# 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

## A Report of the American College of Cardiology/American Heart Association Task Force on **Clinical Practice Guidelines**

### WRITING COMMITTEE MEMBERS

Paul K. Whelton, MB, MD, MSc, FAHA, Chair Robert M. Carey, MD, FAHA, Vice Chair

Wilbert S. Aronow, MD, FACC, FAHA\* Donald E. Casey, Jr, MD, MPH, MBA, FAHA<sup>+</sup> Karen J. Collins, MBA‡ Cheryl Dennison Himmelfarb, RN, ANP, PhD, FAHA§ Sondra M. DePalma, MHS, PA-C, CLS, AACC Samuel Gidding, MD, FACC, FAHA¶ Kenneth A. Jamerson, MD# Daniel W. Jones, MD, FAHA<sup>+</sup> Eric J. MacLaughlin, PharmD\*\* Paul Muntner, PhD, FAHA<sup>+</sup>

### Bruce Ovbiagele, MD, MSc, MAS, MBA, FAHA<sup>+</sup> Sidney C. Smith, Jr, MD, MACC, FAHA++ Crystal C. Spencer, JD‡ Randall S. Stafford, MD, PhD‡‡ Sandra J. Taler, MD, FAHA§§ Randal J. Thomas, MD, MS, FACC, FAHA Kim A. Williams, Sr, MD, MACC, FAHA<sup>+</sup> Jeff D. Williamson, MD, MHS¶¶ Association. Jackson T. Wright, Jr, MD, PhD, FAHA##

## **ACC/AHA TASK FORCE MEMBERS**

Glenn N. Levine, MD, FACC, FAHA, Chair Patrick T. O'Gara, MD, MACC, FAHA, Chair-Elect

Sana M. Al-Khatib, MD, MHS, FACC, FAHA Joshua A. Beckman, MD, MS, FAHA Kim K. Birtcher, MS, PharmD, AACC Biykem Bozkurt, MD, PhD, FACC, FAHA\*\*\* Ralph G. Brindis, MD, MPH, MACC\*\*\* Joaquin E. Cigarroa, MD, FACC Lesley H. Curtis, PhD, FAHA\*\*\* Anita Deswal, MD, MPH, FACC, FAHA Lee A. Fleisher, MD, FACC, FAHA

Jonathan L. Halperin, MD, FACC, FAHA, Immediate Past Chair Federico Gentile, MD, FACC Samuel Gidding, MD, FAHA\*\*\* Zachary D. Goldberger, MD, MS, FACC, FAHA Mark A. Hlatky, MD, FACC, FAHA John Ikonomidis, MD, PhD, FAHA José A. Joglar, MD, FACC, FAHA Laura Mauri, MD, MSc, FAHA Susan J. Pressler, PhD, RN, FAHA\*\*\* Barbara Riegel, PhD, RN, FAHA

Duminda N. Wijeysundera, MD, PhD

\*American Society for Preventive Cardiology Representative. \*ACC/AHA Representative. \*Lay Volunteer/Patient Representative. §Preventive Cardiovascular Nurses Association Representative. American Academy of Physician Assistants Representative. ¶Task Force Liaison. #Association of Black Cardiologists Representative. \*\*American Pharmacists Association Representative. ++ACC/AHA Prevention Subcommittee Liaison. ++American College of Preventive Medicine Representative. §§American Society of Hypertension Representative. Performance Measures Liaison. ¶¶American Geriatrics Society Representative. ##National Medical Association Representative. \*\*\*Former Task Force member; current member during the writing effort.

This document was approved by the American College of Cardiology Clinical Policy Approval Committee and the American Heart Association Science Advisory and Coordinating Committee in September 2017, and by the American Heart Association Executive Committee in October 2017.

The Comprehensive RWI Data Supplement table is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYP.0000000000000065/-/DC1.

The online Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYP.0000000000000065/-/DC2.

The American Heart Association requests that this document be cited as follows: Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2017; • :e • • • • • • •

This article has been copublished in the Journal of the American College of Cardiology.

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.acc.org) and the American Heart Association (professional.heart.org). A copy of the document is available at http://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

Expert peer review of AHA Scientific Statements is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit http://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at http://www.heart.org/HEARTORG/General/Copyright-Permission-

Guidelines\_UCM\_300404\_Article.jsp. A link to the "Copyright Permissions Request Form" appears on the right side of the page.

### (Hypertension. 2017;00:e000-e000.)

© 2017 by the American College of Cardiology Foundation and the American Heart Association, Inc.

Hypertension is available at http://hyper.ahajournals.org

Preamble	6
1. Introduction	10
1.1. Methodology and Evidence Review	10
1.2. Organization of the Writing Committee	10
1.3. Document Review and Approval	11
1.4. Scope of the Guideline	12
1.5. Abbreviations and Acronyms	14
2. BP and CVD Risk	17
2.1. Observational Relationship	17
2.2. BP Components	17
2.3. Population Risk	18
2.4. Coexistence of Hypertension and Related Chronic Conditions	19
3. Classification of BP	21
3.1. Definition of High BP	21
3.2. Lifetime Risk of Hypertension	23
3.3. Prevalence of High BP	23
3.4. Awareness, Treatment, and Control	26
4. Measurement of BP	erican
4.1. Accurate Measurement of BP in the Office	sociatio 27
4.2. Out-of-Office and Self-Monitoring of BP	29
4.3. Ambulatory BP Monitoring	31
4.4. Masked and White Coat Hypertension	33
5. Causes of Hypertension	
5.1. Genetic Predisposition	39
5.2. Environmental Risk Factors	39
5.2.1. Overweight and Obesity	40
5.2.2. Sodium Intake	40
5.2.3. Potassium	40
5.2.4. Physical Fitness	41
5.2.5. Alcohol	41
5.3. Childhood Risk Factors and BP Tracking	43
5.4. Secondary Forms of Hypertension	43
5.4.1. Drugs and Other Substances With Potential to Impair BP Control	
5.4.2. Primary Aldosteronism	51
5.4.3. Renal Artery Stenosis	53
5.4.4. Obstructive Sleep Apnea	54
6. Nonpharmacological Interventions	55
6.1. Strategies	55
6.2. Nonpharmacological Interventions	56
7. Patient Evaluation	56
7.1. Laboratory Tests and Other Diagnostic Procedures	
7.2. Cardiovascular Target Organ Damage	67
8. I reatment of High BP	
8.1. Pharmacological Treatment	
8.1.1. Initiation of Pharmacological BP Treatment in the Context of Overall CVD Risk	69

# 2017 High Blood Pressure Clinical Practice Guideline

8.1.2. BP Treatment Threshold and the Use of CVD Risk Estimation to Guide Drug Treatment of	
Hypertension	71
8.1.3. Follow-Up After Initial BP Evaluation	77
8.1.4. General Principles of Drug Therapy	78
8.1.5. BP Goal for Patients With Hypertension	82
8.1.6. Choice of Initial Medication	83
8.2. Achieving BP Control in Individual Patients	88
8.3. Follow-Up of BP During Antihypertensive Drug Therapy	89
8.3.1. Follow-Up After Initiating Antihypertensive Drug Therapy	89
8.3.2. Monitoring Strategies to Improve Control of BP in Patients on Drug Therapy for High BP	90
9. Hypertension in Patients With Comorbidities	90
9.1. Stable Ischemic Heart Disease	91
9.2. Heart Failure	91
9.2.1. Heart Failure With Reduced Ejection Fraction	96
9.2.2. Heart Failure With Preserved Ejection Fraction	97
9.3. Chronic Kidney Disease	. 100
9.3.1. Hypertension After Renal Transplantation	. 105
9.4. Cerebrovascular Disease	. 106
9.4.1. Acute Intracerebral Hemorrhage	107
9.4.2. Acute Ischemic Stroke	. 109
9.4.3. Secondary Stroke Prevention	. 112
9.5. Peripheral Arterial Disease	. 115
9.6. Diabetes Mellitus	.116
9.7. Metabolic Syndrome	. 119
9.8. Atrial Fibrillation	.120
9.9. Valvular Heart Disease	.121
9.10. Aortic Disease	. 122
10. Special Patient Groups	.123
10.1. Race and Ethnicity	. 123
10.1.1 Racial and Ethnic Differences in Treatment	. 125
10.2. Sex-Related Issues	. 127
10.2.1. Women	. 127
10.2.2. Pregnancy	. 127
10.3. Age-Related Issues	. 130
10.3.1. Older Persons	. 130
10.3.2. Children and Adolescents	. 132
11. Other Considerations	.133
11.1. Resistant Hypertension	.133
11.2. Hypertensive Crises—Emergencies and Urgencies	. 137
11.3. Cognitive Decline and Dementia	. 143
11.4. Sexual Dysfunction and Hypertension	. 145
11.5. Patients Undergoing Surgical Procedures	. 146
12. Strategies to Improve Hypertension Treatment and Control	. 149
12.1. Adherence Strategies for Treatment of Hypertension	. 149
12.1.1. Antihypertensive Medication Adherence Strategies	. 150
12.1.2. Strategies to Promote Lifestyle Modification	. 151
12.1.3. Improving Quality of Care for Resource-Constrained Populations	. 152

### 2017 High Blood Pressure Clinical Practice Guideline

12.2. Structured, Team-Based Care Interventions for Hypertension Control	153
12.3. Health Information Technology–Based Strategies to Promote Hypertension Control	155
12.3.1. EHR and Patient Registries	155
12.3.2. Telehealth Interventions to Improve Hypertension Control	155
12.4. Improving Quality of Care for Patients With Hypertension	157
12.4.1. Performance Measures	157
12.4.2. Quality Improvement Strategies	158
12.5. Financial Incentives	159
13. The Plan of Care for Hypertension	160
13.1. Health Literacy	161
13.2. Access to Health Insurance and Medication Assistance Plans	161
13.3. Social and Community Services	162
14. Summary of BP Thresholds and Goals for Pharmacological Therapy	164
15. Evidence Gaps and Future Directions	165
Appendix 1. Author Relationships With Industry and Other Entities (Relevant)	168
Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)	174



Heart

# Preamble

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines (guidelines) with recommendations to improve cardiovascular health. In 2013, the National Heart, Lung, and Blood Institute (NHLBI) Advisory Council recommended that the NHLBI focus specifically on reviewing the highest-quality evidence and partner with other organizations to develop recommendations (1, 2). Accordingly, the ACC and AHA collaborated with the NHLBI and stakeholder and professional organizations to complete and publish 4 guidelines (on assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, management of blood cholesterol in adults, and management of overweight and obesity in adults) to make them available to the widest possible constituency. In 2014, the ACC and AHA, in partnership with several other professional societies, initiated a guideline on the prevention, detection, evaluation, and management of high blood pressure (BP) in adults. Under the management of the ACC/AHA Task Force, a Prevention Subcommittee was appointed to help guide development of the suite of guidelines on prevention of cardiovascular disease (CVD). These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a cornerstone for quality cardiovascular care. The ACC and AHA sponsor the development and publication of guidelines without commercial support, and members of each organization volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA.

### **Intended Use**

Practice guidelines provide recommendations applicable to patients with or at risk of developing CVD. The focus is on medical practice in the United States, but guidelines developed in collaboration with other organizations can have a global impact. Although guidelines may be used to inform regulatory or payer decisions, they are intended to improve patients' quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

### **Clinical Implementation**

Management in accordance with guideline recommendations is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

### Methodology and Modernization

The ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine (3, 4), and on the basis of internal reevaluation. Similarly, the presentation and delivery of guidelines are reevaluated and modified on the basis of evolving technologies and other factors to facilitate optimal dissemination of information to healthcare professionals at the point of care.

Toward this goal, this guideline continues the introduction of an evolved format of presenting guideline recommendations and associated text called the "modular knowledge chunk format." Each modular "chunk" includes a table of related recommendations, a brief synopsis, recommendation-specific supportive text, and when appropriate, flow diagrams or additional tables. References are provided within the modular chunk itself to facilitate quick review. Additionally, this format will facilitate seamless updating of guidelines with focused updates as new evidence is published, as well as content tagging for rapid electronic retrieval of related recommendations on a topic of interest. This evolved approach format was instituted when this guideline was near completion; therefore, the present document represents a

transitional format that best suits the text as written. Future guidelines will fully implement this format, including provisions for limiting the amount of text in a guideline.

Recognizing the importance of cost–value considerations in certain guidelines, when appropriate and feasible, an analysis of the value of a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology (5).

To ensure that guideline recommendations remain current, new data are reviewed on an ongoing basis, with full guideline revisions commissioned in approximately 6-year cycles. Publication of new, potentially practice-changing study results that are relevant to an existing or new drug, device, or management strategy will prompt evaluation by the Task Force, in consultation with the relevant guideline writing committee, to determine whether a focused update should be commissioned. For additional information and policies regarding guideline development, we encourage readers to consult the ACC/AHA guideline methodology manual (6) and other methodology articles (7-10).

### **Selection of Writing Committee Members**

The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds. Writing committee members represent different geographic regions, sexes, ethnicities, races, intellectual perspectives/biases, and scopes of clinical practice. The Task Force may also invite organizations and professional societies with related interests and expertise to participate as partners, collaborators, or endorsers.

### **Relationships With Industry and Other Entities**



The ACC and AHA have rigorous policies and methods to ensure that guidelines are developed without bias or improper influence. The complete relationships with industry and other entities (RWI) policy can be found <u>at http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy</u>. Appendix 1 of the present document lists writing committee members' relevant RWI. For the purposes of full transparency, writing committee members' comprehensive disclosure information is available online (<u>http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYP.00000000000000000005/-/DC1</u>). Comprehensive disclosure information for the Task Force is available at <u>http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces</u>.

### Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data (6-9). Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee (ERC) is commissioned when there are 1 or more questions deemed of utmost clinical importance that merit formal systematic review. The systematic review will determine which patients are most likely to benefit from a drug, device, or treatment strategy and to what degree. Criteria for commissioning an ERC and formal systematic review include: a) the absence of a current authoritative systematic review, b) the feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, c) the relevance to a substantial number of patients, and d) the likelihood that the findings can be translated into actionable recommendations. ERC members may include methodologists, epidemiologists, healthcare providers, and biostatisticians. The recommendations developed by the writing committee on the basis of the systematic review are marked with "SR".

### **Guideline-Directed Management and Therapy**

The term guideline-directed management and therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm the dosage by reviewing product insert material and evaluate the treatment regimen for contraindications and interactions. The recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

### **Class of Recommendation and Level of Evidence**

The Class of Recommendation (COR) indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence that supports the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1) (6-8).

*Glenn N. Levine, MD, FACC, FAHA Chair, ACC/AHA Task Force on Clinical Practice Guidelines* 

> American Heart Association

# Hypertension

### Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated August 2015)

### **CLASS (STRENGTH) OF RECOMMENDATION** CLASS I (STRONG) Benefit >>> Risl Suggested phrases for writing recommendations: Is recommended Is indicated/useful/effective/beneficial Should be performed/administered/other Comparative-Effectiveness Phrases†: • Treatment/strategy A is recommended/indicated in preference to treatment B Treatment A should be chosen over treatment B Suggested phrases for writing recommendations: Is reasonable Can be useful/effective/beneficial Comparative-Effectiveness Phrases†: Treatment/strategy A is probably recommended/indicated in preference to treatment B It is reasonable to choose treatment A over treatment B CLASS IIb (WEAK) Suggested phrases for writing recommendations: May/might be reasonable May/might be considered Usefulness/effectiveness is unknown/unclear/uncertain or not well established Benefit = Risk CLASS III: No Benefit (MODERATE) Suggested phrases for writing recommendations: Is not recommended Is not indicated/useful/effective/beneficial Should not be performed/administered/other CLASS III: Harm (STRONG) **Risk > Benefit** Suggested phrases for writing recommendations:

# Potentially harmful

- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

### LEVEL (QUALITY) OF EVIDENCE<sup>±</sup>

### LEVEL A

- High-quality evidence<sup>‡</sup> from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

### LEVEL B-R

LEVEL B-NR

- Moderate-quality evidence<sup>‡</sup> from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

### (Nonrandomized)

(Randomized)

- Moderate-quality evidencet from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

### Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

- \* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).
- † For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
- ‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

- Gibbons GH, Harold JG, Jessup M, et al. The next steps in developing clinical practice guidelines for prevention. Circulation. 2013;128:1716-7.
- 2. Gibbons GH, Shurin SB, Mensah GA, et al. Refocusing the agenda on cardiovascular guidelines: an announcement from the National Heart, Lung, and Blood Institute. Circulation. 2013;128:1713-5.
- 3. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (U.S.). Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011.

### 2017 High Blood Pressure Clinical Practice Guideline

- Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (U.S.). Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: National Academies Press; 2011.
- Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129:2329-45.
- 6. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association, 2010. Available at: http://assets.cardiosource.com/Methodology\_Manual\_for\_ACC\_AHA\_Writing\_Committees.pdf and http://professional.heart.org/idc/groups/ahamah-
- public/@wcm/@sop/documents/downloadable/ucm\_319826.pdf. Accessed September 15, 2017.
  7. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016;133:1426-8.
- Jacobs AK, Kushner FG, Ettinger SM. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:268-310.
- Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:1208-17.
- 10. Arnett DK, Goodman RA, Halperin JL, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Department of Health and Human Services. Circulation. 2014;130:1662-7.

# 1. Introduction

As early as the 1920s, and subsequently in the 1959 Build and Blood Pressure Study (1) of almost 5 million adults insured between 1934 and 1954, a strong direct relationship was noted between level of BP and risk of clinical complications and death. In the 1960s, these findings were confirmed in a series of reports from the Framingham Heart Study (2). The 1967 and 1970 Veterans Administration Cooperative Study Group reports ushered in the era of effective treatment for high BP (3, 4). The first comprehensive guideline for detection, evaluation, and management of high BP was published in 1977, under the sponsorship of the NHLBI (5). In subsequent years, a series of Joint National Committee (JNC) BP guidelines were published to assist the practice community and improve prevention, awareness, treatment, and control of high BP (5-7). The present guideline updates prior JNC reports.

# 1.1. Methodology and Evidence Review

An extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted between February and August 2015. Key search words included but were not limited to the following: *adherence; aerobic; alcohol intake; ambulatory care; antihypertensive: agents, drug, medication, therapy; beta adrenergic blockers; blood pressure: arterial, control, determination, devices, goal, high, improve, measurement, monitoring, ambulatory; calcium channel blockers; diet; diuretic agent; drug therapy; heart failure: diastolic, systolic; hypertension: white coat, masked, ambulatory, isolated ambulatory, isolated clinic, diagnosis, reverse white coat, prevention, therapy, treatment, control;* 

intervention; lifestyle: measures, modification; office visits; patient outcome; performance measures; physical activity; potassium intake; protein intake; renin inhibitor; risk reduction: behavior, counseling; screening; sphygmomanometers; spironolactone; therapy; treatment: adherence, compliance, efficacy, outcome, protocol, regimen; weight. Additional relevant studies published through June 2016, during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables included in the Online Data Supplement (http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYP.0000000000000065/-/DC2) summarize the evidence used by the writing committee to formulate recommendations.

As noted in the preamble, an independent ERC was commissioned to perform a formal systematic review of 4 critical clinical questions related to hypertension (Table 2), the results of which were considered by the writing committee for incorporation into this guideline. Concurrent with this process, writing committee members evaluated other published data relevant to the guideline. The findings of the ERC and the writing committee members were formally presented and discussed, and then guideline recommendations were developed. The systematic review report, "Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults," is published in conjunction with this guideline (8), and its respective data supplements are available online (http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYP.000000000000067/-/DC2). No writing committee member reported a RWI. Drs. Whelton, Wright, and Williamson had leadership roles in SPRINT (Systolic Blood Pressure Intervention Trial). Dr. Carey chaired committee discussions in which the SPRINT results were considered.

Question Number	Question	Section Number
1	Is there evidence that self-directed monitoring of BP and/or ambulatory BP monitoring are superior to office-based measurement of BP by a healthcare worker for 1) preventing adverse outcomes for which high BP is a risk factor and 2) achieving better BP control?	4.2
2	What is the optimal target for BP lowering during antihypertensive therapy in adults?	8.1.5
		9.3
		9.6
3	In adults with hypertension, do various antihypertensive drug classes differ in their	8.1.6
	comparative benefits and harms?	8.2
4	In adults with hypertension, does initiating treatment with antihypertensive pharmacological monotherapy versus initiating treatment with 2 drugs (including fixed- dose combination therapy), either of which may be followed by the addition of sequential drugs, differ in comparative benefits and/or harms on specific health outcomes?	8.1.6.1

<b>Table 2. Systematic Review</b>	v Questions on	High BP	in Adults
-----------------------------------	----------------	---------	-----------

BP indicates blood pressure.

# **1.2.** Organization of the Writing Committee

The writing committee consisted of clinicians, cardiologists, epidemiologists, internists, an endocrinologist, a geriatrician, a nephrologist, a neurologist, a nurse, a pharmacist, a physician assistant, and 2 lay/patient representatives. It included representatives from the ACC, AHA, American Academy of Physician Assistants (AAPA), Association of Black Cardiologists (ABC), American College of Preventive Medicine (ACPM), American Geriatrics Society (AGS), American Pharmacists Association (APhA), American

Society of Hypertension (ASH), American Society for Preventive Cardiology (ASPC), National Medical Association (NMA), and Preventive Cardiovascular Nurses Association (PCNA).

# 1.3. Document Review and Approval

This document was reviewed by 2 official reviewers nominated by the ACC and AHA; 1 reviewer each from the AAPA, ABC, ACPM, AGS, APhA, ASH, ASPC, NMA, and PCNA; and 38 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC, AHA, AAPA, ABC, ACPM, AGS, APhA, ASH, ASPC, NMA, and PCNA.

# 1.4. Scope of the Guideline

The present guideline is intended to be a resource for the clinical and public health practice communities. It is designed to be comprehensive but succinct and practical in providing guidance for prevention, detection, evaluation, and management of high BP. It is an update of the NHLBI publication, "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure" (JNC 7) (7). It incorporates new information from studies of office-based BP-related risk of CVD, ambulatory blood pressure monitoring (ABPM), home blood pressure monitoring (HBPM), telemedicine, and various other areas. This guideline does not address the use of BP-lowering medications for the purposes of prevention of recurrent CVD events in patients with stable ischemic heart disease (SIHD) or chronic heart failure (HF) in the absence of hypertension; these topics are the focus of other ACC/AHA guidelines (9, 10). In developing the present guideline, the writing committee reviewed prior published guidelines, evidence reviews, and related statements. Table 3 contains a list of publications and statements deemed pertinent to this writing effort and is intended for use as a resource, thus obviating the need to repeat existing guideline recommendations.

litle	Organization	Publication Year
Guidelines		
Lower-extremity peripheral artery	AHA/ACC	2016 (11)
disease		
Management of primary	Endocrine Society	2016 (12)
aldosteronism: case detection,		
diagnosis, and treatment		
Stable ischemic heart disease	ACC/AHA/AATS/PCNA/SCAI/STS	2014 (13)*2012 (9)
Pheochromocytoma and	Endocrine Society	2014 (14)
paraganglioma		
Atrial fibrillation	AHA/ACC/HRS	2014 (15)
Valvular heart disease	ACC/AHA	2017 (16)
Assessment of cardiovascular risk	ACC/AHA	2013 (17)
Hypertension in pregnancy	ACOG	2013 (18)
Heart failure	ACC/AHA	2017 (19)
		2013 (10)
Lifestyle management to reduce	AHA/ACC	2013 (20)
cardiovascular risk		
Management of arterial	ESH/ESC	2013 (21)
hypertension		

Table 3. Associated Guidelines and Stateme
--

Management of overweight and obesity in adults	AHA/ACC/TOS	2013 (22)
ST-elevation myocardial infarction	ΑCC/ΑΗΑ	2013 (23)
Treatment of blood cholesterol to		2013 (24)
reduce atherosclerotic		2013 (24)
cardiovascular risk in adults		
Cardiovascular diseases during	FSC	2011 (25)
pregnancy	200	2011 (23)
Effectiveness-based guidelines for	ΔΗΔ/ΔΟΟ	2011 (26)
the prevention of cardiovascular	, any ree	2011 (20)
disease in women		
Secondary prevention and risk-	AHA/ACC	2011 (27)
reduction therapy for patients with		2011(27)
coronary and other atherosclerotic		
vascular disease		
Assessment of cardiovascular risk in	ACC/AHA	2010 (28)
asymptomatic adults		()
Thoracic aortic disease	ACC/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/	2010 (29)
	STS/SVM	()
Diagnosis, evaluation, and	NHLBI	2004 (30)
treatment of high blood pressure in		American
children and adolescents		Association
Statements		
Salt sensitivity of blood pressure	АНА	2016 (31)
Cardiovascular team-based care and	ACC	2015 (32)
the role of advanced practice		
providers		
Treatment of hypertension in	AHA/ACC/ASH	2015 (33)
patients with coronary artery		
disease		
Ambulatory blood pressure	AHA	2014 (34)
monitoring in children and		
adolescents		
An effective approach to high blood	AHA/ACC/CDC	2014 (35)
pressure control		
Ambulatory blood pressure	ESH	2013 (36)
monitoring		
Performance measures for adults	ACC/AHA/AMA-PCPI	2011 (37)
with coronary artery disease and		
hypertension		
Interventions to promote physical	AHA	2010 (38)
activity and dietary lifestyle changes		
for cardiovascular risk factor		
reduction in adults		
Resistant hypertension: diagnosis,	AHA	2008 (39)
evaluation and treatment		

\*The full-text SIHD guideline is from 2012 (9). A focused update was published in 2014 (13).

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ACOG, American College of Obstetricians and Gynecologists; ACR, American College of Radiology; AHA, American Heart Association; AMA, American Medical Association; ASA, American Stroke Association; ASH, American Society of Hypertension; CDC, Centers for Disease Control and Prevention; ESC, European Society of Cardiology; ESH, European Society of

Hypertension; HRS, Heart Rhythm Society; NHLBI, National Heart, Lung, and Blood Institute; PCNA, Preventive Cardiovascular Nurses Association; PCPI, Physician Consortium for Performance Improvement; SCA, Society of Cardiovascular Anesthesiologists; SCAI, Society for Cardiovascular Angiography and Interventions; SIHD, stable ischemic heart disease; SIR, Society of Interventional Radiology; STS, Society of Thoracic Surgeons; SVM, Society for Vascular Medicine; and TOS, The Obesity Society.

1.5. Ab	breviations	and Acror	ıyms
---------	-------------	-----------	------

Abbreviation/Acronym	Meaning/Phrase	
ABPM	ambulatory blood pressure monitoring	
ACE	angiotensin-converting enzyme	1
AF	atrial fibrillation	
ARB	angiotensin receptor blocker	
BP	blood pressure	1
CCB	calcium channel blocker	
CHD	coronary heart disease	
CKD	chronic kidney disease	
СРАР	continuous positive airway pressure	
CVD	cardiovascular disease	
DBP	diastolic blood pressure	<b>American</b>
DM	diabetes mellitus	Heart Association
ECG	electrocardiogram	Association
ESRD	end-stage renal disease	1
GDMT	guideline-directed management and therapy	1
GFR	glomerular filtration rate	1
НВРМ	home blood pressure monitoring	<b>1</b> 1
EHR	electronic health record	
HF	heart failure	
HFpEF	heart failure with preserved ejection fraction	
HFrEF	heart failure with reduced ejection fraction	
ICH	intracerebral hemorrhage	
JNC	Joint National Commission	
LV	left ventricular	
LVH	left ventricular hypertrophy	
MI	myocardial infarction	
MRI	magnetic resonance imaging	
PAD	peripheral artery disease	
RAS	renin-angiotensin system	
RCT	randomized controlled trial	]
SBP	systolic blood pressure	
SIHD	stable ischemic heart disease	]
TIA	transient ischemic attack	

- 1. Society of Actuaries. Build and Blood Pressure Study. Vol 1. Ann Arbor, MI: The University of Michigan; 1959.
- 2. Dawber TR. The Framingham Study: The Epidemiology of Atherosclerotic Disease. Cambridge, MA: Harvard University Press; 1980.
- 3. Effects of treatment on morbidity in hypertension. I. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967;202:1028-34.

### 2017 High Blood Pressure Clinical Practice Guideline

- 4. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA. 1970;213:1143-52.
- 5. Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A cooperative study. JAMA. 1977;237:255-61.
- 6. Moser M, Roccella EJ. The treatment of hypertension: a remarkable success story. J Clin Hypertens (Greenwich). 2013;15:88-91.
- Chobanian AV, Bakris GL, Black HR, et al; the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-52.
- Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017. In press.
- 9. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354-471.
- 10. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-327.
- 11. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e726-79.
- 12. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101:1889-916.
- 13. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the
- American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2014;130:1749-67.
- 14. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:1915-42.
- 15. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014;130:e199-267.
- Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159-95.
- Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(suppl 2):S49-73.
- 18. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122:1122-31.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137-61.

### 2017 High Blood Pressure Clinical Practice Guideline

- 20. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(suppl 2):S76-99.
- 21. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159-219.
- 22. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129(suppl 2):S102-38.
- 23. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362-425.
- Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(suppl 2):S1-45.
- 25. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147-97.
- 26. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. Circulation. 2011;123:1243-62.
- 27. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. Circulation. 2011;124:2458-73.
- 28. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2010;122:e584-636.
- 29. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121:e266-369.
- National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114:555-76.
- 31. Elijovich F, Weinberger MH, Anderson CAM, et al. Salt sensitivity of blood pressure: a scientific statement from the American Heart Association. Hypertension. 2016;68:e7-46.
- 32. Brush JE Jr, Handberg EM, Biga C, et al. 2015 ACC health policy statement on cardiovascular team-based care and the role of advanced practice providers. J Am Coll Cardiol. 2015;65:2118-36.
- 33. Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Circulation. 2015;131:e435-70.
- 34. Flynn JT, Daniels SR, Hayman LL, et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension. 2014;63:1116-35.
- 35. Go AS, Bauman MA, Coleman King SM, et al. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. Hypertension. 2014;63:878-85.
- 36. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31:1731-68.

### 2017 High Blood Pressure Clinical Practice Guideline

- Drozda J Jr, Messer JV, Spertus J, et al. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with coronary artery disease and hypertension: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. Circulation. 2011;124:248-70.
- 38. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. Circulation. 2010;122:406-41.
- 39. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008;51:1403-19.

# 2. BP and CVD Risk

# 2.1. Observational Relationship

Observational studies have demonstrated graded associations between higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) and increased CVD risk (1, 2). In a meta-analysis of 61 prospective studies, the risk of CVD increased in a log-linear fashion from SBP levels <115 mm Hg to >180 mm Hg and from DBP levels <75 mm Hg to >105 mm Hg (1). In that analysis, 20 mm Hg higher SBP and 10 mm Hg higher DBP were each associated with a doubling in the risk of death from stroke, heart disease, or other vascular disease. In a separate observational study including >1 million adult patients ≥30 years of age, higher SBP and DBP were associated with increased risk of CVD incidence and angina, myocardial infarction (MI), HF, stroke, peripheral artery disease (PAD), and abdominal aortic aneurysm, each evaluated separately (2). An increased risk of CVD associated with higher SBP and DBP has been reported across a broad age spectrum, from 30 years to >80 years of age. Although the relative risk of incident CVD associated with higher SBP and DBP is smaller at older ages, the corresponding high BP–related increase in absolute risk is larger in older persons (≥65 years) given the higher absolute risk of CVD at an older age (1).

### References

- 1. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903-13.
- 2. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383:1899-911.

# 2.2. BP Components

Epidemiological studies have evaluated associations of SBP and DBP, as well as derived components of BP measurements (including pulse pressure, mean BP, and mid-BP), with CVD outcomes (Table 4). When considered separately, higher levels of both SBP and DBP have been associated with increased CVD risk (1, 2). Higher SBP has consistently been associated with increased CVD risk after adjustment for, or within strata of, DBP (3-5). In contrast, after consideration of SBP through adjustment or stratification, DBP has not been consistently associated with CVD risk (6, 7). Although pulse pressure and mid-BP have been associated with increased CVD risk independent of SBP and DBP in some studies, SBP (especially) and DBP are prioritized in the present document because of the robust evidence base for these measures in both observational studies and clinical trials and because of their ease of measurement in practice settings (8-11).

BP Measurement	Definition
SBP	First Korotkoff sound*
DBP	Fifth Korotkoff sound*
Pulse pressure	SBP minus DBP
Mean arterial pressure	DBP plus one third pulse pressure <sup>+</sup>
Mid-BP	Sum of SBP and DBP, divided by 2

### **Table 4. BP Measurement Definitions**

\*See Section 4 for a description of Korotkoff sounds.

<sup>+</sup>Calculation assumes normal heart rate.

BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

### References

- 1. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903-13.
- 2. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383:1899-911.
- 3. Rutan GH, Kuller LH, Neaton JD, et al. Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the Multiple Risk Factor Intervention Trial. Circulation. 1988;77:504-14.
- 4. Sesso HD, Stampfer MJ, Rosner B, et al. Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in men. Hypertension. 2000;36:801-7.
- 5. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. Arch Intern Med. 1993;153:598-615.
- 6. Benetos A, Thomas F, Bean K, et al. Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. Arch Intern Med. 2002;162:577-81.
- 7. Lindenstrom E, Boysen G, Nyboe J. Influence of systolic and diastolic blood pressure on stroke risk: a prospective observational study. Am J. Epidemiol. 1995;142:1279-90.
- 8. Zhao L, Song Y, Dong P, et al. Brachial pulse pressure and cardiovascular or all-cause mortality in the general population: a meta-analysis of prospective observational studies. J Clin Hypertens (Greenwich). 2014;16:678-85.
- 9. Mosley WJ, Greenland P, Garside DB, et al. Predictive utility of pulse pressure and other blood pressure measures for cardiovascular outcomes. Hypertension. 2007;49:1256-64.
- 10. Franklin SS, Lopez VA, Wong ND, et al. Single versus combined blood pressure components and risk for cardiovascular disease: the Framingham Heart Study. Circulation. 2009;119:243-50.
- 11. Kodama S, Horikawa C, Fujihara K, et al. Meta-analysis of the quantitative relation between pulse pressure and mean arterial pressure and cardiovascular risk in patients with diabetes mellitus. Am J Cardiol. 2014;113:1058-65.

# 2.3. Population Risk

In 2010, high BP was the leading cause of death and disability-adjusted life years worldwide (1, 2). In the United States, hypertension (see Section 3.1 for definition) accounted for more CVD deaths than any other modifiable CVD risk factor and was second only to cigarette smoking as a preventable cause of death for any reason (3). In a follow-up study of 23,272 U.S. NHANES (National Health and Nutrition Examination Survey) participants, >50% of deaths from coronary heart disease (CHD) and stroke occurred among individuals with hypertension (4). Because of the high prevalence of hypertension and its associated increased risk of CHD, stroke, and end-stage renal disease (ESRD), the population-attributable risk of these outcomes associated with hypertension is high (4, 5). In the population-based ARIC (Atherosclerosis Risk in Communities) study, 25% of the cardiovascular events (CHD, coronary revascularization, stroke, or HF) were attributable to hypertension. In the Northern Manhattan study, the percentage of events attributable to hypertension was higher in women (32%) than in men (19%) and higher in blacks (36%) than in whites (21%) (6). In 2012, hypertension was the second leading assigned cause of ESRD, behind diabetes mellitus (DM), and accounted for 34% of incident ESRD cases in the U.S. population (7).

### 2017 High Blood Pressure Clinical Practice Guideline

### References

- 1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224-60.
- 2. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at Least 110 to 115 mm Hg, 1990-2015. JAMA. 2017;317:165-82.
- 3. Danaei G, Ding EL, Mozaffarian D, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med. 2009;6:e1000058.
- 4. Ford ES. Trends in mortality from all causes and cardiovascular disease among hypertensive and nonhypertensive adults in the United States. Circulation. 2011;123:1737-44.
- 5. Cheng S, Claggett B, Correia AW, et al. Temporal trends in the population attributable risk for cardiovascular disease: the Atherosclerosis Risk in Communities Study. Circulation. 2014;130:820-8.
- 6. Willey JZ, Moon YP, Kahn E, et al. Population attributable risks of hypertension and diabetes for cardiovascular disease and stroke in the northern Manhattan study. J Am Heart Assoc. 2014;3:e001106.
- 7. Saran R, Li Y, Robinson B, et al. US Renal Data System 2014 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis. 2015;66 Svii:S1-305.

# 2.4. Coexistence of Hypertension and Related Chronic Conditions

Re	Recommendation for Coexistence of Hypertension and Related Chronic Conditions				
Refere	References that support the recommendation are summarized in Online Data Supplement 1.				
COR	LOE	Recommendation Association			
		1. Screening for and management of other modifiable CVD risk factors are			
I	B-NR	recommended in adults with hypertension (1, 2).			

### Synopsis

Many adult patients with hypertension have other CVD risk factors; a list of such modifiable and relatively fixed risk factors is provided in Table 5. Among U.S. adults with hypertension between 2009 and 2012, 15.5% were current smokers, 49.5% were obese, 63.2% had hypercholesterolemia, 27.2% had DM, and 15.8% had chronic kidney disease (CKD; defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m<sup>2</sup> and/or urine albumin:creatinine  $\geq$ 300 mg/g) (3).

Not only are CVD risk factors common among adults with hypertension, a higher percentage of adults with CVD risk factors have hypertension. For example, 71% of U.S. adults with diagnosed DM have hypertension (4). In the Chronic Renal Insufficiency Cohort (CRIC), 86% of the participants had hypertension (5). Also, 28.1% of adults with hypertension and CKD in the population-based REGARDS (Reasons for Geographic and Racial Differences in Stroke) study had apparent resistant hypertension (6). In NHANES 1999–2010, 35.7% of obese individuals had hypertension (7). The presence of multiple CVD risk factors in individuals with hypertension results in high absolute risks for CHD and stroke in this population. For example, among U.S. adults with hypertension between 2009 and 2012, 41.7% had a 10-year CHD risk >20%, 40.9% had a risk of 10% to 20%, and only 18.4% had a risk <10% (3).

Modifiable risk factors for CVD that are common among adults with hypertension include cigarette smoking/tobacco smoke exposure, DM, dyslipidemia (including high levels of low-density lipoprotein cholesterol or hypercholesterolemia, high levels of triglycerides, and low levels of high-density lipoprotein cholesterol), overweight/obesity, physical inactivity/low fitness level, and unhealthy diet (8). The relationship between hypertension and other modifiable risk factors is complex and interdependent, with several sharing mechanisms of action and pathophysiology. CVD risk factors affect BP through over activation of the renin-angiotensin-aldosterone system, activation of the sympathetic nervous system, inhibition of the cardiac natriuretic peptide system, endothelial dysfunction, and other mechanisms (9-11). Treating some of the other modifiable risk factors may reduce BP through modification of shared pathology, and CVD risk may be reduced by treating global risk factor burden.

### **Recommendation-Specific Supportive Text**

1. Observational studies have demonstrated that CVD risk factors frequently occur in combination, with  $\geq$ 3 risk factors present in 17% of patients (1). A meta-analysis from 18 cohort studies involving 257,384 patients identified a lifetime risk of CVD death, nonfatal MI, and fatal or nonfatal stroke that was substantially higher in adults with  $\geq$ 2 CVD risk factors than in those with only 1 risk factor (1, 2).

### Table 5. CVD Risk Factors Common in Patients With Hypertension

Modifiable Risk Factors*	Relatively Fixed Risk Factors <sup>+</sup>
<ul> <li>Current cigarette smoking, secondhand smoking</li> </ul>	• CKD
<ul> <li>Diabetes mellitus</li> </ul>	<ul> <li>Family history</li> </ul>
<ul> <li>Dyslipidemia/hypercholesterolemia</li> </ul>	<ul> <li>Increased age</li> </ul>
<ul> <li>Overweight/obesity</li> </ul>	<ul> <li>Low socioeconomic/educational status</li> </ul>
<ul> <li>Physical inactivity/low fitness</li> </ul>	Male sex
Unhealthy diet	<ul> <li>Obstructive sleep apnea</li> </ul>
	<ul> <li>Psychosocial stress</li> </ul>

\*Factors that can be changed and, if changed, may reduce CVD risk.

<sup>+</sup>Factors that are difficult to change (CKD, low socioeconomic/educational status, obstructive sleep apnea (12)), cannot be changed (family history, increased age, male sex), or, if changed through the use of current intervention techniques, may not reduce CVD risk (psychosocial stress) (12).

CKD indicates chronic kidney disease; and CVD, cardiovascular disease.

- 1. Wilson PW, Kannel WB, Silbershatz H, et al. Clustering of metabolic factors and coronary heart disease. Arch Intern Med. 1999;159:1104-9.
- 2. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. N Engl J Med. 2012;366:321-9.
- 3. Egan BM, Li J, Hutchison FN, et al. Hypertension in the United States, 1999 to 2012: progress toward Healthy People 2020 goals. Circulation. 2014;130:1692-9.
- 4. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its-Burden in the United States. Atlanta, GA: U.S. Department of Health and Human Services; 2014.
- 5. Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2010;55:441-51.
- 6. Tanner RM, Calhoun DA, Bell EK, et al. Prevalence of apparent treatment-resistant hypertension among individuals with CKD. Clin J Am Soc Nephrol. 2013;8:1583-90.
- 7. Saydah S, Bullard KM, Cheng Y, et al. Trends in cardiovascular disease risk factors by obesity level in adults in the United States, NHANES 1999-2010. Obesity (Silver Spring). 2014;22:1888-95.
- 8. Castelli WP. Epidemiology of coronary heart disease: the Framingham study. Am J Med. 1984;76:4-12.
- 9. Sarzani R, Salvi F, Dessi-Fulgheri P, et al. Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. J Hypertens. 2008;26:831-43.
- 10. Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation in obese normotensive subjects. Hypertension. 1995;25:560-3.
- 11. Kim J, Montagnani M, Koh KK, et al. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation. 2006;113:1888-904.
- 12. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375:919-31.

# 3. Classification of BP

# 3.1. Definition of High BP

Recommendation for Definition of High BP			
References that support the recommendation are summarized in Online Data Supplement 2.			
COR	LOE	Recommendation	
I	B-NR	1. BP should be categorized as normal, elevated, or stage 1 or 2 hypertension to prevent and treat high BP (Table 6) (1-20).	

### Synopsis

Although a continuous association exists between higher BP and increased CVD risk (see Section 2.1), it is useful to categorize BP levels for clinical and public health decision making. In the present document, BP is categorized into 4 levels on the basis of average BP measured in a healthcare setting (office pressures): normal, elevated, and stage 1 or 2 hypertension (Table 6). Online Data Supplement C illustrates schematically the SBP and DBP categories defining normal BP, elevated BP, and stages 1 and 2 hypertension. This categorization differs from that previously recommended in the JNC 7 report, with stage 1 hypertension now defined as an SBP of 130–139 or a DBP of 80–89 mm Hg, and with stage 2 hypertension in the present document corresponding to stages 1 and 2 in the JNC 7 report (21). The rationale for this categorization is based on observational data related to the association between SBP/DBP and CVD risk, RCTs of lifestyle modification to lower BP, and RCTs of treatment with antihypertensive medication to prevent CVD. The increased risk of CVD among adults with stage 2 hypertension is well established. An increasing number of individual studies and meta-analyses of observational data have reported a gradient of progressively higher CVD risk going from normal BP to elevated BP and stage 1 hypertension (4-10, 12, 13, 16). In many of these meta-analyses, the hazard ratios for CHD and stroke were between 1.1 and 1.5 for the comparison of SBP/DBP of 120–129/80– 84 mm Hg versus <120/80 mm Hg and between 1.5 and 2.0 for the comparison of SBP/DBP of 130–139/85– 89 mm Hg versus <120/80 mm Hg. This risk gradient was consistent across subgroups defined by sex and race/ethnicity. The relative increase in CVD risk associated with higher BP was attenuated but still present among older adults (1). The prevalence of severe hypertension has been declining over time, but approximately 12.3% of U.S. adults with hypertension have an average SBP ≥160 mm Hg or average DBP ≥100 mm Hg (22). Lifestyle modification and pharmacological antihypertensive treatment recommendations for individuals with elevated BP and stages 1 and 2 hypertension are provided in Sections 6 and 8, respectively. The relationship of this classification schema with measurements obtained by ambulatory BP recording and home BP measurements is discussed in Section 4.2.

### **Recommendation-Specific Supportive Text**

1. As was the case in previous BP classification systems, the choice and the naming of the categories were based on a pragmatic interpretation of BP-related CVD risk and benefit of BP reduction in clinical trials. Metaanalyses of observational studies have demonstrated that elevated BP and hypertension are associated with increased risk of CVD, ESRD, subclinical atherosclerosis, and all-cause death (1-17). The recommended BP classification system is most valuable in untreated adults as an aid in decisions about prevention or treatment of high BP. However, it is also useful in assessing the success of interventions to reduce BP.

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Table 6. Categories of BP in Adults\*

\*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category. BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in Section 4); DBP, diastolic blood pressure; and SBP systolic blood pressure.

- 1. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903-13.
- 2. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383:1899-911.
- 3. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957-67.
- 4. Guo X, Zhang X, Guo L, et al. Association between pre-hypertension and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Curr Hypertens Rep. 2013;15:703-16.
- 5. Guo X, Zhang X, Zheng L, et al. Prehypertension is not associated with all-cause mortality: a systematic review and meta-analysis of prospective studies. PLoS ONE. 2013;8:e61796.
- 6. Huang Y, Cai X, Li Y, et al. Prehypertension and the risk of stroke: a meta-analysis. Neurology. 2014;82:1153-61.
- 7. Huang Y, Cai X, Liu C, et al. Prehypertension and the risk of coronary heart disease in Asian and Western populations: a meta-analysis. J Am Heart Assoc. 2015;4:e001519.
- 8. Huang Y, Cai X, Zhang J, et al. Prehypertension and incidence of ESRD: a systematic review and meta-analysis. Am J Kidney Dis. 2014;63:76-83.
- 9. Huang Y, Su L, Cai X, et al. Association of all-cause and cardiovascular mortality with prehypertension: a metaanalysis. Am Heart J. 2014;167:160-8.e1.
- 10. Huang Y, Wang S, Cai X, et al. Prehypertension and incidence of cardiovascular disease: a meta-analysis. BMC Med. 2013;11:177.
- Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
- 12. Lee M, Saver JL, Chang B, et al. Presence of baseline prehypertension and risk of incident stroke: a meta-analysis. Neurology. 2011;77:1330-7.
- 13. Shen L, Ma H, Xiang M-X, et al. Meta-analysis of cohort studies of baseline prehypertension and risk of coronary heart disease. Am J Cardiol. 2013;112:266-71.
- 14. Sundstrom J, Arima H, Jackson R, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Ann Intern Med. 2015;162:184-91.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels--overview and meta-analyses of randomized trials. J Hypertens. 2014;32:2296-304.
- 16. Wang S, Wu H, Zhang Q, et al. Impact of baseline prehypertension on cardiovascular events and all-cause mortality in the general population: a meta-analysis of prospective cohort studies. Int J Cardiol. 2013;168:4857-60.
- 17. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387:435-43.
- 18. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich). 2002;4:393-404.

### 2017 High Blood Pressure Clinical Practice Guideline

- 19. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359:995-1003.
- 20. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: metaanalysis on 11,000 participants from 42 trials. Am J Med. 2009;122:290-300.
- 21. Chobanian AV, Bakris GL, Black HR, et al; the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-52.
- 22. Yoon SS, Gu Q, Nwankwo T, et al. Trends in blood pressure among adults with hypertension: United States, 2003 to 2012. Hypertension. 2015;65:54-61.

# 3.2. Lifetime Risk of Hypertension

Observational studies have documented a relatively high incidence of hypertension over periods of 5 to 10 years of follow-up (1, 2). Thus, there is a much higher long-term population burden of hypertension as BP progressively increases with age. Several studies have estimated the long-term cumulative incidence of developing hypertension (3, 4). In an analysis of 1132 white male medical students (mean age: approximately 23 years at baseline) in the Johns Hopkins Precursors study, 0.3%, 6.5%, and 37% developed hypertension at age 25, 45, and 65 years, respectively (5). In MESA (Multi-Ethnic Study of Atherosclerosis), the percentage of the population developing hypertension over their lifetimes was higher for African Americans and Hispanics than for whites and Asians (3). For adults 45 years of age without hypertension, the 40-year risk of developing hypertension was 93% for African-American, 92% for Hispanic, 86% for white, and 84% for Chinese adults (3). In the Framingham Heart Study, approximately 90% of adults free of hypertension at age 55 or 65 years developed hypertension during their lifetimes (4). All of these estimates were based on use of the 140/90– mm Hg cutpoint for recognition of hypertension and would have been higher had the 130/80–mm Hg cutpoint been used.

### References

- 1. Muntner P, Woodward M, Mann DM, et al. Comparison of the Framingham Heart Study hypertension model with blood pressure alone in the prediction of risk of hypertension: the Multi-Ethnic Study of Atherosclerosis. Hypertension. 2010;55:1339-45.
- 2. Parikh NI, Pencina MJ, Wang TJ, et al. A risk score for predicting near-term incidence of hypertension: the Framingham Heart Study. Ann Intern Med. 2008;148:102-10.
- 3. Carson AP, Howard G, Burke GL, et al. Ethnic differences in hypertension incidence among middle-aged and older adults: the multi-ethnic study of atherosclerosis. Hypertension. 2011;57:1101-7.
- 4. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. JAMA. 2002;287:1003-10.
- 5. Shihab HM, Meoni LA, Chu AY, et al. Body mass index and risk of incident hypertension over the life course: the Johns Hopkins Precursors Study. Circulation. 2012;126:2983-9.

# 3.3. Prevalence of High BP

Prevalence estimates are greatly influenced by the choice of cutpoints to categorize high BP, the methods used to establish the diagnosis, and the population studied (1, 2). Most general population prevalence estimates are derived from national surveys. Table 7 provides estimates for prevalence of hypertension in the U.S. general adult population ( $\geq$ 20 years of age) that are based on the definitions of hypertension recommended in the present guideline and in the JNC 7 report. The prevalence of hypertension among U.S. adults is substantially higher when the definition in the present guideline is used versus the JNC 7 definition (46% versus 32%). However, as described in Section 8.1, nonpharmacological treatment (not antihypertensive medication) is recommended for most U.S. adults who have hypertension as defined in the present guideline but who would not meet the JNC 7 definition for hypertension. As a consequence, the new definition results

in only a small increase in the percentage of U.S. adults for whom antihypertensive medication is recommended in conjunction with lifestyle modification.

The prevalence of hypertension rises dramatically with increasing age and is higher in blacks than in whites, Asians, and Hispanic Americans. NHANES estimates of JNC 7–defined hypertension prevalence have remained fairly stable since the early 2000s (1). Most contemporary population surveys, including NHANES, rely on an average of BP measurements obtained at a single visit (2), which is likely to result in an overestimate of hypertension prevalence compared with what would be found by using an average of  $\geq$ 2 readings taken on  $\geq$ 2 visits (1), as recommended in current and previous BP guidelines (3-5). The extent to which guideline recommendations for use of BP averages from  $\geq$ 2 occasions is followed in practice is unclear. Adding self-report of previously diagnosed hypertension yields a 5% to 10% higher estimate of prevalence (1, 6, 7). Most individuals who were added by use of this expanded definition have been diagnosed as having hypertension by a health professional on >1 occasion, and many have been advised to change their lifestyle (2, 6).

American Heart Association

# Hypertension

	SBP/DBP ≥130/80 mm Hg or Self-		SBP/DBP ≥140/90 mm Hg or Self-	
	Reported Antihypertensive		Reported Antihypertensive Medication‡	
	Medication <sup>+</sup>			
Overall, crude	46%		32%	
	Men (n=4717)	Women (n=4906)	Men (n=4717)	Women (n=4906)
Overall, age-sex	48%	43%	31%	32%
adjusted				
Age group, y				
20–44	30%	19%	11%	10%
45–54	50%	44%	33%	27%
55–64	70%	63%	53%	52%
65–74	77%	75%	64%	63%
75+	79%	85%	71%	78%
Race-ethnicity§				
Non-Hispanic white	47%	41%	31%	30%
Non-Hispanic black	59%	56%	42%	46%
Non-Hispanic Asian	45%	36%	29%	27% American Heart
Hispanic	44%	42%	27%	32% Association.

### Table 7. Prevalence of Hypertension Based on 2 SBP/DBP Thresholds\*†

The prevalence estimates have been rounded to the nearest full percentage.

\*130/80 and 140/90 mm Hg in 9623 participants (≥20 years of age) in NHANES 2011–2014.

<sup>+</sup>BP cutpoints for definition of hypertension in the present guideline.

**‡**BP cutpoints for definition of hypertension in JNC 7.

§Adjusted to the 2010 age-sex distribution of the U.S. adult population.

BP indicates blood pressure; DBP, diastolic blood pressure; NHANES, National Health and Nutrition Examination Survey; and SBP, systolic blood pressure.

- 1. Whelton PK. The elusiveness of population-wide high blood pressure control. Annu Rev Public Health. 2015;36:109-30.
- 2. Crim MT, Yoon SSS, Ortiz E, et al. National surveillance definitions for hypertension prevalence and control among adults. Circ Cardiovasc Qual Outcomes. 2012;5:343-51.
- Chobanian AV, Bakris GL, Black HR, et al; the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-52.
- 4. Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A cooperative study. JAMA. 1977;237:255-61.
- 5. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med. 1993;153:154-83.
- 6. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension. 1995;25:305-13.
- 7. Gee ME, Campbell N, Sarrafzadegan N, et al. Standards for the uniform reporting of hypertension in adults using population survey data: recommendations from the World Hypertension League Expert Committee. J Clin Hypertens (Greenwich). 2014;16:773-81.

# 3.4. Awareness, Treatment, and Control

Prevalence estimates for awareness, treatment, and control of hypertension are usually based on self-reports of the hypertension diagnosis (awareness), use of BP-lowering medications in those with hypertension (treatment), and achievement of a satisfactory SBP/DBP during treatment of hypertension (control). Before the present publication, awareness and treatment in adults were based on the SBP/DBP cutpoints of 140/90 mm Hg, and control was based on an SBP/DBP <140/90 mm Hg. In the U.S. general adult population, hypertension awareness, treatment, and control have been steadily improving since the 1960s (1-4), with NHANES 2009 to 2012 prevalence estimates for men and women, respectively, being 80.2% and 85.4% for awareness, 70.9% and 80.6% for treatment (88.4% and 94.4% in those who were aware), 69.5% and 68.5% for control in those being treated, and 49.3% and 55.2% for overall control in adults with hypertension (5). The NHANES experience may underestimate awareness, treatment, and control of hypertension because it is based on BP estimates derived from an average of readings obtained at a single visit, whereas guidelines recommend use of BP averages of  $\geq 2$  readings obtained on  $\geq 2$  occasions. In addition, the current definition of control excludes the possibility of control resulting from lifestyle change or nonpharmacological interventions. NHANES hypertension control rates have been consistently higher in women than in men (55.3% versus 38.0%) in 2009–2012); in whites than in blacks and Hispanics (41.3% versus 31.1% and 23.6%, respectively, in men, and 57.2% versus 43.2% and 52.9%, respectively, in women, for 2009–2012); and in older than in younger adults (50.5% in adults ≥60 years of age versus 34.4% in patients 18 to 39 years of age for 2011–2012) up to the seventh decade (4, 5), although control rates are considerably lower for those  $\geq$ 75 years (46%) and only 39.8% for adults ≥80 years (6) . In addition, control rates are higher for persons of higher socioeconomic status (43.2% for adults with an income >400% above the U.S. government poverty line versus 30.2% for those below this line in 2003 to 2006) (5). Research studies have repeatedly demonstrated that structured, goal-oriented BP treatment initiatives with feedback and provision of free medication result in a substantial improvement in BP control (7-9). Control rates that are much higher than noted in the general population have been reported in care settings where a systems approach (detailed in Sections 12.2 and 12.3) has been implemented for insured adults (10-12).

- 1. Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the Health Examination Surveys, 1960 to 1991. Hypertension. 1995;26:60-9.
- 2. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA. 2003;290:199-206.
- 3. Egan BM, Li J, Hutchison FN, et al. Hypertension in the United States, 1999 to 2012: progress toward Healthy People 2020 goals. Circulation. 2014;130:1692-9.
- 4. Nwankwo T, Yoon SS, Burt V, et al. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. NCHS Data Brief. 2013;1-8.
- 5. National Center for Health Statistics (U.S.). Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD: National Center for Health Statistics (U.S.); 2014.
- 6. Bromfield SG, Bowling CB, Tanner RM, et al. Trends in hypertension prevalence, awareness, treatment, and control among US adults 80 years and older, 1988-2010. J Clin Hypertens (Greenwich). 2014;16:270-6.
- 7. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-85.
- The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97.
- 9. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA. 2016;315:2673-82.
- 10. Fletcher RD, Amdur RL, Kolodner R, et al. Blood pressure control among US veterans: a large multiyear analysis of blood pressure data from the Veterans Administration health data repository. Circulation. 2012;125:2462-8.

### 2017 High Blood Pressure Clinical Practice Guideline

- 11. Jaffe MG, Lee GA, Young JD, et al. Improved blood pressure control associated with a large-scale hypertension program. JAMA. 2013;310:699-705.
- 12. Jaffe MG, Young JD. The Kaiser Permanente Northern California story: improving hypertension control from 44% to 90% in 13 years (2000 to 2013). J Clin Hypertens (Greenwich). 2016;18:260-1.

# 4. Measurement of BP

# 4.1. Accurate Measurement of BP in the Office

Recommendation for Accurate Measurement of BP in the Office					
COR	LOE	Recommendation			
I	C-EO	<ol> <li>For diagnosis and management of high BP, proper methods are recommended for accurate measurement and documentation of BP (Table 8).</li> </ol>			

### Synopsis

Although measurement of BP in office settings is relatively easy, errors are common and can result in a misleading estimation of an individual's true level of BP. There are various methods for measuring BP in the office. The clinical standard of auscultatory measures calibrated to a column of mercury has given way to oscillometric devices (in part because of toxicological issues with mercury). Oscillometric devices use a sensor that detects oscillations in pulsatile blood volume during cuff inflation and deflation. BP is indirectly calculated from maximum amplitude algorithms that involve population-based data. For this reason, only devices with a validated measurement protocol can be recommended for use (see Section 4.2 for additional details). Many of the newer oscillometric devices automatically inflate multiple times (in 1- to 2-minute intervals), allowing patients to be alone and undisturbed during measurement. Although much of the available BP-related risk information and antihypertensive treatment trial experience have been generated by using "traditional" office methods of BP measurement, there is a growing evidence base supporting the use of automated office BP measurements (1).

### **Recommendation-Specific Supportive Text**

1. Accurate measurement and recording of BP are essential to categorize level of BP, ascertain BP-related CVD risk, and guide management of high BP. Most systematic errors in BP measurement can be avoided by following the suggestions provided in Table 8, including having the patient sit quietly for 5 minutes before a reading is taken, supporting the limb used to measure BP, ensuring the BP cuff is at heart level, using the correct cuff size (Table 9), and, for auscultatory readings, deflating the cuff slowly (2). In those who are already taking medication that affects BP, the timing of BP measurements in relation to ingestion of the patient's medication should be standardized. Because individual BP measurements tend to vary in an unpredictable or random fashion, a single reading is inadequate for clinical decision-making. An average of 2 to 3 BP measurements obtained on 2 to 3 separate occasions will minimize random error and provide a more accurate basis for estimation of BP. In addition to clinicians, other caregivers and patients who perform BP self-monitoring should be trained to follow the checklist in Table 8. Common errors in clinical practice that can lead to inaccurate estimation of BP include failure to allow for a rest period and/or talking with the patient during or immediately before the recording, improper patient positioning (e.g., sitting or lying on an examination table), rapid cuff deflation (for auscultatory readings), and reliance on BPs measured at a single occasion.

Key Steps for Proper BP	Specific Instructions
Measurements	
Step 1: Properly prepare the patient	<ol> <li>Have the patient relax, sitting in a chair (feet on floor, back supported) for &gt;5 min.</li> <li>The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement.</li> <li>Ensure patient has emptied his/her bladder.</li> <li>Neither the patient nor the observer should talk during the rest period or during the measurement.</li> <li>Remove all clothing covering the location of cuff placement.</li> <li>Measurements made while the patient is sitting or lying on an examining</li> </ol>
	table do not fulfill these criteria.
Step 2: Use proper technique for BP measurements	<ol> <li>Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically.*</li> <li>Support the patient's arm (e.g., resting on a desk).</li> <li>Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum).</li> <li>Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used (Table 9).</li> </ol>
	<ol> <li>Either the stethoscope diaphragm or bell may be used for auscultatory readings (5, 6).</li> </ol>
Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	<ol> <li>At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings.</li> <li>Separate repeated measurements by 1–2 min.</li> <li>For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mm Hg above this level for an auscultatory determination of the BP level.</li> <li>For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds.</li> </ol>
Step 4: Properly document accurate BP readings	<ol> <li>Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number.</li> <li>Note the time of most recent BP medication taken before measurements</li> </ol>
Step 5: Average the readings	Use an average of $\geq 2$ readings obtained on $\geq 2$ occasions to estimate the individual's level of BP.
Step 6: Provide BP readings to patient	Provide patients the SBP/DBP readings both verbally and in writing.

### Table 8. Checklist for Accurate Measurement of BP (3, 4)

\*See Section 4.2 for additional guidance.

BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Adapted with permission from Mancia et al. (3) (Oxford University Press), Pickering et al. (2) (American Heart Association, Inc.), and Weir et al. (4) (American College of Physicians, Inc.).

Arm Circumference	Usual Cuff Size
22–26 cm	Small adult
27–34 cm	Adult
35–44 cm	Large adult
45–52 cm	Adult thigh

### Table 9. Selection Criteria for BP Cuff Size for Measurement of BP in Adults

Adapted with permission from Pickering et al. (2) (American Heart Association, Inc.). BP indicates blood pressure.

### References

- 1. Leung AA, Daskalopoulou SS, Dasgupta K, et al. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Can J Cardiol. 2017;33:557-76.
- 2. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation. 2005;111:697-716.
- 3. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159-219.
- 4. Weir MR. In the clinic: hypertension. Ann Intern Med. 2014;161:ITC1-15.
- 5. Liu C, Griffiths C, Murray A, et al. Comparison of stethoscope bell and diaphragm, and of stethoscope tube length, for clinical blood pressure measurement. Blood Press Monit. 2016;21:178-83.
- 6. Kantola I, Vesalainen R, Kangassalo K, et al. Bell or diaphragm in the measurement of blood pressure? J Hypertens. 2005;23:499-503.

# 4.2. Out-of-Office and Self-Monitoring of BP

Recommendation for Out-of-Office and Self-Monitoring of BP			
References that support the recommendation are summarized in Online Data Supplement 3 and			
Systematic Review Report.			
COR	LOE	Recommendation	
I	A <sup>sr</sup>	1. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension (Table 11) and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions (1-4).	

SR indicates systematic review.

### Synopsis

Out-of-office measurement of BP can be helpful for confirmation and management of hypertension. Selfmonitoring of BP refers to the regular measurement of BP by an individual at home or elsewhere outside the clinic setting. Among individuals with hypertension, self-monitoring of BP, without other interventions, has shown limited evidence for treatment-related BP reduction and achievement of BP control (1, 5, 6). However, with the increased recognition of inconsistencies between office and out-of-office BPs (see Section 4.4) and greater reduction in BP being recommended for hypertension control, increased attention is being paid to out-of-office BP readings. Although APBM is generally accepted as the best out-of-office measurement method, HBPM is often a more practical approach in clinical practice. Recommended procedures for the collection of HBPM data are provided in Table 10. If self-monitoring is used, it is important to ensure that the BP measurement device used has been validated with an internationally accepted protocol and the results have been published in a peer-reviewed journal (7). A guide to the relationship between HBPM BP readings

and corresponding readings obtained in the office and by ABPM is presented in Table 11. The precise relationships between office readings, ABPM, and HBPM are unsettled, but there is general agreement that office BPs are often higher than ABPM or HBPM BPs, especially at higher BPs.

### **Recommendation-Specific Supportive Text**

1. Ambulatory BP monitoring (ABPM) is used to obtain out-of-office BP readings at set intervals, usually over a period of 24 hours. Home BP monitoring (HBPM) is used to obtain a record of out-of-office BP readings taken by a patient. Both ABPM and HBPM typically provide BP estimates that are based on multiple measurements. A systematic review conducted by the U.S. Preventive Services Task Force reported that ABPM provided a better method to predict long-term CVD outcomes than did office BPs. It incorporates new information from studies of home blood pressure monitoring (HBPM), ambulatory blood pressure monitoring (ABPM), the relationship of overall CVD risk to the effectiveness of blood pressure lowering, clinical outcomes related to different blood pressure goals, strategies to improve blood pressure control and various other areas.. A small body of evidence suggested, but did not confirm, that HBPM could serve as a similar predictor of outcomes (4). Meta-analyses of RCTs have identified clinically useful reductions in SBP and DBP and achievement of BP goals at 6 months and 1 year when self-monitoring of BP has been used in conjunction with other interventions, compared with usual care. Meta-analyses of RCTs have identified only small net reductions in SBP and DBP at 6 months and 1 year for use of self-monitoring of BP on its own, as compared with usual care (1, 5, 6). See Section 4.4 for additional details of diagnostic classification and Section 12 for additional details of telehealth and out-of-office BP measurement for management of high BP.

### Table 10. Procedures for Use of HBPM (8-10)

### Patient training should occur under medical supervision, including:

- Information about hypertension
- Selection of equipment
- Acknowledgment that individual BP readings may vary substantially
- Interpretation of results

### Devices:

- Verify use of automated validated devices. Use of auscultatory devices (mercury, aneroid, or other) is not generally useful for HBPM because patients rarely master the technique required for measurement of BP with auscultatory devices.
- Monitors with provision for storage of readings in memory are preferred.
- Verify use of appropriate cuff size to fit the arm (Table 9).
- Verify that left/right inter-arm differences are insignificant. If differences are significant, instruct patient to measure BPs in the arm with higher readings.

### Instructions on HBPM procedures:

- Remain still:
  - Avoid smoking, caffeinated beverages, or exercise within 30 min before BP measurements.
  - Ensure ≥5 min of quiet rest before BP measurements.
- Sit correctly:
  - Sit with back straight and supported (on a straight-backed dining chair, for example, rather than a sofa).
  - Sit with feet flat on the floor and legs uncrossed.
  - Keep arm supported on a flat surface (such as a table), with the upper arm at heart level.
- Bottom of the cuff should be placed directly above the antecubital fossa (bend of the elbow).
- Take multiple readings:
  - Take at least 2 readings 1 min apart in morning before taking medications and in evening before supper. Optimally, measure and record BP daily. Ideally, obtain weekly BP readings beginning 2 weeks after a change in the treatment regimen and during the week before a clinic visit.
- Record all readings accurately:
  - Monitors with built-in memory should be brought to all clinic appointments.
  - BP should be based on an average of readings on ≥2 occasions for clinical decision making.

### The information above may be reinforced with videos available online:

http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/SymptomsDiagnosisMonitoringofHighBloodPressure/Home-Blood-Pressure-Monitoring\_UCM\_301874\_Article.jsp#.WcQNfLKGMnM

See Table 11 for HBPM targets.

BP indicates blood pressure; and HBPM, home blood pressure monitoring.

# Table 11. Corresponding Values of SBP/DBP for Clinic, HBPM, Daytime, Nighttime, and 24-Hour ABPM Measurements

Clinic	НВРМ	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; DBP diastolic blood pressure; HBPM, home blood pressure monitoring; and SBP, systolic blood pressure.

### References

- 1. Uhlig K, Balk EM, Patel K, et al. Self-Measured Blood Pressure Monitoring: Comparative Effectiveness. Rockville, MD: Agency for Healthcare Research and Quality (U.S.); 2012.
- 2. Margolis KL, Asche SE, Bergdall AR, et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial. JAMA. 2013;310:46-56.
- 3. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. JAMA. 2014;312:799-808.
- 4. Siu AL. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:778-86.
- 5. Yi SS, Tabaei BP, Angell SY, et al. Self-blood pressure monitoring in an urban, ethnically diverse population: a randomized clinical trial utilizing the electronic health record. Circ Cardiovasc Qual Outcomes. 2015;8:138-45.
- 6. Agarwal R, Bills JE, Hecht TJW, et al. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. Hypertension. 2011;57:29-38.
- 7. O'Brien E, Stergiou GS. The pursuit of accurate blood pressure measurement: a 35-year travail. J Clin Hypertens (Greenwich). 2017;19:746-52.
- 8. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159-219.
- 9. Pickering TG, Miller NH, Ogedegbe G, et al. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. Hypertension. 2008;52:10-29.
- 10. National Clinical Guideline Centre (UK). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. London, UK: Royal College of Physicians (UK); 2011.

# 4.3. Ambulatory BP Monitoring

All of the major RCTs have been based on use of clinic BP readings. However, ABPM is often used to supplement BP readings obtained in office settings (1). The monitors are usually programmed to obtain readings every 15 to 30 minutes throughout the day and every 15 minutes to 1 hour during the night. ABPM is conducted while individuals go about their normal daily activities. ABPM can a) provide estimates of mean BP over the entire monitoring period and separately during nighttime and daytime, b) determine the daytime-to-nighttime BP ratio to identify the extent of nocturnal "dipping," c) identify the early-morning BP surge pattern, d) estimate BP variability, and e) allow for recognition of symptomatic hypotension. The U.S. Centers for Medicaid & Medicare Services and other agencies provide reimbursement for ABPM in patients with

suspected white coat hypertension (2). Medicare claims for ABPM between 2007 and 2010 were reimbursed at a median of \$52 and were submitted for <1% of beneficiaries (3, 4). A list of devices validated for ABPM is available (5, 6).

ABPM and HBPM definitions of high BP use different BP thresholds than those used by the previously mentioned office-based approach to categorize high BP identified in Section 3.1. Table 11 provides best estimates for corresponding home, daytime, nighttime, and 24-hour ambulatory levels of BP, including the values recommended for identification of hypertension with office measurements. Typically, a clinic BP of 140/90 mm Hg corresponds to home BP values of 135/85 mm Hg and to ABPM values defined as a daytime SBP/DBP of 135/85 mm Hg, a nighttime SBP/DBP of 120/70 mm Hg, and a 24-hour SBP/DBP of 130/80 mm Hg (7, 8). These thresholds are based on data from European, Australian, and Asian populations, with few data available for establishing appropriate thresholds for U.S. populations (9-13). They are provided as a guide but should be interpreted with caution. Higher daytime SBP measurements from ABPM can be associated with an increased risk of CVD and all-cause death independent of clinic-measured BP (14). A meta-analysis of observational studies that included 13,844 individuals suggested nighttime BP is a stronger risk factor for CHD and stroke than either clinic or daytime BP (15).

Methodological issues complicate the interpretation of data from studies that report office and outof-office BP readings. Definitions and diagnostic methods for identifying white coat hypertension and masked hypertension (see Section 4.4) have not been standardized. The available studies have differed with regard to number of office readings obtained, use of 24-hour ABPM, use of daytime-only ABPM, inclusion of daytime and nighttime BP readings as separate categories, HBPM for monitoring out-of-office BP levels, and even the BP thresholds used to define hypertension with ABPM or HBPM readings. In addition, there are few data that address reproducibility of these hypertension profiles over time, with several studies suggesting progression of white coat hypertension and especially of masked hypertension to sustained office-measured hypertension (16-22).

- 1. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med. 2006;354:2368-74.
- 2. Tunis SR. Decision Memo for Ambulatory Blood Pressure Monitoring (CAG-00067N). Centers for Medicare and Medicaid Services; October 17, 2001.
- 3. Shimbo D, Kent ST, Diaz KM, et al. The use of ambulatory blood pressure monitoring among Medicare beneficiaries in 2007-2010. J Am Soc Hypertens. 2014;8:891-7.
- 4. Kent ST, Shimbo D, Huang L, et al. Rates, amounts, and determinants of ambulatory blood pressure monitoring claim reimbursements among Medicare beneficiaries. J Am Soc Hypertens. 2014;8:898-908.
- 5. Dabl Educational Trust. Information on validated blood pressure devices and monitors. Available at: http://www.dableducational.org. Accessed September 17, 2017.
- 6. British Hypertension Society. BP Monitors. Available at: http://www.bhsoc.org/bp-monitors/bp-monitors. Accessed September 17, 2017.
- 7. Pickering TG, White WB, American Society of Hypertension Writing Group. ASH position paper: home and ambulatory blood pressure monitoring. When and how to use self (home) and ambulatory blood pressure monitoring. J Clin Hypertens (Greenwich). 2008;10:850-5.
- 8. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31:1731-68.
- 9. Kikuya M, Hansen TW, Thijs L, et al. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10year cardiovascular risk. Circulation. 2007;115:2145-52.
- Niiranen TJ, Asayama K, Thijs L, et al. Outcome-driven thresholds for home blood pressure measurement: international database of home blood pressure in relation to cardiovascular outcome. Hypertension. 2013;61:27-34.
- 11. Head GA, Mihailidou AS, Duggan KA, et al. Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: prospective cohort study. BMJ. 2010;340:c1104.
- 12. Hansen TW, Kikuya M, Thijs L, et al. Diagnostic thresholds for ambulatory blood pressure moving lower: a review based on a meta-analysis-clinical implications. J Clin Hypertens (Greenwich). 2008;10:377-81.

### 2017 High Blood Pressure Clinical Practice Guideline

- 13. Ravenell J, Shimbo D, Booth JN 3rd, et al. Thresholds for ambulatory blood pressure among African Americans in the Jackson Heart Study. Circulation. 2017;135:2470-80.
- 14. Hansen TW, Kikuya M, Thijs L, et al. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. J Hypertens. 2007;25:1554-64.
- 15. Roush GC, Fagard RH, Salles GF, et al. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13,844 patients with hypertension. J Hypertens. 2014;32:2332-40.
- 16. Mancia G, Bombelli M, Facchetti R, et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. Hypertension. 2009;54:226-32.
- 17. Ben-Dov IZ, Ben-Arie L, Mekler J, et al. Reproducibility of white-coat and masked hypertension in ambulatory BP monitoring. Int J Cardiol. 2007;117:355-9.
- 18. Bidlingmeyer I, Burnier M, Bidlingmeyer M, et al. Isolated office hypertension: a prehypertensive state? J Hypertens. 1996;14:327-32.
- 19. Muxfeldt ES, Fiszman R, de Souza F, et al. Appropriate time interval to repeat ambulatory blood pressure monitoring in patients with white-coat resistant hypertension. Hypertension. 2012;59:384-9.
- 20. Palatini P, Winnicki M, Santonastaso M, et al. Prevalence and clinical significance of isolated ambulatory hypertension in young subjects screened for stage 1 hypertension. Hypertension. 2004;44:170-4.
- 21. Trudel X, Milot A, Brisson C. Persistence and progression of masked hypertension: a 5-year prospective study. Int J Hypertens. 2013;2013:836387.
- 22. Ugajin T, Hozawa A, Ohkubo T, et al. White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama study. Arch Intern Med. 2005;165:1541-6.



# 4.4. Masked and White Coat Hypertension

### **Recommendations for Masked and White Coat Hypertension** References that support recommendations are summarized in Online Data Supplements 4, 5, and 6. COR LOE Recommendation In adults with an untreated SBP greater than 130 mm Hg but less than 160 1. mm Hg or DBP greater than 80 mm Hg but less than 100 mm Hg, it is **B-NR** lla reasonable to screen for the presence of white coat hypertension by using either daytime ABPM or HBPM before diagnosis of hypertension (1-8). 2. In adults with white coat hypertension, periodic monitoring with either C-LD ABPM or HBPM is reasonable to detect transition to sustained hypertension lla (2, 5, 7). 3. In adults being treated for hypertension with office BP readings not at goal lla C- LD and HBPM readings suggestive of a significant white coat effect, confirmation by ABPM can be useful (9, 10). 4. In adults with untreated office BPs that are consistently between 120 mm Hg and 129 mm Hg for SBP or between 75 mm Hg and 79 mm Hg for DBP, lla **B-NR** screening for masked hypertension with HBPM (or ABPM) is reasonable (3, 4, 6, 8, 11). 5. In adults on multiple-drug therapies for hypertension and office BPs within llb C-LD 10 mm Hg above goal, it may be reasonable to screen for white coat effect with HBPM (or ABPM) (3, 7, 12). 6. It may be reasonable to screen for masked uncontrolled hypertension with llb C-EO HBPM in adults being treated for hypertension and office readings at goal, in the presence of target organ damage or increased overall CVD risk. In adults being treated for hypertension with elevated HBPM readings 7. suggestive of masked uncontrolled hypertension, confirmation of the llb C-EO diagnosis by ABPM might be reasonable before intensification of antihypertensive drug treatment.

	Office/Clinic/Healthcare Setting	Home/Nonhealthcare/ABPM Setting
Normotensive	No hypertension	No hypertension
Sustained hypertension	Hypertension	Hypertension
Masked hypertension	No hypertension	Hypertension
White coat hypertension	Hypertension	No hypertension

ABPM indicates ambulatory blood pressure monitoring; and BP, blood pressure.

### Synopsis

The availability of noninvasive BP monitoring techniques has resulted in differentiation of hypertension into several clinically useful categories that are based on the place of BP measurement (Table 12) (1, 13, 14). These include masked hypertension and white coat hypertension, in addition to sustained hypertension. White coat hypertension is characterized by elevated office BP but normal readings when measured outside the office with either ABPM or HBPM. In contrast, masked hypertension is characterized by office readings suggesting normal BP but out-of-office (ABPM/HBPM) readings that are consistently above normal (15). In sustained hypertension, BP readings are elevated in both office and out-of-office settings.

In patients treated for hypertension, both "white coat effect" (higher office BPs than out-of-office BPs) and "masked uncontrolled hypertension" (controlled office BPs but uncontrolled BPs in out-of-office settings) categories have been reported (5, 15, 16). The white coat effect (usually considered clinically significant when office SBP/DBPs are >20/10 mm Hg higher than home or ABPM SBP/DBPs) has been implicated in "pseudo-resistant hypertension" (see Section 11.1) and results in an underestimation of office BP control rates (17, 18). The prevalence of masked hypertension varies from 10% to 26% (mean 13%) in population-based surveys and from 14% to 30% in normotensive clinic populations (6, 16, 19-21).

The risk of CVD and all-cause mortality in persons with masked hypertension is similar to that noted in those with sustained hypertension and about twice as high as the corresponding risk in their normotensive counterparts (3, 4, 6, 8, 11). The prevalence of masked hypertension increases with higher office BP readings (20, 22, 23).

The prevalence of white coat hypertension is higher with increasing age (24), female versus male sex, nonsmoking versus current smoking status, and routine office measurement of BP by clinician observers versus unattended BP measurements. Many, but not all, studies (4, 6, 8, 25, 26) have identified a minimal increase in risk of CVD complications or all-cause mortality in patients who have white coat hypertension. This has resulted in a recommendation by some panels to screen for white coat hypertension with ABPM (or HBPM) to avoid initiating antihypertensive drug treatment in such individuals (2, 5, 27). The white coat effect and masked uncontrolled hypertension appear to follow the risk profiles of their white coat hypertension and masked hypertension counterparts, respectively (3, 12).

There are no data on the risks and benefits of treating white coat and masked hypertension. Despite these methodological differences, the data are consistent in indicating that masked hypertension and masked uncontrolled hypertension are associated with an increased prevalence of target organ damage and risk of CVD, stroke, and mortality compared with normotensive individuals and those with white coat hypertension.

Figure 1 is an algorithm on the detection of white coat hypertension or masked hypertension in patients not on drug therapy. Figure 2 is an algorithm on detection of white coat effect or masked uncontrolled hypertension in patients on drug therapy. Table 12 is a summary of BP patterns based on office and out-of-office measurements.

### Recommendation-Specific Supportive Text

1. White coat hypertension prevalence averages approximately 13% and as high as 35% in some hypertensive populations (1, 2), and ABPM and HBPM are better predictors of CVD risk due to elevated BP than are office BP measurements, with ABPM being the preferred measurement option. The major clinical relevance of white coat hypertension is that it has typically been associated with a minimal to only slightly increased risk of CVD and all-cause mortality risk (3, 4, 7, 11, 24). If ABPM resources are not readily available, HBPM provides a reasonable but less desirable alternative to screen for white coat hypertension, although the overlap with ABPM is only 60% to 70% for detection of white coat hypertension (5, 9, 27-30).

2. The incidence of white coat hypertension converting to sustained hypertension (justifying the addition of antihypertensive drug therapy to lifestyle modification) is 1% to 5% per year by ABPM or HBPM, with a higher incidence of conversion in those with elevated BP, older age, obesity, or black race (2, 7).

3. The overlap between HBPM and both daytime and 24-hour ABPM in diagnosing white coat hypertension is only 60% to 70%, and the data for prediction of CVD risk are stronger with ABPM than with office measurements (5, 9, 27-30). Because a diagnosis of white coat hypertension may result in a decision not to treat or intensify treatment in patients with elevated office BP readings, confirmation of BP control by ABPM in addition to HBPM provides added support for this decision.

4. In contrast to white coat hypertension, masked hypertension is associated with a CVD and all-cause mortality risk twice as high as that seen in normotensive individuals, with a risk range similar to that of patients with sustained hypertension (3, 4, 6, 8, 11, 31). Therefore, out-of-office readings are reasonable to confirm BP control seen with office readings.

5. The white coat effect has been implicated in office-measured uncontrolled hypertension and pseudoresistant hypertension, which may result in BP control being underestimated when subsequently assessed by ABPM (17, 18). The risk of vascular complications in patients with office-measured uncontrolled hypertension with a white coat effect is similar to the risk in those with controlled hypertension (3, 4, 7, 11, 12). White coat hypertension and white coat effect raise the concern that unnecessary antihypertensive drug therapy may be initiated or intensified. Because a diagnosis of white coat hypertension or white coat effect would result in a decision to not treat elevated office BP readings, confirmation of BP control by HBPM (or ABPM) provides more definitive support for the decision not to initiate antihypertensive drug therapy or accelerate treatment.

6. Analogous to masked hypertension in untreated patients, masked uncontrolled hypertension is defined in treated patients with hypertension by office readings suggesting adequate BP control but out-of-office readings (HBPM) that remain consistently above goal (3, 15, 16, 32, 33). The CVD risk profile for masked uncontrolled hypertension appears to follow the risk profile for masked hypertension (3, 12, 34). Although the evidence is consistent in identifying the increased risk of masked uncontrolled hypertension, evidence is lacking on whether the treatment of masked hypertension or masked uncontrolled hypertension reduces clinical outcomes. A suggestion for assessing CVD risk is provided in Section 8.

7. Although both ABPM and HBPM are better predictors of CVD risk than are office BP readings, ABPM confirmation of elevated BP by HBPM might be reasonable because of the more extensive documentation of CVD risk with ABPM. However, unlike the documentation of a significant white coat effect to justify the decision to not treat an elevated clinic BP, it is not mandatory to confirm masked uncontrolled hypertension determined by HBPM.



Figure 1. Detection of White Coat Hypertension or Masked Hypertension in Patients Not on Drug Therapy

Colors correspond to Class of Recommendation in Table 1.

ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; and HBPM, home blood pressure monitoring.




Figure 2. Detection of White Coat Effect or Masked Uncontrolled Hypertension in Patients on Drug Therapy

Colors correspond to Class of Recommendation in Table 1.

See Section 8 for treatment options.

ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; CVD, cardiovascular disease; and HBPM, home blood pressure monitoring.

- 1. Pickering TG, James GD, Boddie C, et al. How common is white coat hypertension? JAMA. 1988;259:225-8.
- 2. Piper MA, Evans CV, Burda BU, et al. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015;162:192-204.
- 3. Ohkubo T, Kikuya M, Metoki H, et al. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. J Am Coll Cardiol. 2005;46:508-15.

- 4. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. J Hypertens. 2007;25:2193-8.
- 5. National Clinical Guideline Centre (UK). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. London, UK: Royal College of Physicians (UK); 2011.
- Asayama K, Thijs L, Li Y, et al. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. Hypertension 2014;64:935-42.
- 7. Mancia G, Bombelli M, Brambilla G, et al. Long-term prognostic value of white coat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. Hypertension. 2013;62:168-74.
- 8. Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. Am J Hypertens. 2011;24:52-8.
- Viera AJ, Hinderliter AL, Kshirsagar AV, et al. Reproducibility of masked hypertension in adults with untreated borderline office blood pressure: comparison of ambulatory and home monitoring. Am J Hypertens. 2010;23:1190-7.
- 10. Viera AJ, Lin F-C, Tuttle LA, et al. Reproducibility of masked hypertension among adults 30 years or older. Blood Press Monit. 2014;19:208-15.
- 11. Stergiou GS, Asayama K, Thijs L, et al. Prognosis of white-coat and masked hypertension: International Database of Home Blood Pressure in Relation to Cardiovascular Outcome. Hypertension. 2014;63:675-82.
- 12. Tomiyama M, Horio T, Yoshii M, et al. Masked hypertension and target organ damage in treated hypertensive patients. Am J Hypertens. 2006;19:880-6.
- 13. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. JAMA. 1983;249:2792-8.
- 14. Pickering TG, Davidson K, Gerin W, et al. Masked hypertension. Hypertension. 2002;40:795-6.
- 15. Banegas JR, Ruilope LM, de la Sierra A, et al. High prevalence of masked uncontrolled hypertension in people with treated hypertension. Eur Heart J. 2014;35:3304-12.
- 16. Gorostidi M, Vinyoles E, Banegas JR, et al. Prevalence of white-coat and masked hypertension in national and international registries. Hypertens Res. 2015;38:1-7.
- 17. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008;51:1403-19.
- 18. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31:1731-68.
- 19. Wang YC, Shimbo D, Muntner P, et al. Prevalence of masked hypertension among US Adults with nonelevated clinic blood pressure. Am J Epidemiol. 2017;185:194-202.
- 20. Peacock J, Diaz KM, Viera AJ, et al. Unmasking masked hypertension: prevalence, clinical implications, diagnosis, correlates and future directions. J Hum Hypertens. 2014;28:521-8.
- 21. Conen D, Aeschbacher S, Thijs L, et al. Age-specific differences between conventional and ambulatory daytime blood pressure values. Hypertension. 2014;64:1073-9.
- 22. Alwan H, Pruijm M, Ponte B, et al. Epidemiology of masked and white-coat hypertension: the family-based SKIPOGH study. PLoS ONE. 2014;9:e92522.
- 23. Shimbo D, Newman JD, Schwartz JE. Masked hypertension and prehypertension: diagnostic overlap and interrelationships with left ventricular mass: the Masked Hypertension Study. Am J Hypertens. 2012;25:664-71.
- 24. Franklin SS, Thijs L, Asayama K, et al. The cardiovascular risk of white-coat hypertension. J Am Coll Cardiol. 2016;68:2033-43.
- 25. Tientcheu D, Ayers C, Das SR, et al. Target organ complications and cardiovascular events associated with masked hypertension and white-coat hypertension: analysis from the Dallas Heart Study. J Am Coll Cardiol. 2015;66:2159-69.
- 26. Briasoulis A, Androulakis E, Palla M, et al. White-coat hypertension and cardiovascular events: a meta-analysis. J Hypertens. 2016;34:593-9.
- 27. Siu AL, U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:778-86.
- 28. Bayo J, Cos FX, Roca C, et al. Home blood pressure self-monitoring: diagnostic performance in white-coat hypertension. Blood Press Monit. 2006;11:47-52.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 29. Nasothimiou EG, Tzamouranis D, Rarra V, et al. Diagnostic accuracy of home vs. ambulatory blood pressure monitoring in untreated and treated hypertension. Hypertens Res. 2012;35:750-5.
- Sega R, Trocino G, Lanzarotti A, et al. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). Circulation. 2001;104:1385-92.
- 31. Hansen TW, Kikuya M, Thijs L, et al. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. J Hypertens. 2007;25:1554-64.
- 32. Diaz KM, Veerabhadrappa P, Brown MD, et al. Prevalence, determinants, and clinical significance of masked hypertension in a population-based sample of African Americans: the Jackson Heart Study. Am J Hypertens. 2015;28:900-8.
- 33. Andalib A, Akhtari S, Rigal R, et al. Determinants of masked hypertension in hypertensive patients treated in a primary care setting. Intern Med J. 2012;42:260-6.
- 34. Terawaki H, Metoki H, Nakayama M, et al. Masked hypertension determined by self-measured blood pressure at home and chronic kidney disease in the Japanese general population: the Ohasama study. Hypertens Res. 2008;31:2129-35.

# 5. Causes of Hypertension

# 5.1. Genetic Predisposition

Hypertension is a complex polygenic disorder in which many genes or gene combinations influence BP (1, 2). Although several monogenic forms of hypertension have been identified, such as glucocorticoid-remediable aldosteronism, Liddle's syndrome, Gordon's syndrome, and others in which single-gene mutations fully explain the pathophysiology of hypertension, these disorders are rare (3). The current tabulation of known genetic variants contributing to BP and hypertension includes more than 25 rare mutations and 120 single-nucleotide polymorphisms (3, 4). However, even with the discovery of multiple single-nucleotide polymorphisms influencing control of BP since completion of the Human Genome Project in 2003, the associated variants have only small effects. Indeed, at present, the collective effect of all BP loci identified through genome-wide association studies accounts for only about 3.5% of BP variability (4). The presence of a high number of small-effect alleles associated with higher BP results in a more rapid increase in BP with age (5). Future studies will need to better elucidate genetic expression, epigenetic effects, transcriptomics, and proteomics that link genotypes with underlying pathophysiological mechanisms.

American

#### References

- 1. Kaplan NM. Primary hypertension: pathogenesis. In: Kaplan's Clinical Hypertension. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:50-121.
- 2. Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. Circ Res. 2015;116:937-59.
- 3. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell. 2001;104:545-56.
- 4. Dominiczak AF, Kuo D. Hypertension: update 2017. Hypertension. 2017;69:3-4.
- 5. Ference BA, Julius S, Mahajan N, et al. Clinical effect of naturally random allocation to lower systolic blood pressure beginning before the development of hypertension. Hypertension. 2014;63:1182-8.

# 5.2. Environmental Risk Factors

Various environmental exposures, including components of diet, physical activity, and alcohol consumption, influence BP. Many dietary components have been associated with high BP (1, 2). Some of the diet-related factors associated with high BP include overweight and obesity, excess intake of sodium, and insufficient intake of potassium, calcium, magnesium, protein (especially from vegetables), fiber, and fish fats. Poor diet, physical inactivity, and excess intake of alcohol, alone or in combination, are the underlying cause of a large proportion of hypertension. Gut microbiota have also been linked to hypertension, especially in experimental

#### 2017 High Blood Pressure Clinical Practice Guideline

animals. (3) Some of the best-proven environmental relationships with high BP are briefly reviewed below, and nonpharmacological interventions to lower BP are discussed in Section 6.2.

#### References

- 1. Savica V, Bellinghieri G, Kopple JD. The effect of nutrition on blood pressure. Annu Rev Nutr. 2010;30:365-401.
- 2. Chan Q, Stamler J, Griep LMO, et al. An update on nutrients and blood pressure. J Atheroscler Thromb. 2016;23:276-89.
- 3. Tang WHW, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120:1183-96.

# 5.2.1. Overweight and Obesity

Insurance industry actuarial reports have identified a striking relationship between body weight and high BP (1) and a direct relationship between overweight/obesity and hypertension (2). Epidemiological studies, including the Framingham Heart Study (3) and the Nurses' Health Study (4), have consistently identified a direct relationship between body mass index and BP that is continuous and almost linear, with no evidence of a threshold (5, 6). The relationship with BP is even stronger for waist-to-hip ratio and computed tomographic measures of central fat distribution (7). Attributable risk estimates from the Nurses' Health Study suggest that obesity may be responsible for about 40% of hypertension, and in the Framingham Offspring Study, the corresponding estimates were even higher (78% in men and 65% in women) (8, 9). The relationship between obesity at a young age and change in obesity status over time is strongly related to future risk of hypertension. In combined data from 4 longitudinal studies begun in adolescence with repeat examination in young adulthood to early middle age, being obese continuously or acquiring obesity was associated with a relative risk of 2.7 for developing hypertension. Becoming normal weight reduced the risk of developing hypertension to a level similar to those who had never been obese (10).

## 5.2.2. Sodium Intake

Sodium intake is positively associated with BP in migrant (11), cross-sectional (12-14), and prospective cohort studies (15) and accounts for much of the age-related increase in BP (11, 16). In addition to the well-accepted and important relationship of dietary sodium with BP, excessive consumption of sodium is independently associated with an increased risk of stroke (17, 18), CVD (19), and other adverse outcomes (20). Certain groups with various demographic, physiological, and genetic characteristics tend to be particularly sensitive to the effects of dietary sodium on BP (21-23). Salt sensitivity is a quantitative trait in which an increase in sodium load disproportionately increases BP (21, 24). Salt sensitivity is especially common in blacks, older adults, and those with a higher level of BP or comorbidities such as CKD, DM, or the metabolic syndrome (25). In aggregate, these groups constitute more than half of all U.S. adults (26). Salt sensitivity may be a marker for increased CVD and all-cause mortality risk independently of BP (27, 28), and the trait has been demonstrated to be reproducible (29). Current techniques for recognition of salt sensitivity are impractical in routine clinical practice, so salt sensitivity is best considered as a group characteristic.

# 5.2.3. Potassium

Potassium intake is inversely related to BP in migrant (30), cross-sectional (13, 16, 31, 32), and prospective cohort (33) studies. It is also inversely related to stroke (34-36). A higher level of potassium seems to blunt the effect of sodium on BP (37), with a lower sodium–potassium ratio being associated with a lower level of BP than that noted for corresponding levels of sodium or potassium on their own (38). Likewise, epidemiological studies suggest that a lower sodium–potassium ratio may result in a reduced risk of CVD as compared with the pattern for corresponding levels of either cation on its own (39).

# 5.2.4. Physical Fitness

Epidemiological studies have demonstrated an inverse relationship between physical activity and physical fitness and level of BP and hypertension (40). Even modest levels of physical activity have been associated with a decrease in the risk of incident hypertension (41). In several observational studies, the relationship between physical activity and BP has been most apparent in white men (40). With the advent of electronic activity trackers and ABPM, it has become increasingly feasible to conduct studies that relate physical activity and BP (42). Physical fitness, measured objectively by graded exercise testing, attenuates the rise of BP with age and prevents the development of hypertension. In the CARDIA (Coronary Artery Risk Development in Young Adults) study (43), physical fitness measured at 18 to 30 years of age in the upper 2 deciles of an otherwise healthy population was associated with one third the risk of developing hypertension 15 years later, and one half the risk after adjustment for body mass index, as compared with the lowest quintile. Change in fitness assessed 7 years later further modified risk (43). In a cohort of men 20 to 90 years of age who were followed longitudinally for 3 to 28 years, higher physical fitness decreased the rate of rise in SBP over time and delayed the time to onset of hypertension (44).

# 5.2.5. Alcohol

The presence of a direct relationship between alcohol consumption and BP was first reported in 1915 (45) and has been repeatedly identified in contemporary cross-sectional and prospective cohort studies (46). Estimates of the contribution of alcohol consumption to population incidence and prevalence of hypertension vary according to level of intake. In the United States, it seems likely that alcohol may account for close to 10% of the population burden of hypertension (higher in men than in women). In contrast to its detrimental effect on BP, alcohol intake is associated with a higher level of high-density lipoprotein cholesterol and, within modest ranges of intake, a lower level of CHD than that associated with abstinence (35).

- 1. Bray GA. Life insurance and overweight. Obes Res. 1995;3:97-9.
- Harsha DW, Bray GA. Weight loss and blood pressure control (Pro). Hypertension. 2008;51:1420-5; discussion 1425.
- Hubert HB, Feinleib M, McNamara PM, et al. Obesity as an independent risk factor for cardiovascular disease: a 26year follow-up of participants in the Framingham Heart Study. Circulation. 1983;67:968-77.
- 4. Huang Z, Willett WC, Manson JE, et al. Body weight, weight change, and risk for hypertension in women. Ann Intern Med. 1998;128:81-8.
- 5. Hall JE. The kidney, hypertension, and obesity. Hypertension. 2003;41:625-33.
- 6. Jones DW, Kim JS, Andrew ME, et al. Body mass index and blood pressure in Korean men and women: the Korean National Blood Pressure Survey. J Hypertens. 1994;12:1433-7.
- 7. Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. Obes Res. 2000;8:270-8.
- 8. Garrison RJ, Kannel WB, Stokes J 3rd, et al. Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. Prev Med. 1987;16:235-51.
- 9. Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. JAMA. 2009;302:401-11.
- 10. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med. 2011;365:1876-85.
- 11. Klag MJ, He J, Coresh J, et al. The contribution of urinary cations to the blood pressure differences associated with migration. Am J Epidemiol. 1995;142:295-303.
- 12. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. BMJ. 1988;297:319-28.
- 13. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med. 2014;371:601-11.

- 14. Elliott P, Stamler J, Nichols R, et al. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. BMJ. 1996;312:1249-53.
- 15. Takase H, Sugiura T, Kimura G, et al. Dietary sodium consumption predicts future blood pressure and incident hypertension in the Japanese normotensive general population. J Am Heart Assoc. 2015;4:e001959.
- 16. Stamler J. The INTERSALT study: background, methods, findings, and implications. Am J Clin Nutr. 1997;65:626S-42S.
- 17. Strazzullo P, D'Elia L, Kandala NB, et al. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ. 2009;339:b4567.
- 18. Whelton PK. Sodium, potassium, blood pressure, and cardiovascular disease in humans. Curr Hypertens Rep. 2014;16:465.
- 19. Whelton PK, Appel LJ, Sacco RL, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. Circulation. 2012;126:2880-9.
- 20. Institute of Medicine. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. Washington, DC: The National Academies Press; 2005.
- 21. Weinberger MH, Miller JZ, Luft FC, et al. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension. 1986;8:II127-34.
- 22. Sanada H, Jones JE, Jose PA. Genetics of salt-sensitive hypertension. Curr Hypertens Rep. 2011;13:55-66.
- 23. Carey RM, Schoeffel CD, Gildea JJ, et al. Salt sensitivity of blood pressure is associated with polymorphisms in the sodium-bicarbonate cotransporter. Hypertension. 2012;60:1359-66.
- 24. Elijovich F, Weinberger MH, Anderson CAM. Salt sensitivity of blood pressure: a scientific statement from the American Heart Association. Hypertension. 2016;68:e7-46.
- 25. Weinberger MH. Salt sensitivity of blood pressure in humans. Hypertension. 1996;27:481-90.
- 26. Cogswell ME, Zhang Z, Carriquiry AL, et al. Sodium and potassium intakes among US adults: NHANES 2003-2008. Am J Clin Nutr. 2012;96:647-57.
- 27. Weinberger MH, Fineberg NS, Fineberg SE, et al. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. Hypertension. 2001;37:429-32.
- 28. Morimoto A, Uzu T, Fujii T, et al. Sodium sensitivity and cardiovascular events in patients with essential hypertension. Lancet. 1997;350:1734-7.
- 29. Gu D, Zhao Q, Chen J, et al. Reproducibility of blood pressure responses to dietary sodium and potassium interventions: the GenSalt study. Hypertension. 2013;62:499-505.
- 30. Poulter N, Khaw KT, Hopwood BE, et al. Blood pressure and associated factors in a rural Kenyan community. Hypertension. 1984;6:810-3.
- 31. He J, Tell GS, Tang YC, et al. Relation of electrolytes to blood pressure in men. The Yi people study. Hypertension. 1991;17:378-85.
- 32. Zhang Z, Cogswell ME, Gillespie C, et al. Association between usual sodium and potassium intake and blood pressure and hypertension among U.S. adults: NHANES 2005-2010. PLoS ONE. 2013;8:e75289.
- 33. Kieneker LM, Gansevoort RT, Mukamal KJ, et al. Urinary potassium excretion and risk of developing hypertension: the prevention of renal and vascular end-stage disease study. Hypertension. 2014;64:769-76.
- 34. D'Elia L, Barba G, Cappuccio FP, et al. Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. J Am Coll Cardiol. 2011;57:1210-9.
- 35. D'Elia L, Iannotta C, Sabino P, et al. Potassium-rich diet and risk of stroke: updated meta-analysis. Nutr Metab Cardiovasc Dis. 2014;24:585-7.
- 36. Vinceti M, Filippini T, Crippa A, et al. Meta-analysis of potassium intake and the risk of stroke. J Am Heart Assoc. 2016;5:e004210.
- 37. Rodrigues SL, Baldo MP, Machado RC, et al. High potassium intake blunts the effect of elevated sodium intake on blood pressure levels. J Am Soc Hypertens. 2014;8:232-8.
- 38. Khaw KT, Barrett-Connor E. The association between blood pressure, age, and dietary sodium and potassium: a population study. Circulation. 1988;77:53-61.
- 39. Cook NR, Obarzanek E, Cutler JA, et al. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. Arch Intern Med. 2009;169:32-40.
- 40. Lesniak KT, Dubbert PM. Exercise and hypertension. Curr Opin Cardiol. 2001;16:356-9.
- 41. Hayashi T, Tsumura K, Suematsu C, et al. Walking to work and the risk for hypertension in men: the Osaka Health Survey. Ann Intern Med. 1999;131:21-6.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 42. Leary AC, Donnan PT, MacDonald TM, et al. The influence of physical activity on the variability of ambulatory blood pressure. Am J Hypertens. 2000;13:1067-73.
- 43. Carnethon MR, Gidding SS, Nehgme R, et al. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. JAMA. 2003;290:3092-100.
- 44. Liu J, Sui X, Lavie CJ, et al. Effects of cardiorespiratory fitness on blood pressure trajectory with aging in a cohort of healthy men. J Am Coll Cardiol. 2014;64:1245-53.
- 45. Lian C. L'alcoholisme cause d'hypertension arterielle. Bull Acad Med (Paris). 1915;74:525-8.
- 46. Klatsky AL. Alcohol and cardiovascular mortality: common sense and scientific truth. J Am Coll Cardiol. 2010;55:1336-8.

# 5.3. Childhood Risk Factors and BP Tracking

BP distribution in the general population increases with age. Multiple longitudinal studies have investigated the relationship of childhood BP to adult BP. A meta-analysis of 50 such studies showed correlation coefficients of about 0.38 for SBP and 0.28 for DBP, with BPs in the upper range of the pediatric distribution (particularly BPs obtained in adolescence) predicting hypertension in adulthood (1). Several factors, including genetic factors and development of obesity, increase the likelihood that a high childhood BP will lead to future hypertension (2). Premature birth is associated with a 4–mm Hg higher SBP and a 3–mm Hg higher DBP in adulthood, with somewhat larger effects in women than in men (3). Low birth weight from other causes also contributes to higher BP in later life (4).

#### References



- 1. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation. 2008;117:3171-80.
- 2. Juhola J, Oikonen M, Magnussen CG, et al. Childhood physical, environmental, and genetic predictors of adult hypertension: the cardiovascular risk in young Finns study. Circulation. 2012;126:402-9.
- 3. Parkinson JRC, Hyde MJ, Gale C, et al. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Pediatrics. 2013;131:e1240-63.
- 4. de Jong F, Monuteaux MC, van Elburg RM, et al. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. Hypertension. 2012;59:226-34.

# 5.4. Secondary Forms of Hypertension

Recommendations for Secondary Forms of Hypertension					
COR	LOE	Recommendations			
I	C-EO	<ol> <li>Screening for specific form(s) of secondary hypertension is recommended when the clinical indications and physical examination findings listed in Table 13 are present or in adults with resistant hypertension.</li> </ol>			
llb	C-EO	2. If an adult with sustained hypertension screens positive for a form of secondary hypertension, referral to a physician with expertise in that form of hypertension may be reasonable for diagnostic confirmation and treatment.			

#### Synopsis

A specific, remediable cause of hypertension can be identified in approximately 10% of adult patients with hypertension (1). If a cause can be correctly diagnosed and treated, patients with secondary hypertension can achieve a cure or experience a marked improvement in BP control, with reduction in CVD risk. All new patients with hypertension should be screened with a history, physical examination, and laboratory investigations, as recommended in Section 7, before initiation of treatment.

Secondary hypertension can underlie severe elevation of BP, pharmacologically resistant hypertension, sudden onset of hypertension, increased BP in patients with hypertension previously controlled

on drug therapy, onset of diastolic hypertension in older adults, and target organ damage disproportionate to the duration or severity of the hypertension. Although secondary hypertension should be suspected in younger patients (<30 years of age) with elevated BP, it is not uncommon for primary hypertension to manifest at a younger age, especially in blacks (2), and some forms of secondary hypertension, such as renovascular disease, are more common at older age. Many of the causes of secondary hypertension are strongly associated with clinical findings or groups of findings that suggest a specific disorder.

Figure 3 is an algorithm on screening for secondary hypertension. Table 13 is a detailed list of clinical indications and diagnostic screening tests for secondary hypertension, and Table 14 is a list of drugs that can induce secondary hypertension.

#### **Recommendation-Specific Supportive Text**

1. The causes of secondary hypertension and recommended screening tests are provided in Table 13, and drugs that can induce secondary hypertension are provided in Table 14.

2. Diagnosis of many of these disorders requires a complex set of measurements, specialized technical expertise, and/or experience in data interpretation. Similarly, specific treatment often requires a level of technical training and experience.







Colors correspond to Class of Recommendation in Table 1.

TOD indicates target organ damage (e.g., cerebrovascular disease, hypertensive retinopathy, left ventricular hypertrophy, left ventricular dysfunction, heart failure, coronary artery disease, chronic kidney disease, albuminuria, peripheral artery disease).

			Physical	Screening	Additional/ Confirmatory
	Prevalence	Clinical Indications	Examination	Tests	Tests
Common causes					
Renal parenchymal disease (1, 3)	1%-2%	Urinary tract infections; obstruction, hematuria; urinary frequency and nocturia; analgesic abuse; family history of polycystic kidney disease; elevated serum creatinine; abnormal urinalysis	Abdominal mass (polycystic kidney disease); skin pallor	Renal ultrasound	Tests to evaluate cause of renal disease
Renovascular disease (4)	5%-34%*	Resistant hypertension; hypertension of abrupt onset or worsening or increasingly difficult to control; flash pulmonary edema (atherosclerotic); early-onset hypertension, especially in women (fibromuscular hyperplasia)	Abdominal systolic-diastolic bruit; bruits over other arteries (carotid – atherosclerotic or fibromuscular dysplasia), femoral	Renal Duplex Doppler ultrasound; MRA; abdominal CT	Bilateral selective renal intra-arterial angiography
Primary aldosteronism (5, 6)	8%-20%†	Resistant hypertension; hypertension with hypokalemia (spontaneous or diuretic induced); hypertension and muscle cramps or weakness; hypertension and incidentally discovered adrenal mass; hypertension and obstructive sleep apnea; hypertension and family history of early-onset hypertension or stroke	Arrhythmias (with hypokalemia); especially atrial fibrillation	Plasma aldosterone/r enin ratio under standardized conditions (correction of hypokalemia and withdrawal of aldosterone antagonists for 4–6 wk)	Oral sodium loading test (with 24-h urine aldosterone) or IV saline infusion test with plasma aldosterone at 4 h of infusion Adrenal CT scan, adrenal vein sampling.
Obstructive sleep apnea (7)‡	25%–50%	Resistant hypertension; snoring; fitful sleep; breathing pauses during sleep; daytime sleepiness	Obesity, Mallampati class III–IV; loss of normal nocturnal BP fall	Berlin Questionnaire (8); Epworth Sleepiness Score (9); overnight oximetry	Polysomnograp hy
Drug or alcohol induced (10)§	2%-4%	Sodium-containing antacids; caffeine; nicotine (smoking); alcohol; NSAIDs; oral contraceptives; cyclosporine or tacrolimus; sympathomimetics (decongestants, anorectics); cocaine, amphetamines and other illicit drugs; neuropsychiatric agents; erythropojesis-stimulating	Fine tremor, tachycardia, sweating (cocaine, ephedrine, MAO inhibitors); acute abdominal pain (cocaine)	Urinary drug screen (illicit drugs)	Response to withdrawal of suspected agent

Table 13. Causes	of Secondary Hype	rtension With	<b>Clinical Indications</b>	and Diagnostic S	Screening Tests
	0.00001001, 11, 20				

		agents; clonidine withdrawal; herbal agents (Ma Huang, ephedra)			
Uncommon causes			- 		
Pheochromocytoma/pa raganglioma (11)	0.1%-0.6%	Resistant hypertension; paroxysmal hypertension or crisis superimposed on sustained hypertension; "spells," BP lability, headache, sweating, palpitations, pallor; positive family history of pheochromocytoma/ paraganglioma; adrenal incidentaloma	Skin stigmata of neurofibromato sis (café-au-lait spots; neurofibromas); Orthostatic hypotension	24-h urinary fractionated metanephrine s or plasma metanephrine s under standard conditions (supine position with indwelling IV cannula)	CT or MRI scan of abdomen/pelvis
Cushing's syndrome (12)	<0.1%	Rapid weight gain, especially with central distribution; proximal muscle weakness; depression; hyperglycemia	Central obesity, "moon" face, dorsal and supraclavicular fat pads, wide (1-cm) violaceous striae, hirsutism	Overnight 1- mg dexamethaso ne suppression test	24-h urinary free cortisol excretion (preferably multiple); midnight salivary cortisol
Hypothyroidism (10)	<1%	Dry skin; cold intolerance; constipation; hoarseness; weight gain	Delayed ankle reflex; periorbital puffiness; coarse skin; cold skin; slow movement; goiter	Thyroid- stimulating hormone; free thyroxine	None
Hyperthyroidism (10)	<1%	Warm, moist skin; heat intolerance; nervousness; tremulousness; insomnia; weight loss; diarrhea; proximal muscle weakness	Lid lag; fine tremor of the outstretched hands; warm, moist skin	Thyroid- stimulating hormone; free thyroxine	Radioactive iodine uptake and scan
Aortic coarctation (undiagnosed or repaired) (13)	0.1%	Young patient with hypertension (<30 y of age)	BP higher in upper extremities than in lower extremities; absent femoral pulses; continuous murmur over patient's back, chest, or abdominal bruit; left thoracotomy scar (postoperative)	Echocardiogra m	Thoracic and abdominal CT angiogram or MRA
Primary hyperparathyroidism (14)	Rare	Hypercalcemia	Usually none	Serum calcium	Serum parathyroid hormone
hyperplasia (15)	Ndle	hypertension and	virilization (11-	and	elevated

		(11-beta-hydroxylase deficiency [11-beta-OH]); incomplete masculinization in males and primary amenorrhea in females (17-alpha- hydroxylase deficiency [17-alpha-OH])	beta-OH) or incomplete masculinization (17-alpha-OH)	hypokalemia with low or normal aldosterone and renin	deoxycorticoste rone (DOC), 11- deoxycortisol, and androgens17- alpha-OH; decreased androgens and estrogen; elevated deoxycorticoste rone and corticosterone
Mineralocorticoid excess syndromes other than primary aldosteronism (15)	Rare	Early-onset hypertension; resistant hypertension; hypokalemia or hyperkalemia	Arrhythmias (with hypokalemia)	Low aldosterone and renin	Urinary cortisol metabolites; genetic testing
Acromegaly (16)	Rare	Acral features, enlarging shoe, glove, or hat size; headache, visual disturbances; diabetes mellitus	Acral features; large hands and feet; frontal bossing	Serum growth hormone ≥1 ng/mL during oral glucose load	Elevated age- and sex- matched IGF-1 level; MRI scan of the pituitary

\*Depending on the clinical situation (hypertension alone, 5%; hypertension starting dialysis, 22%; hypertension and peripheral vascular disease, 28%; hypertension in the elderly with congestive heart failure, 34%). Association.

\*8% in general population with hypertension; up to 20% in patients with resistant hypertension.

‡Although obstructive sleep apnea is listed as a cause of secondary hypertension, RCTs on the effects of continuous positive airway pressure on lowering BP in patients with hypertension have produced mixed results (see Section 5.4.4 for details).

§For a list of frequently used drugs causing hypertension and accompanying evidence, see Table 14. BP indicates blood pressure; CT, computed tomography; DOC, 11-deoxycorticosterone; IGF-1, insulin-like growth factor-1; IV, intravenous; MAO, monamine oxidase; MRI, magnetic resonance imaging; MRA, magnetic resonance arteriography; NSAIDs, nonsteroidal anti-inflammatory drugs; OH, hydroxylase; and RCT, randomized clinical trial.

- Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008;51:1403-19.
- Selassie A, Wagner CS, Laken ML, et al. Progression is accelerated from prehypertension to hypertension in blacks. 2. Hypertension. 2011;58:579-87.
- 3. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70.
- Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 practice guidelines for the management of patients with 4. peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). Circulation. 2006;113:e463-654.
- 5. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93:3266-81.
- 6. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101:1889-916.
- 7. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58:811-7.
- Kump K, Whalen C, Tishler PV, et al. Assessment of the validity and utility of a sleep-symptom questionnaire. Am J. 8. Respir Crit Care Med. 1994;150:735-41.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 9. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540-5.
- 10. Grossman E, Messerli FH. Drug-induced hypertension: an unappreciated cause of secondary hypertension. Am J Med. 2012;125:14-22.
- 11. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:1915-42.
- 12. Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93:1526-40.
- 13. Lurbe E, Cifkova R, Cruickshank JK, et al. Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. J Hypertens. 2009;27:1719-42.
- 14. Berglund G, Andersson O, Wilhelmsen L. Prevalence of primary and secondary hypertension: studies in a random population sample. Br Med J. 1976;2:554-6.
- 15. Hassan-Smith Z, Stewart PM. Inherited forms of mineralocorticoid hypertension. Curr Opin Endocrinol Diabetes Obes. 2011;18:177-85.
- 16. Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:3933-51.

# 5.4.1. Drugs and Other Substances With Potential to Impair BP Control

Numerous substances, including prescription medications, over-the-counter medications, herbals, and food substances, may affect BP (Table 14) (1-6). Changes in BP that occur because of drugs and other agents have been associated with the development of hypertension, worsening control in a patient who already has hypertension, or attenuation of the BP-lowering effects of antihypertensive therapy. A change in BP may also result from drug–drug or drug–food interactions (2, 4). In the clinical assessment of hypertension, a careful history should be taken with regard to substances that may impair BP control, with close attention paid to not only prescription medications, but also over-the-counter substances, illicit drugs, and herbal products. When feasible, drugs associated with increased BP should be reduced or discontinued, and alternative agents should be used.

Agent	Possible Management Strategy
Alcohol	• Limit alcohol to ≤1 drink daily for women and ≤2 drinks for
	men (7)
Amphetamines (e.g., amphetamine,	• Discontinue or decrease dose (8)
methylphenidate dexmethylphenidate,	<ul> <li>Consider behavioral therapies for ADHD (9)</li> </ul>
dextroamphetamine)	
Antidepressants (e.g., MAOIs, SNRIs, TCAs)	<ul> <li>Consider alternative agents (e.g., SSRIs) depending on</li> </ul>
	indication
	<ul> <li>Avoid tyramine-containing foods with MAOIs</li> </ul>
Atypical antipsychotics (e.g., clozapine,	Discontinue or limit use when possible
olanzapine)	Consider behavior therapy where appropriate
	<ul> <li>Recommend lifestyle modification (see Section 6.2)</li> </ul>
	Consider alternative agents associated with lower risk of
	weight gain, diabetes mellitus, and dyslipidemia (e.g.,
	aripiprazole, ziprasidone) (10, 11)
Caffeine	<ul> <li>Generally limit caffeine intake to &lt;300 mg/d</li> </ul>
	<ul> <li>Avoid use in patients with uncontrolled hypertension</li> </ul>
	Coffee use in patients with hypertension is associated with
	acute increases in BP; long-term use is not associated with
	increased BP or CVD (12)
Decongestants (e.g., phenylephrine,	<ul> <li>Use for shortest duration possible, and avoid in severe or</li> </ul>
pseudoephedrine)	uncontrolled hypertension

Table 14. Frequently Used Medications and Other Substances That May Cause Elevated BP\*

	Consider alternative therapies (e.g. pasal saline intrapasal
	corticosteroids antihistamines) as appropriate
Herbal supplements (e.g., Ma Huang [ephedra], St. John's wort [with MAO inhibitors, yohimbine])	Avoid use
Immunosuppressants (e.g., cyclosporine)	• Consider converting to tacrolimus, which may be associated with fewer effects on BP (13-15)
Oral contraceptives	<ul> <li>Use low-dose (e.g., 20–30 mcg ethinyl estradiol) agents (16) or a progestin-only form of contraception, or consider alternative forms of birth control where appropriate (e.g., barrier, abstinence, IUD)</li> <li>Avoid use in women with uncontrolled hypertension (16)</li> </ul>
NSAIDs	<ul> <li>Avoid systemic NSAIDs when possible</li> <li>Consider alternative analgesics (e.g., acetaminophen, tramadol, topical NSAIDs), depending on indication and risk</li> </ul>
Recreational drugs (e.g., "bath salts" [MDPV], cocaine, methamphetamine, etc.)	Discontinue or avoid use
Systemic corticosteroids (e.g., dexamethasone, fludrocortisone, methylprednisolone, prednisone, prednisolone)	<ul> <li>Avoid or limit use when possible</li> <li>Consider alternative modes of administration (e.g., inhaled, not topical) when feasible</li> </ul>
Angiogenesis inhibitor (e.g., bevacizumab) and tyrosine kinase inhibitors (e.g., sunitinib, sorafenif)	Initiate or intensify antihypertensive therapy

\*List is not all inclusive.

ADHD indicates attention-deficit/hyperactivity disorder; BP, blood pressure; CVD, cardiovascular disease; IUD, intrauterine device; MAOI, monoamine-oxidase inhibitors; MDPV, methylenedioxypyrovalerone; NSAIDs, nonsteroidal antiinflammatory drugs; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; and TCA, tricyclic antidepressant.

- 1. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med. 1993;153:154-83.
- Grossman E, Messerli FH. Drug-induced hypertension: an unappreciated cause of secondary hypertension. Am J Med. 2012;125:14-22.
- 3. Ong SLH, Whitworth JA. How do glucocorticoids cause hypertension: role of nitric oxide deficiency, oxidative stress, and eicosanoids. Endocrinol Metab Clin North Am. 2011;40:393-407, ix.
- 4. Rossi GP, Seccia TM, Maniero C, et al. Drug-related hypertension and resistance to antihypertensive treatment: a call for action. J Hypertens. 2011;29:2295-309.
- 5. Tachjian A, Maria V, Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. J Am Coll Cardiol. 2010;55:515-25.
- Grossman E, Messerli FH. Secondary hypertension: interfering substances. J Clin Hypertens (Greenwich). 2008;10:556-66.
- Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:517-84.
- Cortese S, Holtmann M, Banaschewski T, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry. 2013;54:227-46.
- 9. Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128:1007-22.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 10. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. J Clin Psychiatry. 2007;68(suppl 1):20-7.
- 11. Willey JZ, Moon YP, Kahn E, et al. Population attributable risks of hypertension and diabetes for cardiovascular disease and stroke in the northern Manhattan study. J Am Heart Assoc. 2014;3:e001106.
- 12. Mesas AE, Leon-Munoz LM, Rodriguez-Artalejo F, et al. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. Am J Clin Nutr. 2011;94:1113-26.
- 13. Liu Y, Yang M-S, Yuan J-Y. Immunosuppressant utilization and cardiovascular complications among Chinese patients after kidney transplantation: a systematic review and analysis. Int Urol Nephrol. 2013;45:885-92.
- 14. Penninga L, Penninga EI, Moller CH, et al. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. Cochrane Database Syst Rev. 2013;5:CD008817.
- 15. Xue W, Zhang Q, Xu Y, et al. Effects of tacrolimus and cyclosporine treatment on metabolic syndrome and cardiovascular risk factors after renal transplantation: a meta-analysis. Chin Med J. 2014;127:2376-81.
- 16. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159-219.

	Recommendations for Primary Aldosteronism						
COR	LOE	Recommendations					
I	C-EO	1. In adults with hypertension, screening for primary aldosteronism is recommended in the presence of any of the following concurrent conditions: resistant hypertension, hypokalemia (spontaneous or substantial, if diuretic induced), incidentally discovered adrenal mass, family history of early-onset hypertension, or stroke at a young age (<40 years).					
I	C-LD	2. Use of the plasma aldosterone: renin activity ratio is recommended when adults are screened for primary aldosteronism (1).					
I	C-EO	3. In adults with hypertension and a positive screening test for primary aldosteronism, referral to a hypertension specialist or endocrinologist is recommended for further evaluation and treatment.					

# 5.4.2. Primary Aldosteronism

#### Synopsis

Primary aldosteronism is defined as a group of disorders in which aldosterone production is inappropriately high for sodium status, is relatively autonomous of the major regulators of secretion (angiotensin II and potassium), and cannot be suppressed with sodium loading (2, 3). The increased production of aldosterone induces hypertension; cardiovascular and kidney damage; sodium retention; suppressed plasma renin activity; and increased potassium excretion, which, if prolonged and severe, may cause hypokalemia. However, hypokalemia is absent in the majority of cases and has a low negative predictive value for the diagnosis of primary aldosteronism (4). In about 50% of the patients, primary aldosteronism is due to increased unilateral aldosterone production (usually aldosterone-producing adenoma or, rarely, unilateral adrenal hyperplasia); in the remaining 50%, primary aldosteronism is due to bilateral adrenal hyperplasia (idiopathic hyperaldosteronism) (2, 3).

#### **Recommendation-Specific Supportive Text**

1. Primary aldosteronism is one of the most frequent disorders (occurring in 5% to 10% of patients with hypertension and 20% of patients with resistant hypertension) that causes secondary hypertension (5, 6). The toxic tissue effects of aldosterone induce greater target organ damage in primary aldosteronism than in primary hypertension. Patients with primary aldosteronism have a 3.7-fold increase in HF, a 4.2-fold increase in stroke, a 6.5-fold increase in MI, a 12.1-fold increase in atrial fibrillation (AF), increased left ventricular

hypertrophy (LVH) and diastolic dysfunction, increased stiffness of large arteries, widespread tissue fibrosis, increased remodeling of resistance vessels, and increased kidney damage as compared with patients with primary hypertension matched for BP level (6-8). Because the deleterious effects of aldosterone overproduction are often reversible with unilateral laparoscopic adrenalectomy or treatment with mineralocorticoid receptor antagonists (i.e., spironolactone or eplerenone), screening of patients with hypertension at increased risk of primary aldosteronism is beneficial (2, 3). These include hypertensive patients with adrenal "incidentaloma," an incidentally discovered adrenal lesion on a computed tomography or magnetic resonance imaging (MRI) scan performed for other purposes. Patients with hypertension and a history of early onset hypertension and/or cerebrovascular accident at a young age may have primary aldosteronism due to glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type-1) and therefore warrant screening (2, 3).

2. The aldosterone:renin activity ratio is currently the most accurate and reliable means of screening for primary aldosteronism (1). The most commonly used cutoff value is 30 when plasma aldosterone concentration is reported in nanograms per deciliter (ng/dL) and plasma renin activity in nanograms per milliliter per hour (ng/mL/h) (3). Because the aldosterone:renin activity ratio can be influenced by the presence of very low renin levels, the plasma aldosterone concentration should be at least 10 ng/dL to interpret the test as positive (3). Patients should have unrestricted salt intake, serum potassium in the normal range, and mineralocorticoid receptor antagonists (e.g., spironolactone or eplerenone) withdrawn for at least 4 weeks before testing (2, 3).

3. The diagnosis of primary aldosteronism generally requires a confirmatory test (intravenous saline suppression test or oral salt-loading test) (2, 3). If the diagnosis of primary aldosteronism is confirmed (and the patient agrees that surgery would be desirable), the patient is referred for an adrenal venous sampling procedure to determine whether the increased aldosterone production is unilateral or bilateral in origin. If unilateral aldosterone production is documented on adrenal venous sampling, the patient is referred for unilateral laparoscopic adrenalectomy, which improves BP in virtually 100% of patients and results in a complete cure of hypertension in about 50% (2, 3). If the patient has bilaterally increased aldosterone secretion on adrenal venous sampling or has a unilateral source of excess aldosterone production but cannot undergo surgery, the patient is treated with spironolactone or eplerenone as agent of choice (2, 3). Both adrenalectomy and medical therapy are effective in lowering BP and reversing LVH. Treating primary aldosteronism, either by mineralocorticoid receptor antagonists or unilateral adrenalectomy (if indicated), resolves hypokalemia, lowers BP, reduces the number of antihypertensive medications required, and improves parameters of impaired cardiac and kidney function (9, 10).

- Montori VM, Young WF Jr. Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism. A systematic review of the literature. Endocrinol Metab Clin North Am. 2002;31:619-32, xi.
- 2. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93:3266-81.
- 3. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101:1889-916.
- 4. Mulatero P, Stowasser M, Loh K-C, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocrinol Metab. 2004;89:1045-50.
- 5. Hannemann A, Wallaschofski H. Prevalence of primary aldosteronism in patient's cohorts and in population-based studies--a review of the current literature. Horm Metab Res. 2012;44:157-62.
- 6. Rossi GP, Bernini G, Desideri G, et al. Renal damage in primary aldosteronism: results of the PAPY Study. Hypertension. 2006;48:232-8.
- 7. Milliez P, Girerd X, Plouin P-F, et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol. 2005;45:1243-8.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 8. Mulatero P, Monticone S, Bertello C, et al. Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. J Clin Endocrinol Metab. 2013;98:4826-33.
- 9. Rossi GP, Cesari M, Cuspidi C, et al. Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. Hypertension. 2013;62:62-9.
- 10. Fourkiotis V, Vonend O, Diederich S, et al. Effectiveness of eplerenone or spironolactone treatment in preserving renal function in primary aldosteronism. Eur J Endocrinol. 2013;168:75-81.

# 5.4.3. Renal Artery Stenosis

Recommendations for Renal Artery Stenosis					
COR	LOE	Recommendations			
I.	А	1. Medical therapy is recommended for adults with atherosclerotic renal artery stenosis (1, 2).			
lib	C-EO	2. In adults with renal artery stenosis for whom medical management has failed (refractory hypertension, worsening renal function, and/or intractable HF) and those with nonatherosclerotic disease, including fibromuscular dysplasia, it may be reasonable to refer the patient for consideration of revascularization (percutaneous renal artery angioplasty and/or stent placement).			

#### Synopsis

Heart Association

Renal artery stenosis refers to a narrowing of the renal artery that can result in a restriction of blood flow. Atherosclerotic disease (90%) is by far the most common cause of renal artery stenosis, whereas nonatherosclerotic disease (of which fibromuscular dysplasia is the most common) is much less prevalent and tends to occur in younger, healthier patients (3). Renal artery stenosis is a common form of secondary hypertension. Relieving ischemia and the ensuing postischemic release of renin by surgical renal artery reconstruction is an invasive strategy with a postoperative mortality as high as 13% (4). With the advent of endovascular procedures to restore blood flow, several trials were designed to test the efficacy of these procedures against medical therapy, but they suggested no benefit over medical therapy alone (1, 2).

#### **Recommendation-Specific Supportive Text**

1. Atherosclerotic disease in the renal arteries represents systemic disease and higher risk of both renal failure and cardiovascular morbidity and mortality. No RCT to date has demonstrated a clinical advantage of renal artery revascularization (with either angioplasty or stenting) over medical therapy (2). On the basis of the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial, the recommended medical approach encompasses optimal management of hypertension with an antihypertensive regimen that includes a reninangiotensin system (RAS) blocker, in addition to low-density lipoprotein cholesterol reduction with a highintensity statin, smoking cessation, hemoglobin A1c reduction in patients with DM, and antiplatelet therapy (1).

2. Revascularization may be considered for those who do not respond to medical therapy and for those who have nonatherosclerotic disease (e.g., Takayasu arteritis in Asian populations, fibromuscular dysplasia in other populations). Fibromuscular dysplasia occurs over the lifespan of women (mean: 53 years of age) with almost equal frequency in the renal and carotid circulations (3). Percutaneous transluminal angioplasty alone (without stenting) can improve BP control and even normalize BP, especially in patients with recent onset of hypertension or resistant hypertension (5).

#### References

1. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med. 2014;370:13-22.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 2. Riaz IB, Husnain M, Riaz H, et al. Meta-analysis of revascularization versus medical therapy for atherosclerotic renal artery stenosis. Am J Cardiol. 2014;114:1116-23.
- 3. Olin JW, Froehlich J, Gu X, et al. The United States Registry for Fibromuscular Dysplasia: results in the first 447 patients. Circulation. 2012;125:3182-90.
- 4. Lamawansa MD, Bell R, House AK. Short-term and long-term outcome following renovascular reconstruction. Cardiovasc Surg. 1995;3:50-5.
- 5. Trinquart L, Mounier-Vehier C, Sapoval M, et al. Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis. Hypertension. 2010;56:525-32.

# 5.4.4. Obstructive Sleep Apnea

Recommendation for Obstructive Sleep Apnea				
COR	LOE	Recommendations		
llb	B-R	1. In adults with hypertension and obstructive sleep apnea, the effectiveness of continuous positive airway pressure (CPAP) to reduce BP is not well established (1-5).		

#### Synopsis

Obstructive sleep apnea is a common chronic condition characterized by recurrent collapse of upper airways during sleep, inducing intermittent episodes of apnea/hypopnea, hypoxemia, and sleep disruption (6). Obstructive sleep apnea is a risk factor for several CVDs, including hypertension, coronary and cerebrovascular diseases, HF, and AF (6-9). Observational studies have shown that the presence of obstructive sleep apnea is associated with increased risk of incident hypertension (10, 11). Obstructive sleep apnea is highly prevalent in adults with resistant hypertension ( $\geq$ 80%) (12, 13), and it has been hypothesized that treatment with CPAP may have more pronounced effects on BP reduction in resistant hypertension (6).

#### **Recommendation-Specific Supportive Text**

1. CPAP is an efficacious treatment for improving obstructive sleep apnea. However, studies of the effects of CPAP on BP have demonstrated only small effects on BP (e.g., 2– to 3–mm Hg reductions), with results dependent on patient compliance with CPAP use, severity of obstructive sleep apnea, and presence of daytime sleepiness in study participants (1-5). Although many RCTs have been reported that address the effects of CPAP on BP in obstructive sleep apnea, most of the patients studied did not have documented hypertension, and the studies were too small and the follow-up period too short to allow for adequate evaluation. In addition, a well-designed RCT demonstrated that CPAP plus usual care, compared with usual care alone, did not prevent cardiovascular events in patients with moderate–severe obstructive sleep apnea and established CVD (14).

- 1. Barbe F, Duran-Cantolla J, Capote F, et al. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. Am J Respir Crit Care Med. 2010;181:718-26.
- Martinez-Garcia MA, Capote F, Campos-Rodriguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA. 2013;310:2407-15.
- 3. Lozano L, Tovar JL, Sampol G, et al. Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial. J Hypertens. 2010;28:2161-8.
- 4. Muxfeldt ES, Margallo V, Costa LMS, et al. Effects of continuous positive airway pressure treatment on clinic and ambulatory blood pressures in patients with obstructive sleep apnea and resistant hypertension: a randomized controlled trial. Hypertension. Hypertension. 2015;65:736-42.
- 5. Pedrosa RP, Drager LF, de Paula LKG, et al. Effects of OSA treatment on BP in patients with resistant hypertension: a randomized trial. Chest. 2013;144:1487-94.

#### 2017 High Blood Pressure Clinical Practice Guideline

- Parati G, Lombardi C, Hedner J, et al. Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological research) ACTION B26 on obstructive sleep apnea. J Hypertens. 2012;30:633-46.
- Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoeahypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046-53.
- 8. Marshall NS, Wong KKH, Liu PY, et al. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. Sleep. 2008;31:1079-85.
- 9. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000;283:1829-36.
- 10. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342:1378-84.
- 11. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA. 2012;307:2169-76.
- 12. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58:811-7.
- 13. Muxfeldt ES, Margallo VS, Guimaraes GM, et al. Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. Am J Hypertens. 2014;27:1069-78.
- 14. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375:919-31.



# 6. Nonpharmacological Interventions

Correcting the dietary aberrations, physical inactivity, and excessive consumption of alcohol that cause high BP is a fundamentally important approach to prevention and management of high BP, either on their own or in combination with pharmacological therapy. Prevention of hypertension and treatment of established hypertension are complementary approaches to reducing CVD risk in the population, but prevention of hypertension provides the optimal means of reducing risk and avoiding the harmful consequences of hypertension (1-3). Nonpharmacological therapy alone is especially useful for prevention of hypertension, including in adults with elevated BP, and for management of high BP in adults with milder forms of hypertension (4, 5).

#### References

- 1. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program. JAMA. 2002;288:1882-8.
- 2. National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. Arch Intern Med. 1993;153:186-208.
- 3. Whelton PK. Hypertension curriculum review: epidemiology and the prevention of hypertension. J Clin Hypertens (Greenwich). 2004;6:636-42.
- Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA. 1998;279:839-46.
- 5. Whelton PK. The elusiveness of population-wide high blood pressure control. Annu Rev Public Health. 2015;36:109-30.

# 6.1. Strategies

Nonpharmacological interventions can be accomplished by means of behavioral strategies aimed at lifestyle change, prescription of dietary supplements, or implementation of kitchen-based interventions that directly modify elements of the diet. At a societal level, policy changes can enhance the availability of healthy foods and facilitate physical activity. The goal can be to modestly reduce BP in the general population or to

#### 2017 High Blood Pressure Clinical Practice Guideline

undertake more intensive targeted lowering of BP in adults with hypertension or at high risk of developing hypertension (1). The intent of the general population approach is to achieve a small downward shift in the general population distribution of BP, which would be expected to result in substantial health benefits (2). The targeted approach focuses on BP reduction in adults at greatest risk of developing BP-related CVD, including individuals with hypertension, as well as those at increased risk of developing hypertension, especially blacks and adults who are overweight, consume excessive amounts of dietary sodium, have a high intake of alcohol, or are physically inactive. The targeted approach tends to be intensive, with a more ambitious goal for BP reduction. Both approaches are complementary and mutually reinforcing, and modeling studies suggest they are likely to provide similar public health benefit (3, 4). However, as the precision of risk prediction tools increases, targeted prevention strategies that focus on high-risk individuals seem to become more efficient than population-based strategies (5).

#### References

- 1. National High Blood Pressure Education Program Working Group report on primary prevention of hypertension. Arch Intern Med. 1993;153:186-208.
- 2. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the Trials of Hypertension Prevention (TOHP). BMJ. 2007;334:885-8.
- 3. Rodgers A, MacMahon S. Blood pressure and the global burden of cardiovascular disease. Clin Exp Hypertens. 1999;21:543-52.
- 4. Qin X, Jackson R, Marshall R, et al. Modelling the potential impact of population-wide and targeted high-risk blood pressure-lowering strategies on cardiovascular disease in China. Eur J Cardiovasc Prev Rehabil. 2009;16:96-101.
- 5. Zulman DM, Vijan S, Omenn GS, et al. The relative merits of population-based and targeted prevention strategies. Milbank Q. 2008;86:557-80.

	Recommendations for Nonpharmacological Interventions						
Refer	ences that	support recommendations are summarized in Online Data Supplements 9-21.					
COR	LOE	Recommendations					
I.	А	1. Weight loss is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese (1-4).					
I	А	2. A heart-healthy diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension (5-7).					
I	Α	<b>3.</b> Sodium reduction is recommended for adults with elevated BP or hypertension (8-12).					
I	А	4. Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or hypertension, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion (13-17).					
I.	А	5. Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension (3, 4, 12, 18-22).					
I	Α	6. Adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than 2 and 1 standard drinks* per day, respectively (23-28).					

# 6.2. Nonpharmacological Interventions

\*In the United States, 1 "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol) (29).

#### Synopsis

Nonpharmacological interventions are effective in lowering BP, with the most important interventions being weight loss (1), the DASH (Dietary Approaches to Stop Hypertension) diet (5-7, 30), sodium reduction (8-11), potassium supplementation (13, 17), increased physical activity (18-20, 22, 31), and a reduction in alcohol consumption (23, 24). Various other nonpharmacological interventions have been reported to lower BP, but the extent and/or quality of the supporting clinical trial experience is less persuasive. Such interventions include consumption of probiotics (32, 33, 34); increased intake of protein (35-37), fiber (38, 39), flaxseed (40), or fish oil (41); supplementation with calcium (42, 43) or magnesium (44, 45); and use of dietary patterns other than the DASH diet, including low-carbohydrate and vegetarian diets (5, 7, 46-49), (18-20, 22, 23, 31, 50). Stress reduction is intuitively attractive but insufficiently proved (51), as are several other interventions, including consumption of garlic (52), dark chocolate (53, 54), tea (55), or coffee (56). Behavioral therapies, including guided breathing, yoga, transcendental meditation, and biofeedback, lack strong evidence for their long-term BP-lowering effect (51, 57-61). The best proven nonpharmacological measures to prevent and treat hypertension are summarized in Table 15 (62).

The nonpharmacological interventions presented in Table 15 may be sufficient to prevent hypertension and meet goal BP in managing patients with stage 1 hypertension, and they are an integral part of the management of persons with stage 2 hypertension. To a lesser extent, the Mediterranean diet (49, 63) (which incorporates the basics of healthy eating but emphasizes consumption of legumes and monounsaturated fat, avoidance of red meats, and moderate intake of wine) has been effective in reducing BP, as well as improving lipid profile.

Table 15 is a summary of best proven nonpharmacological interventions for prevention and treatment of hypertension.

#### **Recommendation-Specific Supportive Text**

1. Weight loss is a core recommendation and should be achieved through a combination of reduced calorie intake and increased physical activity (1). The BP-lowering effect of weight loss in patients with elevated BP is consistent with the corresponding effect in patients with established hypertension, with an apparent dose–response relationship of about 1 mm Hg per kilogram of weight loss. Achievement and maintenance of weight loss through behavior change are challenging (64-66) but feasible over prolonged periods of follow-up (64). For those who do not meet their weight loss goals with nonpharmacological interventions, pharmacotherapy or minimally invasive and bariatric surgical procedures can be considered (67, 68). Surgical procedures tend to be more effective but are usually reserved for those with more severe and intractable obesity because of the frequency of complications. (69)

2. The DASH eating plan is the diet best demonstrated to be effective for lowering BP. Because the DASH diet is high in fruits, vegetables, and low-fat dairy products, it provides a means to enhance intake of potassium, calcium, magnesium, and fiber. In hypertensive and nonhypertensive adults, the DASH diet has produced overall reductions in SBP of approximately 11 mm Hg and 3 mm Hg, respectively (7), and the diet was especially effective in blacks (70). When combined with weight loss (6) or a reduction in sodium intake (5, 30), the effect size was substantially increased. Most of the clinical trial experience comes from short-term feeding studies (7), but lifestyle change with the DASH diet has been successful in at least 2 trials that used a behavioral intervention over a 4-month (30) or 6-month (6) period of follow-up. Websites and books provide advice on implementation of the DASH diet. (13, 71-74) Counseling by a knowledgeable nutritionist can be helpful. Several other diets, including diets that are low in calories from carbohydrates (46), high-protein diets (75), vegetarian diets (48), and a Mediterranean dietary pattern (49, 63), have been shown to lower BP.

3. Sodium reduction interventions prevent hypertension and lower BP in adults with hypertension, especially in those with higher levels of BP, blacks, older persons, and others who are particularly susceptible to the

effects of sodium on BP (8-11). Sodium reduction interventions may prevent CVD (76, 77). Lifestyle change (behavioral) interventions usually reduce sodium intake by about 25% (approximately 1,000 mg per day) and result in an average of about a 2-mm Hg to 3-mm Hg reduction in SBP in nonhypertensive individuals, though the reduction can be more than double this in more susceptible individuals, those with hypertension, and those concurrently on the DASH diet (5) or following a weight loss intervention (12). Sodium reduction in adults with hypertension who are already being treated with BP-lowering medications further reduces SBP by about 3 mm Hg and can facilitate discontinuation of medication, although this requires maintenance of the lifestyle change and warrants careful monitoring (12). When combined with weight loss, the reduction in BP is almost doubled. A reduction in sodium intake may also lower SBP significantly in individuals with resistant hypertension who are taking multiple antihypertensive medications (78) (see Section 11.1). Reduced dietary sodium has been reported to augment the BP-lowering effects of RAS blocker therapy (79). Maintenance of the lifestyle changes necessary to reduce sodium intake is challenging (2-4, 12), but even a small decrement in sodium consumption is likely to be safe (2, 4, 9, 12, 80) and beneficial (8, 81), especially in those whose BP is salt sensitive (82). In the United States, most dietary sodium comes from additions during food processing or during commercial food preparation at sit-down and fast-food restaurants (83, 84). Person-specific and policy approaches can be used to reduce dietary sodium intake (85, 86). Individuals can take action to reduce their dietary intake of sodium by choice of fresh foods, use of food labels to choose foods that are lower in sodium content, choice of foods with a "no added sodium" label, judicious use of condiments and sodiuminfused foods, use of spices and low-sodium flavorings, careful ordering when eating out, control of food portion size, and avoiding or minimizing use of salt at the table. Dietary counseling by a nutritionist with expertise in behavior modification can be helpful. A reduction in the amount of sodium added during food processing, as well as fast food and restaurant food preparation, has the potential to substantially reduce sodium intake without the need for a conscious change in lifestyle (81, 85, 87).

 Dietary potassium is inversely related to BP and hypertension in migrant studies (88), cross-sectional reports (89-91), and prospective cohort studies (92). Likewise, dietary potassium (93-96) and a high intake of fruits and vegetables are associated with a lower incidence of stroke (97). Potassium interventions have been effective in lowering BP (13, 14, 16, 81), especially in adult patients consuming an excess of sodium (13, 74, 98) and in blacks (13). The typical BP-lowering effect of a 60-mmol (1380-mg) administration of potassium chloride has been about 2 mm Hg and 4 to 5 mm Hg in adults with normotension and hypertension, respectively, although the response is up to twice as much in persons consuming a high-sodium diet. A reduction in the sodium/potassium index may be more important than the corresponding changes in either electrolyte alone (99). Some but not all studies suggest that the intervention effect may be restricted to adult patients with a low (1500-mg to 2000-mg) daily intake of potassium (92, 100). Most of the intervention experience comes from trials of relatively short duration (median of 5 to 6 weeks) (13, 14), but the BP-lowering effect of potassium in adult patients consuming a high-sodium diet has been reproduced after an interval of 4.4 years (98). In most trials, potassium supplementation was achieved by administration of potassium chloride pills, but the BP response pattern was similar when dietary modification was used (13). Because potassium-rich diets tend to be heart healthy, they are preferred over use of pills for potassium supplementation. The 2015 Dietary Guidelines for Americans (101) encourage a diet rich in potassium and identify the adequate intake level for adult patients as 4700 mg/day (102). The World Health Organization recommends a potassium intake of at least 90 mmol (3510 mg) per day from food for adult patients (15). Good sources of dietary potassium include fruits and vegetables, as well as low-fat dairy products, selected fish and meats, nuts, and soy products. Four to five servings of fruits and vegetables will usually provide 1500 to >3000 mg of potassium. This can be achieved by a diet, such as the DASH diet, that is high in potassium content (6).

5. A BP-lowering effect of increased physical activity has been repeatedly demonstrated in clinical trials, especially during dynamic aerobic exercise (18, 20, 22), but also during dynamic resistance training (18, 21) and static isometric exercise (18, 19, 31). The average reductions in SBP with aerobic exercise are

approximately 2 to 4 mm Hg and 5 to 8 mm Hg in adult patients with normotension and hypertension, respectively (18). Most trials have been of relatively short duration, but increased physical activity has been an intrinsic component of longer-term weight reduction interventions used to reduce BP and prevent hypertension (3, 4, 12). BP-lowering effects have been reported with lower- and higher-intensity exercise and with continuous and interval exercise training (18, 103). Meta-analyses suggest isometric exercise results in substantial lowering of BP (18, 19, 31).

6. In observational studies, there is a strong, predictable direct relationship between alcohol consumption and BP, especially above an intake of 3 standard drinks per day (approximately 36 ounces of regular beer, 15 ounces of wine, or 4.5 ounces of distilled spirits) (29, 104, 105). Meta-analyses of RCTs that have studied the effect of reduced alcohol consumption on BP in adults have identified a significant reduction in SBP and DBP (23, 24). The benefit has seemed to be consistent across trials, but confined to those consuming  $\geq$ 3 drinks/day, as well as dose dependent, with those consuming  $\geq$ 6 drinks/day at baseline reducing their alcohol intake by about 50% and experiencing an average reduction in SBP/DBP of approximately 5.5/4.0 mm Hg (23, 24). Only limited information is available on the effect of alcohol reduction on BP in blacks (23, 106). In contrast to its effect on BP, alcohol seems to have a beneficial effect on several biomarkers for CVD risk, including high-density lipoprotein cholesterol (107, 108). Observational studies have shown a relatively consistent finding of an inverse relationship between alcohol intake and CHD (109, 110), within a moderate range (approximately 12–14 and  $\leq$ 9 standard drinks/week for men and women, respectively). On balance, it seems reasonable for those who are consuming moderate quantities of alcohol ( $\leq$ 2 drinks/day) to continue their moderate consumption of alcohol.

# Hypertension

	Nonpharmacological	Dose	Approximate Impact on SBP		
	Intervention		Hypertension	Normotension	Reference
Weight loss Healthy diet	Weight/body fat DASH dietary pattern	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight. Consume a diet rich in fruits, vegetables, whole grains, and	Hypertension -5 mm Hg -11 mm Hg	Normotension -2/3 mm Hg -3 mm Hg	Reference (1) (6, 7)
Reduced	Dietary sodium	low-fat dairy products, with reduced content of saturated and total fat. Optimal goal is <1500	-5/6 mm Hg	-2/3 mm Hg	American Heart (9. 10) sociation.
intake of dietary sodium		mg/d, but aim for at least a 1000-mg/d reduction in most adults.	5, 5 mm ng		(0) 10)
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	-4/5 mm Hg	-2 mm Hg	
Physical activity	Aerobic	<ul> <li>90–150 min/wk</li> <li>65%–75% heart rate reserve</li> </ul>	-5/8 mm Hg	-2/4 mm Hg	(18, 22)
	Dynamic resistance	<ul> <li>90–150 min/wk</li> <li>50%–80% 1 rep maximum</li> <li>6 exercises, 3 sets/exercise, 10 repetitions/set</li> </ul>	-4 mm Hg	-2 mm Hg	(18)
	Isometric resistance	<ul> <li>4 × 2 min (hand grip), 1 min rest</li> <li>between exercises,</li> <li>30%–40% maximum</li> <li>voluntary</li> <li>contraction, 3</li> <li>sessions/wk</li> <li>8–10 wk</li> </ul>	-5 mm Hg	-4 mm Hg	(19, 31)
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, reduce alcohol† to: • Men: ≤2 drinks daily	-4 mm Hg	-3 mm Hg	(22-24)

## Table 15. Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension\*

	● Women: ≤1 drink		
	daily		

\*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension. DASH indicates Dietary Approaches to Stop Hypertension; and SBP, systolic blood pressure. Resources:

Your Guide to Lowering Your Blood Pressure With DASH—How Do I Make the DASH? Available at:

https://www.nhlbi.nih.gov/health/resources/heart/hbp-dash-how-to. Accessed September 15, 2017. (72) Top 10 Dash Diet Tips. Available at: http://dashdiet.org/dash\_diet\_tips.asp. Accessed September 15, 2017. (73) †In the United States, one "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol) (29).

- 1. Neter JE, Stam BE, Kok FJ, et al. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2003;42:878-84.
- 2. Whelton PK, Kumanyika SK, Cook NR, et al. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group. Am J Clin Nutr. 1997;65:652S-60S.
- 3. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA. 1992;267:1213-20.
- 4. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. Arch Intern Med. 1997;157:657-67.
- Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344:3-10.
- 6. Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. JAMA. 2003;289:2083-93.
- 7. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997;336:1117-24.
- 8. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. N Engl J Med. 2014;371:624-34.
- 9. Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: systematic review and metaanalyses. BMJ. 2013;346:f1326.
- 10. He FJ, Li J, MacGregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ. 2013;346:f1325.
- 11. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low-sodium diet vs. high-sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride (Cochrane Review). Am J Hypertens. 2012;25:1-15.
- 12. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA. 1998;279:839-46.
- 13. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA. 1997;277:1624-32.
- 14. Geleijnse JM, Kok FJ, Grobbee DE. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. J Hum Hypertens. 2003;17:471-80.
- 15. World Health Organization. Guideline: Potassium Intake for Adults and Children. Geneva, Switzerland: World Health Organization; 2012.
- 16. Whelton PK, He J. Health effects of sodium and potassium in humans. Curr Opin Lipidol. 2014;25:75-9.
- 17. Aburto NJ, Hanson S, Gutierrez H, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ. 2013;346:f1378.
- 18. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc. 2013;2:e004473.

- 19. Carlson DJ, Dieberg G, Hess NC, et al. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. Mayo Clin Proc. 2014;89:327-34.
- 20. Garcia-Hermoso A, Saavedra JM, Escalante Y. Effects of exercise on resting blood pressure in obese children: a meta-analysis of randomized controlled trials. Obes Rev. 2013;14:919-28.
- 21. Rossi AM, Moullec G, Lavoie KL, et al. The evolution of a Canadian Hypertension Education Program recommendation: the impact of resistance training on resting blood pressure in adults as an example. Can J Cardiol. 2013;29:622-7.
- 22. Whelton SP, Chin A, Xin X, et al. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2002;136:493-503.
- 23. Xin X, He J, Frontini MG, et al. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2001;38:1112-7.
- 24. Roerecke M, Kaczorowski J, Tobe SW, et al. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. Lancet Public Health. 2017;2:e108-20.
- 25. Stewart SH, Latham PK, Miller PM, et al. Blood pressure reduction during treatment for alcohol dependence: results from the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study. Addiction. 2008;103:1622-8.
- 26. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J Hypertens. 2006;24:215-33.
- 27. Wallace P, Cutler S, Haines A. Randomised controlled trial of general practitioner intervention in patients with excessive alcohol consumption. BMJ. 1988;297:663-8.
- 28. Lang T, Nicaud V, Darne B, et al. Improving hypertension control among excessive alcohol drinkers: a randomised controlled trial in France. The WALPA Group. J Epidemiol Community Health. 1995;49:610-6.
- 29. National Institute on Alcohol Abuse and Alcoholism (NIAAA). What Is A Standard Drink? Available at: <u>https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink</u>. Accessed August 16, 2017.
- 30. Blumenthal JA, Babyak MA, Hinderliter A, et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. Arch Intern Med. 2010;170:126-35.
- 31. Inder JD, Carlson DJ, Dieberg G, et al. Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. Hypertens Res. 2016;39:88-94.
- 32. Khalesi S, Sun J, Buys N, et al. Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. Hypertension. 2014;64:897-903.
- 33. Dong J-Y, Szeto IMY, Makinen K, et al. Effect of probiotic fermented milk on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr. 2013;110:1188-94.
- 34. Cicero AFG, Gerocarni B, Laghi L, et al. Blood pressure lowering effect of lactotripeptides assumed as functional foods: a meta-analysis of current available clinical trials. J Hum Hypertens. 2011;25:425-36.
- 35. Rebholz CM, Friedman EE, Powers LJ, et al. Dietary protein intake and blood pressure: a meta-analysis of randomized controlled trials. Am J Epidemiol. 2012;176(suppl 7):S27-43.
- Tielemans SM a. J, Altorf-van der Kuil W, Engberink MF, et al. Intake of total protein, plant protein and animal protein in relation to blood pressure: a meta-analysis of observational and intervention studies. J Hum Hypertens. 2013;27:564-71.
- 37. Dong J-Y, Zhang Z-L, Wang P-Y, et al. Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in type 2 diabetes: meta-analysis of randomised controlled trials. Br J Nutr. 2013;110:781-9.
- 38. Whelton SP, Hyre AD, Pedersen B, et al. Effect of dietary fiber intake on blood pressure: a meta-analysis of randomized, controlled clinical trials. J Hypertens. 2005;23:475-81.
- 39. Streppel MT, Arends LR, van't Veer P, et al. Dietary fiber and blood pressure: a meta-analysis of randomized placebo-controlled trials. Arch Intern Med. 2005;165:150-6.
- 40. Rodriguez-Leyva D, Weighell W, Edel AL, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. Hypertension. 2013;62:1081-9.
- 41. Campbell F, Dickinson HO, Critchley JA, et al. A systematic review of fish-oil supplements for the prevention and treatment of hypertension. Eur J Prev Cardiol. 2013;20:107-20.
- 42. van Mierlo L a. J, Arends LR, Streppel MT, et al. Blood pressure response to calcium supplementation: a metaanalysis of randomized controlled trials. J Hum Hypertens. 2006;20:571-80.

- 43. Cormick G, Ciapponi A, Cafferata ML, et al. Calcium supplementation for prevention of primary hypertension. Cochrane Database Syst Rev. 2015;6:CD010037.
- 44. Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. Eur J Clin Nutr. 2012;66:411-8.
- 45. Zhang X, Li Y, Del Gobbo LC, et al. Effects of magnesium supplementation on blood pressure: a meta-analysis of randomized double-blind placebo-controlled trials. Hypertension. 2016;68:324-33.
- 46. Bazzano LA, Hu T, Reynolds K, et al. Effects of low-carbohydrate and low-fat diets: a randomized trial. Ann Intern Med. 2014;161:309-18.
- 47. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166:285-93.
- 48. Yokoyama Y, Nishimura K, Barnard ND, et al. Vegetarian diets and blood pressure: a meta-analysis. JAMA Intern Med. 2014;174:577-87.
- 49. Nordmann AJ, Suter-Zimmermann K, Bucher HC, et al. Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. Am J Med. 2011;124:841-51.
- 50. Rossi GP, Seccia TM, Maniero C, et al. Drug-related hypertension and resistance to antihypertensive treatment: a call for action. J Hypertens. 2011;29:2295-309.
- 51. Nagele E, Jeitler K, Horvath K, et al. Clinical effectiveness of stress-reduction techniques in patients with hypertension: systematic review and meta-analysis. J Hypertens. 2014;32:1936-44.
- 52. Rohner A, Ried K, Sobenin IA, et al. A systematic review and metaanalysis on the effects of garlic preparations on blood pressure in individuals with hypertension. Am J Hypertens. 2015;28:414-23.
- 53. Egan BM, Laken MA, Donovan JL, et al. Does dark chocolate have a role in the prevention and management of hypertension? Commentary on the evidence. Hypertension. 2010;55:1289-95.
- 54. Ried K, Sullivan T, Fakler P, et al. Does chocolate reduce blood pressure? A meta-analysis. BMC Med. 2010;8:39.
- 55. Liu G, Mi X-N, Zheng X-X, et al. Effects of tea intake on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr. 2014;112:1043-54.
- 56. Steffen M, Kuhle C, Hensrud D, et al. The effect of coffee consumption on blood pressure and the development of hypertension: a systematic review and meta-analysis. J Hypertens. 2012;30:2245-54.
- 57. Wang J, Xiong X, Liu W. Yoga for essential hypertension: a systematic review. PLoS ONE. 2013;8:e76357.
- 58. Dickinson H, Campbell F, Beyer F, et al. Relaxation therapies for the management of primary hypertension in adults: a Cochrane review. J Hum Hypertens. 2008;22:809-20.
- 59. Lee MS, Pittler MH, Guo R, et al. Qigong for hypertension: a systematic review of randomized clinical trials. J Hypertens. 2007;25:1525-32.
- 60. Yeh GY, Wang C, Wayne PM, et al. The effect of tai chi exercise on blood pressure: a systematic review. Prev Cardiol. 2008;11:82-9.
- 61. Canter PH, Ernst E. Insufficient evidence to conclude whether or not transcendental meditation decreases blood pressure: results of a systematic review of randomized clinical trials. J Hypertens. 2004;22:2049-54.
- 62. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program. JAMA. 2002;288:1882-8.
- 63. Estruch R, Ros E, Martinez-Gonzalez MA. Mediterranean diet for primary prevention of cardiovascular disease. N Engl J Med. 2013;369:676-7.
- 64. Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369:145-54.
- 65. Aucott L, Rothnie H, McIntyre L, et al. Long-term weight loss from lifestyle intervention benefits blood pressure? A systematic review. Hypertension 2009;54:756-62.
- 66. Straznicky N, Grassi G, Esler M, et al. European Society of Hypertension Working Group on Obesity Antihypertensive effects of weight loss: myth or reality? J Hypertens. 2010;28:637-43.
- 67. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129(suppl 2):S102-38.
- 68. Ryan DH. The pharmacological and surgical management of adults with obesity. J Fam Pract. 2014;63:S21-6.
- 69. Chang S-H, Stoll CRT, Song J, et al. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg. 2014;149:275-87.

- Svetkey LP, Simons-Morton D, Vollmer WM, et al. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. Arch Intern Med. 1999;159:285-93.
- 71. Filippini T, Violi F, D'Amico R, et al. The effect of potassium supplementation on blood pressure in hypertensive subjects: a systematic review and meta-analysis. Int J Cardiol. 2017;230:127-35.
- 72. National Heart, Lung, and Blood Institute. Your Guide to Lowering Your Blood Pressure With DASH--How Do I Make the DASH? Available at: <u>https://www.nhlbi.nih.gov/health/resources/heart/hbp-dash-how-to</u>. Accessed September 18, 2017.
- 73. Top 10 DASH Diet Tips. Available at: <u>http://dashdiet.org/dash\_diet\_tips.asp</u>. Accessed September 18, 2017.
- 74. van Bommel E, Cleophas T. Potassium treatment for hypertension in patients with high salt intake: a meta-analysis. Int J Clin Pharmacol Ther. 2012;50:478-82.
- 75. He J, Wofford MR, Reynolds K, et al. Effect of dietary protein supplementation on blood pressure. Circulation. 2011;124:589-95.
- 76. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. Circulation. 2014;129:981-9.
- 77. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the Trials of Hypertension Orevention (TOHP). BMJ. 2007;334:885-8.
- 78. Pimenta E, Gaddam KK, Oparil S, et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. Hypertension 2009;54:475-81.
- 79. Huggins CE, Margerison C, Worsley A, et al. Influence of dietary modifications on the blood pressure response to antihypertensive medication. Br J Nutr. 2011;105:248-55.
- 80. He FJ, Fan S, Macgregor GA, et al. Plasma sodium and blood pressure in individuals on haemodialysis. J Hum Hypertens. 2013;27:85-9.
- 81. Whelton PK. Sodium, potassium, blood pressure, and cardiovascular disease in humans. Curr Hypertens Rep. 2014;16:465.
- 82. Weinberger MH, Miller JZ, Luft FC, et al. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension. 1986;8:II127-34.
- 83. Mattes RD, Donnelly D. Relative contributions of dietary sodium sources. J Am Coll Nutr. 1991;10:383-93.
- 84. Anderson CAM, Appel LJ, Okuda N, et al. Dietary sources of sodium in China, Japan, the United Kingdom, and the United States, women and men aged 40 to 59 years: the INTERMAP study. J Am Diet Assoc. 2010;110:736-45.
- 85. Whelton PK, Appel LJ, Sacco RL, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. Circulation. 2012;126:2880-9.
- 86. Cobb LK, Appel LJ, Anderson CAM. Strategies to reduce dietary sodium intake. Curr Treat Options Cardiovasc Med. 2012;14:425-34.
- 87. McGuire S. Institute of Medicine. 2010. Strategies to Reduce Sodium Intake in the United States. Washington, DC: The National Academies Press. Adv Nutr. 2010;1:49-50.
- He J, Tell GS, Tang YC, et al. Effect of migration on blood pressure: the Yi People Study. Epidemiology. 1991;2:88-97.
- Stamler J. The INTERSALT Study: background, methods, findings, and implications. Am J Clin Nutr. 1997;65:626S-42S.
- 90. Zhang Z, Cogswell ME, Gillespie C, et al. Association between usual sodium and potassium intake and blood pressure and hypertension among U.S. adults: NHANES 2005-2010. PLoS ONE. 2013;8:e75289.
- 91. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med. 2014;371:601-11.
- 92. Kieneker LM, Gansevoort RT, Mukamal KJ, et al. Urinary potassium excretion and risk of developing hypertension: the prevention of renal and vascular end-stage disease study. Hypertension. 2014;64:769-76.
- 93. Bazzano LA, He J, Ogden LG, et al. Dietary potassium intake and risk of stroke in US men and women: National Health and Nutrition Examination Survey I epidemiologic follow-up study. Stroke. 2001;32:1473-80.
- 94. Ascherio A, Rimm EB, Hernan MA, et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation. 1998;98:1198-204.
- 95. Seth A, Mossavar-Rahmani Y, Kamensky V, et al. Potassium intake and risk of stroke in women with hypertension and nonhypertension in the Women's Health Initiative. Stroke. 2014;45:2874-80.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 96. D'Elia L, Barba G, Cappuccio FP, et al. Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. J Am Coll Cardiol. 2011;57:1210-9.
- Bazzano LA, He J, Ogden LG, et al. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Am J Clin Nutr. 2002;76:93-9.
- 98. Gu D, Zhao Q, Chen J, et al. Reproducibility of blood pressure responses to dietary sodium and potassium interventions: the GenSalt study. Hypertension. 2013;62:499-505.
- 99. Cook NR, Obarzanek E, Cutler JA, et al. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. Arch Intern Med. 2009;169:32-40.
- 100. Whelton PK, Buring J, Borhani NO, et al. The effect of potassium supplementation in persons with a high-normal blood pressure. Results from phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. Ann Epidemiol. 1995;5:85-95.
- 101. Dietary Guidelines Advisory Committee. Dietary Guidelines for Americans, 2015-2020. Washington, DC: Department of Health and Human Services (U.S.), Department of Agriculture (U.S); 2015.
- 102.Institute of Medicine. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. Washington, DC: The National Academies Press; 2005.
- 103.Cornelissen VA, Arnout J, Holvoet P, et al. Influence of exercise at lower and higher intensity on blood pressure and cardiovascular risk factors at older age. J Hypertens. 2009;27:753-62.
- 104. Klatsky AL, Gunderson E. Alcohol and hypertension: a review. J Am Soc Hypertens 2008;2:307-17.
- 105. National Institute on Alcohol Abuse and Alcoholism (NIAAA). A Pocket Guide for Alcohol Screening and Brief Intervention. Rockville, MD: NIAAA; 2005. Available at:

https://pubs.niaaa.nih.gov/publications/practitioner/pocketguide/pocket\_guide.htm. Accessed September 18, 2017.

- 106.Cushman WC, Cutler JA, Hanna E, et al. Prevention and Treatment of Hypertension Study (PATHS): effects of an alcohol treatment program on blood pressure. Arch Intern Med. 1998;158:1197-207.
- 107. Rimm EB, Williams P, Fosher K, et al. Moderate alcohol intake and lower risk of coronary heart disease: metaanalysis of effects on lipids and haemostatic factors. BMJ. 1999;319:1523-8.
- 108. Mukamal KJ. Understanding the mechanisms that link alcohol and lower risk of coronary heart disease. Clin Chem. 2012;58:664-6.
- 109.Klatsky AL. Alcohol and cardiovascular mortality: common sense and scientific truth. J Am Coll Cardiol. 2010;55:1336-8.
- 110.Mukamal KJ, Chen CM, Rao SR, et al. Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. J Am Coll Cardiol. 2010;55:1328-35.

# 7. Patient Evaluation

The patient evaluation is designed to identify target organ damage and possible secondary causes of hypertension and to assist in planning an effective treatment regimen. Historical features are relevant to the evaluation of the patient (Table 16). The pattern of BP measurements and changes over time may differentiate primary from secondary causes of hypertension. A rise in BP associated with weight gain, lifestyle factors (such as a job change requiring travel and meals away from home), reduced frequency or intensity of physical activity, or advancing age in a patient with a strong family history of hypertension would suggest the diagnosis of primary hypertension. An evaluation of the patient's dietary habits, physical activity, alcohol consumption, and tobacco use should be performed, with recommendation of the nonpharmacological interventions detailed in Section 6.2 where appropriate. The history should also include inquiry into possible occurrence of symptoms to indicate a secondary cause (Tables 13 and 16). The patient's treatment goals and risk tolerance should also be elicited. This is especially true for older persons, for whom an assessment of multiple chronic conditions, frailty, and prognosis should be performed, including consideration of the time required to see benefit from intervention, which may not be realized for some individuals.

The physical examination should include accurate measurement of BP (Table 8). Automated oscillometric devices provide an opportunity to obtain repeated measurements without a provider present, thereby minimizing the potential for a white coat effect. Change in BP from seated to standing position should be measured to detect orthostatic hypotension (a decline >20 mm Hg in SBP or >10 mm Hg in DBP after 1 minute is abnormal). For adults  $\leq$ 30 years of age with elevated brachial BP, a thigh BP measurement is indicated; if the thigh measurement is lower than arm pressures, a diagnosis of coarctation of the aorta should be considered. The physical examination should include assessment of hypertension-related target organ damage. Attention should be paid to physical features that suggest secondary hypertension (Table 13).

	Primary Hypertension		Secondary Hypertension
٠	Gradual increase in BP, with slow rate	•	BP lability, episodic pallor and dizziness (pheochromocytoma)
	of rise in BP	•	Snoring, hypersomnolence (obstructive sleep apnea)
٠	Lifestyle factors that favor higher BP	•	Prostatism (chronic kidney disease due to post-renal urinary
	(e.g., weight gain, high-sodium diet,		tract obstruction)
	decreased physical activity, job change	•	Muscle cramps, weakness (hypokalemia from primary
	entailing increased travel, excessive		aldosteronism or secondary aldosteronism due to
	consumption of alcohol)		renovascular disease)
٠	Family history of hypertension	•	Weight loss, palpitations, heat intolerance (hyperthyroidism)
		•	Edema, fatigue, frequent urination (kidney disease or failure)
		•	History of coarctation repair (residual hypertension associated
			with coarctation)
		•	Central obesity, facial rounding, easy bruisability (Cushing's
			syndrome)
		•	Medication or substance use (e.g., alcohol, NSAIDS, cocaine,
			amphetamines)
		•	Absence of family history of hypertension

able 16. Historical Features	<b>Favoring Hypertension Cause</b>
------------------------------	------------------------------------

BP indicates blood pressure; and NSAIDs, nonsteroidal anti-inflammatory drugs.

# 7.1. Laboratory Tests and Other Diagnostic Procedures

Laboratory measurements should be obtained for all patients with a new diagnosis of hypertension to facilitate CVD risk factor profiling, establish a baseline for medication use, and screen for secondary causes of hypertension (Table 17). Optional tests may provide information on target organ damage. Monitoring of serum sodium and potassium levels is helpful during diuretic or RAS blocker titration, as are serum creatinine and urinary albumin as markers of CKD progression (1). Measurement of thyroid-stimulating hormone is a simple test to easily detect hypothyroidism and hyperthyroidism, 2 remediable causes of hypertension. A decision to conduct additional laboratory testing would be appropriate in the context of increased hypertension severity, poor response to standard treatment approaches, a disproportionate severity of target organ damage for the level of BP, or historical or clinical clues that support a secondary cause.

Basic testing	Fasting blood glucose*	
	Complete blood count	
	Lipid profile	
	Serum creatinine with eGFR*	
	Serum sodium, potassium, calcium*	
	Thyroid-stimulating hormone	

#### 2017 High Blood Pressure Clinical Practice Guideline

	Urinalysis	
	Electrocardiogram	
Optional testing	Echocardiogram	
	Uric acid	
	Urinary albumin to creatinine ratio	

\*May be included in a comprehensive metabolic panel. eGFR indicates estimated glomerular filtration rate.

#### Reference

1. Chang AR, Sang Y, Leddy J, et al. Antihypertensive medications and the prevalence of hyperkalemia in a large health system. Hypertension. 2016; 67:1181-8.

#### 7.2. Cardiovascular Target Organ Damage

Pulse-wave velocity, carotid intima-media thickness, and coronary artery calcium score provide noninvasive estimates of vascular target organ injury and atherosclerosis (1). High BP readings, especially when obtained several years before a noninvasive measurement, are associated with an increase in subclinical CVD risk (2-4). Although carotid intima-media thickness values and coronary artery calcium scores are associated with cardiovascular events, inadequate or absent information on the effect of improvement in these markers on cardiovascular events prevents their routine use as surrogate markers in the treatment of hypertension.

LVH is a secondary manifestation of hypertension and independently predicts future CVD events. LVH is commonly measured by electrocardiography, echocardiography, or MRI (5, 6). Left ventricular (LV) mass is associated with body size (particularly lean body mass), tobacco use, heart rate (inverse), and long-standing DM (7-9). BP lowering leads to a reduction in LV mass. In TOMHS (Treatment of Mild Hypertension Study), the long-acting diuretic chlorthalidone was slightly more effective in reducing LVH than were a calcium channel blocker (CCB) (amlodipine), ACE inhibitor (enalapril), alpha-receptor blocker (doxazosin), or beta-receptor blocker (acebutolol) (10). Beta blockers are inferior to angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and CCBs in reducing LVH (11).

Hypertension adversely impacts other echocardiographic markers of cardiac structure and function, including left atrial size (both diameter and area; left atrial size is also a precursor of AF); diastolic function (many parameters; a precursor of HF with preserved ejection fraction [HF*p*EF]); cardiac structure; and subclinical markers of LV systolic function, such as myocardial strain assessment with echocardiography and MRI.

Assessment of LVH by means of echocardiography or MRI is not universally recommended during evaluation and management of hypertension in adults because there are limited data on the cost and value of these measures for CVD risk reclassification and changes in type or intensity of treatment. Assessment of LVH is most useful in adults who are young (≤18 years of age) or have evidence of secondary hypertension, chronic uncontrolled hypertension, or history of symptoms of HF. Electrocardiographic criteria for LVH correlate weakly with echocardiographic or MRI definitions of LVH and are less strongly related to CVD outcomes (12-15). Imprecision in lead placement accounts, in part, for the poor correlation of electrocardiographic measurements with direct imaging results. However, electrocardiographic LVH has been valuable in predicting CVD risk in some reports (16, 17). Electrocardiography may also be useful in the assessment of comorbidities, such as rhythm disturbances and prior MI.

LVH, as assessed by electrocardiography, echocardiography, or MRI, is an independent predictor of CVD complications (18, 19). Reduction in LVH can predict a reduction in CVD risk, independent of change in BP (20). When used in CVD risk predictor models, echocardiographic LVH has a small but significant independent effect on CVD risk in younger patients. At older ages, LVH measured by electrocardiography or MRI provides no independent contribution to prediction of CVD risk (21-23). Patients can be classified into 4

#### 2017 High Blood Pressure Clinical Practice Guideline

groups on the basis of the presence or absence of LVH and a determination of whether the LVH has an eccentric (normal relative wall thickness) or concentric geometry (6, 22).

- 1. Persu A, De Plaen J-F. Recent insights in the development of organ damage caused by hypertension. Acta Cardiol. 2004;59:369-81.
- 2. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. JAMA. 2014;311:490-7.
- 3. Pletcher MJ, Bibbins-Domingo K, Lewis CE, et al. Prehypertension during young adulthood and coronary calcium later in life. Ann Intern Med. 2008;149:91-9.
- Juhola J, Magnussen CG, Berenson GS, et al. Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis: the International Childhood Cardiovascular Cohort Consortium. Circulation. 2013;128:217-24.
- 5. Santos M, Shah AM. Alterations in cardiac structure and function in hypertension. Curr Hypertens Rep. 2014;16:428.
- 6. Devereux RB, Roman MJ. Left ventricular hypertrophy in hypertension: stimuli, patterns, and consequences. Hypertens Res. 1999;22:1-9.
- 7. Gidding SS, Liu K, Colangelo LA, et al. Longitudinal determinants of left ventricular mass and geometry: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Circ Cardiovasc Imaging. 2013;6:769-75.
- 8. Fox ER, Musani SK, Samdarshi TE, et al. Clinical correlates and prognostic significance of change in standardized left ventricular mass in a community-based cohort of African Americans. J Am Heart Assoc. 2015;4:e001224.
- Lieb W, Xanthakis V, Sullivan LM, et al. Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the framingham offspring study. Circulation. 2009;119:3085-92.
- 10. Liebson PR, Grandits GA, Dianzumba S, et al. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). Circulation. 1995;91:698-706.
- 11. Fagard RH, Celis H, Thijs L, et al. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. Hypertension. 2009;54:1084-91.
- 12. Norman JE Jr, Levy D. Improved electrocardiographic detection of echocardiographic left ventricular hypertrophy: results of a correlated data base approach. J Am Coll Cardiol. 1995;26:1022-9.
- 13. da Costa W, Riera ARP, Costa F de A, et al. Correlation of electrocardiographic left ventricular hypertrophy criteria with left ventricular mass by echocardiogram in obese hypertensive patients. J Electrocardiol. 2008;41:724-9.
- 14. Bacharova L, Schocken D, Estes EH, et al. The role of ECG in the diagnosis of left ventricular hypertrophy. Curr Cardiol Rev. 2014;10:257-61.
- 15. Bang CN, Devereux RB, Okin PM. Regression of electrocardiographic left ventricular hypertrophy or strain is associated with lower incidence of cardiovascular morbidity and mortality in hypertensive patients independent of blood pressure reduction--a LIFE review. J Electrocardiol. 2014;47:630-5.
- 16. Pewsner D, Juni P, Egger M, et al. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. BMJ. 2007;335:711.
- 17. Rautaharju PM, Soliman EZ. Electrocardiographic left ventricular hypertrophy and the risk of adverse cardiovascular events: a critical appraisal. J Electrocardiol. 2014;47:649-54.
- 18. Armstrong AC, Gidding S, Gjesdal O, et al. LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice. JACC Cardiovasc Imaging. 2012;5:837-48.
- 19. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2010;122:e584-636.
- 20. Devereux RB, Wachtell K, Gerdts E, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA. 2004;292:2350-6.
- 21. Armstrong AC, Jacobs DR Jr, Gidding SS, et al. Framingham score and LV mass predict events in young adults: CARDIA study. Int J Cardiol. 2014;172:350-5.
- 22. Okwuosa TM, Soliman EZ, Lopez F, et al. Left ventricular hypertrophy and cardiovascular disease risk prediction and reclassification in blacks and whites: the Atherosclerosis Risk in Communities Study. Am Heart J. 2015;169:155-61.

#### 2017 High Blood Pressure Clinical Practice Guideline

23. Zalawadiya SK, Gunasekaran PC, Bavishi CP, et al. Left ventricular hypertrophy and risk reclassification for coronary events in multi-ethnic adults. Eur J Prev Cardiol. 2015;22:673-9.

# 8. Treatment of High BP

Clinicians managing adults with high BP should focus on overall patient health, with a particular emphasis on reducing the risk of future adverse CVD outcomes. All patient risk factors need to be managed in an integrated fashion with a comprehensive set of nonpharmacological (see Section 6) and pharmacological strategies. As patient BP and risk of future CVD events increase, BP management should be intensified.

# 8.1. Pharmacological Treatment

# 8.1.1. Initiation of Pharmacological BP Treatment in the Context of Overall CVD Risk

For any specific difference in BP, the relative risk of CVD is constant across groups that differ in absolute risk of atherosclerotic CVD (1-4), albeit with some evidence of lesser relative risk but greater excess risk in older than in younger adults (5-8). Thus, there are more potentially preventable CVD events attributable to elevated BP in individuals with higher than with lower risk of CVD and in older than in younger adults. The relative risk reduction for CVD prevention with use of BP-lowering medications is fairly constant for groups that differ in CVD risk across a wide range of estimated absolute risk (9, 10) and across groups defined by sex, age, body mass index, and the presence or absence of DM, AF, and CKD (5, 11-21). As a consequence, the absolute CVD risk reduction attributable to BP lowering is greater at greater absolute levels of CVD risk (9, 10, 12, 15-19, 22, 23). Put another way, for a given magnitude of BP reduction due to antihypertensive medications, fewer individuals at high CVD risk would need to be treated to prevent a CVD event (i.e., lower number needed to treat) than those at low CVD risk.

- 1. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. JAMA. 2005;294:466-72.
- 2. Ozyilmaz A, Bakker SJL, de Zeeuw D, et al. Screening for albuminuria with subsequent screening for hypertension and hypercholesterolaemia identifies subjects in whom treatment is warranted to prevent cardiovascular events. Nephrol Dial Transplant. 2013;28:2805-15.
- 3. Peters SAE, Huxley RR, Woodward M. Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. Stroke. 2013;44:2394-401.
- 4. Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. Semin Arthritis Rheum. 2013;43:77-95.
- 5. Lawes CMM, Bennett DA, Lewington S, et al. Blood pressure and coronary heart disease: a review of the evidence. Semin Vasc Med. 2002;2:355-68.
- 6. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903-13.
- 7. Takashima N, Ohkubo T, Miura K, et al. Long-term risk of BP values above normal for cardiovascular mortality: a 24year observation of Japanese aged 30 to 92 years. J Hypertens. 2012;30:2299-306.
- 8. Murakami Y. Meta-analyses using individual participant data from cardiovascular cohort studies in Japan: current status and future directions. J Epidemiol. 2014;24:96-101.
- van Dieren S, Kengne AP, Chalmers J, et al. Effects of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes. Diabetes Res Clin Pract. 2012;98:83-90.
- 10. Sundstrom J, Arima H, Woodward M, et al. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384:591-8.

- 11. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005;165:1410-9.
- 12. Wang J-G, Staessen JA, Franklin SS, et al. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. Hypertension. 2005;45:907-13.
- 13. Turnbull F, Woodward M, Neal B, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. Eur Heart J. 2008;29:2669-80.
- 14. Turnbull F, Neal B, Ninomiya T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ. 2008;336:1121-3.
- 15. Du X, Ninomiya T, de Galan B, et al. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. Eur Heart J. 2009;30:1128-35.
- Czernichow S, Ninomiya T, Huxley R, et al. Impact of blood pressure lowering on cardiovascular outcomes in normal weight, overweight, and obese individuals: the Perindopril Protection Against Recurrent Stroke Study trial. Hypertension. 2010;55:1193-8.
- 17. Heerspink HJL, Ninomiya T, Perkovic V, et al. Effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes and chronic kidney disease. Eur Heart J. 2010;31:2888-96.
- 18. Ninomiya T, Zoungas S, Neal B, et al. Efficacy and safety of routine blood pressure lowering in older patients with diabetes: results from the ADVANCE trial. J Hypertens. 2010;28:1141-9.
- 19. Collier DJ, Poulter NR, Dahlof B, et al. Impact of amlodipine-based therapy among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). J Hypertens. 2011;29:583-91.
- 20. Ninomiya T, Perkovic V, Turnbull F, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. Blood Pressure Lowering Treatment Trialists' Collaboration. BMJ. 2013;347:f5680.
- 21. Redon J, Mancia G, Sleight P, et al. Safety and efficacy of low blood pressures among patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). J Am Coll Cardiol. 2012;59:74-83.
- 22. Ogden LG, He J, Lydick E, et al. Long-term absolute benefit of lowering blood pressure in hypertensive patients according to the JNC VI risk stratification. Hypertension. 2000;35:539-43.
- 23. van der Leeuw J, Visseren FLJ, Woodward M, et al. Predicting the effects of blood pressure-lowering treatment on major cardiovascular events for individual patients with type 2 diabetes mellitus: results from Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation. Hypertension. 2015;65:115-21.

# 8.1.2. BP Treatment Threshold and the Use of CVD Risk Estimation to Guide Drug Treatment of Hypertension

Recommendations for BP Treatment Threshold and Use of Risk Estimation* to Guide Drug						
	Treatment of Hypertension					
Refe	References that support recommendations are summarized in Online Data Supplement 23.					
COR	LOE	Recommendations				
I	SBP: A DBP:	1. Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher (1-9).				
I	C-LD	<ol> <li>Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk &lt;10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher (3, 10-13).</li> </ol>				

\*ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-Risk-Estimator/) (13a) to estimate 10-year risk of atherosclerotic CVD. ASCVD was defined as a first CHD death, non-fatal MI or fatal or non-fatal stroke.

#### Synopsis

Whereas treatment of high BP with BP-lowering medications on the basis of BP level alone is considered cost effective (14), use of a combination of absolute CVD risk and BP level to guide such treatment is more efficient and cost effective at reducing risk of CVD than is use of BP level alone (15-24). Practical approaches have been developed to translate evidence from RCTs into individual patient treatment recommendations that are based on absolute net benefit for CVD risk (25), and several national and international guidelines recommend basing use of BP-lowering medications on a combination of absolute risk of CVD and level of BP instead of relying solely on level of BP (26-31).

Attempts to use absolute risk to guide implementation of pharmacological treatment to prevent CVD have had mixed results, with many reports of improvements in provider prescribing behaviors, patient adherence, and reductions in risk (32-38), but with others showing no impact on provider behaviors (39, 40). Use of global CVD risk assessment is infrequent in routine clinical practice (41-46), which suggests that intensive efforts would be required to achieve universal implementation. The choice of specific risk calculators for estimation of risk and risk threshold has been an important source of variability, ambiguity, and controversy (47-54). In addition, implementation of a standard (worldwide) absolute CVD risk threshold for initiating use of BP-lowering medications would result in large variations in medication use at a given level of BP across countries (48, 54, 55). Future research in this area should focus on issues related to implementation of a risk-based approach to CVD prevention, including the use of BP-lowering medications. Although several CVD risk assessment tools are available, on the basis of current knowledge, we recommend use of the ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-Risk-Estimator/) to estimate 10-year risk of atherosclerotic CVD (ASCVD) to establish the BP threshold for treatment (56, 57). It should be kept in mind that the ACC/AHA Pooled Cohort Equations are validated for U.S. adults ages 45 to 79 years in the absence of concurrent statin therapy (56). For those older than age 79, the 10-year ASCVD risk is generally >10%, and thus the SBP threshold for antihypertensive drug treatment for patients >79 years old is 130 mm Hg. Two recent reviews have highlighted the importance of using predicted CVD risk together with BP to guide antihypertensive drug therapy (22, 23).

Figure 4 is an algorithm on BP thresholds and recommendations for treatment and follow-up.

#### **Recommendation-Specific Supportive Text**

1. For the purposes of secondary prevention, clinical CVD is defined as CHD, congestive HF, and stroke. Several meta-analyses of RCTs support the value of using BP-lowering medications, in addition to nonpharmacological treatment, in patients with established CVD in the absence of hypertension, defined previously by an SBP  $\geq$ 140 mm Hg or a DBP ≥90 mm Hg (1, 6, 7, 9). Many RCTs of BP lowering in adults without CVD have used inclusion criteria designed to increase the level of CVD risk in the study populations to increase trial efficiency by facilitating shorter duration and a smaller sample size. As a consequence, few relatively low-risk adults with hypertension have been included in the trials. Trial results provide evidence of CVD prevention from use of BP-lowering medications in adults with an average SBP ≥130 mm Hg or an average DBP ≥80 mm Hg and clinical CVD; 5-year risk of CVD (defined as stroke, CHD, HF, or other CVD death) of approximately 6% to 7% (3, 5); an estimated 10-year CVD death rate of approximately 4.5% (4); or an annual rate of major CVD events of approximately 0.9% per year (7). In the absence of clinical CVD, these risk estimates are roughly equivalent to a 10-year risk of ASCVD exceeding 10% as per the ACC/AHA Pooled Cohort Equations (56). SPRINT (Systolic Blood Pressure Intervention Trial) provides additional support for the use of BP-lowering medications in patients without CVD at SBP levels ≥130 mm Hg; however, it is important to note that few SPRINT participants had untreated SBP between 130 mm Hg and 139 mm Hg at baseline. Furthermore, SPRINT used a Framingham 10-year risk of general CVD exceeding 15% to identify increased CVD risk (8). Although this level of risk is lower than the levels described previously, being roughly equivalent to a 6% to 7% 10-year ASCVD risk per the ACC/AHA Pooled Cohort Equations, most of the participants in SPRINT had a much higher level of CVD risk. This recommendation differs from JNC 7 in its use of CVD risk, rather than diabetes or CKD, to recognize patients, including older adults, with a SBP/DBP <140/90 mm Hg who are likely to benefit from BP lowering drug therapy in addition to nonpharmacological antihypertensive treatment. In JNC 7, the BP threshold for initiation of antihypertensive drug therapy was  $\geq$  140/90 mm Hg for the general adult population and  $\geq$  130/80 mm Hg for adults with diabetes or CKD. Since the publication of JNC 7 in 2003, we have gained additional experience with risk assessment and new data from randomized trials, observational studies and simulation analyses have demonstrated that antihypertensive drug treatment based on overall ASCVD risk assessment combined with BP levels may prevent more CVD events than treatment based on BP levels alone (15-24). According to an analysis of NHANES 2011-2014, the new definition results in only a small increase in the percentage of U.S. adults for whom antihypertensive medication is recommended in conjunction with lifestyle modification. The previously cited meta-analyses are consistent with the conclusion that lowering of BP results in benefit in higher-risk individuals, regardless of their baseline treated or untreated BP ≥130/80 mm Hg and irrespective of the specific cause of their elevated risk. These analyses indicate that the benefit of treatment outweighs the potential harm at threshold BP  $\geq$ 130/80 mm Hg.

2. This recommendation is consistent with prior guidelines, such as JNC 7. In addition, for those for whom nonpharmacological therapy has been ineffective, antihypertensive drug treatment should be added in patients with an SBP  $\geq$ 140 mm Hg or a DBP  $\geq$ 90 mm Hg, even in adults who are at lower risk than those included in RCTs. The rationale for drug treatment in patients with an SBP  $\geq$ 140 mm Hg or a DBP  $\geq$ 90 mm Hg and an estimated 10-year risk of CVD <10% is based on several lines of evidence. First, the relationship of SBP with risk of CVD is known to be continuous across levels of SBP and similar across groups that differ in level of absolute risk (10). Second, the relative risk reduction attributable to BP-lowering medication therapy is consistent across the range of absolute risk observed in trials (3, 11, 58), supporting the contention that the relative risk reduction may be similar at lower levels of absolute risk. This is the case even in a meta-analysis of trials in adults without clinical CVD and an average SBP/DBP of 146/84 mm Hg (5). Finally, modeling studies support the effectiveness and cost-effectiveness of treatment of younger, lower-risk patients over the course of their life spans (12, 13). Although the numbers needed to treat with BP-lowering medications to prevent a CVD event in the short term are greater in younger, lower-risk individuals with hypertension than in older, higher-risk adults with hypertension, the estimated gains in life expectancy attributable to long-term use of
BP-lowering medications are correspondingly greater in younger, lower-risk individuals than in older adults with a higher risk of CVD (12, 13). Indirect support is also provided by evidence from trials using BP-lowering medications to reduce the risk of developing higher levels of BP (59-61) and, in one case, to achieve a reduction in LV mass (62). In the HOPE-3 (Heart Outcomes Prevention Evaluation-3) BP Trial, there was no evidence of short-term benefit during treatment of adults (average age 66 years) with a relatively low risk of CVD (3.8% CVD event rate during 5.6 years of follow-up). However, subgroup analysis suggested benefit in those with an average SBP approximately >140 mm Hg (and a CVD risk of 6.5% during the 5.6 years of follow-up) (63). We acknowledge the importance of excluding white coat hypertension before initiating pharmacological therapy in hypertensive patients with low ASCVD risk. This may be accomplished (as described in Section 4) by HBPM or ABPM as appropriate.



### Figure 4. Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up

Colors correspond to Class of Recommendation in Table 1.

\*Using the ACC/AHA Pooled Cohort Equations (57). Note that patients with DM or CKD are automatically placed in the high-risk category. For initiation of RAS inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2 to 4 weeks after initiating therapy.

<sup>+</sup>Consider initiation of pharmacological therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP  $\geq$ 160/100 mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (e.g., older or with postural symptoms), identification of white coat hypertension or a white coat effect, documentation of adherence, monitoring of the

### 2017 High Blood Pressure Clinical Practice Guideline

response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target.

ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; and RAS, renin-angiotensin system.

- Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
- 2. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016; 387:957-67.
- 3. Sundstrom J, Arima H, Woodward M, et al. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384:591-8.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels--overview and meta-analyses of randomized trials. J Hypertens. 2014;32:2296-304.
- 5. Sundstrom J, Arima H, Jackson R, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Ann Intern Med. 2015;162:184-91.
- 6. Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA. 2011;305:913-22.
- 7. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387:435-43.
- 8. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. SPRINT Research Group. N Engl J Med. 2015;373:2103-16.
- 9. Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. J Hypertens. 2011;29:4-16.
- 10. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903-13.
- van Dieren S, Kengne AP, Chalmers J, et al. Effects of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes. Diabetes Res Clin Pract. 2012;98:83-90.
- 12. Montgomery AA, Fahey T, Ben-Shlomo Y, et al. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: a Markov decision analysis. J Hypertens. 2003;21:1753-9.
- 13. Kassai B, Boissel J-P, Cucherat M, et al. Treatment of high blood pressure and gain in event-free life expectancy. Vasc Health Risk Manag. 2005;1:163-9.
- 13a. ACC/AHA Pooled Cohort Equations. Available at: http://tools.acc.org/ASCVD-Risk-Estimator/. Accessed November 3, 2017.
- 14. Rubinstein A, Colantonio L, Bardach A, et al. Estimation of the burden of cardiovascular disease attributable to modifiable risk factors and cost-effectiveness analysis of preventative interventions to reduce this burden in Argentina. BMC Public Health. 2010;10:627.
- 15. Baker S, Priest P, Jackson R. Using thresholds based on risk of cardiovascular disease to target treatment for hypertension: modelling events averted and number treated. BMJ. 2000;320:680-5.
- 16. Gaziano TA, Steyn K, Cohen DJ, et al. Cost-effectiveness analysis of hypertension guidelines in South Africa: absolute risk versus blood pressure level. Circulation. 2005;112:3569-76.
- 17. Eddy DM, Adler J, Patterson B, et al. Individualized guidelines: the potential for increasing quality and reducing costs. Ann Intern Med. 2011;154:627-34.
- 18. Marchant I, Nony P, Cucherat M, et al. The global risk approach should be better applied in French hypertensive patients: a comparison between simulation and observation studies. PLoS ONE. 2011;6:e17508.
- 19. Cadilhac DA, Carter R, Thrift AG, et al. Organized blood pressure control programs to prevent stroke in Australia: would they be cost-effective? Stroke. 2012;43:1370-5.

### 2017 High Blood Pressure Clinical Practice Guideline

- 20. Cobiac LJ, Magnus A, Barendregt JJ, et al. Improving the cost-effectiveness of cardiovascular disease prevention in Australia: a modelling study. BMC Public Health. 2012;12:398.
- 21. Cobiac LJ, Magnus A, Lim S, et al. Which interventions offer best value for money in primary prevention of cardiovascular disease? PLoS ONE. 2012;7:e41842.
- 22. Karmali KN, Lloyd-Jones DM. Global risk assessment to guide blood pressure management in cardiovascular disease prevention. Hypertension. 2017;69:e2-9.
- 23. Muntner P, Whelton PK. Using predicted cardiovascular disease risk in conjunction with blood pressure to guide antihypertensive medication treatment. J Am Coll Cardiol. 2017;69:2446-56.
- 24. Sussman J, Vijan S, Hayward R. Using benefit-based tailored treatment to improve the use of antihypertensive medications. Circulation. 2013;128:2309-17.
- 25. van der Leeuw J, Ridker PM, van der Graaf Y, et al. Personalized cardiovascular disease prevention by applying individualized prediction of treatment effects. Eur Heart J. 2014;35:837-43.
- 26. Mendis S, Lindholm LH, Mancia G, et al. World Health Organization (WHO) and International Society of Hypertension (ISH) risk prediction charts: assessment of cardiovascular risk for prevention and control of cardiovascular disease in low and middle-income countries. J Hypertens. 2007;25:1578-82.
- van Dis I, Geleijnse JM, Verschuren WMM, et al. Cardiovascular risk management of hypertension and hypercholesterolaemia in the Netherlands: from unifactorial to multifactorial approach. Neth Heart J. 2012;20:320-5.
- 28. Nelson MR, Doust JA. Primary prevention of cardiovascular disease: new guidelines, technologies and therapies. Med J Aust. 2013;198:606-10.
- 29. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014;100(suppl 2):ii1-67.
- 30. World Health Organization. Prevention of Cardiovascular Disease. Guidelines for Assessment and Management of Cardiovascular Risk. Geneva, Switzerland: World Health Organization; 2007.
- 31. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129:2329-45.
- 32. Sheridan SL, Crespo E. Does the routine use of global coronary heart disease risk scores translate into clinical benefits or harms? A systematic review of the literature. BMC Health Serv Res. 2008;8:60.
- 33. Sheridan SL, Viera AJ, Krantz MJ, et al. The effect of giving global coronary risk information to adults: a systematic review. Arch Intern Med. 2010;170:230-9.
- 34. Viera AJ, Sheridan SL. Global risk of coronary heart disease: assessment and application. Am Fam Physician. 2010;82:265-74.
- 35. Sheridan SL, Draeger LB, Pignone MP, et al. A randomized trial of an intervention to improve use and adherence to effective coronary heart disease prevention strategies. BMC Health Serv Res. 2011;11:331.
- 36. Brett T, Arnold-Reed D, Phan C, et al. The Fremantle Primary Prevention Study: a multicentre randomised trial of absolute cardiovascular risk reduction. Br J Gen Pract. 2012;62:e22-8.
- 37. Sekaran NK, Sussman JB, Xu A, et al. Providing clinicians with a patient's 10-year cardiovascular risk improves their statin prescribing: a true experiment using clinical vignettes. BMC Cardiovasc Disord. 2013;13:90.
- Sheridan SL, Draeger LB, Pignone MP, et al. The effect of a decision aid intervention on decision making about coronary heart disease risk reduction: secondary analyses of a randomized trial. BMC Med Inform Decis Mak. 2014;14:14.
- 39. Jansen J, Bonner C, McKinn S, et al. General practitioners' use of absolute risk versus individual risk factors in cardiovascular disease prevention: an experimental study. BMJ Open. 2014;4:e004812.
- Vagholkar S, Zwar N, Jayasinghe UW, et al. Influence of cardiovascular absolute risk assessment on prescribing of antihypertensive and lipid-lowering medications: a cluster randomized controlled trial. Am Heart J. 2014;167:28-35.
- 41. Rafter N, Connor J, Hall J, et al. Cardiovascular medications in primary care: treatment gaps and targeting by absolute risk. N Z Med J. 2005;118:U1676.
- 42. Yong TY, Phillipov G, Phillips PJ. Management outcomes of patients with type 2 diabetes: targeting the 10-year absolute risk of coronary heart disease. Med J Aust. 2007;186:622-4.
- 43. Webster RJ, Heeley EL, Peiris DP, et al. Gaps in cardiovascular disease risk management in Australian general practice. Med J Aust. 2009;191:324-9.

### 2017 High Blood Pressure Clinical Practice Guideline

- 44. Frikke-Schmidt R, Tybjærg-Hansen A, Schnohr P, et al. Common clinical practice versus new PRIM score in predicting coronary heart disease risk. Atherosclerosis. 2010;213:532-8.
- 45. Heeley EL, Peiris DP, Patel AA, et al. Cardiovascular risk perception and evidence--practice gaps in Australian general practice (the AusHEART study). Med J Aust. 2010;192:254-9.
- 46. Shillinglaw B, Viera AJ, Edwards T, et al. Use of global coronary heart disease risk assessment in practice: a crosssectional survey of a sample of U.S. physicians. BMC Health Serv Res. 2012;12:20.
- 47. Game FL, Bartlett WA, Bayly GR, et al. Comparative accuracy of cardiovascular risk prediction methods in patients with diabetes mellitus. Diabetes Obes Metab. 2001;3:279-86.
- 48. Bastuji-Garin S, Deverly A, Moyse D, et al. The Framingham prediction rule is not valid in a European population of treated hypertensive patients. J Hypertens. 2002;20:1973-80.
- 49. Menotti A, Puddu PE, Lanti M. The estimate of cardiovascular risk. Theory, tools and problems. Ann Ital Med Int. 2002;17:81-94.
- de Visser CL, Bilo HJG, Thomsen TF, et al. Prediction of coronary heart disease: a comparison between the Copenhagen risk score and the Framingham risk score applied to a Dutch population. J Intern Med. 2003;253:553-62.
- 51. Persson M, Carlberg B, Weinehall L, et al. Risk stratification by guidelines compared with risk assessment by risk equations applied to a MONICA sample. J Hypertens. 2003;21:1089-95.
- 52. Doust J, Sanders S, Shaw J, et al. Prioritising CVD prevention therapy--absolute risk versus individual risk factors. Aust Fam Physician. 2012;41:805-9.
- 53. Allan GM, Nouri F, Korownyk C, et al. Agreement among cardiovascular disease risk calculators. Circulation. 2013;127:1948-56.
- 54. Diverse Populations Collaborative Group. Prediction of mortality from coronary heart disease among diverse populations: is there a common predictive function? Heart. 2002;88:222-8.
- 55. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, et al. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. N Engl J Med. 2000;342:1-8.
- Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(suppl 2):S49-73.
- 57. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(suppl 2):S1-45.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk--overview and meta-analyses of randomized trials. J Hypertens. 2014;32:2305-14.
- 59. Julius S, Nesbitt SD, Egan BM, et al. Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med. 2006;354:1685-97.
- 60. Julius S, Kaciroti N, Egan BM, et al. TROPHY study: outcomes based on the Seventh Report of the Joint National Committee on Hypertension definition of hypertension. J Am Soc Hypertens. 2008;2:39-43.
- 61. Luders S, Schrader J, Berger J, et al. The PHARAO study: prevention of hypertension with the angiotensinconverting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. J Hypertens. 2008;26:1487-96.
- 62. Fuchs SC, Poli-de-Figueiredo CE, Figueiredo Neto JA, et al. Effectiveness of chlorthalidone plus amiloride for the prevention of hypertension: the PREVER Prevention Randomized Clinical Trial. J Am Heart Assoc. 2016;5:e004248.
- 63. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2009-20.

# 8.1.3. Follow-Up After Initial BP Evaluation

Recommendations for Follow-Up After Initial BP Elevation							
Refe	References that support recommendations are summarized in Online Data Supplement 24.						
COR	LOE	Recommendations					
I	B-R	1. Adults with an elevated BP or stage 1 hypertension who have an estimated 10-year ASCVD risk less than 10% should be managed with nonpharmacological therapy and have a repeat BP evaluation within 3 to 6 months (1, 2).					
I	B-R	2. Adults with stage 1 hypertension who have an estimated 10-year ASCVD risk of 10% or higher should be managed initially with a combination of nonpharmacological and antihypertensive drug therapy and have a repeat BP evaluation in 1 month (1, 2).					
I	B-R	3. Adults with stage 2 hypertension should be evaluated by or referred to a primary care provider within 1 month of the initial diagnosis, have a combination of nonpharmacological and antihypertensive drug therapy (with 2 agents of different classes) initiated, and have a repeat BP evaluation in 1 month (1, 2).					
I	B-R	<ol> <li>For adults with a very high average BP (e.g., SBP ≥180 mm Hg or DBP ≥110 mm Hg), evaluation followed by prompt antihypertensive drug treatment is recommended (1, 2).</li> </ol>					
lla	C-EO	5. For adults with a normal BP, repeat evaluation every year is reasonable.					

### Synopsis

An important component of BP management in hypertensive patients is follow-up. Different periods of time for follow-up are recommended depending on the stage of hypertension, the presence or absence of target organ damage, treatment with antihypertensive medications, and the level of BP control. Recommendations for follow-up are summarized in Figure 4.

### **Recommendation-Specific Supportive Text**

1. Nonpharmacological therapy (see Section 6.2) is the preferred therapy for adults with elevated BP and an appropriate first-line therapy for adults with stage 1 hypertension who have an estimated 10-year ASCVD risk of <10%. Adherence to and impact of nonpharmacological therapy should be assessed within 3 to 6 months.

2. Nonpharmacological therapy can help reduce BP in patients with stage 1 hypertension with an estimated 10-year ASCVD risk of  $\geq$ 10% and should be used in addition to pharmacological therapy as first-line therapy in such patients (see Section 6.2).

3. Prompt evaluation and treatment of patients with stage 2 hypertension with a combination of drug and nonpharmacological therapy are important because of the elevated risk of CVD events in this subgroup, especially those with multiple ASCVD risk factors or target organ damage (1, 2).

4. Prompt management of very high BP is important to reduce the risk of target organ damage (see Section 11.2). The rapidity of the treatment needed is dependent on the patient's clinical presentation (presence of new or worsening target organ damage) and presence or absence of CVD complications, but treatment should be initiated within at least 1 week.

5. Given that the lifetime risk of hypertension exceeds 80% in U.S. adults (3), it is likely that individuals with a normal BP will develop elevated BP in the future. BP may change over time because of changes in BP-related lifestyle factors, such as degree of sedentary lifestyle, dietary sodium intake, body weight, and alcohol intake.

### 2017 High Blood Pressure Clinical Practice Guideline

Less commonly, secondary causes of hypertension can occur over time and lead to an increase in BP. Periodic BP screening can identify individuals who develop elevated BP over time. More frequent BP screening may be particularly important for individuals with elevated ASCVD risk.

### References

- Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials. 2014;11:532-46.
- 2. Cushman WC, Grimm RH Jr, Cutler JA, et al. Rationale and design for the blood pressure intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007;99:44i-55i.
- 3. Carson AP, Howard G, Burke GL, et al. Ethnic differences in hypertension incidence among middle-aged and older adults: the Multi-Ethnic study of Atherosclerosis. Hypertension. 2011;57:1101-7.

# 8.1.4. General Principles of Drug Therapy

	Recommendation for General Principle of Drug Therapy				
Refe	References that support recommendations are summarized in Online Data Supplement 25.				
COR	LOE	Recommendation			
III: Harm	Α	1. Simultaneous use of an ACE inhibitor, ARB, and/or renin inhibitor is potentially harmful and is not recommended to treat adults with hypertension (1-3).			

### Synopsis

Pharmacological agents, in addition to lifestyle modification (see Section 6.2), provide the primary basis for treatment of high BP. A large number of clinical trials have demonstrated that antihypertensive pharmacotherapy not only lowers BP but reduces the risk of CVD, cerebrovascular events, and death (4-7).

Numerous classes of antihypertensive agents are available to treat high BP (Table 18). Agents that have been shown to reduce clinical events should be used preferentially. Therefore, the primary agents used in the treatment of hypertension include thiazide diuretics, ACE inhibitors, ARBs, and CCBs (8-11) (see Section 8.1.6). Although many other drugs and drug classes are available, either confirmation that these agents decrease clinical outcomes to an extent similar to that of the primary agents is lacking, or safety and tolerability may relegate their role to use as secondary agents. In particular, there is inadequate evidence to support the initial use of beta blockers for hypertension in the absence of specific cardiovascular comorbidities (see Section 9).

When the initial drug treatment of high BP is being considered, several different strategies may be contemplated. Many patients can be started on a single agent, but consideration should be given to starting with 2 drugs of different classes for those with stage 2 hypertension (see Section 8.1.6.1). In addition, other patient-specific factors, such as age, concurrent medications, drug adherence, drug interactions, the overall treatment regimen, out-of-pocket costs, and comorbidities, should be considered. From a societal perspective, total costs must be taken into account. Shared decision making, with the patient influenced by clinician judgment, should drive the ultimate choice of antihypertensive agent(s).

Many patients started on a single agent will subsequently require  $\geq 2$  drugs from different pharmacological classes to reach their BP goals (12, 13, 14). Knowledge of the pharmacological mechanisms of action of each agent is important. Drug regimens with complementary activity, where a second antihypertensive agent is used to block compensatory responses to the initial agent or affect a different pressor mechanism, can result in additive lowering of BP. For example, thiazide diuretics may stimulate the renin-angiotensin-aldosterone system. By adding an ACE inhibitor or ARB to the thiazide, an additive BPlowering effect may be obtained (13). Use of combination therapy may also improve adherence. Several 2and 3-fixed-dose drug combinations of antihypertensive drug therapy are available, with complementary

mechanisms of action among the components (Online Data Supplement D). However, it should be noted that many triple-dose combinations may contain a lower-than-optimal dose of thiazide diuretic.

Table 18 is a summary of oral antihypertensive drugs.

### **Recommendation-Specific Supportive Text**

1. Drug combinations that have similar mechanisms of action or clinical effects should be avoided. For example, 2 drugs from the same class should not be administered together (e.g., 2 different beta blockers, ACE inhibitors, or nondihydropyridine CCBs). Likewise, 2 drugs from classes that target the same BP control system are less effective and potentially harmful when used together (e.g., ACE inhibitors, ARBs). Exceptions to this rule include concomitant use of a thiazide diuretic, K-sparing diuretic, and/or loop diuretic in various combinations. Also, dihydropyridine and nondihydropyridine CCBs can be combined. High-quality RCT data demonstrate that simultaneous administration of RAS blockers (i.e., ACE inhibitor with ARB; ACE inhibitor or ARB with renin inhibitor aliskiren) increases cardiovascular and renal risk (1-3).



### Table 18. Oral Antihypertensive Drugs

Class	Drug	Usual Dose, Range (mg/d)*	Daily Frequency		Comments
Primary agents					
Thiazide or	Chlorthalidone	12.5–25	1	•	Chlorthalidone is preferred on the basis of
thiazide-type	Hydrochlorothiazide	25-50	1		prolonged half-life and proven trial reduction of
diuretics	Indapamide	1.25-2.5	1		CVD.
	Metolazone	2.5-10	1	•	Monitor for hyponatremia and hypokalemia, uric
					acid and calcium levels.
				٠	Use with caution in patients with history of acute
					gout unless patient is on uric acid–lowering therapy.
ACE inhibitors	Benazepril	10-40	1 or 2	•	Do not use in combination with ARBs or direct renin
	Captopril	12.5-150	2 or 3		inhibitor.
	Enalapril	5–40	1 or 2	•	There is an increased risk of hyperkalemia, especially
	Fosinopril	10-40	1		in patients with CKD or in those on K <sup>+</sup> supplements
	Lisinopril	10-40	1		or K <sup>+</sup> -sparing drugs.
	Moexipril	7.5-30	1 or 2	•	There is a risk of acute renal failure in patients with
	Perindopril	4-16	1	-	Severe bildleral renal artery steriosis.
	Quinapril	10-80	1 or 2	•	ACE inhibitors
	Ramipril	2.5-10	1 or 2		Avoid in programov
400-	Trandolapril	1-4	1	-	Avoid in pregnancy.
ARBS	Aziisartan	40-80	1	•	Do not use in combination with ACE inhibitors or
	Candesartan	8-32	1	-	direct renin inhibitor.
	Eprosartan	600-800	1 OF 2	•	in these on Kt supplements or Kt sparing drugs
	Irbesartan	150-300	1		In those on K <sup>+</sup> supplements or K <sup>+</sup> -sparing drugs.
	Losartan	50-100	1 or 2	•	sovere bilateral renal actory steposic
	Telmiserten	20-40		1	Do not use if nationt has history of angioedema
	Veleerter	20-80	1	-	with ARBs. Patients with a history of angioedema
	valsartan	80-320			with an ACE inhibitor can receive an ARB beginning 6
					weeks after ACE inhibitor is discontinued.
				•	Avoid in pregnancy.
CCB—	Amlodipine	2.5–10	1	•	Avoid use in patients with HFrEF; amlodipine or
dihydropyridin	Felodipine	5–10	1		felodipine may be used if required.
es	Isradipine	5–10	2	•	They are associated with dose-related pedal edema.
	Nicardipine SR	5–20	1		which is more common in women than men.
	Nifedipine LA	60–120	1		
	Nisoldipine	30–90	1		
CCB—	Diltiazem SR	180–360	2	•	Avoid routine use with beta blockers because of
nondihydropyri	Diltiazem ER	120–480	1		increased risk of bradycardia and heart block.
dines	Verapamil IR	40-80	3	•	Do not use in patients with HFrEF.
	Verapamil SR	120–480	1 or 2	•	There are drug interactions with diltiazem and
	Verapamil-delayed	100–480	1 (in the		verapamil (CYP3A4 major substrate and moderate
	onset ER (various		evening)		inhibitor).
	forms)				
Secondary agent	S		I	r	
Diuretics—	Bumetanide	0.5–4	2	•	These are preferred diuretics in patients with
Іоор	Furosemide	20–80	2	4	symptomatic HF. They are preferred over thiazides
	Torsemide	5–10	1		in patients with moderate-to-severe CKD (e.g., GFR <30 mL/min).
Diuretics—	Amiloride	5–10	1 or 2	•	These are monotherapy agents and minimally
potassium	Triamterene	50-100	1 or 2	1	effective antihypertensive agents.
sparing				•	Combination therapy of potassium-sparing diuretic
				1	with a thiazide can be considered in patients with
				1	hypokalemia on thiazide monotherapy.

				• Avoid in patients with significant CKD (e.g., GFR <45
			10	mL/min).
Diuretics—	Eplerenone	50-100	12	These are preferred agents in primary aldosteronism
aldosterone	Spironolactone	25-100	1	and resistant hypertension.
antagonists				Spironolactone is associated with greater risk of
				gynecomastia and impotence as compared with
				epierenone.
				This is common add-on therapy in resistant
				hypertension.
				<ul> <li>Avoid use with K<sup>+</sup> supplements, other K<sup>+</sup>-sparing</li> </ul>
				diuretics, or significant renal dysfunction.
				Eplerenone often requires twice-daily dosing for
				adequate BP lowering.
Beta	Atenolol	25-100	12	Beta blockers are not recommended as first-line
blockers—	Betaxolol	5–20	1	agents unless the patient has IHD or HF.
cardioselective	Bisoprolol	2.5–10	1	These are preferred in patients with bronchospastic
	Metoprolol tartrate	100-400	2	airway disease requiring a beta blocker.
	Metoprolol succinate	50-200	1	Bisoprolol and metoprolol succinate are preferred in
				patients with HFrEF.
				Avoid abrupt cessation.
Beta	Nebivolol	5–40	1	Nebivolol induces nitric oxide-induced vasodilation.
blockers—				<ul> <li>Avoid abrupt cessation.</li> </ul>
cardioselective				Heart
and				Association.
vasodilatory				
Beta	Nadolol	40–120	1	Avoid in patients with reactive airways disease.
blockers—	Propranolol IR	160-480	2	<ul> <li>Avoid abrupt cessation.</li> </ul>
noncardioselec	Propranolol LA	80–320	1	
Beta	Acebutolol	200-800	2	Generally avoid, especially in patients with IHD or
blockers—	Carteolol	2.5-10	1	HF.
intrinsic	Penhutolol	10-40	1	Avoid abrupt cessation.
sympathomim	Pindolol	10-60	2	
etic activity		10 00	-	
Beta	Carvedilol	12.5-50	2	• Carvedilol is preferred in patients with HFrEF.
blockers—	Carvedilol phosphate	20-80	1	Avoid abrupt cessation.
combined	Labetalol	200-800	2	
alpha- and				
beta-receptor				
Direct renin	Aliskiren	150-300	1	• Do not use in combination with ACE inhibitors or
inhibitor				ARBs.
				Aliskiren is very long acting.
				• There is an increased risk of hyperkalemia in CKD or
				in those on K <sup>+</sup> supplements or K <sup>+</sup> -sparing drugs.
				Aliskiren may cause acute renal failure in patients
				with severe bilateral renal artery stenosis.
				Avoid in pregnancy.
Alpha-1	Doxazosin	1-8	1	These are associated with orthostatic hypotension,
blockers	Prazosin	2–20	2 or 3	especially in older adults.
	Terazosin	1–20	1 or 2	• They may be considered as second-line agent in
				patients with concomitant BPH.
Central alpha <sub>1</sub> -	Clonidine oral	0.1–0.8	2	These are generally reserved as last-line because of
agonist and	Clonidine patch	0.1-0.3	1 weekly	significant CNS adverse effects, especially in older
other centrally	Methyldopa	250-1000	2	adults.
acting drugs	Guanfacine	0.5–2	1	Avoid abrupt discontinuation of clonidine, which
				may induce hypertensive crisis; clonidine must be
	1			tapered to avoid rebound hypertension.

### 2017 High Blood Pressure Clinical Practice Guideline

Direct	Hydralazine	250-200	2 or 3	These are associated with sodium and water		
vasodilators	Minoxidil	5–100	1 -3	retention and reflex tachycardia; use with a diuretic		
				and beta blocker.		
				<ul> <li>Hydralazine is associated with drug-induced lupus-</li> </ul>		
				like syndrome at higher doses.		
				<ul> <li>Minoxidil is associated with hirsutism and requires a</li> </ul>		
				loop diuretic. Minoxidil can induce pericardial		
				effusion.		

\*Dosages may vary from those listed in the FDA approved labeling (available at https://dailymed.nlm.nih.gov/dailymed/). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; BPH, benign prostatic hyperplasia; CCB, calcium channel blocker; CKD, chronic kidney disease; CNS, central nervous system; CVD, cardiovascular disease; ER, extended release; GFR, glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; IR, immediate release; LA, long-acting; and SR, sustained release. From Chobanian et al. JNC 7. (15)

- 1. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. ONTARGET Investigators. N Engl J Med. 2008;358:1547-59.
- 2. Parving H-H, Brenner BM, McMurray JJV, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367:2204-13.
- 3. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892-903.
- 4. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967;202:1028-34.
- 5. Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. JAMA. 1979;242:2562-71.
- 6. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991;265:3255-64.
- 7. Kostis JB, Cabrera J, Cheng JQ, et al. Association between chlorthalidone treatment of systolic hypertension and long-term survival. JAMA. 2011;306:2588-93.
- Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels--overview and meta-analyses of randomized trials. J Hypertens. 2014;32:2296-304.
- Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. J Hypertens. 2011;29:4-16.
- 11. Fretheim A, Odgaard-Jensen J, Brors O, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med. 2012;10:33.
- 12. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich). 2002;4:393-404.
- 13. Gradman AH, Basile JN, Carter BL, et al. Combination therapy in hypertension. J Clin Hypertens (Greenwich). 2011;13:146-54.
- 14. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. ACCORD Study Group. N Engl J Med. 2010;362:1575-85.
- 15. Chobanian AV, Bakris GL, Black HR, et al; the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-52.

# 8.1.5. BP Goal for Patients With Hypertension

	Recommendations for BP Goal for Patients With Hypertension						
Refere	References that support recommendations are summarized in Online Data Supplement 26 and						
		Systematic Review Report.					
COR	DR LOE Recommendations						
	SBP:	1. For adults with confirmed hypertension and known CVD or 10-year ASCVD					
	B-R <sup>SR</sup>	event risk of 10% or higher (see Section 8.1.2), a BP target of less than 130/80					
•	DBP:	mm Hg is recommended (1-5).					
	C-EO						
	SBP:	2. For adults with confirmed hypertension, without additional markers of					
llb	B-NR	increased CVD risk, a BP target of less than 130/80 mm Hg may be					
	DBP:	reasonable (6-9).					
	C-EO						

SR indicates systematic review.

### Synopsis



Refer to the "Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" for the complete systematic evidence review for additional data and analyses (10). Several trials have tested whether more intensive BP control improves major CVD outcomes. Meta-analyses and systematic reviews of these trials provide strong support for the more intensive approach, but the data are less clear in identification of a specific optimal BP target (1-5, 7, 11-13). Recent trials that address optimal BP targets include SPRINT and ACCORD (Action to Control Cardiovascular Risk in Diabetes), with targets for more intensive (SBP <120 mm Hg) and standard (SBP <140 mm Hg) treatment (14, 15), and SPS-3, with a more intensive target of <130/80 mm Hg (16). These trials yielded mixed results in achieving their primary endpoints. SPRINT was stopped early, after a median follow-up of 3.26 years, when more intensive treatment resulted in a significant reduction in the primary outcome (a CVD composite) and in all-cause mortality rate. In ACCORD, more intensive BP treatment failed to demonstrate a significant reduction in the primary outcome (a CVD composite). However, the incidence of stroke, a component of the primary outcome, was significantly reduced. The standard glycemia subgroup did show significant benefit in ACCORD, and a meta-analysis of the only 2 trials (ACCORD and SPRINT) testing an SBP goal of <120 mm Hg showed significant reduction in CVD events (17). SPS-3 failed to demonstrate benefit for the primary endpoint of recurrent stoke (p=0.08) but found a significant reduction in a subgroup with hemorrhagic stroke. Pooling of the experience from 19 trials (excluding SPRINT) that randomly assigned participants to different BP treatment targets identified a significant reduction in CVD events, MI, and stroke in those assigned to a lower (average achieved SBP/DBP was 133/76 mm Hg) versus a higher BP treatment target (2). Similar patterns of benefit were reported in 3 other meta-analyses of trials in which participants were randomly assigned to different BP targets (3-5) and in larger meta-analyses that additionally included trials that compared different intensities of treatment (12). Data from the most recent meta-analysis (42 trials and 144,220 patients) (5) demonstrate a linear association between mean achieved SBP and risk of CVD mortality with the lowest risk at 120 to 124 mm Hg. The totality of the available information provides evidence that a lower BP target is generally better than a higher BP target and that some patients will benefit from an SBP treatment goal <120 mm Hg, especially those at high risk of CVD (15). The specific inclusion and exclusion criteria of any RCT may limit extrapolation to a more general population with hypertension. In addition, all of the relevant trials have been efficacy studies in which BP measurements were more consistent with guideline recommendations than is common in clinical practice, resulting in lower

### 2017 High Blood Pressure Clinical Practice Guideline

absolute values for SBP. For both of these reasons, the SBP target recommended during BP lowering (<130 mm Hg) is higher than that which was used in SPRINT.

### **Recommendation-Specific Supportive Text**

1. Meta-analysis and systematic review of trials that compare more intensive BP reduction to standard BP reduction report that more intense BP lowering significantly reduces the risk of stroke, coronary events, major cardiovascular events, and cardiovascular mortality (1). In a stratified analysis of these data, achieving an additional 10–mm Hg reduction in SBP reduced CVD risk when compared with an average SBP of 158/82 to 143/76 mm Hg, 144/85 to 137/81 mm Hg, and 134/79 to 125/76 mm Hg. Patients with DM and CKD were included in the analysis (1, 2, 11-13, 18). (Specific management details are in Section 9.3 for CKD and Section 9.6 for DM.)

2. The treatment of patients with hypertension without elevated risk has been systematically understudied because lower-risk groups would require prolonged follow-up to have a sufficient number of clinical events to provide useful information. Although there is clinical trial evidence that both drug and nondrug therapy will interrupt the progressive course of hypertension (6), there is no trial evidence that this treatment decreases CVD morbidity and mortality. The clinical trial evidence is strongest for a target BP of 140/90 mm Hg in this population. However, observational studies suggest that these individuals often have a high lifetime risk and would benefit from BP control earlier in life (19, 20).

### References

 Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels--updated overview and meta-analyses of randomized trials. J Hypertens. 2016; 34:613-22.

Heart

- 2. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387:435-43.
- 3. Verdecchia P, Angeli F, Gentile G, et al. More versus less intensive blood pressure-lowering strategy: cumulative evidence and trial sequential analysis. Hypertension. 2016;68:642-53.
- 4. Bangalore S, Toklu B, Gianos E, et al. Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. Am J Med. 2017;30:707-19.e8.
- 5. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol. 2017;2:775-81.
- 6. Julius S, Nesbitt SD, Egan BM, et al. Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med. 2006;354:1685-97.
- 7. Lawes CMM, Bennett DA, Lewington S, et al. Blood pressure and coronary heart disease: a review of the evidence. Semin Vasc Med. 2002;2:355-68.
- 8. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2009-20.
- 9. Neaton JD, Grimm RH Jr, Prineas RJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA. 1993;270:713-24.
- Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Circulation. 2017. In press.
- 11. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ. 2016;352:i717.
- 12. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957-67.
- 13. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ. 2013;185:949-57.
- 14. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. ACCORD Study. N Engl J Med. 2010;362:1575-85.

### 2017 High Blood Pressure Clinical Practice Guideline

- 15. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. SPRINT Research Group. N Engl J Med. 2015;373:2103-16.
- 16. Taler SJ, Textor SC, Canzanello VJ, et al. Role of steroid dose in hypertension early after liver transplantation with tacrolimus (FK506) and cyclosporine. Transplantation. 1996;62:1588-92.
- 17. Perkovic V, Rodgers A. Redefining blood-pressure targets--SPRINT starts the marathon. N Engl J Med. 2015;373:2175-8.
- 18. Lawes CMM, Rodgers A, Bennett DA, et al. Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens. 2003;21:707-16.
- 19. Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. JAMA. 2014;311:490-7.
- 20. Ference BA, Julius S, Mahajan N, et al. Clinical effect of naturally random allocation to lower systolic blood pressure beginning before the development of hypertension. Hypertension. 2014;63:1182-8.

# 8.1.6. Choice of Initial Medication

	Recommendation for Choice of Initial Medication				
Referei	References that support the recommendation are summarized in Online Data Supplement 27 and				
	Systematic Review Report.				
COR	LOE	Recommendation			
I.	A <sup>SR</sup>	1. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. (1, 2)			

SR indicates systematic review.

### Synopsis

The overwhelming majority of persons with BP sufficiently elevated to warrant pharmacological therapy may be best treated initially with 2 agents (see Section 8.1.6.1). When initiation of pharmacological therapy with a single medication is appropriate, primary consideration should be given to comorbid conditions (e.g., HF, CKD) for which specific classes of BP-lowering medication are indicated (see Section 9) (1, 3). In the largest headto-head comparison of first-step drug therapy for hypertension (4, 5), the thiazide-type diuretic chlorthalidone was superior to the CCB amlodipine and the ACE inhibitor lisinopril in preventing HF, a BP-related outcome of increasing importance in the growing population of older persons with hypertension (6-9). Additionally, ACE inhibitors were less effective than thiazide diuretics and CCBs in lowering BP and in prevention of stroke. For black patients, ACE inhibitors were also notably less effective than CCBs in preventing HF (5, 10) and in the prevention of stroke (11, 12) (see Section 10.1). ARBs may be better tolerated than ACE inhibitors in black patients, with less cough and angioedema, but according to the limited available experience they offer no proven advantage over ACE inhibitors in preventing stroke or CVD in this population, making thiazide diuretics (especially chlorthalidone) or CCBs the best initial choice for single-drug therapy. For stroke, in the general population, beta blockers were less effective than CCBs (36% lower risk) and thiazide diuretics (30% lower risk). CCBs have been shown to be as effective as diuretics for reducing all CVD events other than HF, and CCBs are a good alternative choice for initial therapy when thiazide diuretics are not tolerated. Alpha blockers are not used as first-line therapy for hypertension because they are less effective for prevention of CVD than other first-step agents, such as thiazide diuretics (4, 13).

### **Recommendation-Specific Supportive Text**

1. The overall goal of treatment should be reduction in BP, in the context of underlying CVD risk. Five drug classes have been shown, in high-quality RCTs, to prevent CVD as compared with placebo (diuretics, ACE inhibitors, ARBs, CCBs, and beta blockers) (14, 15). In head-to-head comparisons of first-step therapy, different drug classes have been reported to provide somewhat divergent capacity to prevent specific CVD events. Interpretation of meta-analyses comparing agents from different drug classes is challenging because the

relevant RCTs were conducted in different time periods, during which concurrent antihypertensive therapy was less or more common, and the efficacy of agents from certain drug classes may have changed. In recognition of this, some (2) but not all (14, 15) meta-analyses, as well as the largest individual RCT that compared first-step agents (4), have suggested that diuretics, especially the long-acting thiazide-type agent chlorthalidone, may provide an optimal choice for first-step drug therapy of hypertension. In contrast, some meta-analyses have suggested that beta blockers may be less effective, especially for stroke prevention in older adults, but interpretation is hampered by inclusion of RCTs that used beta blockers that are now considered to be inferior for prevention of CVD (16, 17). In a systematic review and network meta-analysis conducted for the present guideline, beta blockers were significantly less effective than diuretics for prevention of HF. There were some other nonsignificant differences between diuretics, ACE inhibitors, ARBs, and CCBs, but the general pattern was for similarity in effect. As indicated in Section 8.1.6.1, most adults with hypertension require more than one drug to control their BP. As recommended in Section 10.1, for black adults with hypertension (without HF or CKD), initial antihypertensive treatment should include a thiazide diuretic or CCB.

- Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017. In press.
- 2. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA. 2003;289:2534-44.
- 3. Peart S. Results of MRC (UK) trial of drug therapy for mild hypertension. Clin Invest Med. 1987;10:616-20.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97.
- 5. Julius S, Weber MA, Kjeldsen SE, et al. The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial: outcomes in patients receiving monotherapy. Hypertension. 2006;48:385-91.
- 6. Ferrucci L, Guralnik JM, Pahor M, et al. Hospital diagnoses, Medicare charges, and nursing home admissions in the year when older persons become severely disabled. JAMA. 1997;277:728-34.
- 7. Curtis LH, Whellan DJ, Hammill BG, et al. Incidence and prevalence of heart failure in elderly persons, 1994-2003. Arch Intern Med. 2008;168:418-24.
- 8. Bleumink GS, Knetsch AM, Sturkenboom MCJM, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J. 2004;25:1614-9.
- 9. Bertoni AG, Hundley WG, Massing MW, et al. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes Care. 2004;27:699-703.
- Ogedegbe G, Shah NR, Phillips C, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitorbased treatment on cardiovascular outcomes in hypertensive blacks versus whites. J Am Coll Cardiol. 2015;66:1224-33.
- 11. Leenen FHH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Hypertension 2006;48:374-84.
- 12. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. J Hypertens. 2006;24:2163-8.
- 13. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension. 2003;42:239-46.
- 14. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.

### 2017 High Blood Pressure Clinical Practice Guideline

- 15. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs--overview and meta-analyses. J Hypertens. 2015;33:1321-41.
- Zhang Y, Sun N, Jiang X, et al. Comparative efficacy of β-blockers on mortality and cardiovascular outcomes in patients with hypertension: a systematic review and network meta-analysis. J Am Soc. Hypertens. 2017;11:394-401.
- 17. Larochelle P, Tobe SW, Lacourciere Y. β-Blockers in hypertension: studies and meta-analyses over the years. Can J Cardiol. 2014;30:S16-22.

# 8.1.6.1. Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

Reco	Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug				
	Therapy*				
COR	COR LOE Recommendation				
I	C-EO	1. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.			
lla	C-EO	<ol> <li>Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal &lt;130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.</li> </ol>			

\*Fixed-dose combination antihypertensive medications are listed in Online Data Supplement D.

### Synopsis

Systematic review of the evidence comparing the initiation of antihypertensive treatment with monotherapy and sequential (stepped-care) titration of additional agents versus initiation of treatment with combination therapy (including fixed-dose combinations) did not identify any RCTs meeting the systematic review questions posed in the PICOTS format (P=population, I=intervention, C=comparator, O=outcome, T=timing, S=setting). However, in both ACCORD and SPRINT, 2-drug therapy was recommended for most participants in the intensive- but not standard-therapy groups.

### **Recommendation-Specific Supportive Text**

1. Because most patients with hypertension require multiple agents for control of their BP and those with higher BPs are at greater risk, more rapid titration of antihypertensive medications began to be recommended in patients with BP >20/10 mm Hg above their target, beginning with the JNC 7 report (1). In these patients, initiation of antihypertensive therapy with 2 agents is recommended. Evidence favoring this approach comes mostly from studies using fixed-dose combination products showing greater BP lowering with fixed-dose combination agents than with single agents, as well as better adherence to therapy (2, 3). The safety and efficacy of this strategy have been demonstrated in adults to reduce BPs to <140/90 mm Hg though not compared with other strategies (4-6). In general, this approach is reasonable in the very elderly, those at high CVD risk, or those who have a history of hypotension or drug-associated side effects. However, caution is advised in initiating antihypertensive pharmacotherapy with 2 drugs in older patients because hypotension or orthostatic hypotension may develop in some patients; BP should be carefully monitored.

2. The stepped-care approach defined by the initiation of antihypertensive drug therapy with a single agent followed by the sequential titration of the dose and addition of other agents has been the recommended treatment strategy since the first report of the National High Blood Pressure Education Program (7). This approach is also reasonable in the very elderly or those at risk or who have a history of hypotension or drug-

### 2017 High Blood Pressure Clinical Practice Guideline

associated side effects. This strategy has been used successfully in nearly all hypertension treatment trials but has not been formally tested against other antihypertensive drug treatment strategies for effectiveness in achieving BP control or in preventing adverse outcomes.

### References

- Chobanian AV, Bakris GL, Black HR, et al; the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-52.
- 2. Law MR, Wald NJ, Morris JK, et al. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326:1427.
- 3. Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a metaanalysis. Am J Med.. 2007;120:713-9.
- 4. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359:2417-28.
- 5. Sundstrom J, Arima H, Jackson R, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Ann Intern Med. 2015;162:184-91.
- 6. Luders S, Schrader J, Berger J, et al. The PHARAO study: prevention of hypertension with the angiotensinconverting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. J Hypertens. 2008;26:1487-96.
- Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A cooperative study. JAMA. 1977;237:255-61.



# 8.2. Achieving BP Control in Individual Patients

Recommendations for lifestyle modifications and drug selection are specified in Sections 6.2, 8.1.4, and 8.1.6. Initial drug selections should be based on trial evidence of treatment efficacy, combined with recognition of compelling indications for use of an agent from a specific drug class, as well as the individual patient's lifestyle preferences and traits. For a subset of patients (25% to 50%) (1), the initial drug therapy will be well tolerated and effective in achieving the desired level of BP, with only the need for subsequent monitoring (see Section 8.3 for an appropriate follow-up schedule). For others, the initial drug will not be tolerated or will not be effective, requiring either a change in medication or addition of another medication, followed by BP monitoring (2). Approximately 25% of patients will require additional treatment adjustments. In a minority of this group, achievement of goal BP can be challenging.

In patients who do not respond to or do not tolerate treatment with 2 to 3 medications or medication combinations, additional trials of treatment tend to be ineffective or poorly tolerated. Some patients may become disillusioned and lost to follow-up, whereas others will identify an alternative healthcare provider, including nontraditional healers, or will try popular home remedies. Working with this more demanding subset requires provider expertise, patience, and a mechanism to respond efficiently and sensitively to concerns as they arise. In this setting, team-based care (see Section 12) may be effective, encouraging coupling of nonpharmacological and pharmacological treatments, while improving access to and communication with care providers.

In the setting of medication intolerance, consider allowing a defined period of time to evaluate the effects of lifestyle modification in patients with a relatively low CVD risk (10-year risk of ASCVD <10%, based on the ASCVD Risk Estimator [http://tools.acc.org/ASCVD-Risk-Estimator]), with scheduled follow-up visits for assessment of BP levels, including a review of HBPM data, and an appraisal of lifestyle change goal achievements. For patients with a higher level of CVD risk or with significant elevations in BP (SBP or DBP >20 or >10 mm Hg above target, respectively), medication is usually started even while the patient is pursuing lifestyle change (see Section 8.1.2).

Consideration of patient comorbidities, lifestyle, and preferences may suggest better tolerance or greater effect from one class of medication versus other classes. For example, if hyponatremia is present, it would be important to avoid or stop thiazide diuretic therapy. In this case, a loop diuretic should be used if a

diuretic is required. If hypokalemia is present, primary or secondary aldosteronism should be excluded, after which one should consider a potassium-sparing agent, such as spironolactone, eplerenone, triamterene, or amiloride. In addition, reducing dietary sodium intake will diminish urinary potassium losses. If the patient has chronic cough or a history of ACE inhibitor–induced cough or develops a cough or bronchial responsiveness while on an ACE inhibitor, one should use an ARB in place of an ACE inhibitor. For patients with bronchospastic lung disease, a beta-1-selective blocker (e.g., bisoprolol, metoprolol) should be considered if beta-blocker therapy is required. A patient who is already adherent to lifestyle change recommendations, including diligent reduction in sodium intake, may show a greater response to a RAS blocker. Prior patient experience should be considered, as in the case of cough associated with prior use of an ACE inhibitor, which is likely to reoccur if an agent from the same class is prescribed.

### References

- 1. Neaton JD, Grimm RH Jr, Prineas RJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA. 1993;270:713-24.
- 2. Senn S. Individual response to treatment: is it a valid assumption? BMJ. 2004;329:966-8.

### 8.3. Follow-Up of BP During Antihypertensive Drug Therapy

Appropriate follow-up and monitoring enable assessment of adherence (see Section 12.1) and response to therapy, help identify adverse responses to therapy and target organ damage, and allow assessment of progress toward treatment goals. High-quality RCTs have successfully and safely developed strategies for follow-up, monitoring, and reassessment from which recommendations can be made (Figure 4) (1, 2). A systematic approach to out-of-office BP assessment is an essential part of follow-up and monitoring of BP, to assess response to therapy; check for evidence of white coat hypertension, white coat effect, masked hypertension, or masked uncontrolled hypertension; and help achieve BP targets (see Sections 4 and 12).

### References

- Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials. 2014;11:532-46.
- 2. Cushman WC, Grimm RH Jr, Cutler JA, et al. Rationale and design for the blood pressure intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007;99:44i-55i.

# 8.3.1. Follow-Up After Initiating Antihypertensive Drug Therapy

Refer	<b>Recommendation for Follow-Up After Initiating Antihypertensive Drug Therapy</b> References that support the recommendation are summarized in Online Data Supplement 28.				
COR	LOE	Recommendation			
I	B-R	1. Adults initiating a new or adjusted drug regimen for hypertension should have a follow-up evaluation of adherence and response to treatment at monthly intervals until control is achieved (1-3).			

### **Recommendation-Specific Supportive Text**

1. Components of the follow-up evaluation should include assessment of BP control, as well as evaluation for orthostatic hypotension, adverse effects from medication therapy, adherence to medication and lifestyle therapy, need for adjustment of medication dosage, laboratory testing (including electrolyte and renal function status), and other assessments of target organ damage (1-3).

### 2017 High Blood Pressure Clinical Practice Guideline

### References

- Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials. 2014;11:532-46.
- 2. Cushman WC, Grimm RH Jr, Cutler JA, et al. Rationale and design for the blood pressure intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007;99:44i-55i.
- 3. Xu W, Goldberg SI, Shubina M, et al. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study. BMJ. 2015;350:h158.

# 8.3.2. Monitoring Strategies to Improve Control of BP in Patients on Drug Therapy for High BP

Recom	Recommendation for Monitoring Strategies to Improve Control of BP in Patients on Drug				
	Therapy for High BP				
Refer	ences that	support the recommendation are summarized in Online Data Supplement 29.			
COR	LOE	Recommendation			
I	А	1. Follow-up and monitoring after initiation of drug therapy for hypertension control should include systematic strategies to help improve BP, including use of HBPM, team-based care, and telehealth strategies (1-6).			

### **Recommendation-Specific Supportive Text**

1. Systematic approaches to follow-up have been shown to improve hypertension control and can be adapted and incorporated into clinical practices according to local needs and resource availability (see Section 8.3.1 for time intervals for treatment follow-up and monitoring and Sections 12.2 and 12.3.2 on systematic strategies to improve BP control).

Association.

### References

- 1. Brennan T, Spettell C, Villagra V, et al. Disease management to promote blood pressure control among African Americans. Popul Health Manag. 2010;13:65-72.
- 2. Bosworth HB, Olsen MK, Grubber JM, et al. Two self-management interventions to improve hypertension control: a randomized trial. Ann Intern Med. 2009;151:687-95.
- 3. Bosworth HB, Powers BJ, Olsen MK, et al. Home blood pressure management and improved blood pressure control: results from a randomized controlled trial. Arch Intern Med. 2011;171:1173-80.
- 4. Green BB, Cook AJ, Ralston JD, et al. Effectiveness of home blood pressure monitoring, Web communication, and pharmacist care on hypertension control: a randomized controlled trial. JAMA. 2008;299:2857-67.
- 5. Heisler M, Hofer TP, Schmittdiel JA, et al. Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems: the adherence and intensification of medications cluster randomized, controlled pragmatic trial. Circulation. 2012;125:2863-72.
- 6. Margolis KL, Asche SE, Bergdall AR, et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial. JAMA. 2013;310:46-56.

# 9. Hypertension in Patients With Comorbidities

Certain comorbidities may affect clinical decision-making in hypertension. These include ischemic heart disease, HF with reduced ejection fraction (HFrEF), HFpEF, CKD (including renal transplantation), cerebrovascular disease, AF, PAD, DM, and metabolic syndrome (1). As noted in Section 8.1.2, this guideline generally recommends use of BP-lowering medications for secondary prevention of CVD in patients with clinical CVD (CHD, HF, and stroke) and an average BP  $\geq$ 130/80 mm Hg and for primary prevention of CVD in adults with an estimated 10-year ASCVD risk of  $\geq$ 10% and an average SBP  $\geq$ 130 mm Hg or an average DBP  $\geq$ 80 mm Hg. Although we recommend use of the ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-

### 2017 High Blood Pressure Clinical Practice Guideline

Risk-Estimator/) to estimate 10-year risk of ASCVD to establish the BP threshold for treatment, the vast majority of adults with a co-morbidity are likely to have a 10-year risk of ASCVD that exceeds 10%. In some instances, clinical trial confirmation of treatment in patients with comorbidities is limited to a target BP of 140/90 mm Hg. In addition, the selection of medications for use in treating high BP in patients with CVD is guided by their use for other compelling indications (e.g., beta blockers after MI, ACE inhibitors for HF*r*EF), as discussed in specific guidelines for the clinical condition (2-4). The present guideline does not address the recommendations for treatment of hypertension occurring with acute coronary syndromes.

#### References

- Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. Circulation. 2011;123:2434-506.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-327.
- Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2014;130:1749-67.
- Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e726-79.

Recom	Recommendations for Treatment of Hypertension in Patients With Stable Ischemic Heart						
	Disease (SIHD)						
Refere	nces that	support recommendations are summarized in Online Data Supplements 30-32.					
COR	LOE	Recommendations					
	SBP:	1. In adults with SIHD and hypertension, a BP target of less than 130/80 mm					
	B-R	Hg is recommended (1-5).					
	DBP:						
	C-EO						
	SBP:	2. Adults with SIHD and hypertension (BP ≥130/80 mm Hg) should be treated					
	B-R	with medications (e.g., GDMT (6) beta blockers, ACE inhibitors, or ARBs) for					
		compelling indications (e.g., previous MI, stable angina) as first-line therapy,					
•	DBP:	with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide					
	C-EO	diuretics, and/or mineralocorticoid receptor antagonists) as needed to					
	• - •	further control hypertension (7-10).					
		3. In adults with SIHD with angina and persistent uncontrolled hypertension,					
I	B-NR	the addition of dihydropyridine CCBs to GDMT (6) beta blockers is					
		recommended (8, 11, 12).					
		4. In adults who have had a MI or acute coronary syndrome, it is reasonable to					
lla	B-NR	continue GDMT (6) beta blockers beyond 3 years as long-term therapy for					
		hypertension (13, 14).					
		hypertension (13, 14).					

# 9.1. Stable Ischemic Heart Disease



### Synopsis

Hypertension is a major risk factor for ischemic heart disease. Numerous RCTs have demonstrated the benefits of antihypertensive drug therapy in reducing the risk of ischemic heart disease. The following recommendations apply only to management of hypertension in patients with SIHD without HF. See Section 9.2 for recommendations for the treatment of patients with SIHD and HF.

Figure 5 is an algorithm on management of hypertension in patients with SIHD.

### **Recommendation-Specific Supportive Text**

1. In patients with increased cardiovascular risk, reduction of SBP to <130/80 mm Hg has been shown to reduce CVD complications by 25% and all-cause mortality by 27% (1).

2. After 5 years of randomized therapy in high-CVD-risk patients, ramipril produced a 22% reduction in MI, stroke, or CVD compared with placebo (10). No added benefit on CVD outcomes was seen when compared with CCBs and diuretics (15, 16). After 4.2 years of randomized therapy in patients with SIHD, perindopril reduced CVD death, MI, or cardiac arrest by 20% compared with placebo (7). Beta blockers are effective drugs for preventing angina pectoris, improving exercise time until the onset of angina pectoris, reducing exercise-induced ischemic ST-segment depression, and preventing coronary events (8, 17-22). Because of their compelling indications for treatment of SIHD, these drugs are recommended as a first-line therapy in the treatment of hypertension when it occurs in patients with SIHD. GDMT beta blockers for SIHD that are also effective in lowering BP include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Atenolol is not as effective as other antihypertensive drugs in the treatment of hypertension (23).

3. Dihydropyridine CCBs are effective antianginal drugs that can lower BP and relieve angina pectoris when added to beta blockers in patients in whom hypertension is present and angina pectoris persists despite betablocker therapy (8, 17, 19-22, 24, 25). GDMT beta blockers for SIHD that are also effective in lowering BP include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol.

4. In randomized long-term trials, use of beta blockers after MI reduced all-cause mortality by 23% (13). Given the established efficacy of beta blockers for treating hypertension and SIHD, their use for treatment continuing beyond 3 years after MI is reasonable (6, 25).

5. GDMT beta blockers and CCBs are effective antihypertensive and antianginal agents. CCBs include dihydropyridine and nondihydropyridine agents. CCBs can be used separately or together with beta blockers beginning 3 years after MI in patients with CAD who have both hypertension and angina.





Colors correspond to Class of Recommendation in Table 1.

\*GDMT beta blockers for BP control or relief of angina include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta blockers with intrinsic sympathomimetic activity. The beta blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events. †If needed for BP control.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; GDMT, guideline-directed management and therapy; and SIHD, stable ischemic heart disease.

- 1. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. SPRINT Research Group. N Engl J Med. 2015;373:2103-16.
- 2. Bundy JD, Li C, Stuchlik P, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol. 2017;2:775-81.
- 3. Leenen FHH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertension 2006;48:374-84.
- 4. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. J Hypertens. 2006;24:2163-8.
- 5. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension. 2003;42:239-46.
- 6. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2014;130:1749-67.

### 2017 High Blood Pressure Clinical Practice Guideline

- Fox KM, EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362:782-8.
- Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
- Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327:669-77.
- Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342:145-53.
- 11. Leon MB, Rosing DR, Bonow RO, et al. Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. Am J Cardiol. 1981;48:131-9.
- 12. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997;350:757-64.
- 13. Freemantle N, Cleland J, Young P, et al. Beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318:1730-7.
- de Peuter OR, Lussana F, Peters RJG, et al. A systematic review of selective and non-selective beta blockers for prevention of vascular events in patients with acute coronary syndrome or heart failure. Neth J Med. 2009;67:284-94.
- 15. Bavry AA, Anderson RD, Gong Y, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. Hypertension 2010;55:48-53.
- 16. Piller LB, Simpson LM, Baraniuk S, et al. Characteristics and long-term follow-up of participants with peripheral arterial disease during ALLHAT. J Gen Intern Med. 2014;29:1475-83.
- 17. Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Circulation. 2015;131:e435-70.
- 18. Ekelund LG, Olsson AG, Oro L, et al. Effects of the cardioselective beta-adrenergic receptor blocking agent metoprolol in angina pectoris. Subacute study with exercise tests. Br Heart J. 1976; 38:155-61.
- 19. Aronow WS, Turbow M, Van Camp S, et al. The effect of timolol vs placebo on angina pectoris. Circulation. 1980;61:66-9.
- 20. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. Circulation. 2011;123:2434-506.
- 21. Aronow WS, Frishman WH. Angina pectoris in the elderly. In: Aronow WS, Fleg JL, Rich MW, eds. Tresch and Aronow's Cardiovascular Disease in the Elderly. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2013:215-37.
- 22. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458-73.
- 23. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet. 2004;364:1684-9.
- 24. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159-219.
- 25. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians,

American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354-471.

# 9.2. Heart Failure

	Recommendation for Prevention of HF in Adults With Hypertension					
Refer	References that support the recommendation are summarized in Online Data Supplement 33.					
COR	LOE	Recommendation				
	SBP:	1. In adults at increased risk of HF, the optimal BP in those with hypertension				
I	B-R	should be less than 130/80 mm Hg (1-3).				
	DBP:					
	C-EO					

### Synopsis

Antecedent hypertension is present in 75% of patients with chronic HF (4). In the Cardiovascular Health Study (5) and the Health, Aging and Body Composition Study (6), 11.2% of 4408 persons (53.1% women, with a mean age of 72.8 years, living in the community, and not receiving antihypertensive drugs at baseline) developed HF over 10 years (7). Compared with those with an average SBP <120 mm Hg, the adjusted incidence of HF was increased 1.6, 2.2, and 2.6 times in those with average SBPs between 120 and 139 mm Hg, between 140 and 159 mm Hg, and  $\geq$ 160 mm Hg, respectively (7).

No RCTs are available that compare one BP-lowering agent to another for the management of patients with HF. The following recommendations for treatment of hypertension in HF are based on use of drugs that lower BP and also have compelling indications for management of HF (with HF*r*EF or HF*p*EF) as recommended in current ACC/AHA guidelines (4, 8).

### **Recommendation-Specific Supportive Text**

1. In adults with hypertension (SBP  $\geq$ 130 mm Hg or DBP  $\geq$ 80 mm Hg) and a high risk of CVD, a strong body of evidence supports treatment with antihypertensive medications (see Section 8.1.2) and more-intensive rather than less-intensive intervention (see Section 8.1.5). In SPRINT, a more intensive intervention that targeted an SBP <120 mm Hg significantly reduced the primary outcome (CVD composite) by about 25% (9). The incidence of HF, a component of the primary outcome, was also substantially decreased (hazard ratio: 0.62; 95% confidence interval: 0.45–0.84). Meta-analyses of clinical trials have identified a similar beneficial effect of more-intensive BP reduction on the incidence of HF (2, 10), but the body of information from studies confined to trials that randomly assigned participants to different BP targets is more limited and less compelling (3). In addition, the available trials were efficacy studies in which BP measurements were more consistent with guideline recommendations than is common in clinical practice, resulting in lower absolute values for SBP. For both of these reasons, the SBP target recommended during BP lowering (<130 mm Hg) is higher than that used in SPRINT.

- 1. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ. 2013;185:949-57.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels--updated overview and meta-analyses of randomized trials. J Hypertens. 2016; 34:613-22.
- 3. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387:435-43.
- 4. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the

### 2017 High Blood Pressure Clinical Practice Guideline

American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2016;134:e282-93.

- 5. Visser M, Langlois J, Guralnik JM, et al. High body fatness, but not low fat-free mass, predicts disability in older men and women: the Cardiovascular Health Study. Am J Clin Nutr. 1998;68:584-90.
- 6. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006;61:1059-64.
- 7. Butler J, Kalogeropoulos AP, Georgiopoulou VV, et al. Systolic blood pressure and incident heart failure in the elderly. The Cardiovascular Health Study and the Health, Ageing and Body Composition Study. Heart. 2011;97:1304-11.
- 8. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-327.
- Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure 9. control. SPRINT Research Group. N Engl J Med. 2015;373:2103-16.
- 10. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957-67.

# 9.2.1. Heart Failure With Reduced Ejection Fraction

<b>Recommendations for Treatment of Hypertension in Patients With HFrEF</b> References that support recommendations are summarized in Online Data Supplement 34.		
COR	LOE	Recommendation Association.
I.	C-EO	1. Adults with HFrEF and hypertension should be prescribed GDMT (2) titrated to attain a BP of less than 130/80 mm Hg.
III: No Benefit	B-R	2. Nondihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HFrEF (1).

# Synopsis

Approximately 50% of patients with HF have HFrEF (2-6). Numerous RCTs have shown that treatment of HFrEF with GDMT reduces mortality and HF hospitalizations (7). Large-scale RCTs have shown that antihypertensive drug therapy reduces the incidence of HF in patients with hypertension (8-11). In ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), chlorthalidone reduced the risk of HFrEF more than amlodipine and doxazosin but similarly to lisinopril (12, 13).

### **Recommendation-Specific Supportive Text**

1. This recommendation is based on guidance in the 2017 ACC/AHA/HFSA guideline focused update on heart failure (14) (see figure from the HF focused update that is reproduced in Online Data Supplement A). Lifestyle modification, such as weight loss and sodium reduction, may serve as adjunctive measures to help these agents work better. No RCT evidence is available to support the superiority of one BP-lowering medication with compelling indications for treatment of HFrEF over another. Medications with compelling indications for HF that may be used as first-line therapy to treat high BP include ACE inhibitors or ARBs, angiotensin receptorneprilysin inhibitors, mineralocorticoid receptor antagonists, diuretics, and GDMT beta blockers (carvedilol, metoprolol succinate, or bisoprolol).

Clinical trials evaluating goal BP reduction and optimal BP-lowering agents in the setting of HFrEF and concomitant hypertension have not been performed. However, in patients at higher CVD risk, BP lowering is associated with fewer adverse cardiovascular events (7). GDMT for HFrEF with agents known to lower BP should consider a goal BP reduction consistent with a threshold now associated with improved clinical outcomes but not yet proven by RCTs in an HF population.

### 2017 High Blood Pressure Clinical Practice Guideline

2. Nondihydropyridine CCBs (verapamil, diltiazem) have myocardial depressant activity. Several clinical trials have demonstrated either no clinical benefit or even worse outcomes in patients with HF treated with these drugs (1). Therefore, nondihydropyridine CCBs are not recommended in patients with hypertension and HF*r*EF.

### References

- 1. Goldstein RE, Boccuzzi SJ, Cruess D, et al. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. Circulation. 1991;83:52-60.
- 2. Aronow WS, Ahn C, Kronzon I. Normal left ventricular ejection fraction in older persons with congestive heart failure. Chest. 1998;113:867-9.
- 3. Aronow WS, Ahn C, Kronzon I. Comparison of incidences of congestive heart failure in older African-Americans, Hispanics, and whites. Am J Cardiol. 1999;84:611-2, A9.
- 4. Gottdiener JS, McClelland RL, Marshall R, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med. 2002;137:631-9.
- 5. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251-9.
- Vasan RS, Larson MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999;33:1948-55.
- 7. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2016;134:e282-93.
- 8. Amery A, Birkenhager W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet. 1985;1:1349-54.
- 9. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. JAMA. 1997;278:212-6.
- 10. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887-98.
- 11. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
- 12. Davis BR, Kostis JB, Simpson LM, et al. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation. 2008;118:2259-67.
- 13. Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up of participants with heart failure in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Circulation. 2011;124:1811-8.
- 14. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137-61.

### 9.2.2. Heart Failure With Preserved Ejection Fraction

Recommendations for Treatment of Hypertension in Patients With HFpEF				
References that support recommendations are summarized in Online Data Supplements 35 and 36.				
COR	LOE	Recommendations		
I.	C-EO	1. In adults with HFpEF who present with symptoms of volume overload,		
		diuretics should be prescribed to control hypertension.		
		2. Adults with HFpEF and persistent hypertension after management of		
. I	C-LD	volume overload should be prescribed ACE inhibitors or ARBs and beta		
		blockers titrated to attain SBP of less than 130 mm Hg (1-6).		

### Synopsis

Approximately 50% of patients with HF have HFpEF (2, 7-11). The ejection fraction in these studies has varied from >40% to  $\geq$ 55% (2). Patients with HFpEF are usually older women with a history of hypertension. Obesity, CHD, DM, AF, and hyperlipidemia are also highly prevalent in patients with HFpEF (2, 11, 12). Hypertension is the most important cause of HFpEF, with a prevalence of 60% to 89% in large RCTs, epidemiological studies, and HF registries (2, 13). Patients with HFpEF also have an exaggerated hypertensive response to exercise (14). Hypertensive acute pulmonary edema is an expression of HFpEF (15).

BP control is important for prevention of HF*p*EF in patients with hypertension (2, 16-19). ALLHAT showed that treatment of hypertension with chlorthalidone reduced the risk of HF compared with amlodipine, doxazosin, and lisinopril (19, 20). Improved BP control also reduces hospitalization, CVD events, and mortality (2, 16-19).

### **Recommendation-Specific Supportive Text**

1. Diuretics are the only drugs used for the treatment of hypertension and HF that can adequately control the fluid retention of HF. Appropriate use of diuretics is also crucial to the success of other drugs used for the treatment of hypertension in the presence of HF. The use of inappropriately low doses of diuretics can result in fluid retention. Conversely, the use of inappropriately high doses of diuretics can lead to volume contraction, which can increase the risk of hypotension and renal insufficiency. Diuretics should be prescribed to all patients with hypertension and HF*p*EF who have evidence of, and to most patients with a prior history of, fluid retention.

2. In a trial of patients with HFpEF and MI, patients randomized to propranolol had at 32-month follow-up a 35% reduction in mortality rate (3). After 21 months of treatment in patients with HFrEF and HFpEF, compared with placebo, those randomized to nebivolol had a 14% reduction in mortality or CVD hospitalization if they had HFrEF and a 19% reduction if they had HFpEF (4). In patients with HFpEF, the primary outcome (a composite of CVD death or HF hospitalization) was observed in 22% for candesartan and 24% for placebo (11% reduction), but fewer patients receiving candesartan were hospitalized for HF (5). The use of nitrates in the setting of HFpEF is associated with a signal of harm and in most situations should be avoided. For many other common antihypertensive agents, including alpha blockers, beta blockers, and calcium channel blockers, limited data exist to guide the choice of antihypertensive therapy in the setting of HFpEF (21). Reninangiotensin-aldosterone system inhibition, however, with ACE inhibitor or ARB and especially MRA would represent the preferred choice. A shared decision-making discussion, with the patient influenced by clinician judgment, should drive the ultimate choice of antihypertensive agents.

- Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015;131:34-42.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-327.
- Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol. 1997;80:207-9.
- 4. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol. 2009;53:2150-8.
- 5. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777-81.

### 2017 High Blood Pressure Clinical Practice Guideline

- 6. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456-67.
- 7. Aronow WS, Ahn C, Kronzon I. Normal left ventricular ejection fraction in older persons with congestive heart failure. Chest. 1998;113:867-9.
- 8. Aronow WS, Ahn C, Kronzon I. Comparison of incidences of congestive heart failure in older African-Americans, Hispanics, and whites. Am J Cardiol. 1999;84:611-2, A9.
- Vasan RS, Larson MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999;33:1948-55.
- 10. Gottdiener JS, McClelland RL, Marshall R, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med. 2002;137:631-9.
- 11. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251-9.
- 12. Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. Circulation. 2009;119:3070-7.
- 13. Bhuiyan T, Maurer MS. Heart failure with preserved ejection fraction: persistent diagnosis, therapeutic enigma. Curr Cardiovasc Risk Rep. 2011;5:440-9.
- 14. Kato S, Onishi K, Yamanaka T, et al. Exaggerated hypertensive response to exercise in patients with diastolic heart failure. Hypertens Res. 2008;31:679-84.
- 15. St Gyalai-Korpos I, Tomescu M, Pogorevici A. Hypertensive acute pulmonary oedema as expression of diastolic heart failure. Rom J Intern Med. 2008;46:153-7.
- 16. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. Circulation. 2011;123:2434-506.
- 17. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. JAMA. 1997;278:212-6.
- Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887-98.
- 19. Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up of participants with heart failure in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). Circulation. 2011;124:1811-8.
- 20. Davis BR, Kostis JB, Simpson LM, et al. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation. 2008;118:2259-67.
- 21. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2013;309:1268-77.

# 9.3. Chronic Kidney Disease

Recommendations for Treatment of Hypertension in Patients With CKD				
References that support recommendations are summarized in Online Data Supplements 37 and 38				
and Systematic Review Report.				
COR	LOE	Recommendations		
I	SBP:	1. Adults with hypertension and CKD should be treated to a BP goal of less than		
	B-R <sup>SR</sup>	130/80 mm Hg (1-6).		
	DBP:			
	C-EO			
lla	B-R	<ol> <li>In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression (3, 7-12).</li> </ol>		
llb	C-EO	<ol> <li>In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]) (7, 8), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.</li> </ol>		

SR indicates systematic review.

### Synopsis

Refer to the "Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" for the complete systematic evidence review for additional data and analyses (13). Hypertension is the most common comorbidity affecting patients with CKD. Hypertension has been reported in 67% to 92% of patients with CKD, with increasing prevalence as kidney function declines (14). Hypertension may occur as a result of kidney disease, yet the presence of hypertension may also accelerate further kidney injury; therefore, treatment is an important means to prevent further kidney functional decline. This tight interaction has led to extensive debate about the optimal BP target for patients with CKD (15-18). Masked hypertension may occur in up to 30% of patients with CKD and portends higher risk of CKD progression (19-23). CKD is an important risk factor for CVD (24), and the coexistence of hypertension and CKD further increases the risk of adverse CVD and cerebrovascular events, particularly when proteinuria is present (25). Even as the importance of hypertension treatment is widely accepted, data supporting BP targets in CKD are limited, as patients with CKD were historically excluded from clinical trials. Furthermore, CKD is not included in the CVD risk calculations used to determine suitability for most clinical trials (26-28).

Heart

Until publication of the SPRINT results, most guidelines for BP targets in patients with CKD favored treatment to a BP <140/90 mm Hg (15), with consideration of the lower target of <130/80 mm Hg for those with more severe proteinuria ( $\geq$ 300 mg albuminuria in 24 hours or the equivalent), if tolerated (16-18). Patients with stage 3 to 4 CKD (eGFR of 20 to <60 mL/minute/1.73 m<sup>2</sup>) comprised 28% of the SPRINT study population, and in this group intensive BP management seemed to provide the same benefits for reduction in the CVD composite primary outcome and all-cause mortality as were seen in the full study cohort. Given that most patients with CKD die from CVD complications, this RCT evidence supports a lower target of <130/80 mm Hg for all patients with CKD (Figure 6). It is appropriate to acknowledge that many patients with CKD have additional comorbidities and evidence of frailty that caused them to be excluded from past clinical trials. Observational studies of CKD cohorts indicate a higher risk of mortality at lower systolic pressures and a flat relationship of SBP to event risk in elderly patients with CKD (29, 30), which supports concerns that these complex patients may be at greater risk of complications from intensive BP treatment and may fail to achieve benefits from lower BP targets. In contrast, in the prespecified subgroup analysis of the elderly cohort in

SPRINT, frail elderly patients did sustain benefit from the lower BP target, which supports a lower goal for all patients, including those with CKD (31). In this setting, incremental BP reduction may be appropriate, with careful monitoring of physical and kidney function.

An ACE inhibitor (or an ARB, in case of ACE inhibitor intolerance) is a preferred drug for treatment of hypertension if albuminuria ( $\geq$ 300 mg/day or  $\geq$ 300 mg/g creatinine by first morning void) is present, although the evidence is mixed (10, 11) (Figure 6). In the course of reducing intraglomerular pressure and thereby reducing albuminuria, serum creatinine may increase up to 30% because of concurrent reduction in GFR (32). Further GFR decline should be investigated and may be related to other factors, including volume contraction, use of nephrotoxic agents, or renovascular disease (33). The combination of an ACE inhibitor and an ARB should be avoided because of reported harms demonstrated in several large cardiology trials (34, 35) and in 1 diabetic nephropathy trial (36). Because of the greater risk of hyperkalemia and hypotension and lack of demonstrated benefit, the combination of an ARB (or ACE inhibitor) and a direct renin inhibitor is also contraindicated during management of patients with CKD (37).

Figure 6 is an algorithm on management of hypertension in patients with CKD.

### **Recommendation-Specific Supportive Text**

1. We recommend ASCVD risk assessment in all adults with hypertension, including those with CKD. As a matter of convenience, however, it can be assumed that the vast majority of patients with CKD have a 10-year ASCVD risk ≥10%, placing them in the high risk category that requires initiation of antihypertensive drug therapy at BP ≥130/80 mm Hg (see Section 8.1.2, Figure 4 and Table 23 for BP thresholds for initiating antihypertensive drug treatment). In SPRINT, the participants with CKD who were randomized to intensive antihypertensive therapy (SBP target <120 mm Hg) appeared to derive the same beneficial reduction in CVD events and all-cause mortality that was seen in their counterparts without CKD at baseline. Likewise, intensive therapy was beneficial even in those ≥75 years of age with frailty or the slowest gait speed. There was no difference in the principal kidney outcome (≥50% decline in eGFR or ESRD) between the intensive-and standard-therapy (SBP target <140 mm Hg) groups (26). Three other RCTs (1-3) have evaluated the effect of differing BP goals of <140/90 mm Hg versus 125–130/75–80 mm Hg on CKD progression in patients with CKD. None of these trials demonstrated a benefit for more intensive BP reduction, although post hoc follow-up analyses favored the lower targets in patients with more severe proteinuria (38, 39), and these trials were underpowered to detect differences in CVD event rates. Recent meta-analyses and systematic reviews that included patients with CKD from SPRINT support more intensive BP treatment (40-42) to reduce cardiovascular events but do not demonstrate a reduction in the rate of progression of kidney disease (doubling of serum creatinine or reaching ESRD). More intensive BP treatment may result in a modest reduction in GFR, which is thought to be primarily due to a hemodynamic effect and may be reversible. Electrolyte abnormalities are also more likely during intensive BP treatment. More intensive BP lowering in patients with CKD is also supported by a BP Lowering Treatment Trialists' Collaboration meta-analysis of RCTs in patients with CKD (43).

2. Evidence comes from AASK (The African American Study of Kidney Disease and Hypertension), 2 small trials (1 positive, 1 negative), and a meta-analysis (3, 6, 10, 11). Albuminuria is quantified by 24-hour urine collection. A 10% to 25% increase in serum creatinine may occur in some patients with CKD as a result of ACE inhibitor therapy.

3. ARBs were shown to be noninferior to ACE inhibitors in clinical trials in the non-CKD population (35). A 10% to 25% increase in serum creatinine may occur in some patients with CKD as a result of ARB therapy.



Figure 6. Management of Hypertension in Patients With CKD

Colors correspond to Class of Recommendation in Table 1.

\*CKD stage 3 or higher or stage 1 or 2 with albuminuria ≥300 mg/d or ≥300 mg/g creatinine. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP blood pressure; and CKD, chronic kidney disease.

- Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994;330:877-84.
- 2. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet. 2005;365:939-46.
- 3. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002;288:2421-31.
- 4. Upadhyay A, Earley A, Haynes SM, et al. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med. 2011;154:541-8.
- 5. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ. 2013;185:949-57.

### 2017 High Blood Pressure Clinical Practice Guideline

- 6. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003;139:244-52.
- Lambers Heerspink HJ, Brantsma AH, de Zeeuw D, et al. Albuminuria assessed from first-morning-void urine samples versus 24-hour urine collections as a predictor of cardiovascular morbidity and mortality. Am J Epidemiol. 2008;168:897-905.
- 8. Lambers Heerspink HJ, Gansevoort RT, Brenner BM, et al. Comparison of different measures of urinary protein excretion for prediction of renal events. J Am Soc Nephrol. 2010;21:1355-60.
- 9. Contreras G, Greene T, Agodoa LY, et al. Blood pressure control, drug therapy, and kidney disease. Hypertension. 2005;46:44-50.
- 10. Esnault VLM, Brown EA, Apetrei E, et al. The effects of amlodipine and enalapril on renal function in adults with hypertension and nondiabetic nephropathies: a 3-year, randomized, multicenter, double-blind, placebo-controlled study. Clin Ther. 2008;30:482-98.
- 11. Marin R, Ruilope LM, Aljama P, et al. A random comparison of fosinopril and nifedipine GITS in patients with primary renal disease. J Hypertens. 2001;19:1871-6.
- 12. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. Ann Intern Med. 1997;127:337-45.
- 13. Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Circulation. 2017. In press.
- 14. Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2010;55:441-51.
- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507-20.
- National Clinical Guideline Centre (UK). Chronic Kidney Disease (Partial Update): Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care. London, UK: National Institute for Health and Care Excellence (UK); 2014.
- 17. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159-219.
- 18. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl (2011). 2012;2(5):337-414.
- 19. Kanno A, Metoki H, Kikuya M, et al. Usefulness of assessing masked and white-coat hypertension by ambulatory blood pressure monitoring for determining prevalent risk of chronic kidney disease: the Ohasama study. Hypertens Res. 2010;33:1192-8.
- 20. Terawaki H, Metoki H, Nakayama M, et al. Masked hypertension determined by self-measured blood pressure at home and chronic kidney disease in the Japanese general population: the Ohasama study. Hypertens Res. 2008;31:2129-35.
- 21. Minutolo R, Gabbai FB, Agarwal R, et al. Assessment of achieved clinic and ambulatory blood pressure recordings and outcomes during treatment in hypertensive patients with CKD: a multicenter prospective cohort study. Am J Kidney Dis. 2014;64:744-52.
- 22. Drawz PE, Alper AB, Anderson AH, et al. Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. Clin J Am Soc Nephrol. 2016;11:642-52.
- 23. Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69:1175-80.
- 24. Navaneethan SD, Schold JD, Arrigain S, et al. Cause-specific deaths in non-dialysis-dependent CKD. J Am Soc Nephrol. 2015;26:2512-20.
- 25. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Chronic Kidney Disease Prognosis Consortium. Lancet. 2010;375:2073-81.

### 2017 High Blood Pressure Clinical Practice Guideline

- 26. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. SPRINT Research Group. N Engl J Med. 2015;373:2103-16.
- 27. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. ACCORD Study Group. N Engl J Med. 2010;362:1575-85.
- Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(suppl 2):S49-73.
- 29. Kovesdy CP, Alrifai A, Gosmanova EO, et al. Age and outcomes associated with BP in patients with incident CKD. Clin J Am Soc Nephrol. 2016;11:821-31.
- 30. Weiss JW, Peters D, Yang X, et al. Systolic BP and mortality in older adults with CKD. Clin J Am Soc Nephrol. 2015;10:1553-9.
- 31. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA. 2016;315:2673-82.
- 32. Holtkamp FA, de Zeeuw D, Thomas MC, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int. 2011;80:282-7.
- 33. Hricik DE, Browning PJ, Kopelman R, et al. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney. N Engl J Med. 1983;308:373-6.
- 34. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893-906.
- 35. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. ONTARGET Investigators. N Engl J Med. 2008;358:1547-59.
- 36. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892-903.
- 37. Parving H-H, Brenner BM, McMurray JJV, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367:2204-13.
- 38. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med. 1995;123:754-62.
- 39. Appel LJ, Wright JT Jr, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010;363:918-29.
- 40. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957-67.
- 41. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels--updated overview and meta-analyses of randomized trials. J Hypertens. 2016;34:613-22.
- 42. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387:435-43.
- 43. Ninomiya T, Perkovic V, Turnbull F, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. BMJ. 2013;347:f5680.

Recommendations for Treatment of Hypertension After Renal Transplantation				
References that support recommendations are summarized in Online Data Supplements 39 and 40.				
COR	LOE	Recommendations		
lla	SBP:	1. After kidney transplantation, it is reasonable to treat patients with		
	B-NR	hypertension to a BP goal of less than 130/80 mm Hg (1).		
	DBP:			
	C-EO			
lla		2. After kidney transplantation, it is reasonable to treat patients with		
	B-R	hypertension with a calcium antagonist on the basis of improved GFR and		
		kidney survival (2).		

# 9.3.1. Hypertension After Renal Transplantation

### Synopsis

After kidney transplantation, hypertension is common because of preexisting kidney disease, the effects of immunosuppressive medications, and the presence of allograft pathology (3). Transplant recipients frequently harbor multiple CVD risk factors and are at high risk of CVD events. Hypertension may accelerate target organ damage and kidney function decline, particularly when proteinuria is present (4-6).

Use of calcineurin inhibitor-based immunosuppression regimens after transplantation is associated with a high (70% to 90%) prevalence of hypertension (7). Hypertension is less common when calcineurin inhibitors have been used without corticosteroids in liver transplantation patients (8), although prevalence rates have not differed in steroid minimization trials after kidney transplantation (9, 10). Reports from long-term belatacept-based immunosuppression studies indicate higher GFR and preservation of kidney function. However, hypertension was still present in the majority of patients, although fewer agents were needed to achieve BP goals (11). Severity of hypertension and intensity of treatment may differ somewhat depending on the type of organ transplanted; however, most concepts relevant to kidney transplant recipients will apply to the other solid organ recipients as well.

BP targets change over time after transplantation. Initially, it is important to maintain ample organ perfusion with less stringent BP targets (<160/90 mm Hg) to avoid hypotension and risk of graft thrombosis. Beyond the first month, BP should be controlled to prevent target organ damage as in the nontransplantation setting (12, 13). Hypertension after transplantation is often associated with altered circadian BP rhythm with loss of the normal nocturnal BP fall (14, 15) and, in some, a nocturnal BP rise. These changes may return to normal after a longer period of follow-up (16).

### **Recommendation-Specific Supportive Text**

1. Although treatment targets for hypertension after transplantation should probably be similar to those for other patients with CKD, there are no trials in post-transplantation patients comparing different BP targets. As kidney transplant recipients generally have a single functioning kidney and CKD, BP targets should be similar to those for the general CKD population.

2. Limited studies have compared drug choice for initial antihypertensive therapy in patients after kidney transplantation. On the basis of a Cochrane analysis (2), most studies favor CCBs to reduce graft loss and maintain higher GFR, with some evidence suggesting potential harm from ACE inhibitors because of anemia, hyperkalemia, and lower GFR. In recognition of this concern, RAS inhibitors may be reserved for the subset of patients with hypertension and additional comorbidities that support the need for ACE inhibitor therapy (i.e., proteinuria or HF after transplantation). With appropriate potassium and creatinine monitoring, this has been demonstrated to be safe (17).

### 2017 High Blood Pressure Clinical Practice Guideline

### References

- 1. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. SPRINT Research Group. N Engl J Med. 2015;373:2103-16.
- 2. Cross NB, Webster AC, Masson P, et al. Antihypertensive treatment for kidney transplant recipients. Cochrane Database Syst Rev. 2009;CD003598.
- 3. Cosio FG, Pelletier RP, Pesavento TE, et al. Elevated blood pressure predicts the risk of acute rejection in renal allograft recipients. Kidney Int. 2001;59:1158-64.
- 4. Peschke B, Scheuermann EH, Geiger H, et al. Hypertension is associated with hyperlipidemia, coronary heart disease and chronic graft failure in kidney transplant recipients. Clin Nephrol. 1999;51:290-5.
- 5. Mange KC, Cizman B, Joffe M, et al. Arterial hypertension and renal allograft survival. JAMA. 2000;283:633-8.
- 6. Mange KC, Feldman HI, Joffe MM, et al. Blood pressure and the survival of renal allografts from living donors. J Am Soc Nephrol. 2004;15:187-93.
- 7. Taler SJ, Textor SC, Canzanello VJ, et al. Cyclosporin-induced hypertension: incidence, pathogenesis and management. Drug Saf. 1999;20:437-49.
- 8. Taler SJ, Textor SC, Canzanello VJ, et al. Role of steroid dose in hypertension early after liver transplantation with tacrolimus (FK506) and cyclosporine. Transplantation. 1996;62:1588-92.
- Woodle ES, First MR, Pirsch J, et al. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg. 2008;248:564-77.
- 10. Vincenti F, Schena FP, Paraskevas S, et al. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant. 2008;8:307-16. can
- 11. Rostaing L, Vincenti F, Grinyo J, et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. Am J Transplant. 2013;13:2875-83.
- 12. Opelz G, Dohler B, Collaborative Transplant Study. Improved long-term outcomes after renal transplantation associated with blood pressure control. Am J Transplant. 2005;5:2725-31.
- 13. Hillebrand U, Suwelack BM, Loley K, et al. Blood pressure, antihypertensive treatment, and graft survival in kidney transplant patients. Transpl Int. 2009;22:1073-80.
- 14. Wadei HM, Amer H, Taler SJ, et al. Diurnal blood pressure changes one year after kidney transplantation: relationship to allograft function, histology, and resistive index. J Am Soc Nephrol.. 2007;18:1607-15.
- 15. Ambrosi P, Kreitmann B, Habib G. Home blood pressure monitoring in heart transplant recipients: comparison with ambulatory blood pressure monitoring. Transplantation. 2014;97:363-7.
- 16. Haydar AA, Covic A, Jayawardene S, et al. Insights from ambulatory blood pressure monitoring: diagnosis of hypertension and diurnal blood pressure in renal transplant recipients. Transplantation. 2004;77:849-53.
- 17. Jennings DL, Taber DJ. Use of renin-angiotensin-aldosterone system inhibitors within the first eight to twelve weeks after renal transplantation. Ann Pharmacother. 2008;42:116-20.

# 9.4. Cerebrovascular Disease

Stroke is a leading cause of death, disability, and dementia (1). Because of its heterogeneous causes and hemodynamic consequences, the management of BP in adults with stroke is complex and challenging (2). To accommodate the variety of important issues pertaining to BP management in the stroke patient, treatment recommendations require recognition of stroke acuity, stroke type, and therapeutic objectives. Future studies should target more narrowly defined questions, such as optimal BP-reduction timing and target, as well as ideal antihypertensive agent therapeutic class by patient type and event type.

- 1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics--2017 update: a report from the American Heart Association. Circulation. 2017;135:e146-603.
- 2. Boan AD, Lackland DT, Ovbiagele B. Lowering of blood pressure for recurrent stroke prevention. Stroke. 2014;45:2506-13.

# 9.4.1. Acute Intracerebral Hemorrhage

Recommendations for Management of Hypertension in Patients With Acute Intracerebral				
Hemorrhage (ICH)				
References that support recommendations are summarized in Online Data Supplement 41.				
COR	LOE	Recommendations		
lla	C-EO	1. In adults with ICH who present with SBP greater than 220 mm Hg, it is reasonable to use continuous intravenous drug infusion (Table 19) and close BP monitoring to lower SBP.		
III: Harm	А	2. Immediate lowering of SBP (Table 19) to less than 140 mm Hg in adults with spontaneous ICH who present within 6 hours of the acute event and have an SBP between 150 mm Hg and 220 mm Hg is not of benefit to reduce death or severe disability and can be potentially harmful (1, 2).		

### Synopsis

Spontaneous, nontraumatic ICH is a significant global cause of morbidity and mortality (3). Elevated BP is highly prevalent in the setting of acute ICH and is linked to greater hematoma expansion, neurological worsening, and death and dependency after ICH.

Association.

Figure 7 is an algorithm on management of hypertension in patients with acute ICH. American Heart

### Recommendation-Specific Supportive Text

1. Information about the safety and effectiveness of early intensive BP-lowering treatment is least well established for patients with markedly elevated BP (sustained SBP >220 mm Hg) on presentation, patients with large and severe ICH, or patients requiring surgical decompression. However, given the consistent nature of the data linking high BP with poor clinical outcomes (4-6) and some suggestive data for treatment in patients with modestly high initial SBP levels (1, 7), early lowering of SBP in ICH patients with markedly high SBP levels (>220 mm Hg) might be sensible. A secondary endpoint in 1 RCT and an overview of data from 4 RCTs indicate that intensive BP reduction, versus BP-lowering guideline treatment, is associated with greater functional recovery at 3 months (1, 7).

2. RCT data have suggested that immediate BP lowering (to <140/90 mm Hg) within 6 hours of an acute ICH was feasible and safe (1, 8, 9), may be linked to greater attenuation of absolute hematoma growth at 24 hours (7), and might be associated with modestly better functional recovery in survivors (1, 7). However, a recent RCT (2) that examined immediate BP lowering within 4.5 hours of an acute ICH found that treatment to achieve a target SBP of 110 to 139 mm Hg did not lead to a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg. Moreover, there were significantly more renal adverse events within 7 days after randomization in the intensive-treatment group than in the standard-treatment group (2). Put together, neither of the 2 key trials (1, 2) evaluating the effect of lowering SBP in the acute period after spontaneous ICH met their primary outcomes of reducing death and severe disability at 3 months.



### Figure 7. Management of Hypertension in Patients With Acute ICH

- 1. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368:2355-65.
- 2. Qureshi Al, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375:1033-43.
- 3. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics--2017 update: a report from the American Heart Association. Circulation. 2017;135:e146-603.
- 4. Zhang Y, Reilly KH, Tong W, et al. Blood pressure and clinical outcome among patients with acute stroke in Inner Mongolia, China J Hypertens. 2008;26:1446-52.
- 5. Rodriguez-Luna D, Pineiro S, Rubiera M, et al. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. Eur J Neurol. 2013;20:1277-83.
- Sakamoto Y, Koga M, Yamagami H, et al. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement-Intracerebral Hemorrhage Study. Stroke. 2013;44:1846-51.
- 7. Tsivgoulis G, Katsanos AH, Butcher KS, et al. Intensive blood pressure reduction in acute intracerebral hemorrhage: a meta-analysis. Neurology. 2014;83:1523-9.
- 8. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators. Antihypertensive treatment of acute cerebral hemorrhage. Crit Care Med. 2010;38:637-48.
- 9. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008;7:391-9.
# 9.4.2. Acute Ischemic Stroke

Recommendations for Management of Hypertension in Patients With Acute Ischemic					
	Stroke				
Refe	erences the	at support recommendations are summarized in Online Data Supplement 42.			
COR	LOE	Recommendations			
I	B-NR	<ol> <li>Adults with acute ischemic stroke and elevated BP who are eligible for treatment with intravenous tissue plasminogen activator should have their BP slowly lowered to less than 185/110 mm Hg before thrombolytic therapy is initiated (1, 2).</li> </ol>			
I	B-NR	2. In adults with an acute ischemic stroke, BP should be less than 185/110 mm Hg before administration of intravenous tissue plasminogen activator and should be maintained below 180/105 mm Hg for at least the first 24 hours after initiating drug therapy (3).			
lla	B-NR	3. Starting or restarting antihypertensive therapy during hospitalization in patients with BP greater than 140/90 mm Hg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated (4, 5).			
lib	C-EO	<ul> <li>contraindicated (4, 5).</li> <li>4. In patients with BP of 220/120 mm Hg or higher who did not receive intravenous alteplase or endovascular treatment and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.</li> </ul>			
III: No Benefit	Α	5. In patients with BP less than 220/120 mm Hg who did not receive intravenous thrombolysis or endovascular treatment and do not have a comorbid condition requiring acute antihypertensive treatment, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an acute ischemic stroke is not effective to prevent death or dependency (4- 9).			

#### Synopsis

Elevated BP is common during acute ischemic stroke (occurring in up to 80% of patients), especially among patients with a history of hypertension (10). However, BP often decreases spontaneously during the acute phase of ischemic stroke, as soon as 90 minutes after the onset of symptoms. Countervailing theoretical concerns about arterial hypertension during acute ischemic stroke include aiming to enhance cerebral perfusion of the ischemic tissue while minimizing the exacerbation of brain edema and hemorrhagic transformation of the ischemic tissue (11, 12). Some studies have shown a U-shaped relationship between the admission BP and favorable clinical outcomes, with an optimal SBP and DBP ranging from 121 to 200 mm Hg and 81 to 110 mm Hg, respectively (13). It is conceivable that an optimal arterial BP range exists during acute ischemic stroke on an individual basis, contingent on the ischemic stroke subtype and other patient-specific comorbidities. Early initiation or resumption of antihypertensive treatment after acute ischemic stroke is indicated only in specific situations: 1) patients treated with tissue-type plasminogen activator (1, 2), and 2) patients with SBP >220 mm Hg or DBP >120 mm Hg. For the latter group, it should be kept in mind that cerebral autoregulation in the ischemic penumbra of the stroke is grossly abnormal and that systemic perfusion pressure is needed for blood flow and oxygen delivery. Rapid reduction of BP, even to lower levels within the hypertensive range, can be detrimental. For all other acute ischemic stroke patients, the advantage of lowering BP early to reduce death and dependency is uncertain (4-9), but restarting antihypertensive therapy

to improve long-term BP control is reasonable after the first 24 hours for patients who have preexisting hypertension and are neurologically stable (4, 5, 14, ).

Figure 8 is an algorithm on management of hypertension in patients with acute ischemic stroke.

#### **Recommendation-Specific Supportive Text**

1. These BP cutoffs correspond to study inclusion criteria in pivotal clinical trials of intravenous thrombolysis for acute ischemic stroke (1).

2. In a large observational study of patients with acute ischemic stroke who received intravenous tissue-type plasminogen activator, high BP during the initial 24 hours was linked to greater risk of symptomatic ICH (3).

3. For the goal of antihypertensive therapy, see Section 8.1.5.

4. Extreme arterial hypertension is detrimental because it can lead to encephalopathy, cardiac compromise, and renal damage. However, hypotension, especially when too rapidly achieved, is potentially harmful because it abruptly reduces perfusion to multiple organs, including the brain.

5. Data from 2 RCTs (5, 9), as well as systematic reviews and meta-analyses (6-8), indicate that antihypertensive agents reduce BP during the acute phase of an ischemic stroke but do not confer benefit with regard to short- and long-term dependency and mortality rate. One RCT did not demonstrate a benefit of continuing prestroke antihypertensive drugs during the first few days after an acute stroke, but it was substantially underpowered to answer the question (4).





#### Figure 8. Management of Hypertension in Patients With Acute Ischemic Stroke

Colors correspond to Class of Recommendation in Table 1.

BP indicates blood pressure; DBP, diastolic blood pressure; IV, intravenous; and SBP, systolic blood pressure.

- 1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-7.
- Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317-29.
- 3. Ahmed N, Wahlgren N, Brainin M, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Stroke. 2009;40:2442-9.
- 4. Robinson TG, Potter JF, Ford GA, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. Lancet Neurol. 2010;9:767-75.
- 5. He J, Zhang Y, Xu T, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA. 2014;311:479-89.
- 6. Wang H, Tang Y, Rong X, et al. Effects of early blood pressure lowering on early and long-term outcomes after acute stroke: an updated meta-analysis. PLoS ONE. 2014;9:e97917.

#### 2017 High Blood Pressure Clinical Practice Guideline

- Zhao R, Liu F-D, Wang S, et al. Blood pressure reduction in the acute phase of an ischemic stroke does not improve short- or long-term dependency or mortality: a meta-analysis of current literature. Medicine (Baltimore). 2015;94:e896.
- 8. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2014;10:CD000039.
- 9. Sandset EC, Bath PMW, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet. 2011;377:741-50.
- 10. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med. 2007;25:32-8.
- 11. Leonardi-Bee J, Bath PM, Phillips SJ, et al. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke. 2002;33:1315-20.
- 12. Castillo J, Leira R, Garcia MM, et al. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. Stroke. 2004;35:520-6.
- 13. Vemmos KN, Tsivgoulis G, Spengos K, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med. 2004;255:257-65.
- 14. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870-947.

American

## 9.4.3. Secondary Stroke Prevention

Reco	Recommendations for Treatment of Hypertension for Secondary Stroke Prevention				
Referen	References that support recommendations are summarized in Online Data Supplements 43 and 44.				
COR	LOE	Recommendations			
I	А	1. Adults with previously treated hypertension who experience a stroke or transient ischemic attack (TIA) should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events (1-3).			
I	Α	2. For adults who experience a stroke or TIA, treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful (1, 3-5).			
I	B-R	3. Adults not previously treated for hypertension who experience a stroke or TIA and have an established BP of 140/90 mm Hg or higher should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular events (1-3).			
I	B-NR	<ol> <li>For adults who experience a stroke or TIA, selection of specific drugs should be individualized on the basis of patient comorbidities and agent pharmacological class (6).</li> </ol>			
llb	B-R	<ol> <li>For adults who experience a stroke or TIA, a BP goal of less than 130/80 mm Hg may be reasonable (6, 7).</li> </ol>			
llb	B-R	6. For adults with a lacunar stroke, a target SBP goal of less than 130 mm Hg may be reasonable (8).			
lib	C-LD	7. In adults previously untreated for hypertension who experience an ischemic stroke or TIA and have a SBP less than 140 mm Hg and a DBP less than 90 mm Hg, the usefulness of initiating antihypertensive treatment is not well established (9).			

#### Synopsis

Each year in the United States, >750,000 adult patients experience a stroke, of which up to 25% are recurrent strokes (10). For an individual who experiences an initial stroke or TIA, the annual risk of a subsequent or

"secondary" stroke is approximately 4% (11), and the case mortality rate is 41% after a recurrent stroke versus 22% after an initial stroke (12). Among patients with a recent stroke or TIA, the prevalence of premorbid hypertension is approximately 70% (13). Risk of recurrent stroke is heightened by presence of elevated BP, and guideline-recommended antihypertensive drug treatment to lower BP has been linked to a reduction in 1-year recurrent stroke risk (14). RCT meta-analyses show an approximately 30% decrease in recurrent stroke risk with BP-lowering therapies (1-3). An issue frequently raised by clinicians is whether the presence of clinically asymptomatic cerebral infarction incidentally noted on brain imaging (computed tomography or MRI scan) in patients without a history of or symptoms of a stroke or TIA warrants implementation of secondary stroke prevention measures. Clinically asymptomatic vascular brain injury is increasingly being considered as an entry point for secondary stroke prevention therapies, because these apparently "silent" brain infarctions are associated with typical stroke risk factors, accumulatively lead to subtle neurological impairments, and bolster risk of future symptomatic stroke events (15). Although the evidence for using antihypertensive treatment to prevent recurrent stroke in stroke patients with elevated BP is compelling (1-3), questions remain about when precisely after an index stroke to initiate it, what specific agent(s) to use (if any), which therapeutic targets to aim for, and whether the treatment approach should vary by index stroke mechanism and baseline level of BP (16).

Figure 9 is an algorithm on management of hypertension in patients with a previous history of stroke (secondary stroke prevention).

#### **Recommendation-Specific Supportive Text**



1. Two overviews of RCTs published through 2009 showed that antihypertensive medications lowered the risk of recurrent vascular events in patients with stroke or TIA (1-3).

2. Specific agents that have shown benefit in either dedicated RCTs or systematic reviews of RCT data include diuretics, ACE inhibitors, and ARBs.

3. Support for this recommendation is based on data from 2 dedicated RCTs, as well as a systematic review and meta-analysis, among patients with a history of stroke or TIA (1-3).

4. Reduction in BP appears to be more important than the choice of specific agents used to achieve this goal. Thus, if diuretic and ACE inhibitor or ARB treatment do not achieve BP target, other agents, such as CCB and/or mineralocorticoid receptor antagonist, may be added.

5. An overview of RCTs showed that larger reductions in SBP tended to be associated with greater reduction in risk of recurrent stroke. However, a separate overview of RCTs in patients who experienced a stroke noted that achieving an SBP level <130 mm Hg was not associated with a lower stroke risk, and several observational studies did not show benefit with achieved SBP levels <120 mm Hg (5).

6. Patients with a lacunar stroke treated to an SBP target of <130 mm Hg versus 130 to 140 mm Hg may be less likely to experience a future ICH.

7. No published RCTs have specifically addressed this question, but a post hoc analysis of an RCT suggests that the effectiveness of antihypertensive treatment for secondary stroke prevention diminishes as initial baseline BP declines (9).

Figure 9. Management of Hypertension in Patients With a Previous History of Stroke (Secondary Stroke Prevention)



Colors correspond to Class of Recommendation in Table 1.

DBP indicates diastolic blood pressure; SBP, systolic blood pressure; and TIA, transient ischemic attack.

- 1. Liu L, Wang Z, Gong L, et al. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. Hypertens Res. 2009;32:1032-40.
- 2. Lakhan SE, Sapko MT. Blood pressure lowering treatment for preventing stroke recurrence: a systematic review and meta-analysis. Int Arch Med. 2009;2:30.
- 3. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033-41.
- PATS Collaborating Group. Post-stroke antihypertensive treatment study. A preliminary result. Chin Med J. 1995;108:710-7.
- 5. Lee M, Saver JL, Hong K-S, et al. Renin-angiotensin system modulators modestly reduce vascular risk in persons with prior stroke. Stroke. 2012;43:113-9.
- 6. Wang W-T, You L-K, Chiang C-E, et al. Comparative effectiveness of blood pressure-lowering drugs in patients who have already suffered from stroke: traditional and Bayesian network meta-analysis of randomized trials. Medicine (Baltimore). 2016;95:e3302.
- 7. Katsanos AH, Filippatou A, Manios E, et al. Blood pressure reduction and secondary stroke prevention: a systematic review and metaregression analysis of randomized clinical trials. Hypertension. 2017;69:171-9.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 8. Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. SPS3 Study Group. Lancet. 2013;382:507-15.
- 9. Arima H, Chalmers J, Woodward M, et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J Hypertens. 2006;24:1201-8.
- 10. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics--2017 update: a report from the American Heart Association. Circulation. 2017;135:e146-603.
- 11. Dhamoon MS, Sciacca RR, Rundek T, et al. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. Neurology. 2006;66:641-6.
- 12. Hardie K, Hankey GJ, Jamrozik K, et al. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke. 2004;35:731-5.
- 13. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology. 2004;62:569-73.
- 14. Toschke AM, Gulliford MC, Wolfe CDA, et al. Antihypertensive treatment after first stroke in primary care: results from the General Practitioner Research Database. J Hypertens. 2011;29:154-60.
- 15. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236.
- 16. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care. 2007;30:162-72.

# 9.5. Peripheral Arterial Disease



<b>Recommendation for Treatment of Hypertension in Patients With PAD</b> References that support the recommendation are summarized in Online Data Supplement 45.				
COR	LOE	Recommendation		
I	B-NR	1. Adults with hypertension and PAD should be treated similarly to patients with hypertension without PAD (1-4).		

#### Synopsis

Patients with PAD are at increased risk of CVD and stroke. Hypertension is a major risk factor for PAD, so these patients are commonly enrolled in trials of antihypertensive drug therapy. However, patients with PAD typically comprise a small fraction of participants, so in the few trials that report results in patients with PAD, subgroup analyses are generally underpowered.

#### **Recommendation-Specific Supportive Text**

1. There is no major difference in the relative risk reduction in CVD from BP-lowering therapy between patients with hypertension and PAD and patients without PAD (1). There is also no evidence that any one class of antihypertensive medication or strategy is superior (2-4). In the INVEST (International Verapamil-Trandolapril) study, the beta blocker atenolol (with or without hydrochlorothiazide) was compared with the CCB verapamil (with or without perindopril). The study showed no significant difference in CVD outcomes between the 2 drug regimens in patients with and without PAD (3). No trials have reported the effects of a higher versus a lower BP goal in patients with PAD. In the 1 trial (ALLHAT) that reported the effects of different classes of BP medications on PAD as an outcome, there was no significant difference by medication class (5).

- 1. Ostergren J, Sleight P, Dagenais G, et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. Eur Heart J. 2004;25:17-24.
- 2. Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA. 2011;305:913-22.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 3. Bavry AA, Anderson RD, Gong Y, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. Hypertension 2010;55:48-53.
- 4. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. J Hypertens. 2006;24:2163-8.
- 5. Piller LB, Simpson LM, Baraniuk S, et al. Characteristics and long-term follow-up of participants with peripheral arterial disease during ALLHAT. J Gen Intern. Med. 2014;29:1475-83.

# 9.6. Diabetes Mellitus

	Recommendations for Treatment of Hypertension in Patients With DM					
Referen	References that support recommendations are summarized in Online Data Supplements 46 and 47					
		and Systematic Review Report.				
COR	LOE	Recommendations				
	SBP:	1. In adults with DM and hypertension, antihypertensive drug treatment				
	B-R <sup>SR</sup>	should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg (1-8).				
	DBP:					
	C-EO					
I	A <sup>SR</sup>	2. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective (1, 9, 10).				
llb	B-NR	3. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria (11, 12).				

SR indicates systematic review.

#### Synopsis

Refer to the "Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" for the complete systematic evidence review for additional data and analyses (13). The prevalence of hypertension among adults with DM is approximately 80%, and hypertension is at least twice as common in persons with type 2 DM than in age-matched individuals without DM (14-16). The coexistence of hypertension and DM markedly increases the risk of developing CVD damage, resulting in a higher incidence of CHD, HF, PAD, stroke, and CVD mortality (17), and may increase risk of microvascular disease, such as nephropathy or retinopathy (16, 18).

There is limited quality evidence to determine a precise BP target in adults with DM. No RCTs have explicitly 1) documented whether treatment to an SBP goal <140 mm Hg versus a higher goal improves clinical outcomes in adults with hypertension and DM or 2) directly evaluated clinical outcomes associated with SBP <130 mm Hg (2). However, 2 high-quality systematic reviews of RCTs support an SBP target of <140 mm Hg (4, 7).

There is little or no available RCT evidence supporting a specific DBP threshold for initiation of pharmacological therapy. Several RCTs, including the HOT (Hypertension Optimal Treatment) trial, UKPDS (United Kingdom Prospective Diabetes Study), and ABCD (Appropriate Blood Pressure Control in Diabetes) trial (19-22), are often cited to support a lower DBP target (e.g., ≤85 or 80 mm Hg) for adults with hypertension and DM. However, these trials were conducted when the diagnostic criteria for DM were more conservative than they are currently (2 fasting glucose levels >140 mg/dL as opposed to 126 mm/dL today).

#### **Recommendation-Specific Supportive Text**

1. We recommend ASCVD risk assessment in all adults with hypertension, including adults with DM. As a matter of convenience, however, it can be assumed that the vast majority of adults with DM have a 10-year ASCVD risk  $\geq$  10%, placing them in the high risk category that requires initiation of antihypertensive drug therapy at BP  $\geq$  130/80 mm Hg (see Section 8.1.2, Figure 4 and Table 23 for BP thresholds for initiating antihypertensive drug treatment). The ACCORD trial (5), which compared CVD outcomes in adults with DM and hypertension who were randomized to an SBP target of <140 mm Hg (standard therapy) or <120 mm Hg (intensive therapy), did not document a significant reduction in the primary outcome (CVD composite) with the lower BP goal, but the trial was underpowered to detect a statistically significant difference between the 2 treatment arms. The ACCORD trial demonstrated a small reduction in absolute risk (1.1%) for stroke, but there were few such events. More adverse events (2% increase in absolute risk) were identified in the lower BP group, especially self-reported hypotension and a reduction in estimated GFR, but these did not result in an excess of stroke or ESRD. The ACCORD trial was a factorial study; secondary analysis demonstrated a significant outcome benefit in the intensive BP/standard glycemic group (3), but benefit in the intensive BP/intensive glycemic control group was no better than in the intensive BP/standard glycemic control group, which suggests a floor benefit beyond which the combined intensive interventions were ineffective (5). An ACCORD secondary analysis suggested that an SBP <120 mm Hg is superior to standard BP control in reducing LVH (6).

A meta-analysis of 73,913 patients with DM reported that an SBP <130 mm Hg reduced stroke by 39%. However, there was no significant risk reduction for MI (23). Two meta-analyses addressing target BP in adults with DM restricted the analysis to RCTs that randomized patients to different BP levels (4, 7). Target BP of 133/76 mm Hg provided significant benefit compared with that of 140/81 mm Hg for major cardiovascular events, MI, stroke, albuminuria, and retinopathy progression (4). Several meta-analyses of RCTs included all trials with a difference in BP (24, 25), but 2 restricted their analyses to trials in which participants were randomized to different BP target levels (4, 7).

SPRINT demonstrated cardiovascular benefit from intensive treatment of BP to a goal of <120 mm Hg as compared with <140 mm Hg but did not include patients with DM. However, the results of ACCORD and SPRINT were generally consistent (26). In addition, a SPRINT substudy demonstrated that patients with prediabetes derived a benefit similar to that of patients with normoglycemia (8). Previous trials have shown similar quantitative benefits from lowering BP in persons with and without DM (9).

2. BP control is more difficult to achieve in patients with DM than in those without DM, necessitating use of combination therapy in the majority of patients (27). All major antihypertensive drug classes (i.e., ACE inhibitors, ARBs, CCBs, and diuretics) are useful in the treatment of hypertension in DM (1, 9). However, in ALLHAT, doxazosin was clearly inferior to chlorthalidone, which also reduced some events more than amlodipine or lisinopril (28).

3. ACE inhibitors and ARBs have the best efficacy among the drug classes on urinary albumin excretion (12) (see Section 9.3). Therefore, an ACE inhibitor or ARB may be considered as part of the combination. A metaanalysis of RCTs of primary prevention of albuminuria in patients with DM demonstrated a significant reduction in progression of moderately to severely increased albuminuria with the use of ACE inhibitors or ARBs (11).

- 1. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and metaanalysis. JAMA. 2015;313:603-15.
- 2. Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. Cochrane Database Syst Rev. 2013;10:CD008277.
- 3. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. ACCORD Study. N Engl J Med. 2010;362:1575-85.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 4. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387:435-43.
- 5. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care. 2014;37:1721-8.
- Soliman EZ, Byington RP, Bigger JT, et al. Effect of intensive blood pressure lowering on left ventricular hypertrophy in patients with diabetes mellitus: Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial. Hypertension. 2015;66:1123-9.
- 7. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ. 2013;185:949-57.
- 8. Bress AP, King JB, Kreider KE, et al. Effect of intensive versus standard blood pressure treatment according to baseline prediabetes status: a post hoc analysis of a randomized trial. Diabetes Care. 2017;40:1401-8.
- 9. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005;165:1410-9.
- 10. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2005;165:1401-9.
- 11. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet. 2015;385:2047-56.
- 12. Schmieder RE, Hilgers KF, Schlaich MP, et al. Renin-angiotensin system and cardiovascular risk. Lancet. 2007;369:1208-19.
- 13. Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Circulation. 2017. In press.
- 14. Kannel WB, Wilson PW, Zhang TJ. The epidemiology of impaired glucose tolerance and hypertension. Am Heart J. 1991;121:1268-73.
- 15. Tarnow L, Rossing P, Gall MA, et al. Prevalence of arterial hypertension in diabetic patients before and after the JNC-V. Diabetes Care. 1994;17:1247-51.
- 16. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000;321:412-9.
- 17. Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16:434-44.
- 18. Do DV, Wang X, Vedula SS, et al. Blood pressure control for diabetic retinopathy. Cochrane Database Syst Rev. 2015;1:CD006127.
- 19. Estacio RO, Jeffers BW, Gifford N, et al. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care. 2000;23(suppl 2):B54-64.
- 20. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med. 1998;338:645-52.
- Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998;317:703-13.
- 22. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-62.
- 23. Reboldi G, Gentile G, Angeli F, et al. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. J Hypertens. 2011;29:1253-69.
- 24. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957-67.
- 25. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ. 2016;352:i717.
- 26. Perkovic V, Rodgers A. Redefining blood-pressure targets--SPRINT starts the marathon. N Engl J Med. 2015;373:2175-8.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 27. Mancia G, Schumacher H, Redon J, et al. Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET). Circulation. 2011;124:1727-36.
- 28. Wright JT Jr, Probstfield JL, Cushman WC, et al. ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. Arch Intern Med. 2009;169:832-42.

## 9.7. Metabolic Syndrome

Metabolic syndrome is a state of metabolic dysregulation characterized by visceral fat accumulation, insulin resistance, hyperinsulinemia, and hyperlipidemia, as well as predisposition to type 2 DM, hypertension, and atherosclerotic CVD (1-3). According to data from the NHANES III and NHANES 1999–2006 (1, 4), the prevalence of metabolic syndrome in the United States was 34.2% in 2006 and has likely increased substantially since that time. The metabolic syndrome is linked to several other disorders, including nonalcoholic steatohepatitis, polycystic ovary syndrome, certain cancers, CKD, Alzheimer's disease, Cushing's syndrome, lipodystrophy, and hyperalimentation (5, 6).

Lifestyle modification, with an emphasis on improving insulin sensitivity by means of dietary modification, weight reduction, and exercise, is the foundation of treatment of the metabolic syndrome. The optimal antihypertensive drug therapy for patients with hypertension in the setting of the metabolic syndrome has not been clearly defined (1). Although caution exists with regard to the use of thiazide diuretics in this population because of their ability to increase insulin resistance, dyslipidemia, and hyperuricemia and to accelerate conversion to overt DM, no data are currently available demonstrating deterioration in cardiovascular or renal outcomes in patients treated with these agents (1). Indeed, as shown in follow-up of ALLHAT, chlorthalidone use was associated with only a small increase in fasting glucose levels (1.5–4.0 mg/dL), and this increase did not translate into increased CVD risk at a later date (7-10). In addition, in post hoc analysis of the nearly two thirds of participants in ALLHAT that met criteria for the metabolic syndrome, chlorthalidone was unsurpassed in reducing CVD and renal outcomes compared with lisinopril, amlodipine, or doxazosin (9, 11). Similarly, high-dose ARB therapy reduces arterial stiffness in patients with hypertension with the metabolic syndrome, but no outcomes data are available from patients in which this form of treatment was used (12). Use of traditional beta blockers may lead to dyslipidemia or deterioration of glucose tolerance, and ability to lose weight (2). In several large clinical trials, the risk of developing DM as a result of traditional betablocker therapy was 15% to 29% (2). However, the newer vasodilating beta blockers (e.g., labetalol, carvedilol, nebivolol) have shown neutral or favorable effects on metabolic profiles compared with the traditional beta blockers (13). Trials using vasodilator beta blockers have not been performed to demonstrate effects on CVD outcomes.

- 1. Lim S, Eckel RH. Pharmacological treatment and therapeutic perspectives of metabolic syndrome. Rev Endocr Metab Disord. 2014;15:329-41.
- 2. Owen JG, Reisin E. Anti-hypertensive drug treatment of patients with and the metabolic syndrome and obesity: a review of evidence, meta-analysis, post hoc and guidelines publications. Curr Hypertens Rep. 2015;17:558.
- 3. Ruderman NB, Shulman GI. Metabolic syndrome. In: Jameson JL, ed. Endocrinology: Adult & Pediatric. Philadelphia, PA: Elsevier Saunders; 2015:752-9.
- 4. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. Diabetes Care. 2011;34:216-9.
- 5. Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med. 2004;140:167-74.
- 6. Chen J, Gu D, Chen C-S, et al. Association between the metabolic syndrome and chronic kidney disease in Chinese adults. Nephrol Dial Transplant. 2007;22:1100-6.
- 7. Barzilay JI, Davis BR, Whelton PK. The glycemic effects of antihypertensive medications. Curr Hypertens Rep. 2014;16:410.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 8. Kostis JB, Wilson AC, Freudenberger RS, et al. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. Am J Cardiol. 2005;95:29-35.
- 9. Wright JT Jr, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2008;168:207-17.
- 10. Wright JT Jr, Probstfield JL, Cushman WC, et al. ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. Arch Intern Med. 2009;169:832-42.
- 11. Black HR, Davis B, Barzilay J, et al. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Diabetes Care. 2008;31:353-60.
- 12. Laurent S, Boutouyrie P, Vascular Mechanism Collaboration. Dose-dependent arterial destiffening and inward remodeling after olmesartan in hypertensives with metabolic syndrome. Hypertension. 2014;64:709-16.
- 13. Reisin E, Owen J. Treatment: special conditions. Metabolic syndrome: obesity and the hypertension connection. J Am Soc Hypertens. 2015;9:156-9; quiz 160.

# 9.8. Atrial Fibrillation

Recommendation for Treatment of Hypertension in Patients With AF				
References that support the recommendation are summarized in Online Data Supplement 48.				
COR	LOE	Recommendation Gal Heart		
lla	B-R	1. Treatment of hypertension with an ARB can be useful for prevention of recurrence of AF (1, 2).		

#### Synopsis –

AF and hypertension are common and often coexistent conditions, both of which increase in frequency with age. AF occurs in 3% to 4% of the population >65 years of age (3). Hypertension is present in more than 80% of patients with AF and is by far the most common comorbid condition, regardless of age (4). AF is associated with systemic thromboembolism, as recognized in the CHADS2 and CHA2DS2-VASc scoring systems for stroke risk (5). It is also associated with gradual worsening of ventricular function, the subsequent development of HF, and increased mortality.

Hypertension has long been recognized as a risk factor for AF because it is associated with LVH, decreased diastolic function with impaired LV filling, rising left atrial pressures with left atrial hypertrophy and enlargement, increased atrial fibrosis, and slowing of intra-atrial and interatrial electrical conduction velocities. Such a distortion of atrial anatomy and physiology increases the incidence of AF (6). Left atrial pressure also increases with ischemic or valvular heart disease and myopathies that are often associated with systemic hypertension, potentially leading to AF.

Although management of AF will continue to revolve around restoration of sinus rhythm when appropriate, rate control when it is not, and anticoagulation, control of hypertension is a key component of therapy (1, 2).

Treatment of hypertension may prevent new-onset AF, especially in patients with LVH or LV dysfunction (1). Five RCTs have compared the value of antihypertensive agents for reduction of new-onset AF (7-11). One study suggested superiority of RAS blockade over a CCB (8), and another reported superiority of RAS blockade over a beta blocker that is no longer recommended for treatment of hypertension (9). In the largest trial, there was no difference in incident AF among adults with hypertension assigned to first-step therapy with a diuretic, ACE inhibitor, or CCB (10). In ALLHAT, the incidence of AF was 23% higher during first-step antihypertensive therapy with the alpha-receptor blocker doxazosin than with chlorthalidone. Furthermore, the occurrence of AF or atrial flutter during the study, either new onset or recurrent, was associated with an increase in mortality of nearly 2.5-fold (10).

#### 2017 High Blood Pressure Clinical Practice Guideline

#### **Recommendation-Specific Supportive Text**

1. Although RAS blockade in theory is the treatment of choice for hypertension in patients with prior AF, relative to other classes of agents, all of the trials that have shown clinical superiority of ARBs over other agents were comparisons with CCBs or beta blockers that are no longer recommended as first-line agents for treatment of hypertension (2). There are no available trials comparing ACE inhibitors with other drugs or any RAS-blocking agents with diuretics.

#### References

- 1. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol. 2005;45:1832-9.
- 2. Zhao D, Wang Z-M, Wang L-S. Prevention of atrial fibrillation with renin-angiotensin system inhibitors on essential hypertensive patients: a meta-analysis of randomized controlled trials. J Biomed Res. 2015;29:475-85.
- 3. Kistler PM, Sanders P, Fynn SP, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. J Am Coll Cardiol. 2004;44:109-16.
- 4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014;130:e199-267.
- 5. Olesen JB, Torp-Pedersen C, Hansen ML, et al. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. Thromb Haemost. 2012;107:1172-9.
- 6. Healey JS, Connolly SJ. Atrial fibrillation: hypertension as a causative agent, risk factor for complications, and potential therapeutic target. Am J Cardiol. 2003;91:9G-14G.
- Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity. The Swedish Trial in Old Patients with Hypertension-2 study. Lancet. 1999;354:1751-6.
- 8. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363:2022-31.
- 9. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol. 2005;45:712-9.
- 10. Haywood LJ, Ford CE, Crow RS, et al. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). J Am Coll Cardiol. 2009;54:2023-31.
- 11. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet. 1999;353:611-6.

# 9.9. Valvular Heart Disease

Recomm	Recommendations for Treatment of Hypertension in Patients With Valvular Heart Disease				
Referen	References that support recommendations are summarized in Online Data Supplements 49 and 50.				
COR	LOE	Recommendation			
		1. In adults with asymptomatic aortic stenosis, hypertension should be treated			
I.	B-NR	with pharmacotherapy, starting at a low dose and gradually titrating upward			
		as needed (1-4).			
		2. In patients with chronic aortic insufficiency, treatment of systolic			
lla	C-LD	hypertension with agents that do not slow the heart rate (i.e., avoid beta			
		blockers) is reasonable (5, 6).			

#### **Recommendation-Specific Supportive Text**

1. Hypertension is a risk factor for the development of aortic stenosis (stage A [e.g., aortic sclerosis or bicuspid aortic valve]) and asymptomatic aortic stenosis (stage B [progressive asymptomatic aortic stenosis]). The

combination of hypertension and aortic stenosis, "2 resistors in series," increases the rate of complications. In patients with asymptomatic mild-to-moderate aortic stenosis, hypertension has been associated with more abnormal LV structure and increased cardiovascular morbidity and mortality (1). There is no evidence that antihypertensive medications will produce an inordinate degree of hypotension in patients with aortic stenosis. Nitroprusside infusion in hypertensive patients with severe aortic stenosis lowers pulmonary and systemic resistance, with improvements in stroke volume and LV end-diastolic pressure (2). Thus, careful use of antihypertensive agents to achieve BP control in patients with hypertensive agents, RAS blockade may be advantageous because of the potentially beneficial effects on LV fibrosis (3), control of hypertension, reduction of dyspnea, and improved effort tolerance (4). Diuretics should be used sparingly in patients with small LV chamber dimensions. Beta blockers may be appropriate for patients with aortic stenosis who have reduced ejection fraction, prior MI, arrhythmias, or angina pectoris. In patients with moderate or severe aortic stenosis, consultation or co-management with a cardiologist is preferred for hypertension management.

2. Vasodilator therapy can reduce the LV volume and mass and improve LV performance in patients with aortic regurgitation (5), but improvement of long-term clinical outcomes, such as time to valve replacement, have been variable (5, 6). Beta blockers may result in increased diastolic filling period because of bradycardia, potentially causing increased aortic insufficiency. Marked reduction in DBP may lower coronary perfusion pressure in patients with chronic severe aortic regurgitation (stage B [progressive asymptomatic aortic regurgitation] and stage C [asymptomatic severe AR]). However, there are no outcomes data to support these theoretical concerns.

#### References

- 1. Rieck ÅE, Cramariuc D, Boman K, et al. Hypertension in aortic stenosis: implications for left ventricular structure and cardiovascular events. Hypertension. 2012;60:90-7.
- 2. Eleid MF, Nishimura RA, Sorajja P, et al. Systemic hypertension in low-gradient severe aortic stenosis with preserved ejection fraction. Circulation. 2013;128:1349-53.
- 3. Bull S, Loudon M, Francis JM, et al. A prospective, double-blind, randomized controlled trial of the angiotensinconverting enzyme inhibitor Ramipril In Aortic Stenosis (RIAS trial). Eur Heart J Cardiovasc Imaging. 2015;16:834-41.
- 4. Chockalingam A, Venkatesan S, Subramaniam T, et al. Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS). Am Heart J. 2004;147:E19.
- 5. Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. N Engl J Med. 1994;331:689-94.
- 6. Evangelista A, Tornos P, Sambola A, et al. Long-term vasodilator therapy in patients with severe aortic regurgitation. N Engl J Med. 2005;353:1342-9.

# 9.10. Aortic Disease

Recommendation for Management of Hypertension in Patients With Aortic Disease			
COR	LOE	Recommendation	
I	C-EO	1. Beta blockers are recommended as the preferred antihypertensive agents in patients with hypertension and thoracic aortic disease (1, 2).	

#### Synopsis

Thoracic aortic aneurysms are generally asymptomatic until a person presents with a sudden catastrophic event, such as an aortic dissection or rupture, which is rapidly fatal in the majority of patients (3, 4). The rationale for antihypertensive therapy is based largely on animal and observational studies associating hypertension with aortic dissection (5, 6). RCTs specifically addressing hypertension and aortic disease are not available, and trials in patients with primary hypertension do not provide insight on either the optimal BP

target or choice of antihypertensive drug therapy in patients with thoracic aortic aneurysm, aortic dissection, or aortic disease (7, 8). A study in 20 humans with hypertension suggested that hypertension is associated with significant changes in the mechanical properties of the aortic wall, with more strain-induced stiffening in hypertension than in normotension, which may reflect destruction of elastin and predisposition to aortic dissection in the presence of hypertension (9). In a retrospective observational study, high BP variability was an independent risk factor for the prognosis of aortic dissection (10). Recommendations for treatment of acute aortic dissection are provided in Section 11.2.

#### **Recommendation-Specific Supportive Text**

1. In patients with chronic aortic dissection, observational studies suggest lower risk for operative repair with beta-blocker therapy (1). In a series of patients with type A and type B aortic dissections, beta blockers were associated with improved survival in both groups, whereas ACE inhibitors did not improve survival (2).

#### References

- 1. Genoni M, Paul M, Jenni R, et al. Chronic beta-blocker therapy improves outcome and reduces treatment costs in chronic type B aortic dissection. Eur J Cardiothorac Surg. 2001;19:606-10.
- 2. Suzuki T, Isselbacher EM, Nienaber CA, et al. Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol. 2012;109:122-7.
- 3. Masuda Y, Yamada Z, Morooka N, et al. Prognosis of patients with medically treated aortic dissections. Circulation. 1991;84:III7-13.
- 4. Rampoldi V, Trimarchi S, Eagle KA, et al. Simple risk models to predict surgical mortality in acute type A aortic dissection: the International Registry of Acute Aortic Dissection score. Ann Thorac Surg. 2007;83:55-61.
- 5. Suzuki T, Mehta RH, Ince H, et al. Clinical profiles and outcomes of acute type B aortic dissection in the current era: lessons from the International Registry of Aortic Dissection (IRAD). Circulation. 2003;108(suppl 1):II312-7.
- 6. Mehta RH, O'Gara PT, Bossone E, et al. Acute type A aortic dissection in the elderly: clinical characteristics, management, and outcomes in the current era. J Am Coll Cardiol. 2002;40:685-92.
- 7. Chan KK, Lai P, Wright JM. First-line beta-blockers versus other antihypertensive medications for chronic type B aortic dissection. Cochrane Database Syst Rev. 2014;2:CD010426.
- 8. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121:e266-369.
- 9. Gaddum NR, Keehn L, Guilcher A, et al. Altered dependence of aortic pulse wave velocity on transmural pressure in hypertension revealing structural change in the aortic wall. Hypertension. 2015;65:362-9.
- 10. Zhang L, Tian W, Feng R, et al. Prognostic impact of blood pressure variability on aortic dissection patients after endovascular therapy. Medicine (Baltimore). 2015;94:e1591.

# **10. Special Patient Groups**

Special attention is needed for specific patient subgroups.

# 10.1. Race and Ethnicity

In the United States, at any decade of life, blacks have a higher prevalence of hypertension than that of Hispanic Americans, whites, Native Americans, and other subgroups defined by race and ethnicity (see Section 3.3). Hypertension control rates are lower for blacks, Hispanic Americans, and Asian Americans than for whites (1). Among men with hypertension, non-Hispanic white (53.8%) adults had a higher prevalence of controlled high blood pressure than did non-Hispanic black (43.8%), non-Hispanic Asian (39.9%), and Hispanic (43.5%) adults. For women with hypertension, the percentage of non-Hispanic white (59.1%) adults with controlled

high blood pressure was higher than among non-Hispanic black (52.3%) and non-Hispanic Asian (46.8%) adults (1). In Hispanic Americans, the lower control rates result primarily from lack of awareness and treatment (2, 3), whereas in blacks, awareness and treatment are at least as high as in whites, but hypertension is more severe and some agents are less effective at BP control (4). Morbidity and mortality attributed to hypertension are also more common in blacks and Hispanic Americans than in Whites. Blacks have a 1.3-times greater risk of nonfatal stroke, 1.8-times greater risk of fatal strokes, 1.5-times greater risk of HF, and 4.2-times greater risk of ESRD (4). Hispanic Americans have lower rates of hypertension awareness and treatment than those of whites and blacks, as well as a high prevalence of comorbid CVD risk factors (e.g., obesity, DM). In 2014, ageadjusted hypertension-attributable mortality rates per 1,000 persons for non-Hispanic white, non-Hispanic black, and Hispanic-American men and women were 19.3 and 15.8, 50.1 and 35.6, and 19.1 and 14.6, respectively (5). However, Hispanics in the United States are a heterogeneous subgroup, and rates of both hypertension and its consequences vary according to whether their ancestry is from the Caribbean, Mexico, Central or South America, or Europe (6-8). Hispanics from Mexico and Central America have lower CVD rates than U.S. whites, whereas those of Caribbean origin have higher rates. Thus, pooling of data for Hispanics may not accurately reflect risk in a given patient. Finally, the excess risk of CKD outcomes in at least some blacks with hypertension may be due to the presence of high-risk APOL1 (apolipoprotein L1) genetic variants (9-11). The rate of renal decline associated with this genotype appears to be largely unresponsive to either BP lowering or RAS inhibition (9-12).



- 1. Yoon SSS, Carroll MD, Fryar CD. Hypertension prevalence and control among adults: United States, 2011-2014. NCHS Data Brief. 2015;1-8.
- 2. Margolis KL, Piller LB, Ford CE, et al. Blood pressure control in Hispanics in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertension. 2007;50:854-61.
- 3. Cooper-DeHoff RM, Aranda JM Jr, Gaxiola E, et al. Blood pressure control and cardiovascular outcomes in high-risk Hispanic patients--findings from the International Verapamil SR/Trandolapril Study (INVEST). Am Heart J. 2006;151:1072-9.
- 4. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics--2017 update: a report from the American Heart Association. Circulation. 2017;135:e146-603.
- Centers for Disease Control and Prevention. Compressed Mortality File: Underlying Cause-of-Death 1999-2013.
   2014. Available at: https://wonder.cdc.gov/mortsql.html. Accessed November 2, 2017.
- 6. Guzman NJ. Epidemiology and management of hypertension in the Hispanic population: a review of the available literature. Am J Cardiovasc Drugs. Am J Cardiovasc Drugs. 2012;12:165-78.
- 7. Sorlie PD, Allison MA, Aviles-Santa ML, et al. Prevalence of hypertension, awareness, treatment, and control in the Hispanic Community Health Study/Study of Latinos. Am J Hypertens. 2014;27:793-800.
- 8. Rodriguez CJ, Allison M, Daviglus ML, et al. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. Circulation. 2014;130:593-625.
- 9. Parsa A, Kao WHL, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013;369:2183-96.
- 10. Lipkowitz MS, Freedman BI, Langefeld CD, et al. Apolipoprotein L1 gene variants associate with hypertensionattributed nephropathy and the rate of kidney function decline in African Americans. Kidney Int. 2013;83:114-20.
- 11. Langefeld CD, Divers J, Pajewski NM, et al. Apolipoprotein L1 gene variants associate with prevalent kidney but not prevalent cardiovascular disease in the Systolic Blood Pressure Intervention Trial. Kidney Int. 2015;87:169-75.
- 12. Grams ME, Rebholz CM, Chen Y, et al. Race, APOL1 risk, and eGFR decline in the general population. J Am Soc Nephrol. 2016;27:2842-50.

	Recommendations for Race and Ethnicity				
Refe	References that support recommendations are summarized in Online Data Supplement 51.				
COR	COR LOE Recommendations				
		1. In black adults with hypertension but without HF or CKD, including those			
1	B-K	diuretic or CCB (1-4).			
I	C-LD         2.         Two or more antihypertensive medications are recommended to achieve BP target of less than 130/80 mm Hg in most adults with hypertension especially in black adults with hypertension (5-7).				

## 10.1.1 Racial and Ethnic Differences in Treatment

#### Synopsis

Lifestyle modification (i.e., weight reduction, dietary modification, and increased physical activity) is particularly important in blacks and Hispanic Americans for prevention and first-line or adjunctive therapy of hypertension (see Sections 12.1.2 and 12.1.3). However, the adoption of lifestyle recommendations is often challenging in ethnic minority patients because of poor social support, limited access to exercise opportunities and healthy foods, and financial considerations. The greater prevalence of lower socioeconomic status may impede access to basic living necessities (8), including medical care and medications. Consideration must also be given to learning styles and preference, personal beliefs, values, and culture (9, 10).

The principles of antihypertensive drug selection discussed in Sections 8.1.4 through 8.1.6 apply to ethnic minorities with a few caveats. In Blacks, thiazide-type diuretics and CCBs are more effective in lowering BP when given as monotherapy or as initial agents in multidrug regimens (11-13). In addition, thiazide-type agents are superior to drugs that inhibit the RAS (i.e., ACE inhibitors, ARBs, renin inhibitors, and beta blockers) for prevention of selected clinical outcomes in blacks (2, 14-16). For optimum endpoint protection, the thiazide chlorthalidone should be administered at a dose of 12.5 to 25 mg/day (or 25-50 mg/d for hydrochlorothiazide) because lower doses are either unproven or less effective in clinical outcome trials (2, 16). The CCB amlodipine is as effective as chlorthalidone and more effective than the ACE inhibitor lisinopril in reducing BP, CVD, and stroke events but less effective in preventing HF. Blacks have a greater risk of angioedema with ACE inhibitors (2, 3), and Asian Americans have a higher incidence of ACE inhibitor-induced cough (17). ACE inhibitors and ARBs are recommended more generally as components of multidrug antihypertensive regimens in blacks with CKD (see Section 9.3), with the addition of beta blockers in those with HF (see Section 9.2). Beta blockers are recommended for treatment of patients with CHD who have had a MI. Most patients with hypertension, especially blacks, require ≥2 antihypertensive medications to achieve adequate BP control. A single-tablet combination that includes either a diuretic or a CCB may be particularly effective in achieving BP control in blacks. Racial and ethnic differences should not be the basis for excluding any class of antihypertensive agent in combination therapy.

#### **Recommendation-Specific Supportive Text**

1. In blacks, thiazide diuretics or CCBs are more effective in lowering BP than are RAS inhibitors or beta blockers and more effective in reducing CVD events than are RAS inhibitors or alpha blockers. RAS inhibitors are recommended in black patients with hypertension, DM, and nephropathy, but they offer no advantage over diuretics or CCBs in hypertensive patients with DM without nephropathy or HF.

2. Four drug classes (thiazide diuretic, CCB, ACE inhibitor, or ARB) lower BP and reduce cardiovascular or renal outcomes (18-21). Thus, except for the combination of ACE inhibitors and ARBs, regimens containing a combination of these classes are reasonable to achieve the BP target (16, 21). Furthermore, the combination of an ACE inhibitor or ARB with a CCB or thiazide diuretic produces similar BP lowering in blacks as in other

#### 2017 High Blood Pressure Clinical Practice Guideline

racial or ethnic groups. For blacks who do not achieve control with 3 drugs, see resistant hypertension (see Section 11.1).

- 1. Leenen FHH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertension 2006;48:374-84.
- 2. Wright JT Jr, Probstfield JL, Cushman WC, et al. ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. Arch Intern Med. 2009;169:832-42.
- 3. Wright JT Jr, Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. JAMA. 2005;293:1595-608.
- 4. Wright JT Jr, Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2008;168:207-17.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97.
- 6. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. SPRINT Research Group. N Engl J Med. 2015;373:2103-16.
- 7. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002;288:2421-31.
- 8. Odedosu T, Schoenthaler A, Vieira DL, et al. Overcoming barriers to hypertension control in African Americans. Cleve Clin J Med. 2012;79:46-56.
- 9. Ferdinand KC. Management of high blood pressure in African Americans and the 2010 ISHIB consensus statement: meeting an unmet need. J Clin Hypertens (Greenwich). 2010;12:237-9.
- 10. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in blacks: an update of the International Society on Hypertension in Blacks consensus statement. Hypertension. 2010;56:780-800.
- 11. Jamerson K, DeQuattro V. The impact of ethnicity on response to antihypertensive therapy. Am J Med. 1996;101:22S-32S.
- 12. Saunders E, Weir MR, Kong BW, et al. A comparison of the efficacy and safety of a beta-blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks. Arch Intern Med. 1990;150:1707-13.
- 13. Cushman WC, Reda DJ, Perry HM, et al. Regional and racial differences in response to antihypertensive medication use in a randomized controlled trial of men with hypertension in the United States. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Arch Intern Med. 2000;160:825-31.
- 14. Brewster LM, van Montfrans GA, Kleijnen J. Systematic review: antihypertensive drug therapy in black patients. Ann Intern Med. 2004;141:614-27.
- 15. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. J Hypertens. 2006;24:2163-8.
- 16. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359:2417-28.
- 17. Woo KS, Nicholls MG. High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. Br J Clin Pharmacol. 1995;40:141-4.
- Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. J Hypertens. 2011;29:4-16.
- 19. Fretheim A, Odgaard-Jensen J, Brors O, et al. Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis. BMC Med. 2012;10:33.
- 20. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003;139:244-52.

21. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.

## 10.2. Sex-Related Issues

The prevalence of hypertension is lower in women than in men until about the fifth decade but is higher later in life (1). Other than special recommendations for management of hypertension during pregnancy, there is no evidence that the BP threshold for initiating drug treatment, the treatment target, the choice of initial antihypertensive medication, or the combination of medications for lowering BP differs for women versus men (2, 3).

#### References

- 1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics--2017 update: a report from the American Heart Association. Circulation. 2017;135:e146-603.
- 2. Gueyffier F, Boutitie F, Boissel JP, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. Ann Intern Med. 1997;126:761-7.

Heart

Association.

3. Turnbull F, Woodward M, Neal B, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. Eur Heart J. 2008;29:2669-80.

## 10.2.1. Women

A potential limitation of RCTs, including SPRINT, is that they are not specifically powered to determine the value of intensive SBP reduction in subgroups, including women in the case of SPRINT. However, in prespecified analyses, there was no evidence of an interaction between sex and treatment effect. Furthermore, no significant differences in CVD outcomes were observed between men and women in a large meta-analysis that included 31 RCTs with about 100,000 men and 90,000 women with hypertension (1). Some have called for a SPRINT-like trial with sufficient power to assess the effects of intensive SBP reduction in women (2). In meta-analyses, there was no convincing evidence that different antihypertensive drug classes exerted sex-related differences in BP lowering or provided distinct CVD protection (1). Calcium antagonists offered slightly greater benefits for stroke prevention than did ACE inhibitors for women than for men, whereas calcium antagonists reduced all-cause deaths compared with placebo in men but not in women. However, these sex-related differences might have been due to chance because of the large number of statistical comparisons that were performed. The Heart Attack Trial and Hypertension Care Computing Project reported that beta blockers were associated with reduced mortality in men but not in women, but this finding was likely due to the low event rates in women (3). Similarly, in the open-label Second Australian National BP study, a significant reduction in CVD events was demonstrated in men but not in women with ACE inhibitors versus diuretics (4).

Adverse effects of antihypertensive therapy were noted twice as often in women as in men in the TOMHS study (5). A higher incidence of ACE inhibitor–induced cough and of edema with calcium antagonists was observed in women than in men (6). Women were more likely to experience hypokalemia and hyponatremia and less likely to experience gout with diuretics (7). Hypertension in pregnancy has special requirements (see Section 10.2.2).

- 1. Turnbull F, Woodward M, Neal B, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. Eur Heart J. 2008;29:2669-80.
- 2. Wenger NK, Ferdinand KC, Bairey Merz CN, et al. Women, hypertension, and the Systolic Blood Pressure Intervention Trial. Am J Med. 2016;129:1030-6.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 3. Fletcher A, Beevers DG, Bulpitt C, et al. Beta adrenoceptor blockade is associated with increased survival in male but not female hypertensive patients: a report from the DHSS Hypertension Care Computing Project (DHCCP). J Hum Hypertens. 1988;2:219-27.
- 4. Jansen J, Bonner C, McKinn S, et al. General practitioners' use of absolute risk versus individual risk factors in cardiovascular disease prevention: an experimental study. BMJ OPEN. 2014;4:e004812.
- Lewis CE, Grandits A, Flack J, et al. Efficacy and tolerance of antihypertensive treatment in men and women with stage 1 diastolic hypertension. Results of the Treatment of Mild Hypertension Study. Arch Intern Med. 1996;156:377-85.
- 6. Kloner RA, Sowers JR, DiBona GF, et al. Sex- and age-related antihypertensive effects of amlodipine. The Amlodipine Cardiovascular Community Trial Study Group. Am J Cardiol. 1996;77:713-22.
- 7. Igho Pemu P, Ofili E. Hypertension in women: part I. J Clin Hypertens (Greenwich). 2008;10:406-10.

	Recommendations for Treatment of Hypertension in Pregnancy			
Referer	References that support recommendations are summarized in Online Data Supplement 53.			
COR	LOE	Recommendations		
I	C-LD	1. Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol (1) during pregnancy (2-6).		
III: Harm	<b>C-LD</b> 2. Women with hypertension who become pregnant should not be treat with ACE inhibitors, ARBs, or direct renin inhibitors (4-6).			

## 10.2.2. Pregnancy

#### Synopsis

BP usually declines during the first trimester of pregnancy and then slowly rises. Hypertension management during pregnancy includes 4 general areas: 1) the newly pregnant mother with existing hypertension; 2) incident hypertension; 3) preeclampsia (a dangerous form of hypertension with proteinuria that has the potential to result in serious adverse consequences for the mother [stroke, HF] and fetus [small for gestational age, premature birth]); and 4) severe hypertension, often in the setting of preeclampsia, requiring urgent treatment to prevent HF, stroke, and adverse fetal outcomes. Hypertension during pregnancy and preeclampsia are recognized as risk factors for future hypertension and CVD (7-9). BP management during pregnancy is complicated by the fact that many commonly used antihypertensive agents, including ACE inhibitors and ARBs, are contraindicated during pregnancy because of potential harm to the fetus (2, 3). The goal of antihypertensive treatment during pregnancy includes prevention of severe hypertension and the possibility of prolonging gestation to allow the fetus more time to mature before delivery.

There are 3 Cochrane database reviews of treatment for mild-to-moderate hypertension during pregnancy (10-12). With regard to the treatment of mild-to-moderate hypertension (SBP of 140–169 or DBP of 90–109 mm Hg), antihypertensive treatment reduces the risk of progression to severe hypertension by 50% compared with placebo but has not been shown to prevent preeclampsia, preterm birth, small for gestational age, or infant mortality. Beta blockers and CCBs appear superior to alpha-methyldopa in preventing preeclampsia (10). An earlier review of 2 small trials did not show improved outcomes with more comprehensive treatment of BP to a target of <130/80 mm Hg (11). Consistent with the results of the Cochrane reviews, a large multinational RCT of treatment in pregnant women with mild-to-moderate hypertension also reported that treatment prevented progression to severe hypertension, but other maternal and infant outcomes were unaffected by the intensity of treatment (13). An earlier review confined to assessing the effect of beta blockers found them generally safe and effective but of no benefit for newborn outcomes, either in placebo-controlled studies or when compared with other antihypertensive agents. There was a suggestion that beta-blocker therapy might be associated with small for gestational age and neonatal bradycardia (12). The largest experience for beta blockers is with labetalol; the largest experience for CCBs is with nifedipine.

Methyldopa and hydralazine may also be used. A review of treatment for pregnancy-associated severe hypertension found insufficient evidence to recommend specific agents; rather, clinician experience was recommended in this setting (14).

Preeclampsia is a potentially dangerous condition for the pregnant woman and fetus, occurring in 3.8% of pregnancies, and preeclampsia and eclampsia account for 9% of maternal deaths in the United States (15). Preeclampsia is associated with an increased risk of preterm delivery, intrauterine growth restriction, placental abruption, and perinatal mortality and is twice as likely to occur in the first pregnancy. The U.S. Preventive Services Task Force has recommended screening all pregnant women for preeclampsia by measuring BP at every prenatal visit (16).

It is beyond the scope of the present guideline to address the management of hypertension during pregnancy in detail. Several international guidelines provide guidance on management of hypertension during pregnancy (2, 3, 17). The American College of Obstetricians and Gynecologists has issued a task force report that includes recommendations for prevention (aspirin in selected cases) and treatment (magnesium for severe hypertension) of hypertension in pregnancy (2). A report detailing treatment of hypertensive emergencies during pregnancy and postpartum has also been released (2, 17, 18).

#### **Recommendation-Specific Supportive Text**

1. ACE inhibitors and ARBs are not approved for use during pregnancy; they are fetotoxic. Among the agents recommended, no specific agent is first choice because there are no data supporting one over another. Therapeutic classes are not recommended because potential toxicity differs among agents within classes.

2. ACE inhibitors and ARBs are fetotoxic in the second and third trimesters of pregnancy. Adverse effects in the first trimester of pregnancy may be secondary to hypertension or the medication (4, 5). Adverse events in the later trimesters have been suggested by observational data and meta-analyses (6). For ARBs, case reports with effects similar to ACE inhibitors have been published (19).

- 1. James PR, Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. Heart. 2004;90:1499-504.
- American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122:1122-31.
- 3. National Clinical Guideline Centre (UK). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. London, UK: Royal College of Physicians (UK); 2011.
- 4. Pucci M, Sarween N, Knox E, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in women of childbearing age: risks versus benefits. Expert Rev Clin Pharmacol. 2015;8:221-31.
- 5. Moretti ME, Caprara D, Drehuta I, et al. The fetal safety of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. Obstet Gynecol Int. 2012;2012:658310.
- 6. Ferrer RL, Sibai BM, Mulrow CD, et al. Management of mild chronic hypertension during pregnancy: a review. Obstet Gynecol. 2000;96:849-60.
- 7. Garovic VD, August P. Preeclampsia and the future risk of hypertension: the pregnant evidence. Curr Hypertens Rep. 2013;15:114-21.
- 8. Kessous R, Shoham-Vardi I, Pariente G, et al. Long-term maternal atherosclerotic morbidity in women with preeclampsia. Heart. 2015;101:442-6.
- 9. Veerbeek JHW, Hermes W, Breimer AY, et al. Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension. Hypertension. 2015;65:600-6.
- 10. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2014;2:CD002252.
- 11. Nabhan AF, Elsedawy MM. Tight control of mild-moderate pre-existing or non-proteinuric gestational hypertension. Cochrane Database Syst Rev. 2011:CD006907.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 12. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2003;CD002863.
- 13. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015;372:407-17.
- 14. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev. 2013;7:CD001449.
- 15. Gulati M. Early identification of pregnant women at risk for preeclampsia: USPSTF recommendations on screening for preeclampsia. JAMA Cardiol. 2017;2:593-5.
- 16. Henderson JT, Thompson JH, Burda BU, et al. Preeclampsia screening: evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2017;317:1668-83.
- 17. Regitz-Zagrosek V, Blomstrom LC, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147-97.
- 18. Committee on Obstetric Practice. Committee Opinion No. 623: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. Obstet Gynecol. 2015;125:521-5.
- 19. Shimada C, Akaishi R, Cho K, et al. Outcomes of 83 fetuses exposed to angiotensin receptor blockers during the second or third trimesters: a literature review. Hypertens Res. 2015;38:308-13.

## 10.3. Age-Related Issues

### **10.3.1. Older Persons**



	Recommendations for Treatment of Hypertension in Older Persons					
Refe	References that support recommendations are summarized in Online Data Supplement 54.					
COR	LOE	Recommendations				
I	A	<ol> <li>Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community- dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher (1).</li> </ol>				
lla	C-EO	<ul> <li>Nigner (1).</li> <li>2. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antibypertensive drugs</li> </ul>				

#### Synopsis

Because of its extremely high prevalence in older adults, hypertension is not only a leading cause of preventable morbidity and mortality but, perhaps more importantly, is under-recognized as a major contributor to premature disability and institutionalization (2-5). Both SBP and DBP increase linearly up to the fifth or sixth decade of life, after which DBP gradually decreases while SBP continues to rise (6). Thus, isolated systolic hypertension is the predominant form of hypertension in older persons (7, 8). RCTs have clearly demonstrated that BP lowering in isolated systolic hypertension (defined as SBP  $\geq$ 160 mm Hg with variable DBP  $\leq$ 90,  $\leq$ 95, or  $\leq$ 110 mm Hg) is effective in reducing the risk of fatal and nonfatal stroke (primary outcome), cardiovascular events, and death (9-12).

Cross-sectional and longitudinal epidemiologic studies in older adults have raised questions about the benefits of more intensive antihypertensive treatment and the relationship between BP lowering and risk of falls (13). Treatment of elevated BP in older persons is challenging because of a high degree of heterogeneity in comorbidity, as well as poly-pharmacy, frailty, cognitive impairment, and variable life expectancy. However, over the past 3 decades, RCTs of antihypertensive therapy have included large numbers of older persons, and in every instance, including when the SBP treatment goal was <120 mm Hg, more intensive treatment has

safely reduced the risk of CVD for persons over the ages of 65, 75, and 80 years (1, 14). Both HYVET (Hypertension in the Very Elderly Trial) and SPRINT included those who were frail but still living independently in the community (1, 14), and both were stopped early for benefit (HYVET after 1.8 years and SPRINT after 3.26 years). In fact, BP-lowering therapy is one of the few interventions shown to reduce mortality risk in frail older individuals. RCTs in noninstitutionalized community-dwelling older persons have also demonstrated that improved BP control does not exacerbate orthostatic hypotension and has no adverse impact on risk of injurious falls (1, 15, 16). It should be noted, however, that SPRINT excluded those with low (<110 mm Hg) standing BP on study entry. Older persons need to be carefully monitored for orthostatic hypotension during treatment. Intensive BP control increases the risk of acute kidney injury, but this is no different from the risk seen in younger adults (1). In summary, despite the complexity of management in caring for older persons with hypertension, RCTs have demonstrated that in many community-dwelling older adults, even adults >80 years of age, BP-lowering goals during antihypertensive treatment need not differ from those selected for persons <65 years of age (17). Importantly, no randomized trial of BP lowering in persons >65 years of age has ever shown harm or less benefit for older versus younger adults. However, clinicians should implement careful titration of BP lowering and monitoring in persons with high comorbidity burden; large RCTs have excluded older persons at any age who live in nursing homes, as well as those with prevalent dementia and advanced HF.

#### **Recommendation-Specific Supportive Text**

1. We recommend ASCVD risk assessment in all adults with hypertension, including older persons. As a matter of convenience, however, it can be assumed that the vast majority of older adults have a 10-year ASCVD risk  $\geq$  10%, placing them in the high risk category that requires initiation of antihypertensive drug therapy at BP  $\geq$ 130/80 mm Hg (see Section 8.1.2, Figure 4 and Table 23 for BP thresholds for initiating antihypertensive drug treatment). Large RCTs using medications to reduce hypertension-related CVD risk with a mean follow-up of ≥2 years have now included a large number of adults ≥65 years of age. These trials have enrolled a broad range of ages ≥65 years, including persons in their 90s and even 100s, as well as those with mild-to-moderate frailty but who were ambulatory and able to travel to a treatment clinic. In these patients, RCTs have shown that BP lowering decreased CVD morbidity and mortality but did not increase the risk of orthostatic hypotension or falls (1, 15, 16). Analysis of the NHANES (2011–2014) data set indicates that 88% of U.S. adults (98% men and 80% women) ≥65 years old have a 10-year predicted ASCVD risk ≥10% or have a history of CVD (CHD, stroke, or HF). For persons ≥75 years of age, 100% have an ASCVD risk score ≥10% or a history of CVD. Therefore, the BP target of ≤130/80 mm Hg would be appropriate (see Section 8.1.2). Initiation of antihypertensive therapy with 2 agents should be undertaken cautiously in older persons, and they need to be monitored carefully for orthostatic hypotension and history of falls. In SPRINT, the benefit was for an SBP goal of <120 mm Hg. Older persons may present with neurogenic orthostatic hypotension associated with supine hypertension. This is particularly common in Parkinson's disease and other neurodegenerative disorders. For management of this problem, the reader is referred to the recommendations of a 2017 consensus panel (18).

American

2. Patients with prevalent and frequent falls, advanced cognitive impairment, and multiple comorbidities may be at risk of adverse outcomes with intensive BP lowering, especially when they require multiple BP-lowering medications. Older persons in this category typically reside in nursing homes and assisting living facilities, are unable to live independently in the community, and have not been represented in RCTs.

- 1. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA. 2016;315:2673-82.
- 2. Ettinger WH Jr, Fried LP, Harris T, et al. Self-reported causes of physical disability in older people: the Cardiovascular Health Study. CHS Collaborative Research Group. J Am Geriatr Soc. 1994;42:1035-44.
- 3. Ferrucci L, Guralnik JM, Pahor M, et al. Hospital diagnoses, Medicare charges, and nursing home admissions in the year when older persons become severely disabled. JAMA. 1997;277:728-34.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 4. den Ouden MEM, Schuurmans MJ, Mueller-Schotte S, et al. Do subclinical vascular abnormalities precede impaired physical ability and ADL disability? Exp Gerontol. 2014;58:1-7.
- 5. Ezzati M, Lopez AD, Rodgers A, et al. Selected major risk factors and global and regional burden of disease. Lancet. 2002;360:1347-60.
- 6. Duprez DA. Systolic hypertension in the elderly: addressing an unmet need. Am J Med. 2008;121:179-84.e3.
- 7. Egan BM, Li J, Hutchison FN, et al. Hypertension in the United States, 1999 to 2012: progress toward Healthy People 2020 goals. Circulation. 2014;130:1692-9.
- 8. Liu X, Rodriguez CJ, Wang K. Prevalence and trends of isolated systolic hypertension among untreated adults in the United States. J Am Soc Hypertens. 2015;9:197-205.
- 9. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991;265:3255-64.
- Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997;350:757-64.
- Liu L, Wang JG, Gong L, et al. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. J Hypertens. 1998;16:1823-9.
- Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887-98.
- 13. Tinetti ME, Han L, Lee DSH, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med. 2014;174:588-95.
- 14. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. BMC Med. 2015;13:78.
- 15. Gangavati A, Hajjar I, Quach L, et al. Hypertension, orthostatic hypotension, and the risk of falls in a communitydwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. J Am Geriatr Soc. 2011;59:383-9.
- 16. Margolis KL, Palermo L, Vittinghoff E, et al. Intensive blood pressure control, falls, and fractures in patients with type 2 diabetes: the ACCORD trial. J Gen Intern Med. 2014;29:1599-606.
- 17. Bavishi C, Bangalore S, Messerli FH. Outcomes of intensive blood pressure lowering in older hypertensive patients. J Am Coll Cardiol. 2017;69:486-93.
- Gibbons CH, Schmidt P, Biaggioni I, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J Neurol. 2017;264:1567-82.

## 10.3.2. Children and Adolescents

Pediatric guidelines are available from other organizations (1, 2). The 2011 report updates the 2004 report for publications through 2008 (antihypertensive medication trials, normative data on pediatric BP) but is otherwise unchanged. In the 2011 guideline (3), BP was stratified into normal, prehypertension (90th percentile to 95th percentile), stage 1 hypertension (95th percentile to >99th percentile), and stage 2 hypertension (above stage 1) by using age-, sex-, and height-based tables beginning at 1 year of age, which were based on the distribution of BP in more than 60,000 healthy children in various population-based studies (1). These definitions were designed to be analogous to definitions in the extant JNC 7 report; for older adolescents (≥14 years), the JNC 7 thresholds generally apply (4). Treatment recommendations are based on hypertension severity, published short-term clinical trials of antihypertensive treatment, age, coexisting CVD risk factors, and risk stratification by presence of LVH on echocardiogram. The treatment goal is to achieve BP <90th percentile. New tables for ambulatory BP distribution in children have been developed. A classification of BP that is based on these ambulatory BP results has been proposed (5, 6). Publication of new evidence-based pediatric guidelines is anticipated in late 2017.

#### 2017 High Blood Pressure Clinical Practice Guideline

#### References

- 1. Moser M, Roccella EJ. The treatment of hypertension: a remarkable success story. J Clin Hypertens (Greenwich). 2013;15:88-91.
- Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Bethesda, MD: National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services; 2012:S1-44. NIH Publication No. 12-7486.
- 3. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128(suppl 5):S213-56.
- 4. Chobanian AV, Bakris GL, Black HR, et al; the National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-52.
- 5. Flynn JT, Daniels SR, Hayman LL, et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension. 2014;63:1116-35.
- 6. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31:1731-68.

# **11. Other Considerations**

## 11.1. Resistant Hypertension

The diagnosis of resistant hypertension is made when a patient takes 3 antihypertensive medications with complementary mechanisms of action (a diuretic should be 1 component) but does not achieve control or when BP control is achieved but requires  $\geq$ 4 medications (1). On the basis of the previous cutoff of 140/90 mm Hg, the prevalence of resistant hypertension is approximately 13% in the adult population (2, 3). Multiple single-cohort studies have indicated that common risk factors for resistant hypertension include older age, obesity, CKD, black race, and DM. Estimates suggest the prevalence would be about 4% higher with the newly recommended control target of <130/80 mm Hg (subject to validation in future study). The prognosis of resistant hypertension (by the previous definition) (1), compared with the prognosis of those who more readily achieve control, has not been fully ascertained; however, risk of MI, stroke, ESRD, and death in adults with resistant hypertension and CHD may be 2- to 6-fold higher than in hypertensive adults without resistant hypertension (4-6). The evaluation of resistant hypertension involves consideration of many patient characteristics, pseudoresistance (BP technique, white coat hypertension, and medication compliance), and screening for secondary causes of hypertension (Figure 10; Section 5.4; Table 13). The term "refractory hypertension" has been used to refer to an extreme phenotype of antihypertensive treatment failure, defined as failure to control BP despite use of at least 5 antihypertensive agents of different classes, including a longacting thiazide-type diuretic, such as chlorthalidone, and a mineralocorticoid receptor antagonist, such as spironolactone (7). The prevalence of refractory hypertension is low; patients with refractory hypertension experience high rates of CVD complications, including LVH, HF, and stroke.

Treatment of resistant hypertension involves improving medication adherence, improving detection and correction of secondary hypertension, and addressing other patient characteristics (8-10). Pharmacological therapy with combinations of medications with complementary mechanisms of action provides an empirical approach that enhances BP control while mitigating untoward effects of potent vasodilators (e.g., fluid retention and reflex tachycardia). CCBs, inhibitors of RAS, and chlorthalidone comprise a common 3-drug regimen (11). Considerable evidence indicates that the addition of spironolactone to multidrug regimens provides substantial BP reduction (12) when compared with placebo. Substantial data also demonstrate the advantage of spironolactone as compared with other active drugs (8, 13-15). In particular, the recent PATHWAY-2 (Optimum Treatment for Drug-Resistant Hypertension) RCT demonstrated the superiority of spironolactone over alpha and beta blockers (13). There is also clinical trial evidence that the addition of hydralazine or minoxidil is effective in achieving BP control in patients resistant to usual

combination therapy (8, 12-16). The dosing of multidrug regimens, occasionally including nighttime dosing, may be best optimized by hypertension specialists.

Several studies have investigated devices that interrupt sympathetic nerve activity (carotid baroreceptor pacing and catheter ablation of renal sympathetic nerves); however, these studies have not provided sufficient evidence to recommend the use of these device in managing resistant hypertension (8-10). In particular, 2 RCTS of renal sympathetic nerve ablation have been negative (8, 9).

American Heart Association.

# Hypertension





Refer to appropriate specialist for known or suspected secondary cause(s) of hypertension Refer to hypertension specialist if BP remains uncontrolled after 6 mo of treatment

\*See additional details in Section 6, Nonpharmacological Intervention.

<sup>+</sup>See Section 5.4.1 and Table 14 for complete list of drugs that elevate BP.

\$See Section 5.4 and Table 13 for secondary hypertension.

BP indicates blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; and SBP, systolic blood pressure.

Adapted with permission from Calhoun et al. (1) (American Heart Association, Inc.).

#### 2017 High Blood Pressure Clinical Practice Guideline

- 1. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension. 2008;51:1403-19.
- 2. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011;57:1076-80.
- 3. Achelrod D, Wenzel U, Frey S. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. Am J Hypertens. 2015;28:355-61.
- 4. Smith SM, Huo T, Delia Johnson B, et al. Cardiovascular and mortality risk of apparent resistant hypertension in women with suspected myocardial ischemia: a report from the NHLBI-sponsored WISE Study. J Am Heart Assoc. 2014;3:e000660.
- 5. Tanner RM, Calhoun DA, Bell EK, et al. Incident ESRD and treatment-resistant hypertension: the reasons for geographic and racial differences in stroke (REGARDS) study. Am J Kidney Dis. 2014;63:781-8.
- 6. Bangalore S, Fayyad R, Laskey R, et al. Prevalence, predictors, and outcomes in treatment-resistant hypertension in patients with coronary disease. Am J Med. 2014;127:71-81.e1.
- 7. Calhoun DA, Booth JN 3rd, Oparil S, et al. Refractory hypertension: determination of prevalence, risk factors, and comorbidities in a large, population-based cohort. Hypertension. 2014;63:451-8.
- 8. Rosa J, Widimsky P, Waldauf P, et al. Role of adding spironolactone and renal denervation in true resistant hypertension: one-year outcomes of randomized PRAGUE-15 Study. Hypertension. 2016;67:397-403.
- 9. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370:1393-401.
- 10. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol. 2011;58:765-73.
- 11. Stergiou GS, Makris T, Papavasiliou M, et al. Comparison of antihypertensive effects of an angiotensin-converting enzyme inhibitor, a calcium antagonist and a diuretic in patients with hypertension not controlled by angiotensin receptor blocker monotherapy. J Hypertens. 2005;23:883-9.
- 12. Liu G, Zheng XX, Xu YL, et al. Effect of aldosterone antagonists on blood pressure in patients with resistant hypertension: a meta-analysis. J Hum Hypertens. 2015;29:159-66.
- 13. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386:2059-68.
- 14. Rodilla E, Costa JA, Perez-Lahiguera F, et al. Spironolactone and doxazosin treatment in patients with resistant hypertension. Rev Esp Cardiol. 2009;62:158-66.
- 15. Dahal K, Kunwar S, Rijal J, et al. The effects of aldosterone antagonists in patients with resistant hypertension: a meta-analysis of randomized and nonrandomized studies. Am J Hypertens. 2015;28:1376-85.
- 16. Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA. 2001;285:2719-28.

# 11.2. Hypertensive Crises—Emergencies and Urgencies

Recommendations for Hypertensive Crises and Emergencies					
Refe	References that support recommendations are summarized in Online Data Supplement 55.				
COR	LOE	Recommendations			
I	B-NR	<ol> <li>In adults with a hypertensive emergency, admission to an intensive care us is recommended for continuous monitoring of BP and target organ dama and for parenteral administration of an appropriate agent (Tables 19 and 2 (1, 2).</li> <li>For adults with a compelling condition (i.e., aortic dissection, seve preeclampsia or eclampsia, or pheochromocytoma crisis), SBP should reduced to less than 140 mm Hg during the first hour and to less than 140 mm Hg in aortic dissection.</li> </ol>			
I	C-EO				
I C-EO		3. For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hour; then, if stable, to 160/100 mm Hg within the next 2 to 6 hours; and then cautiously to normal during the following 24 to 48 hours.			

#### Synopsis

Hypertensive emergencies are defined as severe elevations in BP (>180/120 mm Hg) associated with evidence of new or worsening target organ damage (3-6). The 1-year death rate associated with hypertensive emergencies is >79%, and the median survival is 10.4 months if the emergency is left untreated (7). The actual BP level may not be as important as the rate of BP rise; patients with chronic hypertension can often tolerate higher BP levels than previously normotensive individuals. Hypertensive emergencies demand immediate reduction of BP (not necessarily to normal) to prevent or limit further target organ damage. Examples of target organ damage include hypertensive encephalopathy, ICH, acute ischemic stroke, acute MI, acute LV failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, acute renal failure, and eclampsia. In general, use of oral therapy is discouraged for hypertensive emergencies. Hypertensive emergencies in patients with acute ICH and acute ischemic stroke are discussed in Section 9.4.

American

In contrast, hypertensive urgencies are situations associated with severe BP elevation in otherwise stable patients without acute or impending change in target organ damage or dysfunction. Many of these patients have withdrawn from or are noncompliant with antihypertensive therapy and do not have clinical or laboratory evidence of acute target organ damage. These patients should not be considered as having a hypertensive emergency and instead are treated by reinstitution or intensification of antihypertensive drug therapy and treatment of anxiety as applicable. There is no indication for referral to the emergency department, immediate reduction in BP in the emergency department, or hospitalization for such patients.

Figure 11 is an algorithm on diagnosis and management of a hypertensive crisis. Tables 19 and 20 summarize intravenous antihypertensive drugs for treatment of hypertensive emergencies.

#### **Recommendation-Specific Supportive Text**

1. There is no RCT evidence that antihypertensive drugs reduce morbidity or mortality in patients with hypertensive emergencies (8). However, from clinical experience, it is highly likely that antihypertensive therapy is an overall benefit in a hypertensive emergency (9). There is also no high-quality RCT evidence to inform clinicians as to which first-line antihypertensive drug class provides more benefit than harm in hypertensive emergencies (8). This lack of evidence is related to the small size of trials, the lack of long-term follow-up, and failure to report outcomes. However, 2 trials have demonstrated that nicardipine may be better than labetalol in achieving the short-term BP target (1, 10-12). Several antihypertensive agents in various pharmacological classes are available for the treatment of hypertensive emergencies (Table 19). Because

autoregulation of tissue perfusion is disturbed in hypertensive emergencies, continuous infusion of shortacting titratable antihypertensive agents is often preferable to prevent further target organ damage (5, 6). The selection of an antihypertensive agent should be based on the drug's pharmacology, pathophysiological factors underlying the patient's hypertension (as well as they can be rapidly determined), degree of progression of target organ damage, the desirable rate of BP decline, and the presence of comorbidities (Table 20). The therapeutic goal is to minimize target organ damage safely by rapid recognition of the problem and early initiation of appropriate antihypertensive treatment.

2. Compelling conditions requiring rapid lowering of SBP, usually to <140 mm Hg, in the first hour of treatment include aortic dissection, severe preeclampsia or eclampsia, and pheochromocytoma with hypertensive crisis.

3. There is no RCT evidence comparing different strategies to reduce BP, except in patients with ICH (9, 13). Neither is there RCT evidence to suggest how rapidly or how much BP should be lowered in a hypertensive emergency (9). However, clinical experience indicates that excessive reduction of BP may cause or contribute to renal, cerebral, or coronary ischemia and should be avoided. Thus, comprehensive dosing of intravenous or even oral antihypertensive agents to rapidly lower BP is not without risk. Oral loading doses of antihypertensive agents can engender cumulative effects, causing hypotension after discharge from the emergency department or clinic.

Heart

# Hypertension





Colors correspond to Class of Recommendation in Table 1.

\*Use drug(s) specified in Table 19.

+If other comorbidities are present, select a drug specified in Table 20.

BP indicates blood pressure; DBP, diastolic blood pressure; ICU, intensive care unit; and SBP, systolic blood pressure.

Class	Drug(s)	Usual Dose Range	Comments
CCB— dihydropyridines	Nicardipine	Initial 5 mg/h, increasing every 5 min by 2.5 mg/h to maximum 15 mg/h.	Contraindicated in advanced aortic stenosis; no dose adjustment needed for elderly.
	Clevidipine	Initial 1–2 mg/h, doubling every 90 s until BP approaches target, then increasing by less than double every 5–10 min; maximum dose 32 mg/h; maximum duration 72 h.	Contraindicated in patients with soybean, soy product, egg, and egg product allergy and in patients with defective lipid metabolism (e.g., pathological hyperlipidemia, lipoid nephrosis or acute pancreatitis). Use low-end dose range for elderly patients.
Vasodilators— Nitric-oxide dependent	Sodium nitroprusside	Initial 0.3–0.5 mcg/kg/min; increase in increments of 0.5 mcg/kg/min to achieve BP target; maximum dose 10 mcg/kg/min; duration of treatment as short as possible. For infusion rates ≥4–10 mcg/kg/min or duration >30 min, thiosulfate can be coadministered to prevent cyanide toxicity.	Intra-arterial BP monitoring recommended to prevent "overshoot." Lower dosing adjustment required for elderly. Tachyphylaxis common with extended use. Cyanide toxicity with prolonged use can result in irreversible neurological changes and cardiac arrest.
Hy	Nitroglycerin	Initial 5 mcg/min; increase in increments of 5 mcg/min every 3–5 min to a maximum of 20 mcg/min.	Use only in patients with acute coronary syndrome and/or acute pulmonary edema. Do not use in volume-depleted patients.
Vasodilators—	Hydralazine	Initial 10 mg via slow IV	BP begins to decrease within 10–30
direct		infusion (maximum initial dose 20 mg); repeat every 4–6 h as needed.	min, and the fall lasts 2–4 h. Unpredictability of response and prolonged duration of action do not make hydralazine a desirable first-line agent for acute treatment in most patients.
Adrenergic blockers—beta1 receptor selective antagonist	Esmolol	Loading dose 500–1000 mcg/kg/min over 1 min followed by a 50- mcg/kg/min infusion. For additional dosing, the bolus dose is repeated and the infusion increased in 50- mcg/kg/min increments as needed to a maximum of 200 mcg/kg/min.	Contraindicated in patients with concurrent beta-blocker therapy, bradycardia, or decompensated HF. Monitor for bradycardia. May worsen HF. Higher doses may block beta <sub>2</sub> receptors and impact lung function in reactive airway disease.
Adrenergic blockers— combined alpha <sub>1</sub> and nonselective	Labetalol	Initial 0.3–1.0-mg/kg dose (maximum 20 mg) slow IV injection every 10 min or 0.4–1.0-mg/kg/h IV infusion up to 3 mg/kg/h. Adjust	Contraindicated in reactive airways disease or chronic obstructive pulmonary disease. Especially useful in hyperadrenergic syndromes. May worsen HF and should not be given in

Table 19. Intravenous Antik	nypertensive Drugs for	Treatment of Hypertensive	Emergencies
-----------------------------	------------------------	---------------------------	-------------

beta receptor antagonistrate up to total cumulative dose of 300 mg. This dose can be repeated every 4–6 h.patients with second- or third-degree heart block or bradycardia.Adrenergic blockers— nonselective alpha receptor antagonistPhentolamineIV bolus dose 5 mg. Additional bolus doses every 10 min as needed to lower BP to target.Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, interactions between monamine oxidase inhibitors and other drugs or food, cocaine toxicity, amphetamine overdose, or clonidine withdrawal).Dopamine1- receptor selective agonistFenoldopamInitial 0.1–0.3 mcg/kg/min; may be increased in increments of 0.05–0.1 mcg/kg/min. until target BP is reached. Maximum infusion rate 1.6 mcg/kg/min.Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or intracranial pressure and those with sulfite allergy.ACE inhibitorEnalaprilatInitial 1.25 mg over a 5-min period. Doses can be increased up to 5 mg every 6 h as needed to achieve BP target.Contraindicated in pregnancy and should not be used in acute MI or bilateral renal artery stenosis. Mainly useful in hypertensive emergencies associated with high plasma renin activity. Dose not easily adjusted. Relatively slow onset of action (15 min) and unpredictability of BP response.				
Adrenergic blockers— nonselective alpha receptor antagonistPhentolamineIV bolus dose 5 mg. Additional bolus doses every 10 min as needed to lower BP to target.Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, interactions between monamine oxidase inhibitors and other drugs or food, cocaine toxicity, amphetamine overdose, or clonidine withdrawal).Dopamine1- receptor selective agonistFenoldopamInitial 0.1–0.3 mcg/kg/min; may be increased in increments of 0.05–0.1 mcg/kg/min every 15 min until target BP is reached. Maximum infusion rate 1.6Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or intracranial pressure and those with sulfite allergy.ACE inhibitorEnalaprilatInitial 1.25 mg over a 5-min period. Doses can be increased up to 5 mg every 6 h as needed to achieve BP target.Contraindicated in pregnancy and should not be used in acute MI or bilateral renal artery stenosisACE inhibitorEnalaprilatInitial 1.25 mg over a 5-min period. Doses can be increased up to 5 mg every 6 h as needed to achieve BP target.Contraindicated in pregnancy and should not be used in acute MI or bilateral renal artery stenosis mergencies associated with high plasma renin activity. Dose not easily adjusted. Relatively slow onset of action (15 min) and unpredictability of BP response.	beta receptor antagonist		rate up to total cumulative dose of 300 mg. This dose can be repeated every 4–6 h.	patients with second- or third-degree heart block or bradycardia.
Dopamine1- receptor selective agonistFenoldopamInitial 0.1–0.3 mcg/kg/min; may be increased in increments of 0.05–0.1 mcg/kg/min every 15 min until target BP is reached. Maximum infusion rate 1.6 mcg/kg/min.Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or intracranial pressure and those with sulfite allergy.ACE inhibitorEnalaprilatInitial 1.25 mg over a 5-min period. Doses can be increased up to 5 mg every 6 h as needed to achieve BP target.Contraindicated in pregnancy and 	Adrenergic blockers— nonselective alpha receptor antagonist	Phentolamine	IV bolus dose 5 mg. Additional bolus doses every 10 min as needed to lower BP to target.	Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, interactions between monamine oxidase inhibitors and other drugs or food, cocaine toxicity, amphetamine overdose, or clonidine withdrawal).
ACE inhibitor       Enalaprilat       Initial 1.25 mg over a 5-min period. Doses can be increased up to 5 mg every 6 h as needed to achieve BP target.       Contraindicated in pregnancy and should not be used in acute MI or bilateral renal artery stenosis.         Mainly useful in hypertensive target.       Mainly useful in hypertensive emergencies associated with high plasma renin activity.       Dose not easily adjusted.         Relatively slow onset of action (15 min) and unpredictability of BP response.       Expense bigst blacker U5 heart for the plasma renin with the plasma renormed to	Dopamine <sub>1</sub> - receptor selective agonist	Fenoldopam	Initial 0.1–0.3 mcg/kg/min; may be increased in increments of 0.05–0.1 mcg/kg/min every 15 min until target BP is reached. Maximum infusion rate 1.6 mcg/kg/min.	Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or intracranial pressure and those with sulfite allergy.
response.	ACE inhibitor	Enalaprilat	Initial 1.25 mg over a 5-min period. Doses can be increased up to 5 mg every 6 h as needed to achieve BP target.	Contraindicated in pregnancy and should not be used in acute MI or bilateral renal artery stenosis. Mainly useful in hypertensive emergencies associated with high plasma renin activity. Dose not easily adjusted. Relatively slow onset of action (15 min) and unpredictability of BP
	Dindicates blood areas		baanal blackon UE, baart failur	response.

BP indicates blood pressure; CCB, calcium channel blocker; HF, heart failure; IV, intravenous; and MI, myocardial infarction.

Table 20. Intravenous Antihypertensive Drugs for Treatment of Hypertensive Emergencies in Patients Wit	h
Selected Comorbidities	

Comorbidity	Preferred	Comments
Aguto portio discostion	Drug(s)*	Deguizes repid lowering of CDD to <120 mm Llg
Acute aortic dissection	Esmoloi	Requires rapid lowering of SBP to \$120 mm Hg.
	labetaloi	Beta blockade should precede vasodilator (e.g., picardinine or
		nitronrusside) administration if needed for BP control or to
		prevent reflex tachycardia or inotropic effect: SBP <120 mm Hg
		should be achieved within 20 min.
Acute pulmonary edema	Clevidipine,	Beta blockers contraindicated.
	nitroglycerin	
	nitroprusside	
Acute coronary syndromes	Esmolol <sup>+</sup>	Nitrates given in the presence of PDE-5 inhibitors may induce
	labetalol	profound hypotension. Contraindications to beta blockers
	nicardipine	include moderate-to-severe LV failure with pulmonary edema,
	nitroglycerin†	bradycardia (<60 bpm), hypotension (SBP <100 mm Hg), poor
		peripheral perfusion, second- or third-degree heart block, and
		reactive airways disease.
Acute renal failure	Clevidipine	N/A
	fenoldopam	
	nicardipine	Deswines resid DD levening
Eclampsia or preeclampsia	Hydraiazine	Requires rapid BP lowering.
	nicardinino	ACE Inhibitors, ARBS, renin inhibitors, and hiroprusside
Berioperative hypertension	Clevidinine	Intraggerative hypertension is most frequently seen during
(BP >160/90 mm Hg or SBP	esmolol	anesthesia induction and airway manipulation
elevation >20% of the	nicardinine	anestresia induction and an way manipulation.
preoperative value that	nitroglycerin	
persists for >15 min)		
Acute sympathetic discharge	Clevidipine	Requires rapid lowering of BP.
or catecholamine excess	nicardipine	
states (e.g.,	phentolamine	
pheochromocytoma, post-		
carotid endarterectomy		
status)		
Acute ICH	Section 9.4.1	Section 9.4.1
Acute ischemic stroke	Section 9.4.2	Section 9.4.2

\*Agents are listed in alphabetical order, not in order of preference.

<sup>†</sup>Agent of choice for acute coronary syndromes.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; bpm, beats per minute; ICH, intracerebral hemorrhage; LV, left ventricular; PDE-5, phosphodiesterase type-5; and SBP, systolic blood pressure.

- 1. Farias S, Peacock WF, Gonzalez M, et al. Impact of initial blood pressure on antihypertensive response in patients with acute hypertension. Am J Emerg Med. 2014;32:833-6.
- 2. Peacock WF, Chandra A, Char D, et al. Clevidipine in acute heart failure: results of the A Study of Blood Pressure Control in Acute Heart Failure--A Pilot Study (PRONTO). Am Heart J. 2014;167:529-36.
- 3. Papadopoulos DP, Sanidas EA, Viniou NA, et al. Cardiovascular hypertensive emergencies. Curr Hypertens Rep. 2015;17:5.
- 4. Manning L, Robinson TG, Anderson CS. Control of blood pressure in hypertensive neurological emergencies. Curr. Hypertens Rep. 2014;16:436.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 5. Rhoney D, Peacock WF. Intravenous therapy for hypertensive emergencies, part 1. Am J Health Syst Pharm. 2009;66:1343-52.
- 6. Rhoney D, Peacock WF. Intravenous therapy for hypertensive emergencies, part 2. Am J Health Syst Pharm. 2009;66:1448-57.
- 7. Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. Am J Med Sci. 1974;268:336-45.
- 8. Perez MI, Musini VM. Pharmacological interventions for hypertensive emergencies: a Cochrane systematic review. J Hum Hypertens. 2008;22:596-607.
- 9. Gifford RW Jr. Current practices in general medicine. 7. Treatment of hypertensive emergencies including use of sodium nitroprusside. Proc Staff Meet Mayo Clin. 1959;34:387-94.
- 10. Peacock WF, Varon J, Baumann BM, et al. CLUE: a randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the emergency department. Crit Care. 2011;15:R157.
- 11. Cannon CM, Levy P, Baumann BM, et al. Intravenous nicardipine and labetalol use in hypertensive patients with signs or symptoms suggestive of end-organ damage in the emergency department: a subgroup analysis of the CLUE trial. BMJ OPEN. 2013;3:e002338.
- 12. Varon J, Soto-Ruiz KM, Baumann BM, et al. The management of acute hypertension in patients with renal dysfunction: labetalol or nicardipine? Postgrad Med. 2014;126:124-30.
- 13. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368:2355-65.

## **11.3.** Cognitive Decline and Dementia



Recommendation for Prevention of Cognitive Decline and Dementia			
Refer	ences that	support the recommendation are summarized in Online Data Supplement 56.	
COR	LOE	Recommendation	
lla	B-R	1. In adults with hypertension, BP lowering is reasonable to prevent cognitive decline and dementia (1-6).	

#### Synopsis

Dementia is a leading cause of mortality and placement into nursing homes and assisted living facilities, affecting >46 million individuals globally and 5 million persons in the United States, a number that is expected to double by 2050 (7). A 5-year delay in onset of dementia would likely decrease the number of cases of incident dementia by about 50% after several decades (8). Vascular disease and its risk factors are implicated in a large proportion of patients with dementia, including those with Alzheimer's dementia (9-11). Hypertension is also the primary risk factor for small-vessel ischemic disease and cortical white matter abnormalities (12-15). Most observational studies have suggested that better control of SBP may reduce Alzheimer's disease and other dementias, and the evidence is stronger for BP lowering in middle age than in the elderly (9, 16). Clinical trials with dementia assessment have evaluated all-cause dementia but not Alzheimer's disease specifically. However, all of these trials have methodological issues, such as low power, insufficient follow-up length, and inadequately designed dementia assessment batteries.

#### **Recommendation-Specific Supportive Text**

1. Five clinical trials of BP lowering have included assessment for incident dementia. Of these 5 trials, 4 demonstrated a reduction in dementia incidence, with 2 of these 4 demonstrating statistical significance (746-751). SYST-EUR (Systolic Hypertension in Europe) (17) and PROGRESS (Perindopril Protection Against Recurrent Stroke) (18) both showed statistically significant reductions in incident dementia. SYST-EUR achieved an SBP of 152 mm Hg in the treatment arm (8.3 mm Hg lower than placebo arm) during its blinded phase and an SBP of 149 mm Hg (7.0 mm Hg lower than comparison group) during its open-label follow-up phase (2, 3). PROGRESS achieved an SBP of 138 mm Hg in the treatment group (9 mm Hg lower than the placebo group) and demonstrated dementia prevention in patients with a recent stroke (5). The trial showing

#### 2017 High Blood Pressure Clinical Practice Guideline

no benefit in the direction of dementia reduction achieved an SBP reduction of only 3.2 mm Hg, whereas the other 4 trials achieved SBP reductions of 7 to 15 mm Hg (746-751). When the rate of cognitive decline (not dementia) has been a trial outcome, 7 clinical trials of BP-lowering therapy have been completed, and 2 of these have shown benefit (4-6, 19-22). No randomized trial of BP lowering has demonstrated an adverse impact on dementia incidence or cognitive function. However, the anticipated results from SPRINT, the first adequately powered RCT to test whether intensive BP control reduces dementia, may help clarify this issue in the near future.

- 1. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med. 1994;154:2154-60.
- 2. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998;352:1347-51.
- 3. Forette F, Seux M-L, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med. 2002;162:2046-52.
- 4. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens. 2003;21:875-86.
- Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med. 2003;163:1069-75.
- 6. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7:683-9.
- 7. Prince M, Wimo A, Guerchet M, et al. World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. London, UK: Alzheimer's Disease International; 2015:10-27.
- 8. Brookmeyer R, Corrada MM, Curriero FC, et al. Survival following a diagnosis of Alzheimer disease. Arch Neurol. 2002;59:1764-7.
- 9. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4:487-99.
- 10. Kivipelto M, Helkala EL, Hanninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. Neurology. 2001;56:1683-9.
- 11. Kuller LH, Lopez OL, Jagust WJ, et al. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. Neurology. 2005;64:1548-52.
- 12. Liao D, Cooper L, Cai J, et al. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The ARIC Study. Atherosclerosis Risk in Communities Study. Stroke. 1996;27:2262-70.
- 13. Longstreth WT Jr, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke. 1996;27:1274-82.
- 14. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension. 2005;46:200-4.
- 15. Skoog I. A review on blood pressure and ischaemic white matter lesions. Dement Geriatr Cogn Disord. 1998;9(suppl 1):13-9.
- 16. Hughes TM, Sink KM. Hypertension and its role in cognitive function: current evidence and challenges for the future. Am J Hypertens. 2016;29:149-57.
- 17. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997;350:757-64.
- Czernichow S, Ninomiya T, Huxley R, et al. Impact of blood pressure lowering on cardiovascular outcomes in normal weight, overweight, and obese individuals: the Perindopril Protection Against Recurrent Stroke Study trial. Hypertension. 2010;55:1193-8.
- 19. Bosch J, Yusuf S, Pogue J, et al. Use of ramipril in preventing stroke: double blind randomised trial. BMJ. 2002;324:699-702.
#### 2017 High Blood Pressure Clinical Practice Guideline

- 20. Williamson JD, Launer LJ, Bryan RN, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med. 2014;174:324-33.
- 21. Anderson C, Teo K, Gao P, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol. 2011;10:43-53.
- 22. Diener H-C, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. Lancet Neurol. 2008;7:875-84.

# 11.4. Sexual Dysfunction and Hypertension

An association among sexual dysfunction, atherosclerosis, and hypertension can be constructed from several epidemiology surveys, clinical trials, and cohort studies. Although these data converge to suggest that endothelial dysfunction is a common denominator, the story is complete. Sexual dysfunction represents several domains in desire or interest, as well as physical limitations such as erectile dysfunction. In addition, beta blockers, mineralocorticoid receptor antagonists, and other antihypertensive drugs can have negative effects on libido and erectile function. There are emerging data on the association between erectile dysfunction and CVD compared with other domains of sexual dysfunction. Experimental and clinical studies describe a role for angiotensin II, endothelin, and hydrogen sulfide on cavernous tissue function (1). Many of the signaling pathways for the increased production of oxidative stress and the subsequent deleterious effects of oxidative stress on vascular tissue have been described. Accordingly, it is reasonable to suggest that hypertension might lead to vascular changes that cause erectile dysfunction but, conversely, erectile dysfunction may be part of the causal pathway to CVD (1). Although there is insufficient evidence to recommend screening for CVD risk factors in all men with erectile dysfunction, it has been reported as a sole precursor for CVD in men (2-6).

With the introduction of the phosphodiesterase-5 inhibitors, which can be coadministered with antihypertensive medications, there is now effective therapy for erectile dysfunction that has implications for systemic vascular disease (7). These drugs have additive effects on lowering BP and are recommended as a primary therapy for pulmonary hypertension (8). Although data are available to suggest that some antihypertensive medications affect erectile dysfunction more than others, the use of phosphodiesterase-5 inhibitors make drug class distinctions for erectile dysfunction less relevant (9). The long-term safety and efficacy of chronic administration of phosphodiesterase-5 inhibitors for the mitigation of CVD has yet to be determined and represents an important knowledge gap.

#### References

- 1. Nunes KP, Labazi H, Webb RC. New insights into hypertension-associated erectile dysfunction. Curr Opin Nephrol Hypertens. 2012;21:163-70.
- 2. Johannes CB, Araujo AB, Feldman HA, et al. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol. 2000;163:460-3.
- 3. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. BJU Int. 1999;84:50-6.
- 4. Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. JAMA. 2005;294:2996-3002.
- 5. Shin D, Pregenzer G Jr, Gardin JM. Erectile dysfunction: a disease marker for cardiovascular disease. Cardiol Rev. 2011;19:5-11.
- 6. Martin SA, Atlantis E, Lange K, et al. Predictors of sexual dysfunction incidence and remission in men. J Sex Med. 2014;11:1136-47.
- 7. Vasquez EC, Gava AL, Graceli JB, et al. Novel therapeutic targets for phosphodiesterase 5 inhibitors: current stateof-the-art on systemic arterial hypertension and atherosclerosis. Curr Pharm Biotechnol. 2016;17:347-64.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 8. Ghiadoni L, Versari D, Taddei S. Phosphodiesterase 5 inhibition in essential hypertension. Curr Hypertens Rep. 2008;10:52-7.
- 9. Al Khaja KAJ, Sequeira RP, Alkhaja AK, et al. Antihypertensive drugs and male sexual dysfunction: a review of adult hypertension guideline recommendations. J Cardiovasc Pharmacol Ther. 2016;21:233-44.

# **11.5.** Patients Undergoing Surgical Procedures

Recommendations for Treatment of Hypertension in Patients Undergoing Surgical				
	Procedures			
Referen	ces that su	upport recommendations are summarized in Online Data Supplements 57 and 58.		
COR	LOE	Recommendations		
		Preoperative		
	B-NR	1. In patients with hypertension undergoing major surgery who have been on		
	D-ININ	beta blockers chronically, beta blockers should be continued (1-7).		
lla	C-EO	2. In patients with hypertension undergoing planned elective major surgery, it		
Па	C-LO	is reasonable to continue medical therapy for hypertension until surgery.		
llb	B-NR	3. In patients with hypertension undergoing major surgery, discontinuation of		
		ACE inhibitors or ARBs perioperatively may be considered (8-10).		
		4. In patients with planned elective major surgery and SBP of 180 mm Hg or		
llb	C-LD	higher or DBP of 110 mm Hg or higher, deferring surgery may be considered		
		(11, 12).		
- 11:	B-NR	5. For patients undergoing surgery, abrupt preoperative discontinuation of		
Harm		beta blockers or clonidine is potentially harmful (2, 13).		
- 11:	B-NR	6. Beta blockers should not be started on the day of surgery in beta blocker-		
Harm	D-NIK	naïve patients (14).		
Intraoperative				
		7. Patients with intraoperative hypertension should be managed with		
l I	C-EO	intravenous medications (Table 19) until such time as oral medications can		
		be resumed.		

#### Synopsis

Hypertension in the perioperative period increases the risk of CVD, cerebrovascular events, and bleeding (15, 16). As many as 25% of patients who undergo major noncardiac surgery (17) and 80% of patients who have cardiac surgery experience perioperative hypertension (16, 18). In general, the level of risk is related to the severity of the hypertension.

No high-quality RCTs were identified relating to the treatment of hypertension in patients undergoing major surgical procedures. One analysis evaluated data from 3 prospective, randomized, open-label, parallel-comparison studies in patients undergoing cardiac surgery and concluded that clevidipine is a safe and effective treatment for acute hypertension in patients undergoing cardiac surgery (19). Another systematic review and meta-analysis, including 4 studies, concluded that clevidipine is more effective than other antihypertensive drugs in the management of perioperative hypertension without adverse events (20). Several general strategies and principles based on experience and observation are recommended for this section. In the management of patients with perioperative hypertension, it is important to assess other potential contributing factors, such as volume status, pain control, oxygenation, and bladder distention, when the use of pharmacological therapy to control BP is under consideration. Uncontrolled hypertension is associated with increased perioperative and postoperative complications. Certain medications (e.g., beta blockers, clonidine) may be associated with rebound hypertension if discontinued abruptly (13). Therefore,

several general strategies and principles based on experience and observation are recommended for this section.

These recommendations for beta blockers, ACE inhibitors, and ARBs are generally consistent with the "2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery" and are provided to assist in the management of patients undergoing major noncardiac surgical procedures (21).

#### **Recommendation-Specific Supportive Text**

1. If well tolerated, beta blockers should be continued in patients who are currently receiving them for longitudinal reasons, particularly when longitudinal treatment is provided according to GDMT, such as for MI (22). Multiple observational studies support the benefits of continuing beta blockers in patients who are undergoing surgery and who are on these agents for longitudinal indications (1-7).

2. In the absence of conclusive RCTs, the expert opinion of this writing committee is that control of BP to levels recommended by the present guideline (BP <130/80 mm Hg) or other target levels specified for a particular individual is reasonable before undertaking major elective procedures in either the inpatient or outpatient setting. If the patient is unable to take oral medications, it is reasonable to use intravenous medications (Table 19) as necessary to control BP. Special consideration of placement on parenteral therapy usually occurs for patients taking clonidine or beta blockers because of the risk of stopping these medications acutely. Withdrawal syndromes, accompanied by sympathetic discharge and acute hypertension, can occur on cessation of these agents (13).

3. Data on the potential risk and benefit of ACE inhibitors in the perioperative setting are limited to observational analyses, and this area is controversial. Recent evidence from a large cohort study demonstrates that patients who stopped their ACE inhibitors or ARBs 24 hours before noncardiac surgery were less likely to suffer the primary composite outcome (all-cause death, stroke, or myocardial injury) and intraoperative hypotension than were those continuing these medications until surgery (10).

4. JNC 6 (23) noted conflicting evidence for patients with DBP >110 mm Hg and recommended delay of surgery for gradual reduction in DBP before proceeding with surgery. In a systematic review and meta-analysis of 30 observational studies, preoperative hypertension was associated with a 35% increase in cardiovascular complications (12). An increase in complications, including dysrhythmias, myocardial ischemia or infarction, neurological complications, and renal failure, has been reported in patients with DBP ≥110 mm Hg immediately before surgery (24). In contrast, patients with DBP <110 mm Hg do not appear to be at significantly increased risk (25). The relationship of systolic hypertension to surgical risk is less certain. Among patients undergoing carotid endarterectomy, increased risk of postoperative hypertension and neurological defects were observed (26), and an increased risk of CVD morbidity after coronary artery bypass graft surgery has been observed in patients with isolated systolic hypertension (27). During induction of anesthesia for surgery, sympathetic action can result in a 20- to 30-mm Hg increase in BP and a 15- to 20-bpm increase in heart rate among patients with normal BP (24). Exaggerated responses may occur in patients with poorly treated or untreated hypertension by as much as 90 mm Hg and 40 bpm (24). With further anesthesia, the accompanying inhibition of the sympathetic nervous system and loss of baroreceptor control may result in intraoperative hypotension. Lability in BP appears more likely in patients with poorly controlled hypertension (25), whereas studies have observed that patients with controlled hypertension respond similarly to those who are normotensive (28). Early work indicated that patients with severe hypertension (SBP >210 mm Hg and DBP >105 mm Hg) had exaggerated responses in BP during the induction of anesthesia (28).

5. Although few studies describe risks of withdrawing beta blockers in the perioperative time period (2, 5), longstanding evidence from other settings suggests that abrupt withdrawal of long-term beta blockers is

#### 2017 High Blood Pressure Clinical Practice Guideline

harmful (29-31). There are fewer data to describe whether short-term (1 to 2 days) perioperative use of beta blockers, followed by rapid discontinuation, is harmful (5, 14, 21, 30).

6. The 2014 ACC/AHA perioperative guideline specifically recommends against starting beta blockers on the day of surgery in beta-blocker–naive patients (5, 21, 30), particularly at high initial doses, in long-acting form, and if there are no plans for dose titration or monitoring for adverse events. Data from the POISE (Perioperative Ischemic Evaluation) study demonstrate the risk of initiating long-acting beta blockers on the day of surgery (14).

7. Several antihypertensive agents in a variety of pharmacological classes are available for the treatment of hypertensive emergencies (Table 19).

#### References

- 1. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med. 2005;353:349-61.
- 2. Shammash JB, Trost JC, Gold JM, et al. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. Am Heart J. 2001;141:148-53.
- 3. Wallace AW, Au S, Cason BA. Association of the pattern of use of perioperative β-blockade and postoperative mortality. Anesthesiology. 2010;113:794-805.
- Andersson C, Merie C, Jorgensen M, et al. Association of β-blocker therapy with risks of adverse cardiovascular events and deaths in patients with ischemic heart disease undergoing noncardiac surgery: a Danish nationwide cohort study. JAMA Intern Med. 2014;174:336-44.
- 5. Hoeks SE, Scholte Op Reimer WJM, van Urk H, et al. Increase of 1-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients. Eur J Vasc Endovasc Surg. 2007;33:13-9.
- 6. Barrett TW, Mori M, De Boer D. Association of ambulatory use of statins and beta-blockers with long-term mortality after vascular surgery. J Hosp Med. 2007;2:241-52.
- 7. London MJ, Hur K, Schwartz GG, et al. Association of perioperative β-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. JAMA. 2013;309:1704-13.
- 8. Turan A, You J, Shiba A, et al. Angiotensin converting enzyme inhibitors are not associated with respiratory complications or mortality after noncardiac surgery. Anesth Analg. 2012;114:552-60.
- 9. Rosenman DJ, McDonald FS, Ebbert JO, et al. Clinical consequences of withholding versus administering reninangiotensin-aldosterone system antagonists in the preoperative period. J Hosp Med. 2008;3:319-25.
- Roshanov PS, Rochwerg B, Patel A, et al. Withholding versus continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: an analysis of the Vascular events In noncardiac Surgery patlents cOhort evaluation Prospective Cohort. Anesthesiology. 2017;126:16-27.
- 11. Fleisher LA. Preoperative evaluation of the patient with hypertension. JAMA. 2002;287:2043-6.
- 12. Howell SJ, Sear JW, Foex P. Hypertension, hypertensive heart disease and perioperative cardiac risk. Br J Anaesth. 2004;92:570-83.
- 13. Hart GR, Anderson RJ. Withdrawal syndromes and the cessation of antihypertensive therapy. Arch Intern Med. 1981;141:1125-7.
- 14. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing noncardiac surgery (POISE trial): a randomised controlled trial. POISE Study Group. Lancet. 2008;371:1839-47.
- Charlson ME, MacKenzie CR, Gold JP, et al. The preoperative and intraoperative hemodynamic predictors of postoperative myocardial infarction or ischemia in patients undergoing noncardiac surgery. Ann Surg. 1989;210:637-48.
- 16. Cheung AT. Exploring an optimum intra/postoperative management strategy for acute hypertension in the cardiac surgery patient. J Card Surg. 2006;21(suppl 1):S8-14.
- 17. Dix P, Howell S. Survey of cancellation rate of hypertensive patients undergoing anaesthesia and elective surgery. Br J Anaesth. 2001;86:789-93.
- 18. Haas CE, LeBlanc JM. Acute postoperative hypertension: a review of therapeutic options. Am J Health Syst Pharm. 2004;61:1661-73.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 19. Aronson S, Dyke CM, Stierer KA, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg. 2008;107:1110-21.
- 20. Espinosa A, Ripolles-Melchor J, Casans-Frances R, et al. Perioperative use of clevidipine: a systematic review and meta-analysis. PLoS ONE. 2016;11:e0150625.
- 21. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2215-45.
- 22. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458-73.
- 23. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med. 1997;157:2413-46.
- 24. Wolfsthal SD. Is blood pressure control necessary before surgery? Med Clin North Am. 1993;77:349-63.
- 25. Goldman L, Caldera DL. Risks of general anesthesia and elective operation in the hypertensive patient. Anesthesiology. 1979;50:285-92.
- 26. Towne JB, Bernhard VM. The relationship of postoperative hypertension to complications following carotid endarterectomy. Surgery. 1980;88:575-80.
- 27. Aronson S, Boisvert D, Lapp W. Isolated systolic hypertension is associated with adverse outcomes from coronary artery bypass grafting surgery. Anesth Analg. 2002;94:1079-84.
- 28. Foex P, Meloche R, Prys-Roberts C. Studies of anaesthesia in relation to hypertension. 3. Pulmonary gas exchange during spontaneous ventilation. Br J Anaesth. 1971;43:644-61.
- 29. Gerber JG, Nies AS. Abrupt withdrawal of cardiovascular drugs. N Engl J Med. 1979;301:1234-5.
- 30. Rangno RE, Langlois S. Comparison of withdrawal phenomena after propranolol, metoprolol, and pindolol. Am Heart J. 1982;104:473-8.
- 31. Walker PR, Marshall AJ, Farr S, et al. Abrupt withdrawal of atenolol in patients with severe angina. Comparison with the effects of treatment. Br Heart J. 1985;53:276-82.

# 12. Strategies to Improve Hypertension Treatment and Control

In addition to promoting pharmacological and nonpharmacological treatment adherence in individual patients with hypertension, several population-based systems approaches can play an important role in treatment goals.

# 12.1. Adherence Strategies for Treatment of Hypertension

Therapeutic nonadherence (not following recommended medical or health advice, including failure to "persist" with medications and recommended lifestyle modifications) is a major contributor to poor control of hypertension and a key barrier to reducing CVD deaths. Adherence rates vary substantially in different populations and, in general, are lower for lifestyle change and more behaviorally demanding regimens.

	Recommendations for Antihypertensive Medication Adherence Strategies			
Referen	References that support recommendations are summarized in Online Data Supplements 59 and 60.			
COR	COR LOE Recommendations			
I	B-R	<ol> <li>In adults with hypertension, dosing of antihypertensive medication once daily rather than multiple times daily is beneficial to improve adherence (1- 3).</li> </ol>		
lla	B-NR	2. Use of combination pills rather than free individual components can be useful to improve adherence to antihypertensive therapy (4-7).		

## 12.1.1. Antihypertensive Medication Adherence Strategies

#### Synopsis

Up to 25% of patients do not fill their initial prescription for antihypertensive therapy (8-10). During the first year of treatment, the average patient has possession of antihypertensive medications only 50% of the time, and only 1 in 5 patients has sufficiently high adherence to achieve the benefits observed in clinical trials (11, 12).

Factors contributing to poor adherence are myriad, complex, and multilevel (11, 13, 14). Therefore, solutions to improve adherence may be introduced at patient, provider, and healthcare system levels (13, 15, 16). Several systematic reviews and meta-analyses have assessed the impact of interventions on adherence to antihypertensive medications, including modification of antihypertensive therapy (1-7, 11, 15, 16). No single intervention is uniquely effective, and a sustained, coordinated effort that targets all barriers to adherence in an individual is likely to be the most effective approach. See Online Data Supplement F for barriers to medication adherence and the most successful interventions.

The creation of an encouraging, blame-free environment in which patients are recognized for achieving treatment goals and given "permission" to answer questions related to their treatment honestly is essential to identify and address nonadherence. Patient medication adherence assessment tools (17) are presented in Online Data Supplement A. Members of the hypertension care team may use these self-report tools in a nonthreatening fashion to identify barriers and facilitate behaviors associated with improved adherence to antihypertensive medications. Use of more objective methods (e.g., pill counts, data on medication refills) to assess adherence along with self-report methods is optimal.

#### **Recommendation-Specific Supportive Text**

1. Remembering to take medication is often challenging, particularly for regimens that must be dosed several times daily. Taking medications several times throughout the day requires greater attention to scheduling, as well as additional issues such as transportation or storage, which can be challenging for some patients. The impact of once-daily dosing of antihypertensive drugs versus dosing multiple times daily has been evaluated in several meta-analyses (1-3). Medication adherence was greatest with once-daily dosing (range 71% to 94%) and declined as dosing frequency increased (1, 2).

2. Assessment and possible modification of drug therapy regimens can improve suboptimal adherence. Simplifying medication regimens, either by less frequent dosing (i.e., once daily versus multiple times daily) or use of combination drug therapy, improves adherence. Available fixed-dose combination drug therapy is listed in Online Data Supplement D.

#### References

- 1. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23:1296-310.
- 2. Iskedjian M, Einarson TR, MacKeigan LD, et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Ther. 2002;24:302-16.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 3. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. Arch Intern Med. 2004;164:722-32.
- 4. Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a metaanalysis. Am J Med. 2007;120:713-9.
- 5. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55:399-407.
- 6. Sherrill B, Halpern M, Khan S, et al. Single-pill vs free-equivalent combination therapies for hypertension: a metaanalysis of health care costs and adherence. J Clin Hypertens (Greenwich). 2011;13:898-909.
- 7. Yang W, Chang J, Kahler KH, et al. Evaluation of compliance and health care utilization in patients treated with single pill vs. free combination antihypertensives. Curr Med Res Opin. 2010;26:2065-76.
- 8. Franklin SS, Thijs L, Hansen TW, et al. Significance of white-coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes population. Hypertension. 2012;59:564-71.
- 9. Holland N, Segraves D, Nnadi VO, et al. Identifying barriers to hypertension care: implications for quality improvement initiatives. Dis Manag. 2008;11:71-7.
- 10. Berra E, Azizi M, Capron A, et al. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. Hypertension. 2016;68:297-306.
- 11. Gwadry-Sridhar FH, Manias E, Lal L, et al. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: a systematic review by the ISPOR medication adherence and persistence special interest group. Value Health. 2013;16:863-71.
- 12. Petrilla AA, Benner JS, Battleman DS, et al. Evidence-based interventions to improve patient compliance with antihypertensive and lipid-lowering medications. Int J Clin Pract. 2005;59:1441-51.
- 13. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc. 2011;86:304-14.
- 14. Krousel-Wood MA, Muntner P, Islam T, et al. Barriers to and determinants of medication adherence in hypertension management: perspective of the cohort study of medication adherence among older adults. Med Clin North Am. 2009;93:753-69.
- 15. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;11:CD000011.
- 16. Viswanathan M, Golin CE, Jones CD, et al. Closing the quality gap: revisiting the state of the science (vol. 4: medication adherence interventions: comparative effectiveness). Evid RepTechnol Assess (Full Rep). 2012;1-685.
- 17. Kim MT, Hill MN, Bone LR, et al. Development and testing of the Hill-Bone Compliance to High Blood Pressure Therapy Scale. Prog Cardiovasc Nurs. 2000;15:90-6.

# 12.1.2. Strategies to Promote Lifestyle Modification

Recommendation for Strategies to Promote Lifestyle Modification			
References that support the recommendation are summarized in Online Data Supplement 61.			
COR	LOE	Recommendations	
I	C-EO	1. Effective behavioral and motivational strategies to achieve a healthy lifestyle (i.e., tobacco cessation, weight loss, moderation in alcohol intake, increased physical activity, reduced sodium intake, and consumption of a healthy diet) are recommended for adults with hypertension (1, 2).	

#### Synopsis

The primary lifestyle modification interventions that can help reduce high BP are outlined in Section 6 (healthy diet, weight loss, exercise and moderate alcohol intake). In addition, tobacco cessation is crucial for CVD risk reduction. These modifications are central to good health and require specific motivational and cognitive intervention strategies designed to promote adherence to these healthy behaviors. High-quality evidence supporting some of these strategies is provided in Online Data Supplement G. Additionally, interventions such as goal setting, provision of feedback, self-monitoring, follow-up, motivational interviewing, and promotion of self-sufficiency are most effective when combined. Most individuals have clear expectations about what a

new lifestyle will provide; if their experiences do not match these expectations, they will be dissatisfied and less motivated to maintain a lifestyle change, particularly in environments that do not support healthy choices. Other factors that may influence adoption and maintenance of new physical activity or dietary behaviors include age, sex, baseline health status, and body mass index, as well as the presence of comorbid conditions and depression, which negatively affect adherence to most lifestyle change regimens (1). Primary strategies include cognitive-behavioral strategies for promoting behavior change, intervention processes and delivery strategies, and addressing cultural and social context variables that influence behavioral change.

#### **Recommendation-Specific Supportive Text**

1. It is crucial to translate and implement into practice the most effective evidence-based strategies for adherence to nonpharmacological treatment for hypertension. Both adoption and maintenance of new CVD risk-reducing behaviors pose challenges for many individuals. Success requires consideration of race, ethnicity, and socioeconomic status, as well as individual, provider, and environmental factors that may influence the design of such interventions (1). High-quality evidence has shown that even modest sustained lifestyle changes can substantially reduce CVD morbidity and mortality (1). Because many beneficial effects of lifestyle changes accrue over time, long-term adherence maximizes individual and population benefits. Interventions targeting sodium restriction, other dietary patterns, weight reduction, and new physical activity habits often result in impressive rates of initial behavior changes but frequently are not translated into long-term behavioral maintenance.

#### References

- 1. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. Circulation. 2010;122:406-41.
- Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(suppl 2):S76-99.

# 12.1.3. Improving Quality of Care for Resource-Constrained Populations

The availability of financial, informational, and instrumental support resources can be important though not sole determinants of hypertension control (1, 2). The management of hypertension in resource-constrained populations poses a challenge that will require the implementation of all recommendations discussed in Section 13 (Table 21), with specific sensitivity to challenges posed by limited financial resources, including those related to health literacy, alignment of and potential need to realign healthcare priorities by patients, the convenience and complexity of the management strategy, accessibility to health care, and health-related costs (including medications). Resource-constrained populations are also populations with high representation of groups most likely to manifest health disparities, including racial and ethnic minorities (see Section 10.1), residents located in rural areas, and older adults. The more comprehensive BP targets proposed in the present guideline will present added challenges in these populations.

It is crucial to invest in measures to enhance health literacy and reinforce the importance of adhering to treatment strategies, while paying attention to cultural sensitivities. These measures may include identification of and partnering with community resources and organizations devoted to hypertension control and cardiovascular health. Although comparative-effectiveness data documenting efficacy of various interventions are limited, multidisciplinary team–based approaches and the use of community health workers (see Sections 12.1.1 and 12.2) have shown some utility, as has the use of out-of-office BP monitoring (or no-cost BP control visits), particularly among resource-constrained populations (3-5). Long-acting once-daily medications (e.g., chlorthalidone, amlodipine) that are now available generically and often on discount formularies can often be used to reduce complexity of the regimen and promote adherence by decreasing the effect of missed medication dosages. When possible, prescriptions requiring longer than 30-day refills should

#### 2017 High Blood Pressure Clinical Practice Guideline

be considered, especially once a stable regimen is achieved. Where appropriate, using scored tablets and pill cutters can decrease the cost of medication for patients.

#### References

- 1. Havranek EP, Mujahid MS, Barr DA, et al. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2015;132:873-98.
- Institute of Medicine (U.S.) Committee on Public Health Priorities to Reduce and Control Hypertension. A Population-Based Policy and Systems Change Approach to Prevent and Control Hypertension. Washington, DC: National Academies Press; 2010.
- 3. Margolius D, Bodenheimer T, Bennett H, et al. Health coaching to improve hypertension treatment in a lowincome, minority population. Ann Fam Med. 2012;10:199-205.
- 4. Polgreen LA, Han J, Carter BL, et al. Cost-effectiveness of a physician-pharmacist collaboration intervention to improve blood pressure control. Hypertension. 2015;66:1145-51.
- 5. Brownstein JN, Chowdhury FM, Norris SL, et al. Effectiveness of community health workers in the care of people with hypertension. Am J Prev Med. 2007;32:435-47.

# 12.2. Structured, Team-Based Care Interventions for Hypertension Control

Recommendation for Structured, Team-Based Care Interventions for Hypertension Control				
Refer	References that support the recommendation are summarized in Online Data Supplement 62.			
COR	LOE	Recommendations American		
I	Α	1. A team-based care approach is recommended for adults with hypertension (1-7).		

#### Synopsis

Team-based care to improve BP control is a health systems—level, organizational intervention that incorporates a multidisciplinary team to improve the quality of hypertension care for patients (8-10). Various team-based hypertension care models have been demonstrated to increase the proportion of individuals with controlled BP and to reduce both SBP and DBP (1-7, 11, 12). A team-based care approach is patient centered and is frequently implemented as part of a multifaceted approach, with systems support for clinical decision making (i.e., treatment algorithms), collaboration, adherence to prescribed regimen, BP monitoring, and patient self-management. Team-based care for hypertension includes the patient, the patient's primary care provider, and other professionals, such as cardiologists, nurses, pharmacists, physician assistants, dietitians, social workers, and community health workers. These professionals complement the activities of the primary care provider by providing process support and sharing the responsibilities of hypertension care. Section 13 contains a comprehensive, patient-centered plan of care that should be the basis of all team-based care for hypertension.

Team-based care aims to achieve effective control of hypertension by application of the strategies outlined in Online Data Supplement H (3). Delineation of individual team member roles on the basis of knowledge, skill set, and availability, as well as the patient's needs, allows the primary care provider to delegate routine matters to the team, thereby permitting more time to manage complex and critical patient-care issues. Important implementation aspects, such as type of team member added, role of team members related to medication management, and number of team members, influence BP outcomes (3, 13). Team member roles should be clear to all team members and to patients and families.

Team-based care often requires organizational change and reallocation of resources (14, 15). Systemslevel support, such as use of electronic health records (EHR) (see Section 12.3.1), clinical decision support (i.e., treatment algorithms), technology-based remote monitoring (see Section 12.3.2), self-management support tools, and monitoring of performance, are likely to augment and intensify team-based care efforts to reduce high BP.

#### 2017 High Blood Pressure Clinical Practice Guideline

#### **Recommendation-Specific Supportive Text**

1. RCTs and meta-analyses of RCTs of team-based hypertension care involving nurse or pharmacist intervention demonstrated reductions in SBP and DBP and/or greater achievement of BP goals when compared with usual care (1, 2, 4, 5). Similarly, systematic reviews of team-based care, including a review of studies that included community health workers, for patients with primary hypertension showed reductions in SBP and DBP and DBP and DBP and hypertension medication adherence as compared with usual care (3, 12).

#### References

- 1. Carter BL, Rogers M, Daly J, et al. The potency of team-based care interventions for hypertension: a meta-analysis. Arch Intern Med. 2009;169:1748-55.
- 2. Clark CE, Smith LFP, Taylor RS, et al. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. BMJ. 2010;341:c3995.
- 3. Proia KK, Thota AB, Njie GJ, et al. Team-based care and improved blood pressure control: a community guide systematic review. Am J Prev Med. 2014;47:86-99.
- 4. Santschi V, Chiolero A, Colosimo AL, et al. Improving blood pressure control through pharmacist interventions: a meta-analysis of randomized controlled trials. J Am Heart Assoc. 2014;3:e000718.
- 5. Shaw RJ, McDuffie JR, Hendrix CC, et al. Effects of nurse-managed protocols in the outpatient management of adults with chronic conditions: a systematic review and meta-analysis. Ann Intern Med. 2014;161:113-21.
- 6. Thomas KL, Shah BR, Elliot-Bynum S, et al. Check it, change it: a community-based, multifaceted intervention to improve blood pressure control. Circ Cardiovasc Qual Outcomes. 2014;7:828-34.
- 7. Carter BL, Coffey CS, Ardery G, et al. Cluster-randomized trial of a physician/pharmacist collaborative model to improve blood pressure control. Circ Cardiovasc Qual Outcomes. 2015;8:235-43.
- 8. Himmelfarb CRD, Commodore-Mensah Y, Hill MN. Expanding the role of nurses to improve hypertension care and control globally. Ann Glob Health. 2016;82:243-53.
- 9. The Guide to Community Preventive Services (The Community Guide). Cardiovascular Disease: Team-Based Care to Improve Blood Pressure Control. 2012. Available at: https://www.thecommunityguide.org/findings/cardiovascular-disease-team-based-care-improve-blood-pressure-control. Accessed June 1, 2017.
- 10. Centers for Disease Control and Prevention. Task Force recommends team-based care for improving blood pressure control. Press Release. May 15, 2012. Available at:
- https://www.cdc.gov/media/releases/2012/p0515\_bp\_control.html. Accessed September 17, 2017.
- 11. Tsuyuki RT, Al Hamarneh YN, Jones CA, et al. The effectiveness of pharmacist interventions on cardiovascular risk: The Multicenter Randomized Controlled RxEACH Trial. J Am Coll Cardiol. 2016;67:2846-54.
- 12. Brownstein JN, Chowdhury FM, Norris SL, et al. Effectiveness of community health workers in the care of people with hypertension. Am J Prev Med. 2007;32:435-47.
- 13. Brush JE Jr, Handberg EM, Biga C, et al. 2015 ACC health policy statement on cardiovascular team-based care and the role of advanced practice providers. J Am Coll Cardiol. 2015;65:2118-36.
- 14. Patient-Centered Primary Care Collaborative. The Patient-Centered Medical Home: Integrating Comprehensive Medication Management to Optimize Patient Outcomes: Resource Guide. 2010. Available at: : https://www.pcpcc.org/sites/default/files/media/medmanagement.pdf. Accessed June 15, 2017.
- 15. Dunn SP, Birtcher KK, Beavers CJ, et al. The role of the clinical pharmacist in the care of patients with cardiovascular disease. J Am Coll Cardiol. 2015;66:2129-39.

# **12.3.** Health Information Technology–Based Strategies to Promote Hypertension Control

## 12.3.1. EHR and Patient Registries

Recommendations for EHR and Patient Registries			
Refe	References that support recommendations are summarized in Online Data Supplement 63.		
COR	LOE	Recommendations	
I.	B-NR	1. Use of the EHR and patient registries is beneficial for identification of	
		patients with undiagnosed or undertreated hypertension (1-3).	
I.	B-NR	2. Use of the EHR and patient registries is beneficial for guiding quality	
		improvement efforts designed to improve hypertension control (1-3).	

#### Synopsis

A growing number of health systems are developing or using registries and EHR that permit large-scale queries to support population health management strategies to identify undiagnosed or undertreated hypertension. Such innovations are implemented as ongoing quality improvement initiatives in clinical practice. To reduce undiagnosed hypertension and improve hypertension management, a multipronged approach may include 1) application of hypertension screening algorithms to EHR databases to identify at-risk patients, 2) contacting at-risk patients to schedule BP measurements, 3) monthly written feedback to clinicians about at-risk patients who have yet to complete a BP measurement, and 4) electronic prompts for BP measurements whenever at-risk patients visit the clinic (1, 2).

#### **Recommendation-Specific Supportive Text**

1. A growing number of health systems have implemented secure EHR and are developing databases that permit large-scale queries to support population health management strategies for more effective and accurate identification of patients with hypertension (1-3).

2. A growing number of health systems have implemented secure EHR and are developing databases that permit large-scale quality improvement initiative-designed queries to support population health management strategies for more effective management and control of hypertension (1-3).

#### References

- 1. Rakotz MK, Ewigman BG, Sarav M, et al. A technology-based quality innovation to identify undiagnosed hypertension among active primary care patients. Ann Fam Med. 2014;12:352-8.
- Borden WB, Maddox TM, Tang F, et al. Impact of the 2014 expert panel recommendations for management of high blood pressure on contemporary cardiovascular practice: insights from the NCDR PINNACLE registry. J Am Coll Cardiol. 2014;64:2196-203.
- 3. Jaffe MG, Lee GA, Young JD, et al. Improved blood pressure control associated with a large-scale hypertension program. JAMA. 2013;310:699-705.

# 12.3.2. Telehealth Interventions to Improve Hypertension Control

Recommendation for Telehealth Interventions to Improve Hypertension Control			
Refer	References that support the recommendation are summarized in Online Data Supplement 64.		
COR	LOE	Recommendations	
lla	Α	1. Telehealth strategies can be useful adjuncts to interventions shown to	
		reduce BP for adults with hypertension (1-5).	

#### Synopsis

Telehealth strategies, such as telemedicine, digital health ("eHealth"), and use of mobile computing and communication technologies ("mHealth"), are new and innovative tools to facilitate improvements in managing patients with hypertension. mHealth interventions show promise in reducing SBP in patients with hypertension but with large variability in behavioral targets, intervention components, delivery modalities, and patient engagement (5). In addition, there are important implications for the role of social networks, social media, and electronic technology as viable components of weight management and other lifestyle modification and disease management programs (6).

Commonly used telehealth interventions for hypertension management are listed in Online Data Supplement I. Wireless technologies (Online Data Supplement I) allow linking BP devices and other measurement devices to telephone- or Internet-based transmission systems or to Wi-Fi access points available in users' homes and in communities. Some systems require patients to manually enter data, which is then forwarded to a remote computer or the mobile device of the telehealth provider through a telephone line or the Internet (7). When data are received, they are stored and analyzed, and reports are generated, including variations and averages in BP and other parameters over the recording period.

#### **Recommendation-Specific Supportive Text**

1. Meta-analyses of RCTs of different telehealth interventions have demonstrated greater SBP and DBP reductions (1, 2, 4) and a larger proportion of patients achieving BP control (2) than those achieved with usual care without telehealth. The effect of various telehealth interventions on BP lowering was significantly greater than that of BP self-monitoring without transmission of BP data, which suggests a possible added value of the teletransmission approach (1, 3). Although mHealth interventions in general showed promise in reducing SBP in patients with hypertension, results were inconsistent (5). It is unclear which combination of telehealth intervention features is most effective, and telehealth has not been demonstrated to be effective as a standalone strategy for improving hypertension control.

#### References

- 1. Omboni S, Gazzola T, Carabelli G, et al. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. J Hypertens. 2013;31:455-67; discussion 467-8.
- 2. Verberk WJ, Kessels AGH, Thien T. Telecare is a valuable tool for hypertension management, a systematic review and meta-analysis. Blood Press Monit. 2011;16:149-55.
- 3. Agarwal R, Bills JE, Hecht TJW, et al. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. Hypertension. 2011;57:29-38.
- 4. Liu S, Dunford SD, Leung YW, et al. Reducing blood pressure with Internet-based interventions: a meta-analysis. Can J Cardiol. 2013;29:613-21.
- 5. Burke LE, Ma J, Azar KMJ, et al. Current science on consumer use of mobile health for cardiovascular disease prevention: a scientific statement from the American Heart Association. Circulation. 2015;132:1157-213.
- 6. Li JS, Barnett TA, Goodman E, et al. Approaches to the prevention and management of childhood obesity: the role of social networks and the use of social media and related electronic technologies: a scientific statement from the American Heart Association. Circulation. 2013;127:260-7.
- 7. Omboni S, Ferrari R. The role of telemedicine in hypertension management: focus on blood pressure telemonitoring. Curr Hypertens Rep. 2015;17:535.

# 12.4. Improving Quality of Care for Patients With Hypertension

# 12.4.1. Performance Measures

Recommendation for Performance Measures			
References that support the recommendation are summarized in Online Data Supplement 65.			
COR	LOE	Recommendations	
lla	B-NR	1. Use of performance measures in combination with other quality improvement strategies at patient-, provider-, and system-based levels is reasonable to facilitate optimal hypertension control (1-3).	

#### Synopsis

Efforts to improve suboptimal medical care include the use of performance measures, which are defined as standardized, validated approaches to assess whether correct healthcare processes are being performed and that desired patient outcomes are being achieved (4). Performance measures are often combined with other quality improvement strategies, such as certification or financial incentives tied to higher-quality care (5). Guidelines help define clinical care standards that can be used to develop performance measures. As guidelines evolve over time to incorporate new evidence, related performance measures may also evolve.

Because identification, treatment, and control of hypertension are suboptimal, performance measures for hypertension control have been developed and recommended for use in quality improvement projects aimed at improving hypertension control and related outcomes in clinical practice (6-8). Because the specific methods used in performance measures can have an impact on their accuracy and ultimate impact (e.g., the method of BP measurement used in the assessment), they should be developed, tested, and implemented according to published standards (9). See Online Data Supplement J for publicly available performance measures to assess the quality of hypertension care (generally using JNC 7 criteria).

#### Recommendation-Specific Supportive Text

1. RCTs on the impact of performance measures on hypertension control are lacking; RCTs of quality improvement protocols have shown improvements in hypertension control (1, 2). Furthermore, a large observational study showed that a systematic approach to hypertension control, including the use of performance measures, was associated with significant improvement in hypertension control compared with historical control groups (3).

#### References

- 1. Svetkey LP, Pollak KI, Yancy WS Jr, et al. Hypertension improvement project: randomized trial of quality improvement for physicians and lifestyle modification for patients. Hypertension. 2009;54:1226-33.
- 2. de Lusignan S, Gallagher H, Jones S, et al. Audit-based education lowers systolic blood pressure in chronic kidney disease: the Quality Improvement in CKD (QICKD) trial results. Kidney Int. 2013;84:609-20.
- 3. Jaffe MG, Lee GA, Young JD, et al. Improved blood pressure control associated with a large-scale hypertension program. JAMA. 2013;310:699-705.
- Performance Management and Measurement. U.S. Department of Health and Human Services, Health Resources and Services Administration; 2011. Available at: https://www.hrsa.gov/sites/default/files/quality/toolbox/508pdfs/performancemanagementandmeasurement.pdf
   Accessed October 30, 2017.
- 5. Bardach NS, Wang JJ, De Leon SF, et al. Effect of pay-for-performance incentives on quality of care in small practices with electronic health records: a randomized trial. JAMA. 2013;310:1051-9.
- 6. Navar-Boggan AM, Shah BR, Boggan JC, et al. Variability in performance measures for assessment of hypertension control. Am Heart J. 2013;165:823-7.
- 7. Drozda J Jr, Messer JV, Spertus J, et al. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with coronary artery disease and hypertension: a report of the American College of Cardiology Foundation/American Heart

#### 2017 High Blood Pressure Clinical Practice Guideline

Association Task Force on Performance Measures and the American Medical Association-Physician Consortium for Performance Improvement. Circulation. 2011;124:248-70.

- 8. Powers BJ, Olsen MK, Smith VA, et al. Measuring blood pressure for decision making and quality reporting: where and how many measures? Ann Intern Med. 2011;154:781-8, W-289-90.
- Bonow RO, Douglas PS, Buxton AE, et al. ACCF/AHA methodology for the development of quality measures for cardiovascular technology: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures. Circulation. 2011;124:1483-502.

# 12.4.2. Quality Improvement Strategies

	Recommendation for Quality Improvement Strategies		
Reference	References that support the recommendation are summarized in Online Data Supplements 66 and 67.		
COR	LOE	Recommendations	
lla	B-R	1. Use of quality improvement strategies at the health system, provider, and patient levels to improve identification and control of hypertension can be effective (1-8).	

#### Synopsis

High-quality BP management is multifactorial and requires the engagement of patients, families, providers, and healthcare delivery systems (9). The difference between patient outcomes achieved with current hypertension treatment methods and patient outcomes thought to be possible with best-practice treatment methods is known as a quality gap, and such gaps are at least partly responsible for the loss of thousands of lives each year (10). This includes expanding patient and healthcare provider awareness, appropriate lifestyle modifications, access to care, evidence-based treatment, a high level of medication adherence, and adequate follow-up (9). Quality improvement strategies or interventions aimed at reducing the quality gap for a group of patients who are representative of those encountered in routine practice have been effective in improving the hypertension care and outcomes across a wide variety of clinic and community settings (1-4, 6, 8, 10).

Hypertension quality improvement strategies, with examples of substrategies that have been demonstrated to reduce BP and improve BP, are provided in Online Data Supplement E. Because the effects of the different quality improvement strategies varied across trials, and most trials included >1 quality improvement strategy, it is not possible to discern which specific quality improvement strategies have the greatest effects. Team-based care (see Section 12.4) and an organized system of regular review, with antihypertensive drug therapy implemented via a stepped-care protocol, had a clinically significant effect on reducing SBP and DBP and improving BP control. The assessed strategies in Online Data Supplement E may be beneficial under some circumstances and in varying combinations (1-5). National initiatives such as Million Hearts Make Control Your Goal Blood Pressure Toolkit and Team Up Pressure Down provide quality improvement tools to support hypertension care in communities and clinical settings (11). For other national and regional initiatives to improve hypertension, see Online Data Supplement G.

#### **Recommendation-Specific Supportive Text**

1. Systematic review and meta-analyses of trials of quality improvement interventions at health system, provider, and patient levels have demonstrated greater SBP and DBP reductions and a larger proportion of patients achieving BP control than those observed with no intervention or usual care. Multicomponent and multilevel strategies at the local community and healthcare delivery system levels have been shown to improve BP control (6, 7).

#### References

1. Walsh JME, McDonald KM, Shojania KG, et al. Quality improvement strategies for hypertension management: a systematic review. Med Care. 2006;44:646-57.

#### 2017 High Blood Pressure Clinical Practice Guideline

- 2. Carter BL, Rogers M, Daly J, et al. The potency of team-based care interventions for hypertension: a meta-analysis. Arch Intern Med. 2009;169:1748-55.
- 3. Glynn LG, Murphy AW, Smith SM, et al. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev. 2010;CD005182.
- 4. Proia KK, Thota AB, Njie GJ, et al. Team-based care and improved blood pressure control: a community guide systematic review. Am J Prev Med. 2014;47:86-99.
- 5. Anchala R, Pinto MP, Shroufi A, et al. The role of Decision Support System (DSS) in prevention of cardiovascular disease: a systematic review and meta-analysis. PLoS ONE. 2012;7:e47064.
- 6. Thomas KL, Shah BR, Elliot-Bynum S, et al. Check it, change it: a community-based, multifaceted intervention to improve blood pressure control. Circ Cardiovasc Qual Outcomes. 2014;7:828-34.
- 7. Jaffe MG, Lee GA, Young JD, et al. Improved blood pressure control associated with a large-scale hypertension program. JAMA. 2013;310:699-705.
- 8. Agarwal R, Bills JE, Hecht TJW, et al. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. Hypertension. 2011;57:29-38.
- 9. Go AS, Bauman MA, Coleman King SM, et al. An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. Hypertension. 2014;63:878-85.
- 10. Walsh J, McDonald KM, Shojania KG, et al. Closing the Quality Gap: A Critical Analysis of Quality Improvement Strategies (Vol. 3: Hypertension Care). Rockville, MD: Agency for Healthcare Research and Quality (U.S.), 2005.
- 11. Center for Medicare and Medicaid Services. Million Hearts: Cardiovascular Disease Risk Reduction Model. 2016. Available at: https://innovation.cms.gov/initiatives/Million-Hearts-CVDRRM/. Accessed October 30, 2017.

	Heart	
/		

# 12.5. Financial Incentives

	Recommendations for Financial Incentives				
Refe	References that support recommendations are summarized in Online Data Supplement 68.				
COR	LOE	Recommendations			
lla	B-R	<b>1.</b> Financial incentives paid to providers can be useful in achieving improvements in treatment and management of patient populations with hypertension (1-3).			
lla	B-NR	2. Health system financing strategies (e.g., insurance coverage and copayment benefit design) can be useful in facilitating improved medication adherence and BP control in patients with hypertension (4).			

#### Synopsis

With the evolution of the U.S. health system to reward "value over volume," payment systems have focused on financial incentives to improve quality of care. Use of performance measures promulgated by national organizations, governmental payers, and commercial payers have fostered greater attention to control of high BP among healthcare providers and their patients. These performance measures have formed the basis for determining financial incentives for pay for performance initiatives, commercial insurer "pay-for-value" contracts, and the Medicare Shared Savings Programs developed by the Centers for Medicare & Medicaid Services Innovation for Accountable Care Organizations. In addition, the Centers for Medicare and Medicaid Services has developed The Million Hearts: Cardiovascular Disease Risk Reduction Model, which is an RCT designed to identify and test scalable models of care delivery that reduce CVD risk (5).

Greater attention is being paid to the influence of health insurance coverage and benefit designs focused on reducing patient copayments for antihypertensive medications.

#### **Recommendation-Specific Supportive Text**

1. Moderate-quality evidence with mixed results suggests that population-based payment incentive programs can play an important role in achieving better BP control (1-3).

#### 2017 High Blood Pressure Clinical Practice Guideline

2. Reduced copayments for health care, including for medications, and improved outcomes of hypertension care have been identified in several U.S. studies and in single studies in Finland, Israel, and Brazil (4). This is consistent with other evidence on how copayments reduce uptake of care and has implications for policy makers, particularly because the balance of evidence does not suggest that reducing medication copayments leads to an increase in overall healthcare expenditure.

#### References

- 1. Hysong SJ, Simpson K, Pietz K, et al. Financial incentives and physician commitment to guideline-recommended hypertension management. Am J Manag Care. 2012;18:e378-91.
- 2. Petersen LA, Simpson K, Pietz K, et al. Effects of individual physician-level and practice-level financial incentives on hypertension care: a randomized trial. JAMA. 2013;310:1042-50.
- 3. Karunaratne K, Stevens P, Irving J, et al. The impact of pay for performance on the control of blood pressure in people with chronic kidney disease stage 3-5. Nephrol Dial Transplant. 2013;28:2107-16.
- 4. Maimaris W, Paty J, Perel P, et al. The influence of health systems on hypertension awareness, treatment, and control: a systematic literature review. PLoS Med. 2013;10:e1001490.
- 5. Center for Medicare and Medicaid Services. Million Hearts: Cardiovascular Disease Risk Reduction Model. 2016. Available at: https://innovation.cms.gov/initiatives/Million-Hearts-CVDRRM/. Accessed October 30, 2017.

# **13.** The Plan of Care for Hypertension

		American	
	Recommendation for the Plan of Care for Hypertension		
COR	LOE	Recommendation	
I	C-EO	1. Every adult with hypertension should have a clear, detailed, and current evidence-based plan of care that ensures the achievement of treatment and self-management goals, encourages effective management of comorbid conditions, prompts timely follow-up with the healthcare team, and adheres to CVD GDMT (Table 22).	

#### Synopsis

A specific plan of care for hypertension is essential and should reflect understanding of the modifiable and nonmodifiable determinants of health behaviors, including the social determinants of risk and outcomes. A clinician's sequential flow chart for management of hypertension is presented in Table 21. Detailed evidencebased elements of the plan of care are listed in Table 22. The determinants will vary among demographic subgroups (see Section 10 for additional information).

#### **Recommendation-Specific Supportive Text**

1. Studies demonstrate that implementation of a plan of care for hypertension can lead to sustained reduction of BP and attainment of BP targets over several years (1). Meta-analysis of RCTs shows reductions in BP of patients with hypertension and achievement of BP goals at 6 months and 1 year when compared with usual care.

Clinician's Sequential Flow Chart for the Management of Hypertension				
Measure office BP accurately	Section 4			
Detect white coat hypertension or masked	Section 4			
hypertension by using ABPM and HBPM				
Evaluate for secondary hypertension	Section 5			
Identify target organ damage	Sections 5 and 7			
Introduce lifestyle interventions	Section 6			
Identify and discuss treatment goals	Sections 7 and 8			
Use ASCVD risk estimation to guide BP threshold for	Section 8.1.2			
drug therapy				
Align treatment options with comorbidities	Section 9			
Account for age, race, ethnicity, sex, and special	Sections 10 and 11			
circumstances in antihypertensive treatment				
Initiate antihypertensive pharmacological therapy	Section 8			
Insure appropriate follow-up	Section 8			
Use team-based care	Section 12			
Connect patient to clinician via telehealth	Section 12			
Detect and reverse nonadherence	Section 12			
Detect white coat effect or masked uncontrolled	Section 4			
hypertension	Association.			
Use health information technology for remote	Section 12			
monitoring and self-monitoring of BP				

#### Table 21. Clinician's Sequential Flow Chart for the Management of Hypertension

ABPM indicates ambulatory blood pressure monitoring; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; and HBPM, home blood pressure monitoring.

# 13.1. Health Literacy

Communicating alternative behaviors that support self-management of healthy BP in addition to medication adherence is important. This should be done both verbally and in writing. Today, mobile phones have a recording option. For patients with mobile phones, the phone can be used to inform patients and family members of medical instructions after the doctor's visit as an additional level of communication. Inclusion of a family member or friend that can help interpret and encourage self-management treatment goals is suggested when appropriate. Examples of needed communication for alternative behaviors include a specific regimen relating to physical activity; a specific sodium-reduced meal plan indicating selections for breakfast, lunch, and dinner; lifestyle recommendations relating to sleep, rest, and relaxation; and finally, suggestions and alternatives to environmental barriers, such as barriers that prevent healthy food shopping or limit reliable transportation to and from appointments with health providers and pharmacy visits.

# 13.2. Access to Health Insurance and Medication Assistance Plans

Health insurance and medication plan assistance for patients is especially important to improving access to and affordability of medical care and BP medications. Learning how the patient financially supports and budgets for his or her medical care and medications offers the opportunity to share additional insight relating to cost reductions, including restructured payment plans. Ideally, this would improve the patient's compliance with medication adherence and treatment goals.

# 13.3. Social and Community Services

Health care can be strengthened through local partnerships. Hypertensive patients, particularly patients with lower incomes, have more opportunity to achieve treatment goals with the assistance of strong local partnerships. In patients with low socioeconomic status or patients who are challenged by social situations, integration of social and community services offers complementary reinforcement of clinically identified treatment goals. Social and community services are helpful when explicitly related to medical care. However, additional financial support and financial services are incredibly beneficial to patients, some of whom may choose to skip a doctor's appointment to pay a residential utility bill.



Table 22. Evidence-Base	d Elements of the Pl	an of Care for Pati	ents With Hypertension
-------------------------	----------------------	---------------------	------------------------

Plan of Care	Associated Section(s) of Guideline
	and Other Reference(s)
Pharmacological and nonpharmacological treatments	
Medication selection (initial and ongoing)	Section 8.1
Monitoring for adverse effects and adherence	Sections 8.3.1, 8.3.2, 12.1.1
Nonpharmacological interventions	Sections 6, 12.1.2 (2)
• Diet	
Exercise	
<ul> <li>Weight loss if overweight</li> </ul>	
<ul> <li>Moderate alcohol consumption</li> </ul>	
Management of common comorbidities and conditions	
Ischemic heart disease	Section 9.1 (3, 4)
Heart failure	Section 9.2 (5)
Reduced ejection fraction	
Preserved ejection fraction	
Diabetes mellitus	Section 9.6 (6)
Chronic kidney disease	Section 9.3
Cerebrovascular disease	Section 9.4
Peripheral arterial disease	Section 9.5 Heart
Atrial fibrillation	Section 9.8 Association
Valvular heart disease	Section 9.9
Left ventricular hypertrophy	Section 7.3
Thoracic aortic disease	Section 9.10
Patient and family education	
Achieving BP control and self-monitoring	Sections 4.2, 8.2
Risk assessment and prognosis	Section 8.1.2
Sexual activity and dysfunction	Section 11.4
Special patient groups	
Pregnancy	Section 10.2.2
Older persons	Section 10.3.1
Children and adolescents	Section 10.3.2
Metabolic syndrome	Section 9.7
Possible secondary causes of hypertension	Section 5.4
Resistant hypertension	Section 11.1
Patients with hypertension undergoing surgery	Section 11.5
Renal transplantation	Section 9.3.1
Psychosocial factors	
Sex-specific issues	Section 10.2
Culturally sensitive issues (race and ethnicity)	Section 10.1
Resource constraints	Section 12.5
Clinician follow-up, monitoring, and care coordination	
Follow-up visits	Sections 8.1.3, 8.3.1, 8.3.2
Team-based care	Section 12.2
Electronic health record	Section 12.3.1
Health information technology tools for remote and self-monitoring	Section 12.3.2
Socioeconomic and cultural factors	·
Health literacy	Section 13.1.3
Access to health insurance and medication assistance plans	Section 13.1.3
Social services	Section 13.1.3

Community services	Section 13.1.3
BR indicates blood pressure	

BP indicates blood pressure.

#### References

- 1. Jaffe MG, Young JD. The Kaiser Permanente Northern California story: improving hypertension control from 44% to 90% in 13 years (2000 to 2013). J Clin Hypertens (Greenwich). 2016;18:260-1.
- 2. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458-73.
- 3. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2014;130:1749-67.
- 4. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354-471.
- 5. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-327.
- 6. Standards of Medical Care in Diabetes--2016: Summary of Revisions. Diabetes Care. 2016;39(suppl 1):S4-5.

# 14. Summary of BP Thresholds and Goals for Pharmacological Therapy

Several different BP thresholds and goals for the long-term treatment of hypertension with pharmacological therapy are recommended in this guideline. To provide a quick reference for practicing clinicians, these are summarized for hypertensive patients in general and for those with specific comorbidities in Table 23.

Clinical Condition(s)	BP Threshold, mm	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized,	≥130 (SBP)	<130 (SBP)
ambulatory, community-living adults)		
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

Table 23. BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertensior
According to Clinical Conditions

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.



# **15. Evidence Gaps and Future Directions**

In the present guideline, the writing committee was able to call on the large body of literature on BP and hypertension to make strong recommendations across a broad range of medical conditions. Nonetheless, significant gaps in knowledge exist.

Importantly, there are areas where epidemiological and natural history studies suggest that hypertension prevention or earlier treatment of hypertension might substantially improve outcomes, but clinical trials are lacking to provide guidance. The combination of epidemiological data showing a graded relationship between BP and outcomes, particularly above a BP of 120/80 mm Hg, and the results of the SPRINT trial showing benefit of more comprehensive treatment to a target BP of <120/80 mm Hg, suggests that a lifelong BP below that level will substantially lower CVD and CKD incidence. This is especially the case for younger individuals, those with DM, and those with high lifetime CVD risk based on the presence of multiple risk factors, including high BP. If hard, cardiovascular outcome clinical trials remain the sole driver of evidence-based guidelines, then determining the full benefit of earlier intervention may not be possible because of the cost and length of time needed for intervention. Outcomes may be different if antihypertensive treatment is initiated earlier in the natural history of CVD. DM may provide a population in whom to test this hypothesis. Composite outcomes that include both prevention of events and surrogates, such as prevention of decline in renal function or amelioration of measures of subclinical atherosclerosis, vascular stiffness, or LV structure and function, should be considered. Otherwise, these younger individuals may be undertreated and experience mortality or CVD events before being old enough to enter hard outcome-driven trials such as SPRINT. Replication of SPRINT, especially in younger patients with DM and in countries where nonischemic stroke is the predominant cause of CVD, is highly desirable. Likewise, implementation studies that demonstrate the practicality of SPRINT-like interventions in resource-constrained practice settings are needed.

More information is urgently needed relating hypertensive target organ damage to CVD risk and outcomes. Should the identification of target organ damage and hypertensive heart disease prompt more aggressive BP management (i.e., increase the rationale for instituting pharmacological therapy earlier or more intensively? Should all patients with hypertension be screened with echocardiogram for LVH? Should

echocardiography be repeated once LVH is noted? Is it important to document LVH regression? At present, there are no RCT data to inform guideline recommendations.

ABPM and HBPM provide enhanced ability to both diagnose hypertension and monitor treatment. Although evidence is sufficient to recommend incorporating these tools into clinical practice, more knowledge about them is required. Areas of inquiry include closer mapping of the relationship of outcomes to ambulatory and home BP measurements, so that definitions of hypertension and hypertension severity based on these measures can be developed, including the importance of masked hypertension, white coat hypertension, and nocturnal hypertension. Reproducibility of ambulatory and home BPs must be studied, and cohorts should include a broader range of ethnicities. Trials with entry criteria and treatment goals based on ambulatory or home BP measures should be conducted, including studies of masked and white coat hypertension. The practicality and cost of incorporating ABPM into EHR and routine care should be assessed. The existence of these techniques should not hamper efforts to investigate ways to improve accuracy in the measurement of clinic BP. Further research on improving accuracy of office BP measurements, including number of measurements, training of personnel measuring BP, and device comparisons, will help standardize care and thus improve outcomes. Technology for measurement of BP continues to evolve with the emergence of cuffless devices and other strategies that provide the opportunity for continuous noninvasive assessment of BP. The accuracy, cost, and usefulness of these new technologies will need to be assessed.

The contemporary healthcare environment is dramatically different from the era in which awareness of hypertension as a risk factor and benefits of treatment were discovered. With the advent of the EHR, complex calculations of CVD risk and renal function can be incorporated into routine reports, and many new avenues to support intervention strategies are available to clinicians. Optimizing these approaches will require continued focused research. Recognition that simply applying what we know about BP control would have a large impact on population health, observations on inefficiencies and excessive cost in the U.S. healthcare system, and the growth of information technology have led to promising studies of ways to improve and monitor hypertension care. Results of this research are reflected in this guideline, but further work is required. Examples for study include the effectiveness of multidisciplinary healthcare teams to achieve BP treatment goals at lower cost, social media to maintain contact with patients, information technology to monitor outcomes and decrease practice variability, and incentives to providers to achieve better outcomes for patients. A key goal of these efforts should be to demonstrate reduction in healthcare disparities across ethnicity, sex, social and economic class, and age barriers.

More research on the prevention of the development of hypertension and the benefit of lifetime low BP should be conducted. In this regard, elucidation of genetic expression, epigenetic effects, transcriptomics, and proteomics that link genotypes with longitudinal databases may add considerable knowledge about beneficial outcomes of lifelong lower BP, determinants of rise in BP over time, and identification of new treatment targets through understanding the underlying pathophysiological mechanisms. Research should be directed toward the development of therapies that directly counteract the mechanisms accounting for the development of hypertension and disease progression. Additional research aimed at development of practical approaches to implementation of clinical and population-based strategies to prevent obesity, increase physical fitness, and control excess salt and sugar intake could have significant public health impact. In addition, there are minimal, if any, data on whether treatment of hypertension during pregnancy mitigates risk; thus, there is a need for further research in this area, considering both proximate (during the pregnancy and postpartum period) and distant (CVD prevention) outcomes (1).

In the very old, frailty and higher risk of medication side effects complicate treatment. Additional knowledge of the effects of antihypertensive treatment for patients with dementia and patients who reside in long-term-care facility settings is needed. The best approach to older persons who have supine hypertension but postural hypotension needs to be clarified.

Further research related to shared decision-making with patients and their families is needed. Examples include areas where evidence does not clearly identify one treatment or goal as substantially better

than another, where improved patient knowledge (or improved provider knowledge of the patient's circumstances) might improve compliance, where reliance on patient collaboration improves achievement of outcomes (e.g., HBPM, use of social media), and where there are competing health concerns (e.g., older individuals with frailty).

Finally, clinical guidelines are increasingly required to manage the large body of accumulated knowledge related to diagnosis and management of high BP. However, guidelines often cause controversy and confusion when competing recommendations are made by different "expert" groups or when changes in definitions, treatments, or treatment goals are introduced. Now may be the time to begin the investigation of the impact of guidelines on clinical practice, costs, and patient outcomes, as well as ways to facilitate communication and collaboration between different guideline-developing organizations. This document is, as its name implies, a guide. In managing patients, the responsible clinician's judgment remains paramount.

#### Reference

1. Moser M, Brown CM, Rose CH, et al. Hypertension in pregnancy: is it time for a new approach to treatment? J Hypertens. 2012;30:1092-100.

# Presidents and Staff American College of Cardiology



Mary Norine Walsh, MD, MACC, President Shalom Jacobovitz, Chief Executive Officer

William J. Oetgen, MD, MBA, FACC, Executive Vice President, Science, Education, Quality, and Publishing MaryAnne Elma, MPH, Senior Director, Science, Education, Quality, and Publishing Amelia Scholtz, PhD, Publications Manager, Science, Education, Quality, and Publishing

#### American College of Cardiology/American Heart Association

Katherine A. Sheehan, PhD, Director, Guideline Strategy and Operations Abdul R. Abdullah, MD, Science and Medicine Advisor Naira Tahir, MPH, Associate Guideline Advisor

#### American Heart Association

John J. Warner, MD, President Nancy Brown, Chief Executive Officer Rose Marie Robertson, MD, FAHA, Chief Science and Medicine Officer Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations Jody Hundley, Production Manager, Scientific Publications, Office of Science Operations

**Key Words:** ACC/AHA Clinical Practice Guidelines; blood pressure; hypertension; ambulatory care; antihypertensive agents; behavior modification; risk reduction; treatment adherence; treatment outcomes; Systems of care, hypertension emergency, secondary hypertension, blood pressure, measurement, diabetes, chronic kidney disease, resistant hypertension, nonpharmacologic treatment, lifestyle measures

#### Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (October 2017)

						Institutional,		
				Ownershin/		Organizational,		
			Spoakors	Dwnersnip/ Dortnorship		Einancial	Export	
Committee Member	Employment	Consultant	Bureau	/Principal	Personal Research	Bonofit	Witness	Salary
Daul K. Whalton		Nono	Nono	Nono	Nono	Nono	Nono	Salal y
(Chair)	School of Hygiopo	None	None	None	None	None	None	NOTE
(Chuir)							Ame	erican
	anu rropical Madisina Shaw						He	art
	Church Drofossor							ociation
	of Clobal Dublic							bolation
Debort M. Carov	Health	None	Nono	Nana	Nono	None	Nono	Nana
(Vice Chair)	Virginia Doon	None	None	None	None	None	None	None
(vice chuir)	Virginia—Dean							
	Ementus anu							
	Drofossor							
	Professor,							
	Department of							
Mille and C. Annual and	Medicine	Neg	News	Num	New	News	News	News
wildert S. Aronow	Westchester	None	None	None	None	None	None	None
	Medical Center							
	And New York							
	Collogo							
	College— Drofossor of							
	Modicino							
Danald C. Casay, Jr.	Thomas lofferson	None	Nono	Nono	Nono	None	Nono	Nana
Donalu E. Casey, Ji		None	NOTE	None	None	None	None	NOTE
	College Of Bopulation							
	Hoalth_Adjunct							
	Faculty: Alvaroz 9.							
	Marcal							
	iviaisai Ino/health_							
	Principal and							
	Founder							
	Health—Adjunct Faculty; Alvarez & Marsal Ipo4health— Principal and Founder							

Karen J. Collins	Collins Collaboration— President	None	None	None	None	None	None	None
Cheryl Dennison Himmelfarb	John Hopkins University— Professor of Nursing and Medicine, Institute for Clinical and Translational Research	None	None	None	None	None	None	None
Sondra M. DePalma	PinnacleHealth CardioVascular Institute— Physician Assistant; American Academy of PAs—Director, Regulatory and Professional Practice	None	None	None	None	None	None Hei Hei Ass	None art ociation.
Samuel Gidding	Alfred I. Dupont Hospital for Children—Chief, Division of Pediatric Cardiology, Nemours Cardiac Center	None	None	None	None	None	None	None
David C. Goff, Jr*	Colorado School of Public Health— Professor and Dean, Department of Epidemiology	None	None	None	None	None	None	None

Kenneth A. Jamerson	University of Michigan Health System— Professor of Internal Medicine and Frederick G.L. Huetwell Collegiate Professor of Cardiovascular Medicine	None	None	None	None	None	None	None
Danie W. I Jones	University of Mississippi Medical Center— Professor of Medicine and Physiology; Metabolic Diseases and Nutrition— University	None	None	None	None	None	None Ame Hea Ass	None prican art pciation.
	Sanderson Chair in Obesity Mississippi Center for Obesity Research— Director, Clinical and Population Science			TE		<b>S</b> 1(	$\mathbf{O}$	
Eric J. MacLaughlin	Texas Tech University Health Sciences Center— Professor and Chair, Department of Pharmacy Practice, School of Pharmacy	None	None	None	None	None	None	None

Paul Muntner	University of	None						
	, Alabama at							
	Birmingham—							
	Professor,							
	Department of							
	Epidemiology							
Bruce Ovbiagele	Medical	None						
	University of							
	South Carolina—							
	Pihl Professor							
	and Chairman of							
	Neurology							
Sidney C. Smith Jr	University of	None						
Sidiley C. Sinich, Si	North Carolina at	None						
	Chanel Hill							ar L
	Professor of						ASS	ociation .
	Medicine: Center							
	for							
	Cardiovascular							
	Science and							
	Medicine -							
	Director							
Crystal C Spansor	Sponsor Law	Nono	Nono	None	Nono	None	Nono	Nono
Crystal C. Spencer	DA Attornovist	None						
	PA—Attorney at							
Dandall C. Stafford	Ldw	None	Nana	Nana	Nana	None	None	None
Kanuan S. Stanoru	Drevention	None						
	Prevention							
	Research							
	Center—							
	Professor of							
	Niedicine;							
	Program on							
	Prevention							
	Dutcomes—							
<u> </u>	Director							
Sandra J. Taler		None						
	Professor of							
	Medicine, College							
	of Medicine							

Randal J. Thomas	Mayo Clinic— Medical Director	None	None	None	None	None	None	None
	Cardiac							
	Rehabilitation							
	Program							
Kim A. Williams, Sr	Rush University	None	None	None	None	None	None	None
	Medical Center—							
	James B. Herrick							
	Professor;							
	Division of							
	Cardiology—							
	Chief							
Jeff D. Williamson	Wake Forest	None	None	None	None	None	None Ame	None
	Baptist Medical							art
	Center—						Ass	ociation.
	Professor of							
	Modicino: Soction							
	on Gerontology							
	and Geriatric							
	Medicine—Chief							
Jackson T. Wright, Jr	Case Western	None	None	None	None	None	None	None
	Reserve							
	University—							
	Professor of							
	Medicine;							
	William T. Dahms							
	MD Clinical							
	Research Unit—							
	Program							
	Director;							
	University							
	Hospitals Case							
	Medical Center—							
	Director, Clinical							
	Hypertension							
	Program							

This table represents the relationships of committee members with industry and other entities (RWI) that are considered relevant to this document. Although most ACC/AHA guideline writing committees are constituted such that no more than half the members may have relevant RWI for 1 year before and during development of the guideline, rules for the prevention guidelines require that no members have relevant RWI from 1 year before appointment until 1 year after publication of the guideline. Members' RWI were

reviewed and updated at all meetings and conference calls of the writing committee during the document development period. The complete ACC/AHA policy on RWI is available at <a href="http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy">http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy</a>.

We gratefully acknowledge the contributions of Dr. Lawrence Appel, who served as a member of the Writing Committee from November 2014 to September 2015.

\*Dr. David C. Goff resigned from the writing committee in December 2016 because of a change in employment before the recommendations were balloted. The writing committee thanks him for his contributions, which were extremely beneficial to the development of the draft.

AAPA indicates American Academy of Physician Assistants; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; ABC, Association of Black Cardiologists; NMA, National Medical Association; and PCNA, Preventive Cardiovascular Nurses Association.



# Hypertension

#### Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)—2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (October 2017)

Reviewer	Representati on	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Kim K. Birtcher	Official Reviewer— TFPG Lead Reviewer	University of Houston College of Pharmacy— Clinical Professor, Department of Pharmacy Practice and Translational Research	• Jones & Bartlett Learning	None	None	None	Accreditation Council for Clinical Lipidology†	None	• Walgreens* erican art ociation•
Roger Blumenthal	Official Reviewer— Prevention Subcommitt ee	Johns Hopkins Hospital— Kenneth Jay Pollin Professor of Cardiology; Ciccarone Center for the Prevention of Heart Disease— Director	None	None	None	None	None	None	None

Anna Dominiczak	Official Reviewer— AHA	University of Glasgow— Regius Professor of Medicine; Vice-Principal and Head of College of Medical, Veterinary and Life Sciences	None	None	None	None	None	None	None
Carlos M. Ferrario	Official Reviewer— AHA	Wake Forest School of Medicine— Professor, of Physiology and Pharmacology; Hypertension and Vascular Disease Center— Director	None	None	None	None	None	None Am He Ass	Nonen art ociation.
Eugene Yang	Official Reviewer— ACC-BOG	University of Washington School of Medicine— Associate Clinical Professor of Medicine; UW Medicine Eastside Specialty Center— Medical Director	<ul> <li>RubiconMD*</li> <li>Regeneron*</li> </ul>	None	None	<ul> <li>Amgen Inc.*</li> <li>Gilead Sciences, Inc. (DSMB)*</li> </ul>	None	• Third party, CAD, 2016*	None

Robert Jay Amrien	Organization al Reviewer— AAPA	Massachusetts General Hospital— Clinical Physician Assistant, Chelsea Health Center; Bryant University— Physician Assistant Program	None	None	None	None	None	• Defendant , aortic dissection, 2016*	None
Greg Holzman	Organization al Reviewer —ACPM	Montana Department of Public Health and Human Services—State Medical Officer	None	None	None	None	<ul> <li>American Academy of Family Medicine<sup>†</sup></li> <li>American College of Preventive Medicine<sup>†</sup></li> </ul>	None	None ociation
Martha Gulati	Organization al Reviewer— ASPC	University of Arizona College of Medicine— Professor of Medicine; Chief, Division of Cardiology; University Medicine Cardiovascular Institute in Phoenix— Physician Executive Director, Banner	None	None	None	None	• REATA (spouse)*	None	None

Wallace Johnson	Organization al Reviewer— NMA	University of Maryland Medical Center— Assistant Professor of Medicine	None	None	None	Amgen†	None	None	None
Nancy Houston Miller	Organization al Reviewer— PCNA	The Lifecare Company— Associate Director	<ul> <li>Moving Analytics*</li> </ul>	None	None	None	None	None	None
Aldo J. Peixoto	Organization al Reviewer— ASH	Yale University School of Medicine— Professor of Medicine (Nephrology); Associate Chair for Ambulatory Services Operations and Quality, Department of Internal Medicine; Clinical Chief, Section of Nephrology	• Lundbeck Inc.	None	None	Bayer Healthcare     Pharmaceuticals <sup>+</sup>	• Bayer Healthcare Pharmaceuticals	None Am He Ass	
Carlos Rodriguez	Organization al Reviewer— ABC	Wake Forest University— Professor, Epidemiology and Prevention	• Amgen Inc.	None	None	None	None	None	None

Joseph Saseen	Organization al Reviewer— APhA	University of Colorado Anschutz Medical Campus—Vice- Chair, Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences	None	None	None	None	<ul> <li>National Lipid Association<sup>+</sup></li> </ul>	• Defendant , statin use, 2016	None erican art
Mark Supiano	Organization al Reviewer— AGS	University of Utah School of Medicine—D. Keith Barnes, MD, and Dottie Barnes Presidential Endowed Chair in Medicine; Chief, Division of Geriatrics; VA Salt Lake City Geriatric Research— Director, Education, and Clinical Center; University of Utah Center on Aging Executive— Director	None	None	None	None	<ul> <li>American Geriatrics Society<sup>†</sup></li> <li>Division Chief<sup>†</sup></li> <li>McGraw-Hill Medical</li> </ul>	None	None

Sana M. Al- Khatib	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Duke Clinical Research Institute— Professor of Medicine	None	None	None	<ul> <li>AHRQ*</li> <li>FDA*</li> <li>PCORI*</li> <li>VA Health System (DSMB)</li> </ul>	• Elsevier* • NIH, NHLBI	• Third party, implantabl e cardiverte r defibrillato rs, 2017	None
George Bakris	Content Reviewer	University of Chicago Medicine— Professor of Medicine; Director, Hypertensive Diseases Unit	None	None	None	<ul> <li>AbbVie, Inc.</li> <li>Janssen, Bayer, Relypsa</li> </ul>	None	None	None erican art iociation.
Jan Basile	Content Reviewer	Medical University of South Carolina— Professor of Medicine, Seinsheimer Cardiovascular Health Program; Ralph H Johnson VA Medical Center— Internist	None	<ul> <li>Amgen Inc.</li> <li>Arbor</li> <li>Janssen Pharmace uticals, Inc</li> </ul>	None	<ul> <li>Eli Lilly and Company</li> <li>NHLBI</li> </ul>	None	None	None
Joshua A. Beckman	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Vanderbilt University Medical Center: Director, Cardiovascular Fellowship Program,	<ul> <li>AstraZeneca*</li> <li>Merck*</li> <li>SANOFI*</li> </ul>	None	• EMX† • JanaCare†	• Bristol Myers Squibb*	<ul> <li>Vascular Interventional Advances *</li> </ul>	None	• 2015- Defendant; Venous thromboemb olism*

John Bisognano	Content Reviewer	University of Rochester Medical Center— Cardiologist	• CVRx	None	None	● CVRx* ● NIH*	None	None	None
Biykem Bozkurt	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine— Medical Care Line Executive, Cardiology Chief, Gordon Cain Chair, Professor of Medicine, Debakey	None	None	None	• Novartis Corporation	None	None	None erican art ociation.
David Calhoun	Content Reviewer	University of Alabama, Birmingham School of Medicine— Professor, Department of Cardiovascular Disease	<ul> <li>Novartis</li> <li>Valencia Technologies*</li> </ul>	None	None	MEDTRONIC*     ReCor Medical*	None	None	None
Joaquin E. Cigarroa	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Oregon Health and Science University— Clinical Professor of Medicine	None	None	None	• NIH	<ul> <li>ACC/AHA Taskforce on Clinical Practice Guidelines†</li> <li>AHA, Board of Directors, Western Affiliate†</li> <li>American Stroke Association, Cryptogenic Stroke Initiative Advisory Committee†</li> <li>Catheterization and Cardiovascular Intervention†</li> <li>SCAI Quality Interventional Council†</li> </ul>	<ul> <li>Defendant , CAD, 2011†</li> <li>Defendant , sudden death/CAD , 2010†</li> </ul>	None erican art ociation.
------------------------	--	---	------	------	------	---------	---	--	------------------------------------
William Cushman	Content Reviewer	Memphis VA Medical Center—Chief, Preventive Medicine Section; University of Tennessee College of Medicine— Professor, Medicine, Preventive Medicine, and Physiology	None	None	None	• Lilly	<ul> <li>Novartis Corporation†</li> <li>Takeda†</li> </ul>	None	None

Anita Deswal	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine Associate Professor of Medicine,	None	None	None	• NIH *	<ul> <li>bAurora Health Care Inc.</li> <li>American Heart Association<sup>†</sup></li> <li>AHA Committee on Heart Failure and Transplantation – Chair<sup>†</sup></li> <li>Heart Failure Society of America<sup>†</sup></li> </ul>	None	None
Dave Dixon	Content Reviewer— Cardiovascul ar Team	Virginia Commonwealth University School of Pharmacy— Associate Professor	None	None	None	None	None	None He	None ociation.
Ross Feldman	Content Reviewer	Winnipeg Regional Health Authority— Medical Director, Cardiac Sciences Program; University of Manitoba— Professor of Medicine	<ul> <li>GSK*</li> <li>Servier*</li> <li>Valeant Pharmaceutic als International *</li> </ul>	None	None	None	None	None	None

Keith Ferdinand	Content Reviewer	Tulane University School of Medicine— Professor of Clinical Medicine	<ul> <li>Amgen Inc.*</li> <li>Boehringer Ingelheim*</li> <li>Eli Lilly*</li> <li>Sanofi- Aventis*</li> <li>Novartis</li> <li>Quantum Genomics</li> <li>Sanofi- Aventis*</li> </ul>	None	None	None	• Novartis	None	None
Stephan Fihn	Content Reviewer	University of Washington— Professor of Medicine, Heath Services; Division Head, General Internal Medicine; Director, Office of Analytics and Business Intelligence for the Veterans Health Administration; VA Puget Sound Health Care System— General Internist	None	None	None	None	University of Washington	None Am	Nonen art ociation.

Lawrence Fine	Content Reviewer	National Heart, Lung and Blood Institute— Chief, Clinical Applications and Prevention Branch, Division of Prevention and Population Sciences	None	None	None	None	• NIH*	None	None
John Flack	Content Reviewer	Southern Illinois University School of Medicine— Chair and Professor Department of Internal Medicine; Chief, Hypertension Specialty Services	Regeneron*     NuSirt	None	None	<ul> <li>Bayer Healthcare Pharmaceuticals<sup>†</sup></li> <li>GSK<sup>†</sup></li> </ul>	<ul> <li>American Journal of Hypertension*</li> <li>CardioRenal Medicine†</li> <li>International Journal of Hypertension†</li> <li>Southern Illinois University Department of Medicine*</li> </ul>	None Am Ass	None erican art ociation.
Joseph Flynn	Content Reviewer	Seattle Children's Hospital—Chief of the Division of Nephrology; University of Washington School of Medicine— Professor of Pediatrics	• Ultragenyx, Inc. (DSMB)	None	None	None	UpToDate, Springer*	None	None

Federico Gentile	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Centro Cardiologico	None						
Joel Handler	Content Reviewer	Kaiser Permanente— Physician; National Kaiser Permanente Hypertension— Clinical Leader	None	None	None	None	None	None	None erican art ociation.
Hani Jneid	Content Reviewer— ACC/AHA Task Force on Clinical Data Standards	Baylor College of Medicine— Associate Professor of Medicine, MEDVAMC	None						
José A. Joglar	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	UT Southwestern Medical Center— Professor of Internal Medicine; Cardiovascular Clinical Research Center— Director	None						

Amit Khera	Content Reviewer	University of Texas Southwestern Medical Center— Assistant Professor of Medicine	None	None	None	None	None	None	None
Glenn N. Levine	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine— Professor of Medicine; Director, Cardiac Care Unit	DE	None	None	None	None	<ul> <li>Defendant         <ul> <li>Defendant</li> <li>catherizati             <ul></ul></li></ul></li></ul>	None erican art sociation.

Giuseppe Mancia	Content Reviewer	University of Milan- Bicocca— Professor of Medicine; Chairman, Department of Clinical Medicine, Prevention and Applied Biotechnologies	<ul> <li>Boehringer Ingelheim*</li> <li>CVRx</li> <li>Ferrer</li> <li>MEDTRONIC</li> <li>Menarini International*</li> <li>Recordati</li> <li>Servier International*</li> <li>Actavis</li> </ul>	None	None	None	• Novartis*	None	None
Andrew Miller	Content Reviewer— Geriatric Cardiology Section	Cardiovascular Associates— Cardiologist	None	None	None	<ul> <li>Novartis Corporation<sup>†</sup></li> <li>Pfizer Inc<sup>†</sup></li> </ul>	<ul> <li>Bristol-Myers Squibb Company</li> <li>Janssen Pharmaceuticals , Inc.</li> <li>NIH</li> </ul>	None As	a None ociation.
Pamela Morris	Content Reviewer— Prevention Council, Chair	Seinsheimer Cardiovascular Health Program— Director; Women's Heart Care Medical University of South Carolina— Co- Director	<ul> <li>Amgen Inc.</li> <li>AstraZeneca</li> <li>Sanofi Regeneron</li> </ul>	None	None	• Amgen Inc.	None	None	None

Martin Myers	Content Reviewer	Sunnybrook Health Sciences Centre— Affiliate Scientist; University of Toronto— Professor, Cardiology	• Ideal Life Inc*	None	None	None	None	None	None
Rick Nishimura	Content Reviewer	Mayo Clinic College of Medicine— Judd and Mary Morris Leighton Professor of Medicine; Mayo Clinic— Division of Cardiovascular Diseases	None	None	None	None	None	None	None erican art ociation.
Patrick T. O'Gara	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	Harvard Medical School— Professor of Medicine; Brigham and Women's Hospital— Director, Strategic Planning, Cardiovascular Division	None	None	None	None	MEDTRONIC     NIH*	None	None

Suzanne Oparil	Content Reviewer	University of Alabama at Birmingham— Distinguished Professor of Medicine; Professor of Cell, Developmental and Integrative Biology, Division of Cardiology	<ul> <li>Actelion</li> <li>Lundbeck</li> <li>Novo Nordisk, Inc.</li> </ul>	None	None	<ul> <li>AstraZeneca (Duke University)*</li> <li>Bayer Healthcare Pharmaceuticals, Inc.*</li> <li>Novartis*</li> <li>NIH*</li> </ul>	• NIH/NHLBI, • Takeda WHF/ESH/EPH	None	None
Carl Pepine	Content Reviewer— CV Disease in Women Committee	Shands Hospital at University of Florida— Professor of Medicine, Chief of Cardiovascular Medicine	None	None	None	<ul> <li>Capricor, Inc.</li> <li>NIH</li> <li>Cytori Therapeutics, Inc.</li> <li>Sanofi-Aventis</li> <li>InVentive Health Clinical. LLC</li> </ul>	None	None Ass	None
Mahboob Rahman	Content Reviewer	Case Western Reserve University School of Medicine— Professor of Medicine	None	None	None	None	None	None	None
Vankata Ram	Content Reviewer	UT Southwestern Medical Center; Apollo Institute for Blood Pressure Clinics	None	None	None	None	None	None	None

Barbara Riegel	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	University of Pennsylvania School of Nursing- Professor	None	None	None	<ul> <li>Co-Investigator- mentor<sup>†</sup></li> <li>Co-investigator NIH</li> <li>NIH grant</li> <li>PCORI</li> </ul>	• Novartis Corp †	None	None
Edward Roccella	Content Reviewer	National Heart, Lung, and Blood Institute— Coordinator, National High Blood Pressure Education Program	Medical University of South Carolina	None	None	None	<ul> <li>American Society of Hypertension<sup>†</sup></li> <li>Consortium for Southeast Hypertension Control<sup>†</sup></li> <li>Consortium Southeast Hypertension Control</li> <li>Inter American Society of Hypertension<sup>†</sup></li> </ul>	None	None erican art ociation.
Ernesto Schiffrin	Content Reviewer	Jewish General Hospital— Physician-in- Chief, Chief of the Department of Medicine and Director of the Cardiovascular Prevention Centre; McGill University— Professor, Department of Medicine, Division of Experimental Medicine	• Novartis • Servier	• Novartis	None	<ul> <li>Servier*</li> <li>Canadian Institutes for Health Research*</li> </ul>	• CME Medical Grand Rounds	None	None

Raymond Content Townsend Reviewer	University of Pennsylvania School of Medicine— Professor of Medicine; Director, Hypertension Section, Department of Internal Medicine/Renal ; Institute for	• MEDTRONIC	None	None	• NIH*	• ASN • UpToDate	None	None
	Translational Medicine and Therapeutics— Member						Ass	art ociation.
Michael Content Weber Reviewer	SUNY Downstate College of Medicine— Professor of Medicine	<ul> <li>Ablative Solutions*</li> <li>Allergan, Inc</li> <li>Astellas Pharma US*</li> <li>Boston Scientific*</li> <li>Eli Lilly and Company</li> <li>MEDTRONIC*</li> <li>Novartis</li> </ul>	<ul> <li>Menarini*</li> <li>Merck &amp; Co., Inc.*</li> </ul>	None	None	None	None	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq$ 5% of the voting stock or share of the business entity, or ownership of  $\geq$ 5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. Please refer to http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

\*Significant relationship.

<sup>+</sup>No financial benefit.

AHRQ indicates Agency for Healthcare Research and Quality; AAPA, American Academy of Physician Assistants; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; ABC, Association of Black Cardiologists; BOG, Board of Governors; CME, continuing medical education; DSMB, Data and Safety Monitoring Board; FDA, U.S. Food and Drug Administration; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; NMA, National Medical Association; PCNA, Preventive Cardiovascular Nurses Association; PCORI, Patient-Centered Outcomes Research Institute; SCAI, Society for Cardiovascular Angiography and Interventions; SUNY, State University of New York; TFPG, Task Force on Practice Guidelines; and UT, University of Texas.



# Hypertension





## 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Paul K. Whelton, Robert M. Carey, Wilbert S. Aronow, Donald E. Casey, Jr, Karen J. Collins, Cheryl Dennison Himmelfarb, Sondra M. DePalma, Samuel Gidding, Kenneth A. Jamerson, Daniel W. Jones, Eric J. MacLaughlin, Paul Muntner, Bruce Ovbiagele, Sidney C. Smith, Jr, Crystal C. Spencer, Randall S. Stafford, Sandra J. Taler, Randal J. Thomas, Kim A. Williams, Sr, Jeff D. Williamson and Jackson T. Wright, Jr

*Hypertension.* published online November 13, 2017;

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2017 American Heart Association, Inc. All rights reserved. Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://hyper.ahajournals.org/content/early/2017/11/10/HYP.0000000000000065.citation

## Data Supplement (unedited) at:

http://hyper.ahajournals.org/content/suppl/2017/11/13/HYP.00000000000000065.DC1 http://hyper.ahajournals.org/content/suppl/2017/11/13/HYP.0000000000000065.DC2

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at: http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Hypertension* is online at: http://hyper.ahajournals.org//subscriptions/

Author Relationships With Industry and Other Entities (Comprehensive)—2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (October 2017)

Committee Member	Employment	Consultant	Sneakers Burgan	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Paul K. Whelton ( <i>Chair</i> )	Tulane University School of Hygiene and Tropical Medicine—Show Chwan Professor of Global Public Health	None	None	None	• NIH–SPRINT trial† (PI)	None	None	None
Robert M. Carey (Vice Chair)	University of Virginia—Dean Emeritus and University Professor, Department of Medicine	None	None	None	• NIH†	None	None	None
Wilbert S. Aronow	Westchester Medical Center and New York Medical College—Professor of Medicine	None	None	None	None	None	None	None
Donald E. Casey, Jr	Thomas Jefferson College of Population Health—Adjunct Faculty; Alvarez & Marsal Ipo4health— Principal and Founder	None	None	None	None	None	None	None
Karen J. Collins	Collins Collaboration— President	None	None	None	None	North Carolina A&T State University Alumni Association‡	None	None

Cheryl Dennison Himmelfarb	John Hopkins University— Professor of Nursing and Medicine, Institute for Clinical and Translational Research	MedThink Communicatio ns	None	None	<ul> <li>Helene Fuld Health Trust†</li> <li>NIH†</li> </ul>	• Preventive Cardiovascular Nurses Association‡	None	None
Sondra M. DePalma	PinnacleHealth CardioVascular Institute—Physician Assistant; American Academy of PAs— Director, Regulatory and Professional Practice	• American Society of Hypertension	None	None	None	• Accreditation Council for Clinical Lipidology‡	None	None
Samuel Gidding	Alfred I. Dupont Hospital for Children—Chief, Division of Pediatric Cardiology, Nemours Cardiac Center	<ul> <li>Familial Hypercholester olemia Foundation<sup>‡</sup></li> <li>Regenxbio</li> </ul>	None	None	<ul> <li>Familial Hypercholesterolemia Foundation<sup>‡</sup></li> <li>NIH<sup>†</sup></li> </ul>	• Cardiology Division Head‡	None	None
David C. Goff, Jr*	Colorado School of Public Health— Professor and Dean, Department of Epidemiology	None	None	None	None	None	None	None
Kenneth A. Jamerson	University of Michigan Health System—Professor of Internal Medicine and Frederick G.L. Huetwell Collegiate Professor of Cardiovascular Medicine	• American Society of Hypertension	None	None	• NIH/NIDDK/NHLBI†	<ul> <li>American Society of Hypertension‡</li> <li>International Society of Hypertension In Blacks‡</li> <li>Bayer Healthcare Pharmaceuticals</li> </ul>	None	None

Daniel W. Jones	University of Mississippi Medical Center— Professor of Medicine and Physiology; Metabolic Diseases and Nutrition— University Sanderson Chair in Obesity Mississippi Center for Obesity Research— Director, Clinical and Population Science	None	None	None	None	None	None	None
Eric J. MacLaughlin	Texas Tech University Health Sciences Center— Professor and Chair, Department of Pharmacy Practice, School of Pharmacy	• American Society of Hypertension	None	None	None	<ul> <li>AHA‡</li> <li>American College of Clinical Pharmacy‡</li> <li>American Pharmacists Association‡</li> <li>Texas Tech University Health Sciences Center†</li> <li>NIH</li> </ul>	None	None
Paul Muntner	University of Alabama at Birmingham— Professor, Department of Epidemiology	<ul> <li>Amgen Inc.</li> <li>National Center for Health Statistics†</li> </ul>	None	None	<ul> <li>AHA†</li> <li>Amgen Inc.†</li> <li>NIH†</li> </ul>	None	None	None
Bruce Ovbiagele	Medical University of South Carolina— Pihl Professor and Chairman of Neurology	None	None	None	None	None	None	None
Sidney C. Smith, Jr	University of North Carolina at Chapel Hill—Professor of Medicine; Center for Cardiovascular Science and Medicine—Director	None	None	None	None	None	None	None

Crystal C. Spencer	Spencer Law, PA— Attorney at Law	None	None	None	None	<ul> <li>AHA‡</li> <li>Dermatologic Surgery Associates†</li> <li>Hospital Corporation of America†</li> </ul>	None	None
Randall S. Stafford	Stanford Prevention Research Center— Professor of Medicine; Program on Prevention Outcomes— Director	None	None	None	None	None	None	None
Sandra J. Taler	Mayo Clinic— Professor of Medicine, College of Medicine	None	None	None	None	None	None	<ul> <li>American Society of Hypertension Clinical Specialist Program†</li> <li>American Society of Nephrology†</li> </ul>
Randal J. Thomas	Mayo Clinic— Medical Director, Cardiac Rehabilitation Program	None	None	None	None	None	None	None
Kim A. Williams, Sr	Rush University Medical Center— James B. Herrick Professor; Division of Cardiology— Chief	None	None	None	None	None	None	None
Jeff D. Williamson	Wake Forest Baptist Medical Center— Professor of Internal Medicine; Section on Gerontology and Geriatric Medicine—Chief	None	None	None	None	None	None	None

Jackson T. Wright, Jr	Case Western	None	None	None	None	Northeast Ohio	None	None
	Reserve					Neighborhood		
	University-					Health Centers‡		
	Professor of							
	Medicine; William							
	T. Dahms MD							
	Clinical Research							
	Unit—Program							
	Director; University							
	Hospitals Case							
	Medical Center-							
	Director, Clinical							
	Hypertension							
	Program							

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq$ 5% of the voting stock or share of the business entity, or ownership of  $\geq$ \$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

We gratefully acknowledge the contributions of Dr. Lawrence Appel, who served as a member of the Writing Committee from November 2014 to September 2015.

\*Dr. David C. Goff resigned from the writing committee in December 2016 due to a change in employment before the recommendations were balloted. The writing committee thanks him for his contributions, which were extremely beneficial to the development of the draft.

†Significant relationship. ‡No financial benefit.

AAPA indicates American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; NMA, National Medical Association; PCNA, Preventive Cardiovascular Nurses Association; and PI, principal investigator.

# 2017 Hypertension Guideline Data Supplements

(Section numbers correspond to the full-text guideline.)

## **Table of Contents**

Data Supplement 1. Coexistence of Hypertension and Related Chronic Conditions (Section 2.4)	7
Data Supplement 2. Definition of High BP (Section 3.1)	8
Data Supplement 3. Out-of-Office and Self-Monitoring of BP (Section 4.2)	18
Data Supplement 4. White Coat Hypertension (Section 4.4)	21
Data Supplement 5. White Coat Hypertension (Prevalence) (Section 4.4)	23
Data Supplement 6. White Coat Hypertension (Correlation with Clinical Outcomes) (Section 4.4)	25
Data Supplement 7. Renal Artery Stenosis (Section 5.4.3)	27
Data Supplement 8. RCTs Comparing Obstructive Sleep Apnea (Section 5.4.4)	29
Data Supplement 9. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Dietary Fiber Intake) (Section 6.2)	
Data Supplement 10. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Fish Oil) (Section 6.2)	
Data Supplement 11. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Potassium Supplementation to Placebo or Usual Diet) (Section 6.2)	34
Data Supplement 12. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Protein Intake on BP) (Section 6.2)	
Data Supplement 13. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Sodium Reduction to Placebo or Usual Diet) (Section 6.2)	
Data Supplement 14. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Stress Reduction) (Section 6.2)	43
Data Supplement 15. RCTs and Meta-analyses Studying the Effect of Nonpharmacologic Interventions on BP (Dietary Patterns) (Section 6.2)	
Data Supplement 16. RCTs and Meta-analysis RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Alcohol Reduction) (Section 6.2)	51
Data Supplement 17. RCTs and Meta-analysis RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Calcium Supplementation) (Section 6.2)	55
Data Supplement 18. RCTs and Meta-analyses RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Physical Activity) (Section 6.2)	

© 2017 American College of Cardiology Foundation and American Heart Association, Inc.

## 2017 Hypertension Guideline Data Supplements

Data Supplement 19. RCTs and Meta-analysis RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Magnesium Supplementation) (Section 6.2)	59
Data Supplement 20. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Weight Loss) (Section 6.2)	61
Data Supplement 21. RCTs and Systematic Reviews for RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Section 6.2)	64
Data Supplement 22. Observational Studies of CV Target Organ Damage Including LVH (Section 7.2)	66
Data Supplement 23. RCTs on Use of Risk Estimation to Guide Treatment of Hypertension (Section 8.1.2)	67
Data Supplement 24. Follow-Up After Initial BP Evaluation (Section 8.1.3)	81
Data Supplement 25. RCTs for General Principles of Drug Therapy (Combination Therapies that Inhibit the RAAS) (Section 8.1.4)	
Data Supplement 26. BP Goal for Patients with Hypertension (Section 8.1.5)	
Data Supplement 27. Choice of Initial Medication (Section 8.1.6)	92
Data Supplement 28. Follow-Up After Initiating Antihypertensive Drug Therapy (Section 8.3.1)	95
Data Supplement 29. Monitoring Strategies to Improve Control of BP in Patients on Drug Therapy for High BP (Section 8.3.2)	97
Data Supplement 30. RCTs Comparing Stable Ischemic Heart Disease (Section 9.1)	
Data Supplement 31. Meta-analyses of ischemic heart disease (Section 9.1)	110
Data Supplement 32. Nonrandomized Trials, Observational Studies, and/or Registries of Ischemic Heart Disease (Section 9.1)	111
Data Supplement 33. RCTs Comparing Heart Failure (Section 9.2)	112
Data Supplement 34. RCTs Comparing HFrEF (Section 9.2.1)	113
Data Supplement 35. RCTs Comparing HFpEF (Section 9.2.2)	119
Data Supplement 36. Nonrandomized Trials, Observational Studies, and/or Registries of HFpEF (Section 9.2.2)	122
Data Supplement 37. RCTs Comparing CKD (Section 9.3)	123
Data Supplement 38. Nonrandomized Trials, Observational Studies, and/or Registries of CKD (Section 9.3)	133
Data Supplement 39. RCTs Comparing Hypertension after Renal Transplantation (Section 9.3.1)	137
Data Supplement 40. Nonrandomized Trials, Observational Studies, and/or Registries for Hypertension after Renal Transplantation (Section 9.3.1)	140
Data Supplement 41. RCTs Comparing Acute Intracerebral Hemorrhage Outcomes (Section 9.4.1)	143
Data Supplement 42. RCTs Comparing Acute Ischemic Stroke Outcomes (Section 9.4.2)	147
Data Supplement 43. RCTs Comparing Secondary Stroke Prevention (Section 9.4.3)	
Data Supplement 44. Nonrandomized Trials, Observational Studies, and/or Registries of Secondary Stroke Prevention (Section 9.4.3)	

Data Supplement 45. RCTs and Meta-analysis Comparing PAD (Section 9.5)	168
Data Supplement 46. RCTs and Meta-analyses Comparing BP Targets in DM (Section 9.6)	174
Data Supplement 47. Nonrandomized Trials, Observational Studies, and/or Registries in DM (Section 9.6)	183
Data Supplement 48. Atrial Fibrillation (Section 9.8)	190
Data Supplement 49. Valvular Heart Disease (Section 9.9)	191
Data Supplement 50. RCTs and Meta-analysis Comparing Valvular Heart Disease (Section 9.9)	194
Data Supplement 51. RCTs Comparing Race/Ethnicity (Section 10.1)	197
Data Supplement 52. RCTs Comparing Women With Hypertension (Section 10.2.1)	201
Data Supplement 53. RCTs Comparing Pregnancy (Section 10.2.2)	203
Data Supplement 54. RCT for Older Persons (Section 10.3.1)	204
Data Supplement 55. RCTs Comparing Hypertensive Crises and Emergencies (Section 11.2)	204
Data Supplement 56. RCTs Assessing Impact of Hypertension Therapy on Dementia Incidence (Section 11.3)	207
Data Supplement 57. RCTs for Patients Undergoing Surgical Procedures (Section 11.5)	210
Data Supplement 58. Observational and Nonrandomized Studies for Patients Undergoing Surgical Procedures (Section 11.5)	211
Data Supplement 59. RCTs of Adherence and Compliance with Fixed Dose Combinations Regimens (Section 12.1.1)	213
Data Supplement 60. Nonrandomized Trials, Observational Studies, and/or Registries of Antihypertensive Medication Adherence Strategies (Section 12.1.1)	214
Data Supplement 61. RCTs and Meta-analysis on Strategies to Promote Lifestyle Modification (Section 12.1.2)	220
Data Supplement 62. RCTs, Meta-analyses, and Systematic Reviews on the Effect of Structured, Team-based Care Interventions for Hypertension Control (Section 12.2)	221
Data Supplement 63. Electronic Health Records and Patient Registries (Section 12.3.1)	227
Data Supplement 64. RCTs, Meta-analyses, and Systematic Reviews on the Effect of Telehealth Interventions to Improve Hypertension Control (Section 12.3.2)	232
Data Supplement 65. RCTs and Observational Studies that Report on the Effect of Performance Measures and on Hypertension Control (Section 12.4.1)	236
Data Supplement 66. RCTs, Meta-analyses, and Systematic Reviews on Quality Improvement Strategies on Hypertension Treatment Outcomes (Section 12.4.2)	238
Data Supplement 67. Nonrandomized Trials, Observational Studies, and/or Registries of Effect of Quality Improvement Strategies on Hypertension Treatment Outcomes (Se 12.4.2)	ection 244
Data Supplement 68. RCTs Comparing Financial Incentives (Section 12.5)	245
Additional Data Supplement Tables and Figures	252

Data Supplement A. Treatment of HFrEF Stages C and D	252
Data Supplement B. Medication Adherence Assessment Scales	253
Data Supplement C. Categories Defining Normal BP, Elevated BP, and Stages 1, 2, and 3 Hypertension	253
Data Supplement D. Fixed-Dose Combination Antihypertensive Drugs	255
Data Supplement E. Examples of Hypertension Quality Improvement Strategies	256
Data Supplement F. Barriers and Improvement Strategies in Antihypertensive Medication Adherence (350-354)	257
Data Supplement G. Examples of Strategies to Promote Lifestyle Modification Interventions in Patients With Hypertension (319,320,356-362)	258
Data Supplement H. Responsibilities and Roles of the Hypertension Team	259
Data Supplement I. Examples of Telehealth Strategies and Technologies to Promote Effective Hypertension Management	260
Data Supplement J. Publicly Available Performance Measures Used to Assess Hypertension Care Quality Services (364-368)	261
Data Supplement K. Online Quality Improvement Resources for Treatment and Control of Hypertension	263
References	264

## Search Terms:

An extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted between February and August 2015. Key search words included but were not limited to the following: *adherence; aerobic; alcohol intake; ambulatory care; antihypertensive: agents, drug, medication, therapy; beta adrenergic blockers; blood pressure: arterial, control, determination, devises, goal, high, improve, measurement, monitoring, ambulatory; calcium channel blockers; diet; diuretic agent; drug therapy; heart failure: diastolic, systolic; hypertension: white coat, masked, ambulatory, isolated ambulatory, isolated clinic, diagnosis, reverse white coat, prevention, therapy, treatment, control; intervention; lifestyle: measures, modification; office visits; patient outcome; performance measures; physical activity; potassium intake; protein intake; renin inhibitor; risk reduction: behavior, counseling; screening; sphygmomanometers; spironolactone; therapy; treatment: adherence, compliance, efficacy, outcome, protocol, regimen; weight. Additional relevant studies published through June 2016, during the guideline writing process, were also considered by the writing committee, and added to the evidence tables when appropriate.* 

### **Abbreviations:**

1°, primary; 2°, secondary; AASK, African American Study of Kidney Disease and Hypertension; ABI, ankle-brachial index; ABCD, Appropriate Blood Pressure Control in Diabetes; ABPM, ambulatory blood pressure monitoring; ACCESS, Acute Candesartan Cilexetil Evaluation in Stroke Survivors; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease; AF, atrial fibrillation; AFL, atrial flutter; AHR, adjusted hazard ratio; AIPRD, Angiotensin-Converting Enzyme Inhibition in Progressive Renal Disease; ALLHAT, Antihypertensive Lipid Lowering Treatment to Prevent Heart Attack Trial; AMI, acute myocardial infarction; ARB, angiotensin-receptor blocker; ARIC, Atherosclerosis Risk in Communities; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BB, beta blocker; BMI, body mass index; BP, blood pressure; BPLTTC, Blood Pressure Lowering Treatment Trialists' Collaboration; bpm, beats per minute; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAD, coronary artery disease; CATIS, China Antihypertensive Trial in Acute Ischemic Stroke; CCB, calcium-channel blocker; CCU, coronary care unit; CHD, coronary heart disease; CHF, congestive heart failure; CHHIPS, Controlling Hypertension and Hypotension Immediately Post-Stroke; CI, confidence interval; CKD, chronic kidney disease; COMFORT, Combination Pill of Losartan Potassium and Hydrochlorothiazide for Improvement of Mediation Compliance Trial; COSSACS, the Continue or Stop Post-Stroke Antihypertensives Collaborative Study; CPAP, continuous positive airway pressure; Cr, creatinine; CrCL, creatinine clearance; CRP, c-reactive protein; CR/XL, metoprolol controlled release/extended release; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; DM, diabetes mellitus; DM-1, diabetes mellitus type-1; DM-2, diabetes mellitus type-2; ECG, electrocardiogram; ED, emergency department; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; FC, functional class; FDC, fixed dose combination; FEVER, Felodipine EVent Reduction; GITS, gastrointestinal therapeutic system; GFR, glomerular filtration rate; HBPM, home blood pressure monitoring; HCTZ, hydrochlorthiazide; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HEDIS, Healthcare Effectiveness Data and Information Set; HF, heart failure; HFrEF, reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HIV, human immunodeficiency virus; HR, hazard ratio; HTN, hypertension; ICD, implantable cardioverter-defibrillator; ICH, intracerebral hemorrhage; IDACO, International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome; IHD, ischemic heart disease; IMT, intimal media thickness; INDANA, Individual Data Analysis of Antihypertensive drug intervention trials; INTERACT2, the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; INVEST, International Verapamil-Trandolapril Study; INWEST, the Intravenous Nimodipine West European Stroke Trial; IQI, interquartile interval; IQR, interquartile range; IRR, incident rate ratio; ISDN, isosorbide dinitrate; IV, intravenous; JNC-7, 7th Report of the Joint National Committee; KPNC, Kaiser Permanente Northern California; LDL, low-density lipoprotein; LGSAS, low-gradient severe aortic stenosis; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI; left ventricular mass index; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; MAP, mean arterial pressure; MD, mean difference; MDPIT, Multicenter Dilitiazem Postinfarction Research Group; MDRD, Modification of Diet in Renal Disease; MERIT, Metoprolol CR/XL Randomised Intervention Trial; MESA, Multi-Ethnic Study of Atherosclerosis; MH, masked hypertension; MI, myocardial infarction; MOSES, The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention; MPR, medication possession ratio; MRFIT, Multiple Risk Factor Intervention Trial; MRI, magnetic resonance imaging; N/A, not available; NCQA, National Committee for Quality Assurance; NEMESIS, North East Melbourne Stroke Incidence Study; NHANES, National Health and Nutrition Examination Surveys; NIH, National Institute of Health; NNT, number needed to treat; NR, not relative;

© 2017 American College of Cardiology Foundation and American Heart Association, Inc.

## 2017 Hypertension Guideline Data Supplements

NS, nonsignificant; NSAID, nonsteroidal anti-inflammatory drug; NUTRICODE, Nutrition and Chronic Diseases Expert Group; NYHA, New York Heart Association; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; OR, odds ratio; OSA, obstructive sleep apnea; P4P, pay for performance; PA, pulmonary artery; PAD, peripheral artery disease; PAMELA, Pressione Arteriose Monitorate E Loro Associazioni; PCP, primary care provider; periop, perioperative; PREDIMED, Prevention with a Mediterranean Diet; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROBE, Prospective, randomized, open, blinded endpoint; PROGRESS, The perindopril protection against recurrent stroke study; PRONTO, Prospective Optical Coherence Tomography Imaging of Patients with endovascular Age-Related Macular Degeneration Treated with Intraocular Ranibizumab; pt, patient; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; QI, quality improvement; RAAS, renin angiotensin aldosterone system; RCT, randomized controlled trial; REIN-2, Blood Pressure Control for Renoprotection in Patients with Non-diabetic Renal Disease; RH, relative hazard; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; RR, relative risk; Rx, medical prescription; SAE, severe adverse event; SBP, systolic blood pressure; SCOPE-AS, Symptomatic Cardiac Obstruction – Pilot Study of Enalapril in Aortic Stenosis; SD, standard deviation; SE, stress echocardiography; SH, sustained hypertension; SHEP, Summer Health Enrichment; SITS-ISTR, Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register; SKIPOGH, Swiss Kidney Project on Genes in Hypertension; SPC, single pill combination; SPRINT, Systolic Blood Pressure Intervention Trial; Syst-Eur, Systolic Hypertension in Europe; t-PA, tissue plasminogen activator; TIA, transient ischemic attack; TOHP, Trials of Hypertension Prevention; TOMHS, Treatment of Mild Hypertension Study; TONE, Trial of Nonpharmacologic Intervention in the Elderly; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With Aldosterone Antagonist; TR, target range; UA, unstable angina; U.K., United Kingdom; UKPDS, United Kingdom Prospective Diabetes Study; U.S., United States; VA, Veterans Affairs; VA Coop; Veterans Administration Cooperative Study Group on Antihypertensive Agents; VA NEPHRON-D, Veterans Affairs Nephropathy in Diabetes; VALIANT, Valsartan in Acute Myocardial Infarction Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; WCH, white coat hypertension; and WPW; Wolff-Parkinson-White syndrome.

Data Supploment 1	Convictoric of Uvportori	cion and Dolatod Chi	onic Conditions (	(Saction 2 1)
Data Supplement I.		SIULI ALIU REIALEU ULII		SECTION 2.41

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR RR; & 95% CI)	Summary/Conclusion Comment(s)
Wilson PW, et al., 1999 (1) <u>10335688</u>	Study type: Nonrandomized Size: 2,406 men, 2,569 women (1,759 men, 1,818 women with follow-up)	Inclusion criteria: Men and women 18–74 y and free of CHD at baseline, from the Framingham Offspring Study Exclusion criteria: N/A	<u>1° endpoint</u> : Total CHD (first occurrence of angina, UA, MI, and coronary death), Hard CHD (first MI and coronary death) <u>Results:</u> Presence of ≥3 risk factors was associated with a 2.39 times greater risk of CHD in men (95% CI: 1.56–3.36; p<0.001) and a 5.90 increased risk of CHD in women (95% CI: 2.54–13.73; p<0.001)	• CVD risk factors infrequently occur in isolation (only 28%–30% of the time); presence of ≥3 risk factors occurred 17% of the time in both men and women; presence of ≥3 risk factors associated with high risk of CHD and coronary death (attributable risk of 20% in men and 48% in women)
Berry JD, et al., 2012 (2) <u>22276822</u>	Study type: Nonrandomized Size: 257,384 black and white men and women, including 67,890 pts (from 17 meta-analysis) and 189,494 pts (from MRFIT)	Inclusion criteria: Meta- analysis of 18 cohort studies Exclusion criteria: N/A	1° endpoint: Fatal CHD, nonfatal MI, fatal or nonfatal stroke <u>Results:</u> Participants with optimal RF profile (total cholesterol <180 mg/dL, untreated BP <120 mm Hg systolic, and <80 mm Hg diastolic, nondiabetic, nonsmoker) compared to participants with ≥2 risk factors had lower risk of CVD through the age of 80 y (4.7% vs. 29.6% for men, 6.4% vs. 20.5% for women), lower lifetime risk of fatal heart disease and nonfatal MI (3.6% vs. 37.5% for men, <1% vs. 18.3% for women), and lower lifetime risk of fatal or nonfatal stroke (2.3% vs. 8.3% for men, 5.3% vs. 10.7% for women)	Increased burden of 80 risk factors associated with higher lifetime risk of CVD

Study Acronym; Author; Vear Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and Cl; & 95% Cl)	Summary/Conclusion Comment(s)
Lewington S, et al., 2002 12493255	Study type: Meta-analysis of 61 observational cohort studies	Inclusion criteria: Men and women with no history of previous CVD and record of key study variables. Exclusion criteria: Prior CVD	1° endpoint: Cause-specific mortality         Results: 958,074 persons followed for a mean of 12 y to death (12.7 million person-y at risk.         Number of deaths attributed to:         -Stroke: 11960         -IHD: 34,283         -Other vascular:10092         -Non-vascular: 60797         Above a SBP ≥115 mm Hg and DBP ≥75 mm Hg, there was a progressive rise in vascular death with progressively high BP with no evidence of a J-curve (approximately doubling of stroke and IHD mortality for a 20 mm Hg higher level of SBP or 10 mm Hg higher level of DBP, in those 40–69 y). With progressively higher age, the BP-related proportional risk of vascular mortality was somewhat reduced but the corresponding absolute risk was much higher	<ul> <li>In adults aged 40–89 y, usual BP is strongly related to vascular (and overall) mortality, without evidence of a threshold down to at least an SBP/DBP of 115/75 mm Hg.</li> </ul>
Rapsomaniki E, et al., 2014 <u>24881994</u>	Study type: Observational cohort study Size: 1.25 million patients, in 225 primary care practices in the UK, followed for a median of 5.2 y using electronic medical records.	Inclusion criteria: Men and women ≥30 y, with no previous diagnosis of CVD, who had been registered at their practices for ≥1 year. Exclusion criteria: N/A	1° endpoint: 12 acute and chronic CVD outcomes <u>Results:</u> 83,098 initial CVD events recorded. Within each of 3 age groups (30–59, 60–79, and ≥80 y), the lowest risk for CVD was in those with a SBP 90–114 mm Hg and DBP 60–74 mm Hg. There was a direct relationship between level of BP and most CVD outcomes, with no evidence of J-curve, with the strongest relationship for SBP and stroke and weakest for abdominal aneurysm.	Despite modern treatments, the lifetime burden of BP- related CVD was substantial.
Wilson PW, et al., 1999 (1) <u>10335688</u>	Study type: Nonrandomized	Inclusion criteria: Men and women 18– 74 y and free of CHD at baseline, from the Framingham Offspring Study	<u>1° endpoint</u> : Total CHD (first occurrence of angina, UA, MI, and coronary death), Hard CHD (first MI and coronary death)	• CVD risk factors infrequently occur in isolation (only 28%–30% of the time)

Data Supplement 2. Definition of High BP (Section 3.1)
--

	Size: 2,406 men, 2,569 women (1,759 men, 1,818 women with follow-up)	Exclusion criteria: N/A	Results: Presence of ≥3 risk factors was associated with a 2.39 times greater risk of CHD in men (95% CI: 1.56–3.36; p<0.001) and a 5.90 increased risk of CHD in women (95% CI: 2.54– 13.73; p<0.001)	<ul> <li>Presence of ≥3 risk factors occurred 17% of the time in both men and women</li> <li>Presence of ≥3 risk factors associated with high risk of CHD and coronary death (attributable risk of 20% in men and 48% in women)</li> </ul>
Guo X, et al., 2013 (3) <u>23634212</u>	Study type: Meta- analysis of nonrandomized studies Size: 870,678 pts	Inclusion criteria: Studies reporting adjusted risk for CVD or mortality with pre- HTN Exclusion criteria: N/A	1° endpoint           CVD and all-cause mortality <u>Results:</u> SBP/DBP 120–129/80–84 mm Hg           compared to <120/80 mm Hg:	<ul> <li>SBP/DBP of 120–129/80– 84 mm Hg associated with increased risk for all-cause or CVD mortality.</li> <li>SBP/DBP of 130–139/85– 89 mm Hg associated with an increased risk for CVD mortality.</li> </ul>
Guo X, et al., 2013 (4) <u>24234576</u>	<u>Study type</u> : Meta- analysis of nonrandomized studies <u>Size</u> : 1,010,858 pts	Inclusion criteria: Studies reporting adjusted risk for fatal and nonfatal stroke, CHD, MI and total CVD events with pre- HTN, 120–129/80–84 mm Hg or 130– 139/85–89 mm Hg Exclusion criteria: N/A	1° endpoint: Fatal and nonfatal stroke, CHD, MI and total CVD events <u>Results:</u> SBP/DBP 120-129/80-84 mm Hg compared to <120/80 mm Hg:	• Compared to pts with SBP/DBP<120/80 mm Hg, the RR for CVD, MI and stroke were larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs. SBP/DBP of 120– 129/80–84 mm Hg.
Huang Y, et al., 2013 (5) <u>23915102</u>	Study type: Meta- analysis of nonrandomized studies Size: 468,561 pts from 18 prospective cohort studies	Inclusion criteria: Studies reporting risk for CVD, CHD and stroke, with 120– 139/80–89 mm Hg, 120–129/80–84 mm Hg or130–139/85–89 mm Hg Adults ≥18 y BP evaluated at baseline	<u>1° endpoint</u> : CVD, CHD, and stroke <u>Results:</u> Comparing SBP/DBP 120–129/80–84           mm Hg to <120/80 mm Hg:	• Compared to pts with SBP/DBP <120/80 mm Hg, the RR for CVD was larger for pts with SBP/DBP of 130– 139/85–89 mm Hg vs.

		≥2 y follow-up for outcomes	Comparing SBP/DBP RR: 130–139/85–89 mm Hg	SBP/DBP of 120-129/80-84
		Results reported with adjustment	to <120/80 mm Hg:	mm Hg
			• CVD RR: 1.63; 95% CI: 1.47–1.80;	
		Exclusion criteria: N/A	p value comparing these risk ratios=0.02	
			• The RR comparing CHD and stroke by levels of	
			SBP/DBP: 130–139/85–89 mm Hg and SBP/DBP	
			of 120–129/80–84 mm Hg vs. <120/80 mm Hg	
			were not reported.	
Huang Y, et al.,	Study type: Meta-	Inclusion criteria: Studies reporting	<u>1° endpoint</u> : ESRD	Compared to pts with
2014 (6)	analysis of	adjusted risk for ESRD with 120–139/80–	<b>D</b>	SBP/DBP <120/80 mm Hg,
24074825	nonrandomized studies	89 MM Hg, 120–129/80–84 MM Hg	Results: Comparing SBP/DBP 120-129/80-84	the RR for ESRD was larger
	<b>Sizo:</b> 1,002,702 ptc word	01130-139/03-09 IIIII Fly Adulte >18 y PD evaluated at baseline > 1		120/05 00 mm Liquic
	derived from 6 prospective	x follow-up for ESRD	• ESRD KR: 1.44; 95% CI: 1.19–1.74	SRD/DRD of 120, 120/20, 24
	cohort studies	Results reported with adjustment	<120/80 mm Ha:	mm Ha
		results reported with adjustment	• ESDD DD: 2.02: 05% CI: 1.70, 2.40:	liining
		Exclusion criteria: 1) enrollment	<ul> <li>ESRD RR. 2.02, 95% CI. 1.70-2.40,</li> <li>n value comparing these risk ratios 0.01</li> </ul>	
		depended on having a condition or risk	• p value companing mese risk ratios=0.01	
		factor, 2) the study reported only age- and		
		sex-adjusted RRs,		
		and 3) data were derived from the same		
		cohort or from a 2° analysis		
Huang Y, et al.,	Study type: Meta-	Inclusion criteria: Studies reporting	<u>1° endpoint</u> : Stroke	<ul> <li>Compared to pts with</li> </ul>
2013 (7)	analysis of	adjusted risk for stroke with 120–139/80–		SBP/DBP <120/80 mm Hg,
24623843	nonrandomized studies	89 mm Hg, 120–129/80-84 mm Hg or130–	Results: Comparing SBP/DBP 120–129/80–84	the RR for stroke was larger
	<b>C</b> ' 7(0.000 mls (	139/85–89 mm Hg	mm Hg to <120/80 mm Hg:	for pts with SBP/DBP of 130–
	<u>SIZE</u> : 762,393 pts from 19	• Adults ≥18 y	• Stroke: RR: 1.44; 95% CI: 1.27–1.63	139/85–89 mm Hg vs.
	prospective conort studies	BP evaluated at baseline	Comparing SBP/DBP 130–139/85–89 mm Hg to	SBP/DBP of 120–129/80–84
		• ≥1 y tollow-up for stroke	<120/80 mm Hg:	тт нд
		<ul> <li>Results reported with adjustment</li> </ul>	• Stroke: RR: 1.95; 95% CI: 1.73–2.21	
		Evolution esiteria	<ul> <li>p value comparing these risk ratios ≤0.001</li> </ul>	
		Exclusion criteria:		
		• Enrollment depended on having a		
		other baseline chronic diseases)		
		• The DD was upadjusted or only adjusted		
		for age and sex		
		Data were derived from the same cohort		
		• Data were derived from the same collor		
		or meta-analysis of other conort studies.		

Huang Y, et al.,	Study type: Meta-	Inclusion criteria:	1° endpoint: All-cause and CVD mortality	Compared to pts with
2014 (8)	analysis of	Studies reporting adjusted risk for all-		SBP/DBP $< 120/80$ mm Hg
24439976	nonrandomized studies	cause/CVD mortality with 120–139/80–89	Results: Comparing SBP/DBP 120–129/80-84	the RR for CVD mortality was
		mm Ha. 120-129/80–84 mm Ha or 130–	mm Ha to $<120/80$ mm Ha:	larger for pts with SBP/DBP of
	Size: 1,129,098 pts from	139/85–89 mm Ha	• All-cause mortality RR: 0.96: 95% CI: 0.85–1.08	130–139/85-89 mm Ha vs.
	20 prospective cohort	• Adults ≥18 v	• CVD mortality RR: 1.08: 95% CI: 0.98–1.18	SBP/DBP of 120–129/80-84
	studies	BP evaluated at baseline		mm Hg.
		• $\geq 2$ v follow-up for mortality	Comparing SBP/DBP 130-139/85-89 mm Hg to	• The RR for not all-cause
		Results reported with adjustment	<120/80 mm Hg:	mortality was similar for these
			• All-cause mortality RR: 1.03; 95% CI: 0.95–1.12	2 BP levels.
		Exclusion criteria:	• CVD mortality RR: 1.28; 95% CI: 1.16–1.41	
		Enrollment depended on having a	• p value comparing these risk ratios:	
		specific risk factor condition (e.g., DM or	• All-cause mortality p=0.33	
		other baseline chronic diseases)	• CVD mortality p=0.01	
		• The RR was unadjusted or only adjusted		
		for age and sex		
		• Data were derived from the same cohort		
		or meta-analysis of other cohort studies.		
Huang Y, et al.,	Study type: Meta-	Inclusion criteria:	1° endpoint: CHD	<ul> <li>Compared to pts with</li> </ul>
2015 (9)	analysis of	<ul> <li>Studies reporting adjusted risk for CHD</li> </ul>		SBP/DBP<120/80 mm Hg, the
<u>25699996</u>	nonrandomized studies	with 120–139/80–89 mm Hg, 120–129/80–	Results: Comparing SBP/DBP 120–129/80–84	RR for CHD was larger for pts
		84 mm Hg or130–139/85–89 mm Hg	mm Hg to <120/80 mm Hg:	with SBP/DBP of 130-
	Size: 591,664 pts from 17	<ul> <li>Adults ≥18 y</li> </ul>	• CHD RR: 1.27; 95% CI: 1.07–1.50	139/85–89 mm Hg vs.
	prospective cohort studies	<ul> <li>BP evaluated at baseline</li> </ul>	Comparing SBP/DBP 130-139/85-89 mm Hg to	SBP/DBP of 120-129/80-84
		<ul> <li>Results reported with adjustment</li> </ul>	<120/80 mm Hg:	mm Hg.
			• CHD RR: 1.58; 95% CI: 1.24–2.02	<ul> <li>However, this difference</li> </ul>
		Exclusion criteria:	<ul> <li>p value comparing these RR: 0.15</li> </ul>	was not statistically
		<ul> <li>Enrollment depended on having a</li> </ul>		significant.
		specific risk factor condition (e.g., DM or		
		other baseline chronic diseases)		
		• The RR was unadjusted or only adjusted		
		for age and sex		
		• Data were derived from the same cohort		
		or meta-analysis of other cohort studies.		
Lee M, et al., 2011	Study type: Meta-	Inclusion criteria:	1° endpoint: Incident stroke	<ul> <li>Compared to pts with</li> </ul>
(10)	analysis of	• Studies reporting adjusted risk for stroke		SBP/DBP <120/80 mm Hg,
<u>21956722</u>	nonrandomized studies	with 120–139/80–89 mm Hg, 120–129/80–	Results: Comparing SBP/DBP 120–129/80–84	the RR for stroke was larger
		84 mm Hg or130–139/85–89 mm Hg	mm Hg to <120/80 mm Hg:	for pts with SBP/DBP of 130–
		<ul> <li>Adults ≥18 y</li> </ul>	• Stroke RR: 1.22; 95% CI: 0.95–1.57	139/85–89 mm Hg vs.

	Size: 518,520 pts from 18 prospective cohort studies	<ul> <li>BP evaluated at baseline</li> <li>Results reported with adjustment</li> <li>Exclusion criteria: <ul> <li>Cross-sectional, case-control or retrospective cohort</li> <li>The RR was unadjusted or only adjusted for age and sex</li> <li>95% CI not reported</li> <li>Data were derived from the same cohort or meta-analysis of other cohort studies</li> <li>Results from trial of antihypertensive medication</li> </ul> </li> </ul>	Comparing SBP/DBP 130–139/85–89 mm Hg to <120/80 mm Hg: • Stroke RR: 1.79; 95% CI: 1.49–2.16	SBP/DBP of 120–129/80–84 mm Hg
Shen L, et al., 2013 (11) <u>23608614</u>	Study type: Meta- analysis of nonrandomized studies Size: 934,106 pts from 18 prospective cohort studies	Inclusion criteria: • Studies reporting adjusted risk for CHD with 120–139/80–89 mm Hg, 120–129/80– 84 mm Hg or 130–139/85–89 mm Hg • BP evaluated at baseline • 95% CI was reported Exclusion criteria: N/A	<u>1° endpoint</u> : CHD <u>Results:</u> Comparing SBP/DBP 120–129/80–84 mm Hg to <120/80 mm Hg: • CHD RR: 1.16; 95% CI: 0.96–1.42 Comparing SBP/DBP 130–139/85–89 mm Hg to <120/80 mm Hg: • CHD RR: 1.53; 95% CI: 1.19–1.97)	• Compared to pts with SBP/DBP <120/80 mm Hg, the RR for CHD was larger for pts with SBP/DBP of 130– 139/85–89 mm Hg vs. SBP/DBP of 120–129/80–84 mm Hg
Wang S, et al., 2013 (12) <u>23932039</u>	Study type: Meta- analysis of nonrandomized studies Size: 396,200 pts from 13 prospective cohort studies	Inclusion criteria: • Prospective cohort studies reporting risk for outcomes with 120–139/80–89 mm Hg • Pts free of CVD at baseline, • Follow-up ≥5 y • Adjusted results reported • 95% CI was reported Exclusion criteria: N/A	<u>1° endpoint</u> : CVD, CVD mortality, all-cause mortality <u>Results:</u> Comparing SBP/DBP 120-129/80-84 mm Hg to <120/80 mm Hg:	<ul> <li>Compared to pts with SBP/DBP&lt;120/80 mm Hg, RR for CVD and CVD mortality were larger for pts with SBP/DBP of 130–139/85–89 mm Hg vs. SBP/DBP of 120– 129/80–84 mm Hg.</li> <li>No difference in all-cause mortality was present across BP levels.</li> </ul>
Cushman WC, et al., 2002 (13) <u>12461301</u>	Study type: 2° analysis of an RCT Size: 33,357 pts in the ALLHAT	Inclusion criteria: Men and women ≥55 y with HTN and 1 additional CHD risk factor Exclusion criteria: Pts randomized to doxazosin.	<u>1° endpoint</u> : Achieving SBP/DBP<140/90 mm Hg, use of ≥2 drug classes	<ul> <li>BP control (&lt;140/90 mm</li> <li>Hg) can be achieved in most</li> <li>pts ≥2 or more drug classes</li> <li>are often required.</li> </ul>

			Results: SBP/DBP control was achieved by 66%	
			at 5 v of follow-up and 63% of pts were on $\geq 2$	
			drug classes.	
Dalhof B. et al.	Study type: RCT	Inclusion criteria: Men and women with	1° endpoint: Following a titration schedule to	Pts with a mean SBP/DBP
2002 (14)	<u>oldaj (jpo</u> l no i	FCG signs of LVH Trough sitting SBP	reach a target SBP/DBP<140/90 mm Hg	of 160–200/95–115 mm Hg
11937178	Size: 9,193 pts 55–80 v in	160–200 mm Ha or DBP 95–115 mm Ha		will need >2 classes of
	the Losartan Intervention	after 1–2 wk of placebo.	Results: Mean SBP/DBP at baseline was 174/98	antihypertensive medication
	For Endpoint reduction in		mm Ha Over 90% of hts required >2 drug	to achieve SBP/DBP <140/90
	HTN	Exclusion criteria: 2º HTN, MI/stroke	classes during follow-up	mm Hg
		within 6 mo, angina, HF or LVEF <40%.		initi rig.
Wald DS, et. al.,	Study type: Meta-	Inclusion criteria: Randomized placebo-	1° endpoint: Mean BP reduction.	Combination therapy results
2009 (15)	analysis of RCT	controlled trials comparing 2 of 4	<u> </u>	in substantially larger SBP
19272490	5	(thiazides, BB s, ACEIs, and CCB) drug	<b>Results:</b> Combination therapy vs. monotherapy	and DBP reductions
	Size: 10,968 pts in 42	classes.	produced larger SBP reductions:	compared with monotherapy,
	trials of factorial designs		• Thiazide alone (7.3 mm Hg)	even after dose titration.
	comparing monotherapy,	Exclusion criteria: Trials <2 wk duration,	• Thiazide+second drug class (14.6 mm Hg)	
	combination therapy and	no placebo group, nonrandomized order of	• BB alone (9.3 mm Hg)	
	placebo.	treatment.	• BB +second drug class (18.9 mm Hg)	
			• ACE-inhibitor alone (6.8 mm Hg)	
			• ACE-inhibitor+second drug class (13.9 mm Hg)	
			• CCB alone (8.4 mm Hg)	
			• CCB +second drug class (14.3 mm Hg)	
Lewington S, et al.,	Aim: To describe the age-	Inclusion criteria: Collaboration was	1° endpoint:	Throughout middle and old
2002 (16)	specific relevance of BP to	sought from the investigators of all	Not completely clear, but for our purposes.	age, usual BP is strongly and
12493255	cause-specific mortality	prospective observational studies in which	stroke and IHD death would be co-1°. Also looked	directly related to vascular
	. ,	data on BP, blood cholesterol, date of birth	at other vascular deaths.	(and overall) mortality, without
	Study type: Meta-	(or age), and sex had been recorded at a	HRs for stroke mortality for a 20 mm Hg lower	any evidence of a threshold
	analysis of cohort studies	baseline screening visit, and in which	SBP by age-group	down to at least 115/75 mm
		cause and date of death (or age at death)	40-49: 0.36 (95% CI: 0.32-0.40)	Hg.
	Size: 61 prospective	had been routinely sought for all screens	50–59: 0.38 (95% CI: 0.35–0.40)	
	studies with 12.7 million	during more than 5,000 person-y of follow-	60–69: 0.43 (95% CI: 0.41–0.45)	
	person-y of observation,	up (see appendix A). Relevant studies	70–79: 0.50 (95% CI: 0.48–0.52)	
	56,000 vascular deaths in	were identified through computer searches	80–89: 0.67 (95% CI: 0.63–0.71)	
	40–89 y.	of Medline and Embase, by hand-	<ul> <li>HRs for IHD mortality for a 20 mm Hg lower</li> </ul>	
		searches of meeting abstracts, and by	SBP by age-group	
		extensive discussions with investigators.	40–49: 0.49 (95% CI: 0.45–0.53)	
			50–59: 0.50 (95% CI: 0.49–0.52)	
		Exclusion criteria: I o minimize the	60–69: 0.54 (95% CI: 0.53–0.55)	
		effects of reverse causality (whereby	70–79: 0.60 (95% CI: 0.58–0.61)	

		established disease could change the usual BP), studies were excluded if they had selected pts on the basis of a positive history of stroke or heart disease, and individuals from contributing studies were excluded from the present analyses if they had such a history recorded at baseline.	80–89: 0.67 (95% CI: 0.64–0.70) • HRs for other vascular mortality for a 20 mm Hg lower SBP by age-group 40–49: 0.43 (95% CI: 0.38–0.48) 50–59: 0.50 (95% CI: 0.47–0.54) 60–69: 0.53 (95% CI: 0.51–0.56) 70–79: 0.64 (95% CI: 0.61–0.67) 80–89: 0.70 (95% CI: 0.65–0.75) • Similar results for DBP also in figure 1. • Similar results for men and women separately for stroke figure 2, and HD, figure 5.	
Ettehad D, et al., 2016 (17) 26724178 ain all BF qu re ar ba co ar ph int <u>St</u> ar 61	im: This systematic eview and meta-analysis ims to combine data from Il published large-scale P-lowering trials to uantify the effects of BP eduction on CV outcomes nd death across various aseline BP levels, major omorbidities, nd different harmacological nterventions. Atudy type: Meta- nalysis of RCTs <u>ize:</u> 123 studies with 13,815 pts	<ul> <li>Inclusion criteria:</li> <li>RCTs of BP-lowering treatment that included a minimum of 1,000 pt-y of follow-up in each study arm. No trials were excluded because of presence of baseline comorbidities, and trials of antihypertensive drugs for indications other than HTN were eligible.</li> <li>Eligible studies fell into 3 categories: 1st, random allocation of pts to a BP-lowering drug or placebo; 2nd, random allocation of pts to different BP-lowering drugs; and third, random allocation of pts to different BP-lowering targets.</li> <li>Exclusion criteria: &lt;1,000 pt y of follow-up in each treatment group.</li> <li>Intervention: BP-lowering meds</li> <li>Comparator: Placebo, active comparator or less intensive treatment</li> </ul>	<ul> <li>In Stroke, figure 5, and firb, figure 5.</li> <li>Pendpoint: <ul> <li>CVD.</li> <li>Major CVD events, CHD, stroke, HF, renal failure, and all-cause mortality.</li> <li>Standardized RR for 10 mm Hg difference in SBP</li> <li>CVD RR: 0.80 (95% CI: 0.77–0.83)</li> </ul> </li> <li>Other endpoints: <ul> <li>CHD RR: 0.83 (95% CI: 0.78–0.88)</li> <li>Stroke RR: 0.73 (95% CI: 0.68–0.77)</li> <li>HF RR: 0.72 (95% CI: 0.67–0.78)</li> <li>Total deaths RR: 0.87 (95% CI: 0.84–0.91)</li> </ul> </li> <li>Other results: <ul> <li>Benefit for CVD and other endpoints not different by baseline SBP, including &lt;130 mm Hg fig 4 in paper</li> <li>CVD: 0.63; 95% CI: 0.27–1.57; p=0.38</li> <li>HF: 0.83; 95% CI: 0.41–1.70; p=0.27</li> <li>Total deaths: 0.53; 95% CI: 0.37–0.76; p=0.79</li> <li>More precision around estimates of benefits in SBP 130–139 at baseline, fig 4 in paper</li> <li>Results similar in trials of people with and without CVD at baseline figure 5</li> <li>CVD+ 0.77 (95% CI: 0.71–0.81)</li> </ul></li></ul>	<ul> <li>BP-lowering significantly reduces vascular risk across various baseline BP levels and comorbidities. Our results provide strong support for lowering BP to SBP&lt;130 mm Hg and providing BP-lowering treatment to individuals with a history of CVD, CHD, stroke, DM, HF, and CKD.</li> <li>In stratified analyses, we saw no strong evidence that proportional effects were diminished in trials that included people with lower baseline SBP (&lt;130 mm Hg), and major CV events were clearly reduced in high-risk pts with various baseline comorbidities. Both of these major findings—the efficacy of BP-lowering below 130 mm Hg and the similar proportional effects in high risk populations—are consistent with and extend the findings of the SPRINT trial.</li> </ul>

			<ul> <li>CVD- 0.74 (95% CI: 0.67–0.83)</li> <li>Total deaths</li> <li>CVD+ 0.90 (95% CI: 0.83–0.98)</li> <li>CVD- 0.84 (95% CI: 0.75–0.93)</li> <li>Other outcomes similarly in figure 5</li> <li>In appendix, in general, benefits for CVD prevention seen in groups with and without baseline CHD, Stroke, DM, CKD and HF when examined separately, but no absolute risks provided to enable estimation of how far down the absolute risk curve these findings have been demonstrated.</li> <li>Some evidence of BB inferiority to other med classes in figure 6.</li> <li>Did not report absolute risks so do not know lower level of risk in treated populations.</li> </ul>	<ul> <li>Lack of individual pt data, which would have allowed a more reliable assessment of treatment effects in different pt groups.</li> <li>Interpretation: Lowering of BP into what has been regarded the normotensive range should therefore be routinely considered for the prevention of CVD among those deemed to be of sufficient absolute risk.</li> </ul>
Law MR, et al., 2009 (18) <u>19454737</u>	Study type: Meta- analysis of use of BP- lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of other antihypertensive drugs in CAD included 85,395 pts	Inclusion criteria: The database search used Medline (1966 to Dec. 2007) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analyses and review articles. Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	<u>1° endpoint</u> : CAD events; stroke <u>Results:</u> In 37 trials of pts with a history of CAD, BB reduced CAD events 29% (95% CI: 22%– 34%). In 27 trials in which BBs were used after acute MI, BB reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which BB were used after long-term CAD, BB insignificantly reduced CAD events 13%. In 7 trials, BB reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of ACEIs, insignificantly 14% in 4 trials of angiotensin receptor blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCB. Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEI, and 34% (95% CI: 25%–42%) in 9 trials of CCB.	• With the exception of the extra protective effect of BB given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.
Sundstrom J, et al., 2015 (19) <u>25531552</u>	Aim: To investigate whether pharmacologic BP reduction prevents CV events and deaths in pts with grade 1 HTN.	Inclusion criteria: RCTs of at least 1 y duration; pts ≥18 y, at least 80% of whom had grade 1 HTN and no previous CVD (MI, angina pectoris, CABG, PCI, stroke, TIA, carotid surgery, peripheral arterial	<u>1° endpoint</u> : Total major CV events, comprising stroke (nonfatal stroke or death from cerebrovascular disease), coronary events (nonfatal MI or death from CHD, including sudden death), HF (causing death or resulting in	• BP-lowering therapy is likely to prevent stroke and death in pts with uncomplicated grade 1 HTN.

	<u>Study type:</u> Meta- analysis of RCTs <u>Size:</u> 10 RTCs with 15,266 pts	surgery, intermittent claudication, or renal failure); and compared an antihypertensive drug provided as monotherapy or a stepped-care algorithm vs. placebo or another control regimen. Exclusion criteria: Excluded trials did not contribute an event for any of the outcomes of interest.	hospitalization), or CV death; OR: 0.86 (95% CI: 0.74–1.01) <u>Other endpoints:</u> Each of the above outcomes independently; and total deaths. CHD 0.91 (95% CI: 0.74–1.12) Stroke 0.72 (95% CI: 0.55–0.99) HF 0.80 (95% CI: 0.57–1.12) CVD deaths 0.75 (95% CI: 0.57–0.98) Total deaths 0.78 (95% CI: 0.67–0.92) Only the first event for a pt was used for the analysis of each outcome, but a pt who had >1 outcome type could contribute to more than 1 analysis. They also tabulated overall withdrawals and withdrawals due to adverse events.	• 5 y risks in BPLTTC control groups CVD events 7.4%, CVD deaths 3.1%
Thomopoulos C, et al., 2014 (20) <u>25259547</u>	Aim: Investigating whether all grades of HTN benefit from BP-lowering treatment and which are the target BP levels to maximize outcome reduction. Study type: Meta- analysis of RCTs Size: 32 RCTs with 104,359 pts	Inclusion criteria: Intentional BP-lowering comparing active drug treatment with placebo, or less active treatment (intentional BP-lowering trials), or comparison of an active drug with placebo over baseline antihypertensive treatment, resulting in a BP difference of at least 2 mm Hg in either SBP or DBP (nonintentional BP-lowering trials); enrolling of hypertensive individuals only or a high proportion (at least 40%) of them. Exclusion criteria: N/A	<ul> <li><u>1º endpoint</u>:</li> <li>As some trials were done on low-risk pts, others on higher risk pts, no evaluation of absolute risk-reduction was made. However, a 2º analysis was done including trials or trial subgroups with mean baseline SBP/DBP values in grade 1 range and a low-to-moderate risk (&lt;5% CV deaths in 10 y in controls): FEVER stratum with baseline SBP below the median (&lt;153 mm Hg); HTN Detection and Follow-up Program stratum with baseline DBP 90–94 mm Hg and no CVD; OSLO (e17); TOMHS (e28) and USPHS. Risks of stroke, CHD, the composite of stroke and CHD, and all-cause death were significantly reduced by BP-lowering in these low-to-moderate risk pts (control group: average CV mortality 4.5% in10 y) with a moderate BP elevation (average SBP/DBP 145.5/91 mm Hg) at randomization. Standardized RR associated with 10/5 reduction in BP: stroke 0.33 (95% CI: 0.11–0.98) CHD 0.68 (95% CI: 0.48–0.95)</li> </ul>	<ul> <li>Meta-analyses favor BP-lowering treatment even in grade 1 HTN at low-to-moderate risk, and lowering SBP/DBP to &lt;140/90 mm Hg.</li> <li>Achieving &lt;130/80 mm Hg appears safe, but only adds further reduction in stroke.</li> </ul>

			• • • • • • • • • • • •	
			CVD death 0.57 (95% CI: 0.32–1.02) total death	
			0.53 (95% 0.35–0.80)	
			Compared outcomes of achieved on study SBP	
			<130 vs. ≥130	
			Standardized Risk ratio associated with 10/5	
			reduction in BP: stroke 0.68 (95% CI: 0.57, 0.83)	
			CHD 0.87 (95% CI: 0.76, 1.00)	
			HF 0.92 (95% CI: 0.47, 1.77)	
			CVD 0.81 (95% CI: 0.67, 1.00)	
			CVD death 0.88 (95% CI: 0.77, 1.01) total death	
			0.88 (95% Cl: 0.77, 0.99)	
			• Outcomes of achieved on study SBP 130-139	
			vs. ≥140	
			Standardized RR associated with 10/5 reduction	
			in BP: stroke 0.63 (95% CI: 0.52, 0.77)	
			CHD 0.77 (95% CI: 0.70, 0.86)	
			HF 0.76 (95% CI: 0.47, 1.25)	
			CVD 0.74 (95% CI: 0.62, 0.88)	
			CVD death 0.81 (95% CI: 0.67, 0.97) total death	
			0.87 (95% Cl: 0.75, 1.00)	
			• Similar pattern of results for on treatment DBP.	
Xie X, et al.,	Aim: To assess the	Inclusion criteria: RCTs with at least 6	<u>1° endpoint</u> :	<ul> <li>Intensive BP-lowering,</li> </ul>
2015 (21)	efficacy and safety of	mo follow-up that randomly assigned pts	• CVD, other major CV events, defined as a MI,	including to <130 mm Hg,
<u>26559744</u>	intensive BP-lowering	to more intensive vs. less intensive BP-	stroke, HF, or CV death, separately and	provided greater vascular
	strategies.	lowering treatment, with different BP	combined; nonvascular and all-cause mortality;	protection than standard
		targets or different BP changes from	ESKD, and adverse events. Progression of	regimens.
	Study type: Meta-	baseline. Reference lists from identified	albuminuria (defined as new onset of micro-	<ul> <li>In high-risk pts, there are</li> </ul>
	analysis of RCTs	trials and review articles were manually	albuminuria/macro-albuminuria or a change from	additional benefits from more
		scanned to identify any other relevant	micro-albuminuria to macro-albuminuria)	intensive BP-lowering,
	Size: 19 RC1s with	studies.	and retinopathy (retinopathy progression of 2 or	including for those with SPB
	44,989 pts		more steps) were also recorded for trials that	<140 mm Hg at baseline.
		Exclusion criteria: N/A	were done in pts with DM	<ul> <li>The net absolute benefits of</li> </ul>
			• CVD RR: 0.86 (95% CI: 0.78–0.96)	intensive BP-lowering in high-
		Intervention: BP-lowering meas		risk individuals are large.
		Compositor	Other endpoints:	
		<u>comparator</u> :	MI RR: 0.87 (95% CI: 0.76–1.00) p=0.042	Limitations:
		Less Intensive treatment	Stroke RR: 0.78 (95% CI: 0.68–0.90)	<ul> <li>Lack of individual pt data,</li> </ul>
		• BP difference 6.8/3.5	HF RR: 0.85 (95% CI: 0.66–1.11)	which would have allowed a
		• The mean follow-up BP	CVD death RR: 0.91 (95% CI: 0.74–1.11)	more reliable assessment of
		levels in the less intensive BP-lowering	I otal deaths RR: 0.91 (95% CI: 0.81–1.03)	

reg	gimen group were 140/81 mm Hg,		treatment effects in different pt
con	mpared with	Other results:	groups.
133	3/76 mm Hg in the more intensive	<ul> <li>Benefit for CVD not different by baseline SBP</li> </ul>	<ul> <li>Interpretation: Supports</li> </ul>
trea	eatment group.	120–139: 0.89 (95% CI: 0.76–1.05)	treating pt with and without
		140–160: 0.83 (95% CI: 0.68–1.00)	CVD at threshold of 130 to
		>160: 0.89 (95% CI: 0.73–1.09)	<130. Supports treating at
		p-heterogeneity: 0.60	threshold of about 130 even
		Benefit for CVD not different for more intensive	down to a CVD event rate of
		and less intensive targets in intensive group	0.9% per y.
		<140 or <150 mm Hg: 0.76 (95% CI: 0.60–0.97)	
		<120- <130 mm Hg: 0.91 (95% CI: 0.84-1.00; p-	
		hetero: 0.06)	
		Absolute benefits were proportional to absolute	
		risk.	
		• For trials in which all pts had vascular disease,	
		renal disease, or DM at baseline, the average	
		control group rate of major vascular events was	
		2.9% per y compared with 0.9% per y in other	
		trials, and the numbers needed to treat were 94	
		(95% CI: 44–782) in these trials vs. 186 (95% CI:	
		107–708) in all other trials.	
		<ul> <li>Increase in Severe hypotension: 0.3% vs. 0.1%</li> </ul>	
		per person y OR: 2.68 (95% CI: 1.21–5.89)	

# Data Supplement 3. Out-of-Office and Self-Monitoring of BP (Section 4.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population (N)	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Pickering TG, et al., 1988 (22) <u>3336140</u>	Study type: • Observational Cohort • 24-h ABPM <134/90 • Systematic review • Office vs. ABPM or HBPM Size: 292 pts	N/A	<u>1° endpoint</u> : WCH=21%	<ul> <li>Multiple methodologies used to define MH.</li> <li>Prevalence 8.5%–16.6% (general population),</li> <li>14.7%–30.4% (nonelevated clinic population)</li> </ul>
Uhlig K, et al., 2012 (23) <u>22439158</u>	Study type: • Systematic review • Self-monitoring vs. usual care vs. self- monitoring+support	N/A	<u>1° endpoint</u> : Change in clinic SBP/DBP	<ul> <li>Self-monitoring vs. usual care resulted in lower SBP/DBP (-3.1/-2.0 mm Hg) at 6 mo</li> <li>Self-monitoring + support vs. usual care resulted in lower SBP/DBP SBP/DBP -3.4 - 8.9/-1.94.4 mm Hg up to 12 mo.</li> <li>Self-monitoring may confer a small benefit for BP control.</li> </ul>
--	--	--	---	---
McManus RJ, et al., 2014 (24) <u>25157723</u>	Study type: • RCT • Self-monitoring with self- titration vs. usual care. Size: 552 pts	Inclusion criteria: SBP/DBP ≥130/85 mm Hg	1° endpoint: Change in SBP/DBP at 12 mo	• Self-monitoring with self-titration was associated with SBP and DBP differences of 9.2 mm Hg and 3.4 mm Hg, respectively.
Margolis KL, et al., 2013 (25) <u>23821088</u>	Aim: Assess impact of follow-up and monitoring system including home BP tele-monitoring and pharmacist case management on BP control in pts treated for HTN <u>Study type:</u> Cluster RCT <u>Size</u> : 450 pts	Inclusion criteria: Pts from 16 clinics in integrated health system in Minneapolis, MN	222 pts randomized to 8 usual care clinics and 228 randomized to 8 intervention clinics Intervention included 12 mo of home BP tele-monitoring and pharmacist case management, with 6 mo of follow-up afterward	<ul> <li>Intervention group achieved better BP control compared to usual care during 12 mo of intervention and persisting during 6 mo of follow-up</li> <li>SBP was &lt;140/90 in 57.2% (95% CI: 44.8%, 68.7%) of intervention pts at 6 and 12 mo vs. 30% (95% CI: 23.2%, 37.8%) in usual care (p=0.001)</li> <li>Combination of home BP tele-monitoring and pharmacist case management helped control HTN better than usual care at 6, 12, and 18 mo.24</li> </ul>
Margolis KL, et al., 2013 (25) <u>23821088</u>	Study type: • RCT • Home BP telemonitoring with pharmacist case management vs. usual care. Size: 450 pts	Inclusion criteria: Uncontrolled BP	1° endpoint:SBP/DBP <140/90mm Hg (<130/80 mm Hg in DM or	<ul> <li>Telemonitoring resulted in better BP control (57% vs. 30%) at 6 and 12 mo and larger SBP declines at 6, 12, and 18 mo.</li> <li>Some aspects of pt satisfaction (e.g., clinicians listening carefully) improved with telemonitoring.</li> </ul>
McManus RJ, et al., 2014 (24) <u>25157723</u>	Study type: • RCT • Self-monitoring with self- titration vs. usual care. Size: 552 pts	Inclusion criteria: SBP/DBP ≥130/85 mm Hg	1° endpoint: Change in SBP/DBP at 12 mo	• Self-monitoring with self-titration was associated with SBP and DBP differences of 9.2 mm Hg and 3.4 mm Hg, respectively.

Siu AL, et al., 2015 26458123	Study type: U.S. Preventive Services Task Force commissioned systematic review and meta-analysis of office and out of office BP relationships for diagnostic accuracy of diagnosing high BP after an initial office-based classification of high BP.	Inclusion criteria: • Adults ≥18 y. • 24 studies based on "confirmation" by means of ABPM and 6 by means of HPBM.	<ul> <li><u>1° endpoint</u>: ABPM or HBPM conformation of office-based diagnosis of high BP.</li> <li>CVD risk-relationships for ABPM, HBPM and office-based BPs also reviewed.</li> <li>ABPM was recommended as the best method to confirm an office-based diagnosis of high BP, with HBPM an acceptable alternative, based on "over diagnosis" of high BP with office BP measurements (White coat hypertension) and stronger relationships between out of office BP measurements (especially ABPM) with vascular events.</li> </ul>	• Screen for high BP in adults ≥18 y and confirm office-based high BP using out of office BP measurements 9preferably ABPM).
Uhlig K, et al., 2012 (23) <u>22439158</u>	Study type: • Systematic review • Self-monitoring vs. usual care vs. self- monitoring+support	N/A	<u>1° endpoint</u> : Change in clinic SBP/DBP	<ul> <li>Self-monitoring vs. usual care resulted in lower SBP/DBP (-3.1/-2.0 mm Hg) at 6 mo</li> <li>Self-monitoring + support vs. usual care resulted in lower SBP/DBP SBP/DBP -3.4 - 8.9/-1.94.4 mm Hg up to 12 mo. Self-monitoring may confer a small benefit for BP control.</li> </ul>
Yi SS, et al., 2015 (26) <u>25737487</u>	Study type: • RCT • Self-monitoring of BP vs. usual care. <u>Size</u> : 900 pts	N/A	<ul> <li><u>1° endpoint</u>:</li> <li>Change in clinic SBP/DBP and HTN control (SBP/DBP &lt;140/90 mm Hg)</li> <li>Decline in SBP at 9 mo was 14.7 mm Hg and 14.1 mm Hg in the intervention and usual care groups (p=0.70); HTN was controlled in 38.9% and 39.1% in the intervention and control groups (p=0.91)</li> </ul>	• Self-monitoring of BP by itself does not improve BP above usual care.
Agarwal R, et. al., 2011 (27) <u>21115879</u>	Study type: • Systematic review	N/A	1° endpoint:           • Change in clinic SBP/DBP and MAP	• Self-monitoring is associated with a reduction in BP. This effect is larger when accompanied by telemonitoring.

	<ul> <li>Self-monitoring vs. usual</li> </ul>		<ul> <li>Mean reduction in SBP, DBP</li> </ul>	
	care vs. self-		and MAP with home monitoring	
	monitoring+telemonitoring		was 2.63 mm Hg (95% CI: 4.24–	
			1.02), 1.68 (95% CI: 2.58–0.79),	
	<u>Size</u> : 9,446 pts		4.0 (95% CI: 1.79–6.22). The	
			effect for SBP was larger when	
			accompanied by telemonitoring	
			(3.20; 95% CI: 4.66–1.73 vs.	
			1.26; 95% CI: 2.20–0.31).	
Fagard RH, et. al.,	Study type:	N/A	1° endpoint: CVD events.	<ul> <li>MH is associated with increased CVD risk</li> </ul>
2007 (28)	<ul> <li>Systematic review</li> </ul>		The adjusted HR for CVD events	but WCH is not associated with increased risk.
<u>17921809</u>	<ul> <li>MH and WCH vs.</li> </ul>		was 1.12 (95% CI: 0.84–1.50) for	
	sustained normotension		WCH vs. sustained normotension	
			(p=0.59) and 2.00 (95% CI: 1.58–	
	<u>Size</u> : 11,502 pts		2.52) for MH vs. sustained	
			normotension (p<0.001)	

# Data Supplement 4. White Coat Hypertension (Section 4.4)

Study Acronym; Author; Year Published	Study Type/Design; Definitions	Patient Population (N)	HBPM (%)	Daytime ABPM (%)	24-h ABPM (%)	Results/Comments
Viera AJ, et al., 2010 (29) <u>20671718</u>	Office BP ×3     Duplicate measures of: 24-h ABPM >130/80 Daytime ABPM>135/85 HBPM >135/85	<ul> <li>50 pts</li> <li>Untreated</li> <li>Borderline HTN and BP &gt;110/70 and &lt;160/110</li> </ul>	• MH=43/35	• MH=54/53	• MH=51/45	<ul> <li>For MH diagnosis</li> <li>95% agreement daytime and 24-h ABPM</li> <li>Only 47%–53% agreement between HBPM and either daytime or 24-h ABPM</li> </ul>
Viera AJ, et al., 2014 (30) <u>24842491</u>	Office BP ×3     Duplicate measures of: 24-h ABPM >130/80 Daytime ABPM >135/85 HBPM >135/85	<ul> <li>420 pts</li> <li>Untreated</li> <li>Borderline HTN and BP &gt;120/80 and &lt;149/95</li> </ul>	• MH=15–17	• MH=43-44	• MH=48–50	<ul> <li>For MH Diagnosis</li> <li>92%–94% agreement daytime and 24-h ABPM</li> <li>70% agreement between HBPM and either daytime K=0.3–0.36</li> </ul>
Bayo B, et al., 2006 (31) <u>16534404</u>	<ul><li>Office BP ×3</li><li>HBPM ×3 d</li></ul>	<ul><li>190 untreated pts</li><li>Spanish</li><li>Borderline</li></ul>	• WCH=35 (95% CI: 28–42)		• WCH=42 (95% CI: 34, 48)	• Compared to ABPM, HBPM pulse pressure variation: 59% negative predictive value: 69%

Asayama K, et al., 2015 (32) <u>25135185</u>	Obs (IDACO) database     CV outcomes risk by WCH, MH, NTN ABPM measured: Office BP ×2 >140/90 (office) >130/80 (24-h ABPM) >135/85 (daytime ABPM) >120/70 (nighttime ABPM)	• 8,237 untreated pts	N/A	• WCH=9.1 • MH=13.4	• WCH=10.7 • MH=9.7	<ul> <li>Overlap from daytime to 24-h ABPM: WCH=86% MH=61%</li> </ul>
Conen D, et al., 2014 (33) <u>25185130</u>	<ul> <li>Obs</li> <li>13 IDACO Cohorts</li> <li>Office ×2</li> <li>Awake ABPM &gt;135/85</li> <li>24-h ABP &gt;130/80</li> <li>Analyzed by decade in y</li> </ul>	• 7,506 untreated pts	<ul> <li>WCH=2.2% age 18–30, increasing to 19.5% in both sexes age &gt;70 y</li> <li>MH=inverted U distribution (13% and 11% in 18–30 y 18% and 20% in those 30–50 y</li> <li>Increased prevalence in men</li> </ul>		<ul> <li>WCH=3.0 in age 18–30 increasing to 19.1% both sexes age &gt;70 y</li> <li>MH=inverted U distribution (12% and 9% in youngest and oldest, 19% and 17% in those 30– 50 y</li> <li>Increase prevalence in men</li> </ul>	• Similar prevalence using either 24-h or awake ABPM
Nasothimiou EG, et al., 2012 (34) <u>22357523</u>	<ul> <li>Office BP ×3 × &gt;140/90</li> <li>HBPM &gt;135/85</li> <li>Daytime ABPM &gt;135/85</li> </ul>	• 613 pts (66% untreated, 34% treated)	• WCH=15% • MH=15%	• WCH=14% • MH=16%	N/A	<ul> <li>WCH: 89% agreement daytime ABPM and HBPM, kappa=0.79</li> <li>MH: 88% agreement, kappa=0.56</li> </ul>
Coll de TG, et al., 2011 (35) <u>21183853</u>	<ul> <li>Office ×2 &gt;140/90</li> <li>Daytime ABPM &gt;135/85</li> <li>HBPM &gt;135/85</li> </ul>	403 untreated pts	• WCH=24%	• WCH=8.1%	N/A	N/A
Stergiou GS, et al., 2005 (36) <u>15925734</u>	<ul> <li>Office ×3 ×2 &gt;140/90</li> <li>HBPM ≥135/85 awake •</li> <li>ABPM ≥135/85</li> </ul>	438 untreated/ treated pts	• MH=12% • WCH=16%	• MH=14% • WCH=15%	N/A	<ul> <li>No difference in proportions of pts Dx with MH or WCH by HBPM or awake ABPM</li> <li>No difference between treated and untreated. However, only 44% overlap for MH, but 90%–95% if 5 mm Hg zone of uncertainty added.</li> </ul>

Sega R, et al., 2001 (37) <u>11560854</u>	Population-based     PAMELA Study	• 2,051 pts	● WCH=12% ● MH=9%	• WCH=12% • MH=9%	N/A	<ul> <li>70% agreement between ABPM and HBPM for WCH and 57% for MH</li> </ul>
	• Office ×3 >140/90					
	• HBPM >132/83					
	• ABPM >125/79					
	<ul> <li>LVMI by echo</li> </ul>					

# Data Supplement 5. White Coat Hypertension (Prevalence) (Section 4.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Vinyoles E et al., 2008 (38) <u>18300853</u>	Study type: • Cross-sectional, comparative multicenter descriptive study Size: 6,176 pts	N/A	<u>1° endpoint</u> : WCH=21%	<ul> <li>Multiple methodologies used to define MH.</li> <li>Prevalence 8.5%–16.6% (general population), 14.7%–30.4% (nonelevated clinic population)</li> </ul>
Pickering TG, et al., 1988 (22) <u>3336140</u>	Study type: • Observational cohort • 24-h ABPM <134/90 • Systematic review • Office vs. ABPM or HBPM Size: 292 pts	N/A	<u>1° endpoint</u> : WCH=21%	<ul> <li>Multiple methodologies used to define MH.</li> <li>Prevalence 8.5%–16.6% (general population), 14.7%–30.4% (nonelevated clinic population)</li> </ul>
Piper MA, et al., 2015 (39) <u>25531400</u>	Study type: • Systematic review • Office vs. ABPM or HBPM	N/A	<u>1<sup>o</sup> endpoint</u> : ●WCH=5-35% (ABPM) ● WCH conversion to SH ~1%-5% y	• Prevalence of WCH sufficiently high to require ABPM confirmation of SH in those with elevated clinic BP
Asayama K, et al., 2014 (32) <u>25135185</u>	Study type: • Observational (IDACO) database • ABPM measured: • Office BP ×2 • >140/90 (office) • >130/80 (24-h ABPM) • >135/85 (daytime ABPM) • >120/70 (nighttime ABPM) Size: 8 237	Inclusion criteria: Untreated, >18 y	<u>1° endpoint</u> : ● WCH=6.3%-12.5% ● MH=9.7%-19.6%	• Variable prevalence of both WCH and MH based on method of defining

Conen D, et al., 2014 (33) <u>25185130</u>	Study type: • Observational • 13 IDACO cohorts • Office ×2 • Awake ABPM >135/85 • 24-h ABP >130/80 • Analyzed by decade in y Size: 7.506 pts	Inclusion criteria: >18 y, untreated	<ul> <li><u>1° endpoint</u>:</li> <li>WCH=2.2% age 18–30 y, increasing to 19.5% both sexes age &gt;70 y</li> <li>MH=inverted U distribution (13% and 11% in youngest and oldest, 18% and 20% in those 30–50 y) Increase prevalence in males</li> </ul>	<ul> <li>Increase in WCH prevalence with increasing age in both sexes</li> <li>Peak MH prevalence age 30–50 y with drop at age extremes. Greater prevalence of MH in males.</li> <li>Similar prevalence when 24-h vs. awake ABPM used</li> </ul>
Alwan H, et al., 2014 (40) <u>24663506</u>	Study type: • Observational • SKIPOGH • Office BP ×4 • Daytime ABPM • Office >140/90 • Daytime >135/85 <u>Size:</u> 652	Inclusion criteria: >18 y, untreated	<u>1° endpoint</u> : ● WCH=2.6% ● MH=15.8%	• Pts with pre-HTN had 7 times higher rate of MH
Stergiou GS, et al., 2014 (41) <u>24420553</u>	Study type: • Observational • 5 IDACO cohort Studies • Office ×2 >140/90 • Home >135/85 • Median 8.3-y follow-up Size: 5,007 pts	Inclusion criteria: >18 y, untreated	<u>1° endpoint</u> : Long-term follow-up for CVD events	● WCH=13.8% ● MH=8.1%
Pierdomenico SD, et al., 2011 (42) <u>20847724</u>	Study type: Meta-analysis of observational cohort studies (8 WCH, 5 MH) 24-h ABPM >130/80 Daytime >135/85 Size: 7,961 pts	Inclusion criteria: >18 y, untreated	<u>1° endpoint:</u> Long-term follow-up for CVD events	● WCH=16.1% ● MH=5.8%
Hansen TW, et al., 2007 (43) <u>17620947</u>	Study type: • 4 observational studies • Office <140/90 • 24-h ABPM >135/85 Size: 7,030 pts	<ul> <li>78% untreated</li> </ul>	Study endpoints:           ● F/NF CVD           ● Median follow-up =9.5 y           1° Results:           ● Adj HR vs. NTN           ● WCH=1.22 (CI: 0.96–1.53), p=0.09           ● MH=1.62 (CI: 1.35–1.96), p<0.001	N/A

	• SH=1.80 (CI: 1.59–2.03), p<0.001	

# Data Supplement 6. White Coat Hypertension (Correlation with Clinical Outcomes) (Section 4.4)

Study Acronym;	Study Type/Design;	Patient	Study Endpoints and	Endpoint Results	Summary/Conclusions/
Author; Voar Published	Study Size (N)	Population	Length of Follow-up	(Absolute Event Rates, Divalue: OB or DB: 8.05% CI)	Comment
NICE 2011 (44) 22855971	Study type: Systematic Review 3 Meta-analyses 11 observational studies "best method" comparison of office vs. HBPM or ABPM that best predicted (i.e., statistically significant predictors and higher HR values) clinical outcomes (after adjustment for covariates in multivariate analyses)	<ul> <li>Home vs. office (n=7,685)</li> <li>ABPM vs. office (n=33,158)</li> <li>Home vs. ABPM vs. Office (n=2,442)</li> </ul>	Outcomes of interest: mortality, stroke, MI, HF, DM, vascular procedures, hospitalization for angina, and other MACCE	<ul> <li>P Value; OK of KR; &amp; 95% Cl)</li> <li>For predicting clinical outcomes:</li> <li>ABPM vs. office (9 studies):</li> <li>ABPM superior to office (8 studies)</li> <li>No difference between ABPM and office (1 study)</li> <li>HBPM vs. office (3 studies):</li> <li>HBPM superior to office (2 studies)</li> <li>No difference between HBPM and office (1 study)</li> <li>HBPM vs. ABPM vs. office (2 studies):</li> <li>HBPM similar to ABPM and both superior to office (1 study)</li> <li>No difference between HBPM, ABPM and office (1 study)</li> </ul>	Overall recommendation for ABPM to confirm HTN diagnosis (HBPM recommended if ABPM not practical)
Pierdomenico SD, et al., 2011 (42) <u>20847724</u>	Study type: Meta-analysis (8 studies) • NTN vs. WCH or MH based mostly on daytime ABPM <135/85 Size: 7,961	Inclusion criteria: Untreated	<ul> <li>Follow-up 3.2–12.8 y</li> <li>Composite CVD</li> </ul>	<ul> <li>WCH vs. NTN: OR: 0.96; 95% CI: 0.65–1.42</li> <li>MH vs. NTN: OR: 2.09; 95% CI: 1.55–2.81</li> <li>SH vs. NTN: OR: 2.59; 95% CI: 2.00–3.35</li> </ul>	N/A
Asayama K, et al., 2014 (32) <u>25135185</u>	Study type: Observational (IDACO) database • CV outcomes risk by WCH, MH, NTN • ABPM measured: Office BP ×2 >140/90 (office)	Inclusion criteria: >18 y, untreated	<ul> <li>F/NF CVD/stroke,</li> <li>729 CV events</li> <li>Follow-up 10.6 y</li> </ul>	<ul> <li>WCH adjusted HR: 1.2; 95% CI: 0.93– 1.54; p=0.16</li> <li>MH adjusted HR: 1.81; 95% CI: 1.41– 2.32; p&lt;0.0001</li> <li>SH adjusted HR: 2.31; 95% CI: 1.91– 2.80; p&lt;0.0001</li> </ul>	N/A

	(24-h ABPM) >130/80 (daytime ABPM) >135/85 (nighttime ABPM) >120/70 <u>Size</u> : 8,237				
Verdecchia P, et al., 2005 (45) <u>15596572</u>	Study type: Population- based (4 international cohorts) • Office ×3 >140/90 • Awake ABPM >130/80 Size: 5,955	• 26% NTN	<ul> <li>Stroke</li> <li>Follow-up 5.4 y</li> </ul>	<ul> <li>WCH adjusted HR: 1.15; 95% CI: 0.61– 2.16; p=0.66</li> <li>SH adjusted HR: 2.01; 95% CI: 1.31– 3.08; p&lt;0.001</li> </ul>	• Stroke not increased in WCH but tended to approach systolic HTN risk 6 y after baseline ABPM.
Hansen TW, et al., 2007 (43) <u>17620947</u>	Study type: Observational 4 studies • Office <140/90 • 24-h ABPM >135/85 Size: 7,030	78% untreated	<ul> <li>F/NF CVD</li> <li>Median follow-up=9.5</li> <li>y</li> </ul>	<ul> <li>WCH adjusted HR: 1.22 (95% CI: 0.96, 1.53), p=0.09</li> <li>MH adjusted HR: 1.62; 95% CI: 1.35–1.96; p&lt;0.001</li> <li>SH adjusted HR: 1.80; 95% CI: 1.59–2.03; p&lt;0.001</li> </ul>	N/A
Fagard RH, et al., 2007 (28) <u>17921809</u>	Study type: Meta-analysis 7 studies • Office <140/90 • 24-h ABPM or HBPM Size: 11,502	Treated and untreated	<ul> <li>F or F/NF CVD</li> <li>Follow-up 3.2–12.3 y (mean=8 y)</li> </ul>	<ul> <li>WCH adjusted HR: 1.12 (95% CI: 0.84– 1.50), p=0.59</li> <li>MH adjusted HR: 2.0; 95% CI: 1.58– 2.52; p&lt;0.001</li> <li>Systolic HTN adjusted HR: 2.28; 95% CI: 1.87–2.78; p&lt;0.001</li> </ul>	N/A
Mancia G, et al., 2013 (46) <u>23716584</u>	Study type: Observational PAMELA Study • Office ×3<140/90 • HBPM>135/85 and-24-h • ABPM>130/80 Size: 2,051	22% treated	<ul> <li>CV and all- cause mortality</li> <li>Follow-up 16 y</li> </ul>	<ul> <li>CV mortality in WCH adjusted HR: 2.04 (95% CI: 0.87–4.78), p=0.10</li> <li>All-cause mortality in WCH adjusted HR: 1.50; 95% CI: 1.03–2.18; p=0.03</li> </ul>	<ul> <li>Trend but insignificant increase in CV mortality and significant increase in total mortality in WCH</li> <li>Risk of developing systolic HTN greater in those with WCH</li> </ul>
Tomiyama M, et al., 2006 (47) <u>16942927</u>	Study type: Cross-sectional study assessing target organ damage by BP control status. Control: Office <140/90, daytime <135/85. Size: 332	Treated pts	<ul> <li>LVMI, carotid IMT, UAE</li> <li>Cross-sectional</li> </ul>	• LVMI, carotid IMT and UAE increased in masked uncontrolled HTN compared to controlled HTN. LVMI and UAE increased in SH	• SH and masked uncontrolled HTN but not WCE associated with increased target organ damage

Ohkubo T, et al.,	Study type: Observational	Untreated	CVD mortality/stroke	• WCH RH: 1.28; 95% CI: 0.76–2.14);	Similar results treated and
2005 (46)	$\sim 0$ Office $x^2 > 140/00$	(/0%)	• Follow-up TO y	μ=0.4	untreated, males, and remales
10033700	• Office $\times 2 > 140/90$	• rreated (30%)		• IVIH RH: 2.13; 95% CI:1.38-3.29;	
	• Awake ADPIVI > 155/05				
	<b>Sizo</b> : 1 332			• SH RH: 2.20; 95% CI:1.77-4.54;	
	<u>5126. 1,552</u>			p<0.0001	
Tientcheu D, et al.,	Study type: Observational	<ul> <li>Dallas Heart</li> </ul>	<ul> <li>Clinical CVD incl TIA,</li> </ul>	• WCH adj HR: 2.09; 95% CI: 1.05–4.15;	<ul> <li>Higher CVD with SH, MH and</li> </ul>
2015 (49)	cohort	Study	• UA	p=0.035	WCH (African Americans only).
<u>26564592</u>	<ul> <li>Home readings ×5 ×2</li> </ul>	<ul> <li>54% African</li> </ul>		• MH adj HR: 2.03; 95% CI: 1.36–3.03;	CVD risk not increased in whites
	visits taken by research staff	American		p<0.001	with WCH
	<ul> <li>Office readings ×5</li> </ul>	30%-39%		SH adj HR: 3.12; 95% CI: 2.13–4.56;	
	Ĵ	treated		p<0.001	
	<u>Size</u> : 3,027				

# Data Supplement 7. Renal Artery Stenosis (Section 5.4.3)

Study Acronym (if applicable) Author Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lawes CM, et al., 2003 (50) <u>12658016</u>	<u>Study type:</u> Meta- analysis of RCTs of BP drugs recording CHD events and strokes <u>Size</u> : 464,000 pts	N/A	CHD RR or 46% Stroke 64%	All classes of BP meds confer benefit while BB confer greater benefit in those with CAD
Riaz IB, et al., 2014 (51) <u>25145333</u>	Study type: 540 studies and 7 RCTs Size: 2,139 pts	N/A	• Incidence of nonfatal MI 6.74% in both the stenting and medical therapy groups: OR: 0.99; 95% CI: 0.70–1.43; p=0.99, incidence of renal events in stenting population was found to be 19.58% vs. 20.53% in medical therapy OR: 0.95; 95% CI: 0.76–1.18; p=0.62.	BP effect, CV accident not specifically reported
Cooper CJ, et al., 2014 (52) <u>24245566</u>	Study type: Residential treatment center medical therapy with or without renal stent Size: 947 pts	Inclusion criteria: Atherosclerotic renal artery stenosis	• Composite endpoint of death from CV or renal causes, MI, stroke, hospitalization for congestive HF, progressive renal insufficiency, or the need for renal-replacement therapy. 35.1% and 35.8%, respectively; HR with stenting: 0.94; 95% CI: 0.76–1.17; p=0.58 Difference in SBP favoring the stent group: -2.3 mm Hg; 95% CI: -4.4– 0.2; p=0.03.	N/A

Xie X, et al., 2015 (21) <u>26559744</u>	Study type: MA of RTC that randomly assigned individuals to different target BP levels <u>Size</u> : 44,989 pts	• 19 trials	<ul> <li>Achieved BP 133/76 mm Hg (intensive) 140/81 (less intense)</li> <li>Major CV events: 14%; 95% CI: 4%–22%</li> <li>MI: 13%; 95% CI: 0%–24%</li> <li>Stroke: 22%; 95% CI: 10%–32%</li> <li>Albuminuria: 10%; 95% CI: 3%–16%</li> <li>Retinopathy progression: 19%; 95% CI: 0%–34%.</li> <li>More intensive had no effects on HF: 15%; 95% CI: -11%–34%</li> <li>CV death: 9%; 95% CI: -11%–26%</li> <li>Total mortality: 9%; 95% CI: -3%–19%</li> <li>ESKD: 10%; 95% CI: -6%–23%</li> </ul>	More intensive approach reduced major CV events (stroke and MI) except heat failure, CVD, ESRD, and total mortality.
Brunström M, et al., 2016 (53) <u>26920333</u>	Study type: Meta- analysis of levels of BP control in DM hypertensives. <u>Size</u> : 73,738 pts	• 49 trials ( most pts with DM-2)	Baseline SBP >150 <u>RR for</u> • All death: 0.89; 95% CI:0.80–0.99 • CVD: 0.75; 95% CI: 0.57–0.99 • MI: 0.74; 95% CI: 0.63–0.87 • Stroke: 0.77; 95% CI: 0.65–0.91 • ESRD: 0.82; 95% CI: 0.71–0.94 Baseline SBP140–150 <u>RR of</u> • Death: 0.87; 95% CI: 0.78–0.98) • MI: 0.84; 95% CI: 0.76–0.9 • HF: 0.80; 95% CI: 0.66–0.97 If baseline SBP,140 mm Hg, however, further treatment increased the risk of CV mortality (1.15; 95% CI: 1.00–1.32	BP lowering reduces major CV events in DM. Caution for initiating treatment in diabetics with SBP <140/90
Ettehad D, et al., 2015 (17) <u>26724178</u>	Study type: Meta- analysis of large RTCs of antihypertensive treatment Size: 613,815 pts	123 studies	Every 10 mm Hg reduction in SBP RR: • Major CV events: 0.80; 95% CI: 0.77–0.83 • CHD: 0.83; 95% CI: 0.78–0.88 • Stroke: 0.73; 95% CI: 0.68–0.77), HF (0.72, 0.67–0.78 • All-cause mortality: 0.87; 95% CI: 0.87; 0.84–0.91 • ESRD: 0.95; 0.84–1.07	• BP lowering reduces CV risk across various baseline BP levels and comorbidities. Suggest lowering SBP <130 mm Hg and BP-lowering treatment to pts with a history of CVD, CHD, stroke, DM, HF, and CKD.

Thomopolous C, et al., 2016 (54) <u>26848994</u>	Study type: Meta- analysis of RTCs of more vs. less intense BP control	• 16 trials (52,235 pts) compared more vs. less intense treatment 34 (138,127 pts) active vs. placebo	More intense BP • Stroke RR: 0.71; 95% CI: 0.60–0.84) • CHD RR: 0.80; 95% CI: 0.68–0.95) • Major CV events RR: 0.75; 95% CI: 0.68–0.85 • CV mortality RR: 0.79; 95% CI: 0.63–0.97 Stratification of SBP cutoffs (150,140 and 130 mm Hg) showed that a SBP/DBP difference of 10/5 mm Hg across each cutoff reduced risk of all outcomes	• Intensive BP reduction improves CV outcomes compared to less intense Achieved BP <130/80 may be associated with CV benefit.
Julius S, et al., 2006 (55) <u>16537662</u>	Study type: RCT in pre- HTN; 16 mg candesartan vs. placebo Size: 809 pts	• 58% men	• During the first 2 y, HTN developed in 154 (40.4%) pts in the placebo group compared with only 53 (13.6%) of those in the candesartan group, for RR: 66.3% (p<0.0001). After 4 y, HTN developed in 240 (63.0%) in the placebo group vs. only 208 (53.2%) in the candesartan group RR: 15.6% (p<0.0069).	• 2/3 of those with pre-HTN develop HTN within 4 y. Candesartan interrupts the onset and reduced by 15.6%
Ference BA, et al., 2014 (56) <u>24591335</u>	Study type: Evaluated the effect of 12 polymorphisms (associated with BP) on the odds of CHD and compared it with the effect of lower SBP observed in both prospective cohort studies and BP-lowering randomized trials Size: 199,477 pts	63 studies	• 12 polymorphisms were associated with a 0.32 mm Hg lower SBP (p=1.79×10 <sup>-7</sup> ) and a 0.093-mm Hg/decade slower age-related rise in SBP (p=3.05×10 <sup>-5</sup> ). The effect of long-term exposure to lower SBP on CHD mediated by these polymorphisms was 2-fold greater than that observed in prospective cohort studies (p=0.006) and 3-fold greater than that observed in short-term BP treatment trials (p=0.001).	• SBP may be causally associated with the rate of rise in SBP with age and has a cumulative effect on the risk of CHD.

# Data Supplement 8. RCTs Comparing Obstructive Sleep Apnea (Section 5.4.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Barb F, et al.,	Aim: Assess the	Inclusion	Intervention: CPAP	1° endpoint: Decrease in BP	Limitations: Not blinded; both groups
2010 (57)	effect on BP of 1 y of	criteria: Pts with			consisted of pts with severe sleep-
<u>20007932</u>	treatment with CPAP	HTN (on	Comparator:	Results: At 12 mo, CPAP decreased	apnea.
	in nonsleepy pts with	medications or	Conservative treatment	SBP by 1.89 mm Hg (95% CI: 3.90–0.11	
	HTN and OSA.	≥140/90) and		mm Hg; p=0.065) and DBP 2.19 mm Hg	

	<u>Study type:</u> RCT Size: 359 pts; 12 mo	apnea-hypopnea index >19.	(dietary counseling and sleep hygiene advice).	(95% CI: 3.46– -0.93 mm Hg; p=0.001). The most significant reduction in BP was in pts who used CPAP for more than 5.6 h/night.	Conclusions: CPAP induced a significant reduction in BP, albeit small, in hypertensive pts with OSA.
	of follow-up			5	
Martinez-Garcia MA, et al., 2013 (58) 24327037	<u>Aim:</u> Assess the effect of CPAP on BP in pts with OSA and resistant	Inclusion criteria: Pts with resistant hypertension and	Intervention: CPAP Comparator: No therapy	1° endpoint: Change in 24-h ABPM from baseline to 12 wk.	Limitations: Did not use sham CPAP as placebo; open-label; short follow-up.
	hypertension. <u>Study type:</u> RCT <u>Size:</u> 194 pts; 3 mo follow-up	ÓŚA.		• When the changes in BP were compared between groups by intent to treat, the CPAP group achieved a greater decrease in 24-h mean BP (3.1 mm Hg (95% CI: 0.6, 5.6); p=0.02) and 24-h DBP (3.2 mm Hg (95% CI: 1.0, 5.4; p=0.005) but not in 24-h SBP (3.1 mm Hg (95% CI:	hypertension and OSA, CPAP treatment for 12 wk compared with control resulted in a decrease in 24-h mean and DBP and improvement in nocturnal pressure pattern.
				<ul> <li>-0.6–6.7; p=0.10) compared to control.</li> <li>There was also a greater nocturnal BP dipping pattern in CPAP treated pts than control (35.9% vs. 21.6%; adjusted OR: 2.4; CI: 1.2–5.1; p=0.02).</li> <li>There was a significant positive correlation between h of CPAP use and</li> </ul>	
				the decrease in mean 24-h BP (r=0.29; 0.006), SBP (r=0.25; p=0.02) and DBP (r=0.30; p=0.005).	
Lozano L, et al., 2010 (59) <u>20577130</u>	<u>Aim:</u> Assess effect of CPAP on pts with OSA and resistant	Inclusion criteria: Pts with resistant	Intervention: CPAP + conventional drug treatment	<u>1° endpoint</u> : Decrease in 24-h ABPM from baseline to 12 wk.	Limitations: Small study; only 3 mo follow-up; lack of sham control.
	hypertension. Study type: RCT	hypertension and OSA.	Comparator: Conventional drug	<u>Results:</u> Pts with ABPM confirmed resistant hypertension treated with CPAP, unlike those treated with conventional	<u>Conclusions</u> : CPAP as a complement to usual treatment improved mean 24-h DBP in pts with OSA and ABPM-
	Size: 96 pts; 3 mo of		treatment alone	therapy, showed a decrease in 24-h DBP $(-4.9\pm6.4 \text{ vs. } 0.1\pm7.3 \text{ mm Hg}; p=0.027)$ .	confirmed resistant hypertension.
	tollow-up			Pts who used CPAP >5.8 h showed a greater reduction in daytime DBP (-6.12 mm Hg; 95% CI: -1.45–10.82; p=0.004), 24-h DBP (-6.98 mm Hg; 95% CI: -1.86– - 12.1; p=0.009) and 24-h SBP (-9.71 mm Hg; 95% CI: -0.20– -19.22; p=0.46)	

Muxfeldt FS, et	Aim: Evaluate the	Inclusion	Intervention: CPAP +	1º endpoint: BP reduction at 6 mo via	Limitations: Nonblinded design: per
al 2015 (60)	effect of CPAP on nts	criteria: Pts with	conventional	ARPM	protocol analysis underpowered to show
25601933	with resistant	resistant	antihypertensive		the prespecified outcome of 6–7 mm Ha
20001700	hypertension and	hypertension and	therany	Posults:	SBP differences between CPAP and
			thorupy	• On an intention to treat analysis, there	control groups
	034.	034	Comparator:	• On an intention-to-treat analysis, there was no significant difference in any PD	control groups.
	Study type: DCT		Antibuportonsivo	was no significant unreferice in any DP	<b>Conclusions:</b> CDAD had no significant
	Study type. Not		therany alone	change, fielder in floctumal BP fail,	effect on clinic or ambulatory BP in hts
	Sizo: 131 nts: 6 mo of		Conventional	between CPAP and control groups. The	with resistant hypertension and
	<u>512e.</u> 434 pts, 0 m0 0		antihyportonsiyo	Dest effect of CPAP was on hight-time	modoratoly sovere to sovere OSA
	10110W-up		thorany included	SBP III per-protocol analysis, with greater	However, in the specific subgroup of hts
			spiropolactopo	Feduction of 4.7 mm Hg (95% CI: -1.6%–	with uncontrolled ambulatory PD_CDAD
			spironolacione.	5.8%; p=0.25, in comparison with the	may modestly reduce high time SBD
				control group.	and improve the pocturnal RD fall
				Median use of CPAP was 4.8 h.	nattorn The reason for lack of PD
					reduction in the overall study may have
					hear due to even lent control of PD with
					been due to excellent control of BP with
					median 5 medications, including
	Also Freebooks the	he charten			spironolacione, in the majority of pts.
Pedrosa RP, et	Aim: Evaluate the	Inclusion	Intervention: CPAP +	<u>1º endpoint</u> : BP reduction at 6 mo by	Limitations: Small; but strength was
al., 2013 (61)	effect of CPAP on pts	criteria: Pts with	conventional	ABPM.	rigorous exclusion of pts who were
23598607	with resistant	resistant	antihypertensive		nonadherent; control arm did not
	hypertension and	hypertension and	therapy (n=20)	<u>Results:</u> BP was 162±4/97±2 mm Hg	undergo placebo treatment; nonblinded.
	OSA.	OSA		prior to randomization. CPAP was used	
			Comparator:	for 6 h/night. Compared with the control	Conclusions: Treatment of OSA with
	Study type: RCT with		Antihypertensive	group, awake SBP/DBP decreased	CPAP significantly reduces daytime BP
			therapy alone (n=20).	significantly in the CPAP group (-	in pts with resistant hypertension.
	<u>Size:</u> 40 pts; 6 mo			6.5±3.3/-4.5±1.9 vs. +3.1±3.3/2.1±2/7	
	follow-up			mm Hg; p<0.05). BP changes were	
				significant only when pts were awake but	
				not at night by ABPM.	

### Data Supplement 9. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Dietary Fiber Intake) (Section 6.2)

Study Acronym;	Aim of Study;	Patient Population	Study Intervention (#	Endpoint Results	Relevant 2° Endpoint (if any);
Author;	Study Type;		patients) /	(Absolute Event Rates,	Study Limitations;
Year Published	Study Size (N)		Study Comparator (#	P value; OR or RR; & 95% CI)	Adverse Events
			patients)		

Whelton SP, et al., 2005 (62) <u>15716684</u>	Aim: Study the effect of dietary fiber intake on BP Study type: Systematic review and meta- analysis Size: • 21 RCTs (25 comparisons) with 1,477 pts • 20 of the RCTs were conducted in nonhypertensive persons • 13 double-blind; 3 single blind and 9 open label	Inclusion criteria: • RCT • ≥16 y • English language publication before Feb. 2004 • No concurrent interventions Exclusion criteria: Missing key data	Intervention: Fiber supplementation, either as a pill (8 trials), cereal/fruit/veg (15 trials), Pectin (1 trial), Guar gum (1 trial) <u>Comparator</u> : Placebo or no fiber supplementation	<u>1° endpoint</u> : In a pooled analysis of the overall group (hypertensive and normotensive persons), the mean for change in SBP was -1.15 mm Hg; 95% CI: -2.68–0.39 mm Hg and for DBP was -1.65 mm Hg; 95% CI: -2.70– -0.61 mm Hg. In the subgroup of 20 trials conducted in nonhypertensives, the mean change in SBP was -0.14 mm Hg; 95% CI: -1.10–0.86 mm Hg. In the subgroup of 5 trials conducted in hypertensives, the mean change in BP was -5.95 mm Hg; 95% CI: -9.50– -2.40) mm Hg.	<ul> <li>This is the most detailed and comprehensive review of the topic.</li> <li>It provides limited evidence, overall, that fiber supplementation results in a significant in BP and suggests no evidence in support of an effect in normotensives.</li> </ul>
Streppel MT, et al., 2005 (63) <u>15668359</u>	Aim: Study the effect of fiber supplementation on BP Study type: Systematic review and meta- analysis Size: • 23 RCTs (25 comparisons) in 1,404 pts • Mean duration=9 wk • Mean age=42 y • 16 double-blind, with 14 (67%) of the 21 comparisons conducted in normotensive pts • 3 trials based on plant protein and 4 trials based on animal protein	Inclusion criteria • Human RCT • BP 1° or 2° outcome • Publications between January 1966–January 2003 Exclusion criteria: • Inadequate reporting of the data • Concurrent intervention	Intervention: Fiber supplementation (average dose=11.5 g/d); soluble fiber in 11 trials, insoluble fiber in 7 trials, and a mixture in the remaining trials Comparator: Placebo or no fiber supplementation	<u>1° endpoint</u> : In the overall group (hypertensive and normotensive pts), a pooled analysis identified a MD for change in SBP of -1.13 mm Hg; 95% CI: -2.49–0.23. In a subgroup of 17 trials conducted in "nonhypertensives" (mean baseline BP<140/90 mm Hg or <50% receiving antihypertensive medication), the mean treatment effect was -0.23 mm Hg; 95% CI: -1.43–0.98 in univariate analysis and -1.00 mm Hg; 95% CI: - 1.94– -0.06 mm Hg in multivariate analysis that adjusted for age, sex, study design, duration of intervention, and fiber dose. The corresponding effects in 8 trials conducted in hypertensives were -4.53 mm Hg; 95% CI: -6.69– -2.38 mm Hg; and -2.42 mm Hg; 95% CI: -5.28–0.45 mm Hg. <u>Safety endpoint</u> : N/A	• Findings consistent with experience in the meta-analysis by Whelton et al.

Evans CE, et al., 2011 (64) <u>25668347</u>	Aim: Study the effect of fiber supplementation on BP Study type: Systematic review and meta- analysis Size: 28 trials met the inclusion criteria and reported fiber intake and SBP and/or DBP. 18 trials were included in a meta-analysis.	Inclusion criteria • RCTs, in humans of at least 6 wk duration • Fiber isolate or fiber-rich diet against a control or placebo • Published between 1 January 1990 and 1 December 2013. Exclusion criteria: N/A	Intervention: Fiber supplementation (average dose =11.5 g/d) -soluble fiber in 11 trials, insoluble fiber in 7 trials, and a mixture in the remaining trials Comparator: Placebo or no fiber supplementation	<u>1° endpoint</u> : Studies were categorized into 1 of 12 fiber-type categories. The pooled estimates for all fiber types were -0.9 mm Hg (95% CI: -2.5–0.6 mm Hg) and -0.7 mm Hg (95% CI: -1.9–0.5 mm Hg) for SBP and DBP, respectively. The median difference in total fiber was 6g. Analyses of specific fiber types concluded that diets rich in beta-glucans reduce SBP by 2.9 mm Hg (95% CI: 0.9, 4.9 mm Hg) and DBP by 1.5 mm Hg (95% CI: 0.2–2.7 mm Hg) for a median difference in beta-glucans of 4 g. Heterogeneity for individual fiber types was generally low. <u>Safety endpoint</u> : N/A	<ul> <li>Higher consumption of beta- glucan fiber is associated with lower SBP and DBP.</li> <li>The results of this review are consistent with recommendations to increase consumption of foods rich in dietary fiber, but some additional emphasis on sources of beta-glucans, such as oats and barley, may be warranted.</li> </ul>
---	---	---	--	--	--

# Data Supplement 10. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Fish Oil) (Section 6.2)

Study	Aim of Study;	Patient Population	Study Intervention (#	Endpoint Results	Relevant 2° Endpoint (if any);
Acronym;	Study Type;		patients) /	(ADSOIULE EVENT Rales, Divelue: OD or DD: 8,05% CI)	Study Limitations;
Author, Voar Dublishod	Sludy Size (N)		siduy comparator (#	P value, OR OI RR, & 95% CI	Adverse Events
Campbell F, et al., 2012 (65) <u>22345681</u>	Aim: Study the effect of fish oil supplementation on BP	Inclusion criteria: • RCT • English language publication before	Intervention: Fish oil given in capsule form, with doses varying from 0.8–13.33 g/d.	<u>1° endpoint</u> : In a pooled analysis of the 8 trials conducted in hypertensive pts, the mean for change in SBP was - 2.56 mm Hg; 95% CI: -4.53– -0.58 mm	<ul> <li>This is the most recent of many that have been published.</li> <li>Previous meta-analyses have been conducted by Appel et al</li> </ul>
	Study type: Systematic review and meta-analysis Size: • 17 RCTs (25 comparisons) with 1,524 pts. • 9 trials were conducted in normotensives (1,049	January 2011 • Duration ≥8 wk <u>Exclusion criteria</u> : N/A	<u>Comparator</u> : Placebo (usually corn oil, olive oil, or safflower oil).	Hg. The corresponding SBP change for the 9 trials conducted in normotensives was -0.50 mm Hg; 95% CI: -1.44– 0.45.	<ul> <li>(1993), Morris et al. (1993), Geleijnse et al (2002) and Dickinson et al. (2006).</li> <li>In general, the findings have been fairly consistent in demonstrating a relatively small (2 3/4 mm Hg SBP) but significant effect, with most of this being attributable to the results in trials conducted in hypertensive pts.</li> </ul>

Rodriguez- Leyva D, et al.,	pts with mean age of 47 y). Follow-up varied 2–26 wk. <u>Aim:</u> Study the effect of flaxseed on BP in	Inclusion criteria: • >40 y	Intervention: Pts given 1 food item per day for	<u>1° endpoint</u> : SBP and DBP consistently decreased in the flaxseed	<ul> <li>Based on this 1 RCT, flaxseed appeared to have a significant</li> </ul>
2013 (66)	hypertensive pts	• PAD for >6 mo, ABI	6 mo, containing either	group over the course of the study.	BP lowering effect
24120170	Study type: RCT	<0.9	or placebo. Flaxseed	dropped significantly to $136\pm22$ mm Hg (n=0.04). On the contrary, in the	
	Size: 110 pts with PAD	Inability to walk, bowel disease, moderate to severe renal failure, life	acids, lignans, and fiber.	placebo group, SBP rose slightly to 146±21 mm Hg. After 6 mo of intervention, DBP in the flaxseed group	
		expectancy <2 y with high cardiac risk, allergy to any	Comparator: Placebo	fell to 72±11 mm Hg (p=0.004), whereas DBP in the placebo group remained the same (79±10 mm Hg)	
		who plan to undergo			
		surgery during the course of the trial, and no more than 2 fish meals per wk			

Data Supplement 11. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Potassium Supplementation to Placebo or Usual Diet) (Section 6.2)

	Acronym; Author; Year Published
Whelton PK, et al., 1997 (67)Aim: Study the effect of potassium supplementation on BPInclusion criteria: • Human RCT • Without HTN 	Whelton PK, et al., 1997 (67) <u>9168293</u>

	<ul> <li>Overall, 33 RCT (n=2,609)</li> <li>2 RCTs (n=1,049) in normotensives</li> </ul>		(placebo in 10 RCT and usual diet in 2 RCT)	In the 20 trials conducted in hypertensives, mean: -4.4 mm Hg; 95% CI: -6.6– -2.2 for SBP and -2.5 mm Hg; 95% CI: -4.9– -0.1 for DBP <u>Safety endpoint</u> : N/A	<ul> <li>The 1 RCT conducted in African-Americans (n=87) identified a mean treatment effect size of -6.9 mm Hg; 95% CI: -9.34.4 for SBP (p&lt;0.001) and -2.5 mm Hg; 95% CI: -4.30.8 for DBP (p=0.004).</li> <li>In the entire cohort (trials conducted in pts with HTN and normotension), net changes in SBP and DBP were directly related to level of urinary sodium excretion during the trial.</li> </ul>
Aburto NJ, et al., 2013 (68) <u>23558164</u>	Aim: Study the effect of potassium supplementation on BP Study type: Systematic review and meta-analysis Size: 21 RCTs (n=1,892); 16 in pts with HTN (n=818) and 3 RCTs in pts without HTN (n=757)	Inclusion criteria: • RCT in humans • Duration ≥4 wk • 24-h collections of urinary potassium • No concomitant interventions Exclusion criteria: Pts who were acutely ill, HIV positive, hospitalized, or had impaired urinary excretion of potassium	Intervention: Potassium supplementation in 20 trials, supplements plus diet/education in 1 trial, and diet/education alone in 2 trials. Comparator: No potassium supplementation (placebo or usual diet)	<ul> <li><u>1° endpoint</u>:</li> <li>Overall change in SBP=- 5.93; 95% CI: -10.151.70. After removing outlier trials, the change was -3.49 mm Hg; 95% CI: -5.151.82 mm Hg.</li> <li>In 16 trials conducted in hypertensives, change in SBP was -5.32 mm Hg; 95% CI: -7.203.43.</li> <li>In the 3 trials conducted in persons without HTN, change in SBP was 0.09 mm Hg; 95% CI: -0.77-0.95.</li> </ul>	<ul> <li>1 trial (TOHP Phase I) incorrectly entered twice so only 2 trials really available. However, this does not change overall finding.</li> <li>The negative results for normotensives in this meta-analysis (and difference with the findings by Whelton et al) probably reflects the requirement for a duration of ≥4 wk and the fact that few trials of this duration have been conducted in normotensives.</li> </ul>
Geleijnse JM, et al., 2003 (69) <u>12821954</u>	Aim: Study the effect of potassium supplementation on BP Study type: Systematic review and meta- regression analysis Size: 27 RCTs; 19 in pts with HTN and 11 RCTs in pts without HTN	Inclusion criteria: • RCT in adults • Published after 1966 • Duration ≥2 wk • No concomitant interventions Exclusion criteria: • Disease • Outlier results (1 trial)	Intervention: Potassium supplementation Comparator: No potassium supplementation	<ul> <li><u>1° endpoint</u>:</li> <li>Overall change in SBP=- 2.42; 95% CI: -3.751.08</li> <li>In the 19 trials conducted in hypertensives, change in SBP was -3.51 mm Hg; 95% CI: -5.311.72</li> <li>In the 3 trials conducted in persons without HTN, change in SBP was 0.97 mm Hg; 95% CI: -3.07-1.14</li> <li><u>Safety endpoint</u>: N/A</li> </ul>	<ul> <li>Imputation for missing data</li> <li>In addition to the treatment effect difference by presence/absence of HTN, there was a trend toward a larger treatment effect in older age (≥45 y), and to a lesser extent higher baseline urinary Na (&gt;150 mmol/24 h) and greater increase in urinary K (&gt;44 mmol/24 h)</li> </ul>

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (#	Endpoint Results (Absolute Event Rates, P value; OR or RR; &	Relevant 2° Endpoint (if any); Study Limitations;
Rebholz CM, et al., 2012 (70) 23035142	Aim: Study the effect of protein intake on BP Study type: Systematic review and meta- analysis Size: • 40 RCTs (44 comparisons) with 3,277 pts • 32 comparisons of protein vs. carbohydrate • 12 comparisons of vegetable vs. animal protein • 35 of the RCTs were conducted in normotensive persons (28 with SBP in the prehypertensive range)	Inclusion criteria: • RCT in humans • ≥18 y • Publication between January 1,1950 and April 1, 2011 • No concurrent interventions • No more than 10% difference in calories, sodium, potassium, fiber between the treatment arms • Duration ≥1 wk Exclusion criteria: Missing key data	Intervention: • Protein intake • 1st meta-analysis: any source of protein, with a median protein supplementation dose of 40 g/d (20–66 g/d) • 2nd meta-analysis: specifically vegetable or animal protein Comparator: • 1st meta-analysis: carbohydrate • 2nd meta-analysis: vegetable or animal protein	<ul> <li>1° endpoint: <ul> <li>1st meta-analysis</li> </ul> </li> <li>1st meta-analysis</li> <li>There was a fairly consistent trend for a small BP lowering effect of protein compared to carbohydrate intake (86% of the trials). In a pooled analysis of the overall group (hypertensive and normotensive persons), the mean for change in SBP was -1.76 (95% CI: - 2.331.20). In a subgroup of 15 trials in which none of the participants were receiving antihypertensive medication, the mean change in SBP was -1.95 (95% CI: -2.621.29).</li> <li>2<sup>nd</sup> meta-analysis</li> <li>For the comparison of vegetable vs. animal protein, there was no evidence of a difference in BP. In a pooled analysis of the overall group (hypertensive and normotensive pts) the mean change in SBP was -0.10 (95% CI: -2.31 - 2.11) mm Hg. In a subgroup of 8 trials in which none of the pts were receiving antihypertensive medication, the mean change in SBP was -0.55 (95% CI: -3.06 - 1.96).</li> </ul>	<ul> <li>This is the most detailed and comprehensive review of the topic.</li> <li>It provides strong evidence that protein supplementation results in a significant but modest reduction in BP and suggests that the effect size is similar following supplementation with protein from vegetables or animals.</li> </ul>
Lielemans SM, et al., 2013 (71) <u>23514841</u>	<u>Aim</u> : Study the effect of protein intake on BP	Inclusion criteria • RCTs, in "generally healthy adults"	Intervention: Protein intake	<ul> <li><u>1° endpoint:</u></li> <li>At baseline, the mean for age and SBP were 50 (range: 31–74) and 128</li> </ul>	• Findings consistent with experience in the meta- analysis by Rebholz et al.

# Data Supplement 12. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Protein Intake on BP) (Section 6.2)

	Study type: Systematic review and meta- analysis Size: 16 RCT (210 comparisons) of protein vs. carbohydrate in 1,449 pts, with 14 (67%) of the 21 comparisons conducted in normotensive pts. -3 trials based on plant protein and 4 trials based on animal protein	<ul> <li>Publications between January 1966–January 2012</li> <li><u>Exclusion criteria</u>:</li> <li>Inadequate reporting of the data</li> <li>Concurrent intervention</li> </ul>	Carbohydrate intake	<ul> <li>(range: 112–144). During the trials, the MD in protein intake was 48 g/d (range: 26–74 g/d).</li> <li>In the overall group (hypertensive and normotensive participants), a pooled analysis of comparisons from 14 trials (1,208 pts) identified a MD for change in SBP of -2.11 (95% CI: -2.8– -1.37) for protein vs. carbohydrate. In 3 RCTs that employed plant protein (327 pts), the mean treatment effect was -1.95 (95% CI: -3.21– -0.69) and in 4 RCTs that employed animal protein (574 pts), the corresponding difference was -2.20 (95% CI: -3.36– -1.03).</li> <li>Safety endpoint: N/A</li> </ul>	
Dong JY, et al., 2013 (72) <u>23829939</u>	Aim: Study the effect of protein intake on BP in DM-2 Study type: Systematic review and meta- analysis Size: 9 RCTs with 418 pts	Inclusion criteria: • RCTs in adults with DM-2 • Publications up to August 2012 • High protein diet intervention and ≥5% difference in dietary protein intake between intervention and control groups • Trial duration ≥4 wk Exclusion criteria: Inadequate reporting of key data	Intervention: High protein diet intervention and ≥5% difference in dietary protein intake between intervention and control groups Comparator: N/A	<u>1° endpoint</u> : Pooled experience in the 14 trials identified a nonsignificant reduction in mean SBP of -3.10 (95% Cl: -4.63– -1.56). <u>Safety endpoint</u> : N/A	<ul> <li>Heterogeneous group of open label trials with a range of duration from 4–24 wk (median of 12 wk). In addition to DM-2, all of the participants were overweight or obese.</li> <li>The quality of the trials varied, drop-out rates ranged from 0%–0%, and only 1 trial was analyzed using an intent to treat approach.</li> </ul>
Dong JY, et al., 2013 (73) <u>23823502</u>	Aim: Study the effect of probiotic fermented milk on BP. Study type: Systematic review and meta- analysis. All but 1	Inclusion criteria: • RCTs • Placebo controlled • Published prior to March 2012 Exclusion criteria:	Intervention: Probiotic fermented milk (100– 450 g/d) Comparator: Not specified but all of the trials reported to be	1° endpoint:Pooled experience in the9 trials identified a nonsignificantreduction in mean SBP of -3.59 (95%CI: -7.58–0.40).Safety endpoint:N/A	• The most recent of several meta-analyses conducted by different groups of investigators that have reported a similar effect size following administration of lactopeptides, especially the

(cross-over) trial said to use a parallel design. Antihypertensive drug use reported in 3 trials and in an additional 3 trials mean SBP exceeded 150 mm Hg at baseline.	<ul> <li>Intervention with enzymatically hydrolysed milk</li> <li>Cointervention</li> </ul>	placebo controlled. However, 2 were single blind and 1 was open label.	<ul> <li>lactotripeptides Valine- Proline-Proline and Isolucine- Proline-Proline.</li> <li>These findings may have special relevance for countries, like Japan, where consumption of fermented milk products is common.</li> </ul>
Size: 14 RCTs with 702 pts (median size=40).			

Data Supplement 13. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Sodium Reduction to Placebo or Usual Diet) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
NUTRICODE Mozaffarian D, et al., 2014 (74) <u>25119608</u>	Aim: Study the effect of sodium reduction on BP and CVD mortality Study type: Meta- regression analysis Size: 103 RCTs (107 comparisons) with 6,970 pts; 38 of the 107 comparisons were conducted in normotensive pts	Inclusion criteria: RCT in 2 previous Cochrane meta-analyses Exclusion criteria: • Duration <1 wk • Mean 24-h collections or estimates of urinary sodium reduced <20 mmol in the intervention group compared to control • Concomitant interventions	Intervention: Sodium reduction Comparator: No sodium reduction	<ul> <li><u>1° endpoint</u>:</li> <li>Strong evidence for a linear relationship between reduction in sodium intake and lower levels of SBP throughout the entire distribution of sodium studied, with larger reductions in older persons, blacks (compared to whites) and hypertensives (compared to normotensives). For a white, normotensive population at age 50 y, each reduction of 100 mmol/d (2.3 g/d) in dietary sodium lowered SBP by a mean: 3.74 (95% CI: 5.18–2.29).</li> <li>Modeling based on global estimates of sodium intake, effect of sodium reduction on BP, and effect of BP reduction on CVD mortality attributed 1.65 million CVD deaths annually due sodium intake &gt;2 g/d. this would represent 9.5% (95% CI: 6.4–12.8) of all CVD mortality. Estimates were not</li> </ul>	<ul> <li>RCT meta-regression analysis that provides evidence for BP lowering following a reduction in dietary sodium intake, overall and in normotensive persons, with a more pronounced effect in those who were older, black and had a higher starting level of BP.</li> <li>These findings are consistent with other reports.</li> <li>The modeling analysis suggested sodium reduction would yield important population health benefits but did not specify the magnitude of the potential benefit for pts within the normal BP range.</li> </ul>

Aburto NJ, et al., 2013 (68) <u>23558164</u>	Aim: Study the effect of sodium reduction on BP Study type: Systematic review and meta-analysis Size: Overall study included 36 trials (49 comparisons) conducted in 6,736 pts. Of these, 3,263 were nonhypertensive. The results in normotensives in this table are based on experience in 7 RCTs conducted in 3,067 normotensive pts.	Inclusion criteria: • RCT in humans • Trial duration ≥4 wk • 24-h urinary sodium ≥40 mmol/d less in treatment compared to control group • No concurrent interventions • Not acutely ill <u>Exclusion criteria</u> : Lack of above	Intervention: Sodium reduction Comparator: No sodium reduction	provided separately for hypertensive and normotensive persons. <u>1° Safety endpoint</u> : N/A <u>1° endpoint</u> : In pooled analysis, the overall change in SBP was -3.39 (95% CI: -4.31– - 2.46) mm Hg. In the pts with HTN, the change was -4.06 (95% CI: -5.15– -2.96). In the normotensives, the change was -1.38 (95% CI: -2.74–0.02). <u>Safety endpoint</u> : In the small number of relevant trials, there was no significant effect of sodium reduction on lipid levels (Total cholesterol, LDL-cholesterol, HDL- cholesterol, triglyceride levels; 11 trials) or on plasma (7 trials) or urinary catecholamine levels (2 trials). Experience in 4 trials (3 which could not be included in the meta-analysis) suggested a beneficial effect of sodium reduction on urinary protein excretion.	• Study inclusion/exclusion criteria designed to yield a group of trials that would provide results that have relevance for clinical practice and public health. In this context, reduced sodium intake resulted in a statistically significant but small reduction in SBP.
He FJ, et al., 2013 (75) <u>22437256</u>	Aim: Study the effect of sodium reduction on BP Systematic review, meta-analysis and meta-regression analysis Size: Overall study included 34 trials (37 comparisons) conducted in 3,230	Inclusion criteria: • RCTs • Healthy adults ≥18 y • Trial duration ≥4 wk • Sodium intake only difference between treatment and control group • 24-h urine sodium ≥40 mmol less in treatment compared to control <u>Exclusion criteria</u> : Lack of above	Intervention: Sodium reduction Comparator: No sodium reduction	<ul> <li><u>1° endpoint</u>: In an overall pooled analysis, the change for SBP was -4.18 (95% CI: -5.183.18) mm Hg. In the trials of persons with HTN, the mean change was -5.39 (95% CI: -6.624.15) mm Hg. In the trials conducted in normotensives, the change in SBP was -2.42 (95% CI: -3.561.29) mm Hg.</li> <li>In meta-regression analysis, change in 24-h urinary sodium was significantly associated with reduction in SBP (4.3 mm Hg for a 100 mmol reduction in 24-h urinary sodium).</li> </ul>	<ul> <li>Study inclusion/exclusion criteria designed to yield a group of trials that would provide results that have relevance for clinical practice and public health. In this context, reduced sodium intake resulted in a significant and potentially important reduction in SBP.</li> <li>The meta-regression results were consistent with a dose- response relationship in normotensive pts</li> </ul>

	pts. 12 of the RCTs (14 comparisons) were conducted in 2,240 normotensive pts.			Safety endpoint: In the small number of relevant trials (which included both hypertensive and normotensive pts) that provided safety endpoint measurements (4–14 trials), there was no change in total, LDL- or HDL- cholesterol, or triglyceride levels. There were small significant increases in plasma renin activity, aldosterone, and noradrenaline levels but these were consistent with expected physiologic responses to sodium reduction.	
Graudal NA, et al., 2012 (76) <u>22068710</u>	Aim: Study the effect of sodium reduction on BP Study type: Systematic review and meta-analysis Size: Overall study included 167 trials. Of these, 71 RCTs were conducted in 5,577 normotensive pts, with the following characteristics: • Median age: 27 y (13–67 y) • Median trial duration: 7 d (4– 1,100 d) • 5,292 Whites (71 studies) • 268 Blacks (7 studies) • 215 Asians (3 studies)	Inclusion criteria: • RCTs • 24-h collections or estimates from ≥8 h collections of urinary sodium excretion Exclusion criteria: Systematic studies in unhealthy pts with diseases other than HTN	Intervention: Sodium reduction Comparator: No sodium reduction	<ul> <li><u>1º endpoint</u>: The overall effect of sodium reduction was not presented.</li> <li>A forest plot of 71 comparisons (from 61 trials) in the 4,919 normotensive whites assigned to sodium reduction compared to usual sodium intake identified a trend towards lower SBP in 50 (70%), no difference in 8 (11%), and higher SBP in 13 (19%). In a pooled analysis, sodium reduction compared to usual sodium intake in the normotensives yielded the following MDs in SBP:</li> <li>Whites: -1.27 (95% CI: -1.88– -0.66)</li> <li>Blacks: -4.02 (95% CI: -7.37– -0.68)</li> <li>Asians: -1.27 (95% CI: -3.07– -0.54)</li> <li>A corresponding analysis in the hypertensives yielded the following MDs in SBP:</li> <li>Whites: -5.48 (95% CI: -6.53– -4.43)</li> <li>Blacks: -6.44 (95% CI: -8.85– -4.03)</li> <li>Asians: -10.21 (95% CI: -16.98– -3.44)</li> </ul>	<ul> <li>Heterogeneous group of trials that included many small studies of short duration in young persons.</li> <li>Overall finding of lower BP in those assigned to a reduced intake of dietary sodium, with an apparently greater effect in Blacks compared to Whites and Asians.</li> <li>The hormone changes in this meta-analysis likely reflect a physiologic response to sodium reduction, especially in studies of short duration and rapid changes in sodium intake. The increases in total cholesterol and triglyceride levels were not noted in the meta-analyses conducted by Aburto et al. and He et al.</li> </ul>

				comparisons in both hypertensive and normotensive participants) that provided safety endpoint measurements, significant increases in the standard MD for plasma renin activity (70 trials), aldosterone (51 trials), noradrenaline (31 trials), adrenaline (14 trials), and weighted MD for total cholesterol (24 trials), and triglyceride (18 trials) levels. There was no significant effect of sodium reduction on LDL-cholesterol (15 trials) and HDL-cholesterol (17 trials).	
DASH-Sodium Trial Sacks FM, et al., 2001 (77) <u>11136953</u>	Aim: Study the effect of sodium reduction on BP Study type: Randomized, controlled crossover trial Size: Overall study based on 412 pts, of whom 243 were normotensive	Inclusion criteria: Adults ≥22 y Exclusion criteria: Taking antihypertensive medication, heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements, >14 drinks/wk	Intervention: Feeding study in which pts were randomized to a DASH or control diet at 3 levels of assigned dietary sodium intake (High=210 mmol/d; Intermediate=100 mmol/d; Low=50 mmol/d) <u>Comparator</u> : Each pt served as their own control (crossover design)	<ul> <li><u>1° endpoint</u>:</li> <li>Reduced sodium intake resulted in a significant reduction in SBP, with a greater reduction during assignment to the Low compared to the Intermediate sodium intake diet. At every level of sodium intake, the achieved reduction in SBP was greater on the control group compared to the DASH diet and for Blacks compared to other pts.</li> <li>Reducing sodium intake from the high to intermediate level decreased SBP by 2.1 mm Hg (p&lt;0.001) during the control diet and 1.3 mm Hg (p=0.03) during the DASH diet.</li> <li>Reducing sodium intake from the intermediate low level decreased SBP by a further 4.6 mm Hg (p&lt;0.001) during the control diet and 1.7 mm Hg (p&lt;0.01) during the control diet.</li> <li>Safety endpoint: N/A</li> </ul>	<ul> <li>This trial provides the best (direct) evidence for a dose- response treatment relationship between sodium intake and level of BP.</li> <li>It also suggests the relative effect of reduced sodium intake is greater in persons with a typical U.S. diet but the combination of sodium reduction and consumption of a DASH-type diet results in a lower level of BP than can be achieved with either dietary modification on its own.</li> <li>Consistent with other trials and meta-analyses, it suggests the effect of a reduced sodium intake is greater in Blacks compared to others, especially for those consuming a typical U.S. diet.</li> </ul>
TOHP II Trial	Aim: Study the effect	Inclusion criteria:	Intervention:	<u>1° endpoint</u> :	• This was the largest trial of
(Sodium	of sodium reduction	Healthy community-	Behavior change	Change in SBP	sodium reduction in HTN
component)	on BP and prevention	dwelling adults 30–54 y	intervention aimed at	• Compared to usual care, the sodium	prevention and also provides
	OFFIN.	BMI between 110%	sludying the effects of	reduction group experienced a significant	The longest duration of follow.
ai., 2000 (78)	Study type:	and 165% of desirable	roductions in distance	mean reduction of 51 mmol for 24-h urinary	The assumptions for a main     offocts factorial analysis
10372004	Dandomized	body weight	sodium intako during	excretion and -2.9 (SD: 0.5) mm Hg	(independence of the
	Kanuunnizeu,		soulum make during	(p<0.001) in SBP at 6 mo (-5.1 mm Hg in	(independence of the

	controlled factorial trial. <u>Size</u> : 2,382 pts, of whom 594 were randomized to sodium reduction (alone) and 596 were randomized to usual care.	<ul> <li>Not taking BP-lowering medication</li> <li>Mean SBP &lt;140 mm</li> <li>Hg and DBP 83–89 mm</li> <li>Hg</li> <li>Exclusion criteria: Taking antihypertensive medication, Heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements, &gt;14 drinks/wk.</li> </ul>	up to 48 mo (minimum 36 mo) of follow-up. <u>Comparator</u> : Usual care group	<ul> <li>the sodium reduction group and -2.2 mm Hg in the usual care group).</li> <li>A progressive reduction in effect size for urinary sodium excretion and BP was noted over time, with mean for SBP at 18, 36 mo and termination of -2.0 (SD: 0.5) mm Hg (p&lt;0.001), -1.2 (SD: 0.5) mm Hg (p=0.02), and -1.0 (SD: 0.5) mm Hg (p=0.5).</li> <li><u>Prevention of HTN</u></li> <li>At 6 mo of follow-up the incidence of new onset HTN was 39% lower in the pts randomized to reduced dietary sodium intake compared to the usual care group (p=0.04).</li> <li>During more prolonged follow-up, the effect size decreased but remained significant after 48 mo of follow-up (14% reduction; p=0.04). Overall, the incidence of HTN was reduced by 18% (p=0.048).</li> <li><u>Safety endpoint</u>: N/A</li> </ul>	interventions) were not demonstrated. Given this finding, the most reliable analysis of this trial was comparison of the experience in each active intervention group with the usual care group. This results in a reduction in statistical power. • Consistent with the pattern in the proceeding TOHP I trial sodium reduction reduced BP and the incidence of HTN but the effect sizes for sodium reduction and BP as well as the difficulty of maintaining the intervention in highly motivated and extensively counselled participants underscores the difficulty of achieving sodium reduction in the general population without changes in food processing and restaurant/fast food preparation practicos
TOHP Phase I 1992 (79) <u>1586398</u>	Aim: Study the effect of sodium reduction on BP and prevention of HTN Study type: Randomized, controlled factorial trial. Size: Overall, 2,182 adults, with the 327 assigned to sodium reduction compared	Inclusion criteria: • Community-dwelling adults 30–54 y • Not on antihypertensive medication • DBP 80-89 mm Hg • Healthy Exclusion criteria: • Disease • Inability to comply with the protocol	Intervention: Behavior change intervention Comparator: Usual care	1° endpoint:         Change in DBP         2° endpoint:         Change in SBP         Safety endpoint:         CVD events, symptoms and general and well being	<ul> <li>Significantly lower DBP (0.9 mm Hg; p&lt;0.05) and SBP (1.7 mm Hg; p&lt;0.01) in the sodium reduction group compared to usual care</li> <li>Few CVD events</li> <li>No difference in symptoms</li> <li>Significant improvement in general well-being at 6 and 18 mo (p&lt;0.05)</li> </ul>

	to 417 usual care controls				
Cook NR, et al., 2007 (80) <u>17449506</u>	Aim: Study the effect of sodium reduction on CVD morbidity and mortality. Study type: 10–15 y post-trial follow-up of TOHP I and TOPH II pts that took advantage of the randomized trial design. Vital status was obtained for 100% of the pts and information on morbidity was obtained from 2,415 (77%) of the pts. Size: 744 TOHP Phase I and 2,382 TOHP Phase II pts	Inclusion criteria: Assigned to dietary sodium reduction or control in TOHP Phase I or TOHP Phase II. Exclusion criteria: None	Intervention: Behavior change intervention aimed at studying the effects of modest (25%–30%) reductions in dietary sodium intake during TOHP Phase I or TOHP Phase II. <u>Comparator</u> : No sodium reduction intervention.	<ul> <li><u>1° endpoint</u>:</li> <li>200 CVD events and 77 deaths during follow-up</li> <li>Kaplan-Meier plots identified trends toward less morbidity and mortality in those who had been randomized to sodium reduction compared to usual care, with a consistent pattern for the TOHP I and TOHP II participants</li> <li>Risk of a CVD event was 30% lower (RR: 0.70; 95% CI: 0.53–0.94; p=0.018) among those randomized to sodium reduction compared to usual care, after adjustment for trial, clinic, age, race, sex, baseline weight and sodium excretion</li> <li>RR for total mortality was 0.80 (95% CI: 0.51–1.26).</li> </ul>	• Dietary sodium reduction, previously shown to reduce BP and prevent HTN in the TOHP I and TOHP II trials, appeared to reduce CVD events during extended post-trial follow-up of the pts from these 2 trials.

Data Supplement 14. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Stress Reduction) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Canter PH, et al., 2004 (81) <u>15480084</u>	Aim: Study the effect of transcendental meditation on BP	Inclusion criteria: • RCT in humans • Publication in any language until May	Intervention: • Use of transcendental meditation techniques as taught by Maharishi Mehach Vari	<u>1° endpoint</u> : Statistically significant reduction in SBP reported in 3 of 5 trials that provided such	<ul> <li>Only a handful of RCTs available from the large number of publications on this topic.</li> <li>Trials had methodological weaknesses and were subject to potential bias due to</li> </ul>
	review Size:	No concurrent     interventions	Practiced on a regular basis over an extended period	<u>1° Safety endpoint</u> : N/A	the affiliation of authors to the transcendental meditation organization.

1011 54-150 pts	<ul> <li>6 RCTs with wide rang of pts: young to elderly; healthy volunteers to Blacks with HTN.</li> <li>HTN: 2 trials</li> <li>High normal BP: 2 trial:</li> <li>Normotensive: 1 trial</li> <li>Not stated: 1 trial</li> <li>Sample sizes ranging from 34–156 pts</li> </ul>	Exclusion criteria: N/A	<u>Comparator</u> : No treatment, sham, alternative treatment	<ul> <li>A few trials reported small reductions in SBP but clinical relevance of findings is unclear.</li> <li>Most of the trials were underpowered and could have missed a significant finding.</li> <li>The authors concluded that "there is at present insufficient good quality information to conclude whether or not transcendental meditation has a cumulative positive offect on RP"</li> </ul>
-----------------	---	----------------------------	---	---

# Data Supplement 15. RCTs and Meta-analyses Studying the Effect of Nonpharmacologic Interventions on BP (Dietary Patterns) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Appel LJ, et al., 1997 (82) <u>9099655</u>	Aim: Study the effect of dietary patterns on BP Study type: • Multicenter RCT • 3 arm parallel design • 3 wk pre- randomization run-in phase • Feeding study with 8 wk of intervention Size: 459 adults, mean age 44 y. (326 normotensive)	Inclusion criteria: • Adults ≥22 y • SBP<160 mm Hg and DBP 80–95 mm Hg • No antihypertensive medication Exclusion criteria: • CVD event within 6 mo • Poorly controlled DM or hyperlipidemia • BMI ≥35 • Pregnancy or lactation • Chronic illness that would interfere with participation • Unwillingness to stop taking vitamins, mineral supplements, Ca++ antacids	Intervention: • Diet high in fruits and vegetables • "Combination" diet high in fruits, vegetables, low-fat dairy products, and reduced total fat, saturated fat and cholesterol. <u>Comparator</u> : Usual U.S. diet	<ul> <li><u>1° endpoint</u>: Compared to the control diet, both intervention diets reduced BP, with an overall mean (95% CI) reduction of:</li> <li>Fruits and Veg. Diet: SBP: -2.8 (95% CI: -4.70.9) DBP: -1.1 (95% CI: -2.40.3)</li> <li>Combination Diet: SBP: -5.5 (95% CI: -7.43.7) DBP: -3.0 (95% CI: -4.31.6)</li> <li>The BP changes in the subgroup with HTN were:</li> <li>Fruits and Veg. Diet: SBP: -7.2 (-11.4, -3.0) DBP: -2.8 (-5.4, -0.3)</li> <li>Combination Diet: SBP: -11.4 (-15.9, -6.9) DBP: -5.5 (-8.2, -2.7)</li> </ul>	<ul> <li>This trial was the first of several to document the value of the combination diet (later renamed the DASH diet).</li> <li>The BP reductions noted with the DASH (combination) diet were substantial and well maintained.</li> <li>Generalizability was limited due to the nature of the intervention (feeding study) and the relatively short period of intervention experience (8 wk)</li> </ul>

		● Consuming ≥14		The corresponding changes in the	
		alcoholic drinks with		subaroup of normotensives were:	
		Donal insufficiency		Fruits and Veg. Diet:	
		• Renal insufficiency		SRD: $0.9(2.7, 1.1)$	
				$DD \cdot 0.0 (-2.7, 1.1)$	
				DDF0.3 (-1.9, 1.3)	
				SBP: -3.5 (-5.3, -1.6)	
				DBP: -2.1 (-3.6, -0.5)	
				19 Cofety and points infragrant and	
				<u>is Salety enupoint:</u> innequent and	
				gastrointestinai symptoms in each	
				group	
Sacks FM, et al.,	<u>Aim:</u> Study the effect	Inclusion criteria:	Intervention: 3 levels of	<u>1° endpoint:</u>	I his trial provided additional
2001 (77)	of different levels of	● Adults ≥22 y	dietary sodium while	<ul> <li>At each level of sodium intake,</li> </ul>	documentation of the effectiveness of a
<u>11136953</u>	sodium intake on BP	<ul> <li>Average SBP between</li> </ul>	consuming a DASH or	SBP and DBP were lower during	DASH diet in lowering BP in
	during consumption of	120–159 mm Hg and	usual U.S. diet. The	consumption of the DASH diet	normotensives (and hypertensives) and
	a DASH or usual U.S.	average DBP between	target sodium intake	compared to the usual U.S. diet, the	the complementary benefit of
	diet	80–95 mm Hg	levels for a daily energy	difference being greatest with high	consuming a reduced intake of sodium.
		No use of	intake of 2,100 kcal	sodium intake and lowest with low	
	Study type:	antihypertensive	were:	sodium intake, with the mean SBP	
	Multicenter RCT with	medication	High: 150 mmol (3,450	difference between the DASH and	
	2 parallel diet arms	moulouton	mg)/d	usual US diets during high.	
	(DASH diet or usual	Exclusion criteria	Intermediate: 100 mmol	intermediate and low sodium intake	
	U.S. diet)	Heart disease renal	(2,300 mg)/d	heing -5.9 (95% Cl <sup>·</sup> -8.0– -3.7) -5.0	
	• Within each arm	insufficiency poorly	Low: 50 mmol (1.150	(95% CI: -7 62 5) and -2 2 (95%	
	randomized cross-over	controlled hyperlinidemia	ma)/d	$(13.00 \text{ Cl}; -1.0 \text{2.3})$ , and -2.2 (13.00 Cl}; -1.0 -1). The corresponding	
	trial with 2 poriods	or DM_DM requiring		difforences for DBD were 2.0 (05%	
	tosting different lovels	or Divi, Divi requiring	The mean achieved	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
	of codium intako (no	insuin, special dietaly	levels of sodium during	(14.31.5), -2.5 (957) (14.11.5)	
		requirements, >14	the high intermediate	0.8), and -1.0 (95% CI: -2.5, 0.4).	
	washout)	aiconolic grinks /wk.	and low sodium parioda	• In both the DASH and usual U.S.	
	<b>C</b> = 110		and low Souldin periods	diet arms, SBP and DBP were	
	<u>Size:</u> 412, with 59%		were 144, 107 and 67	significantly lower during	
	(243) being		mmol/d in the DASH	intermediate compared to high	
	normotensive		diel group and 141, 106,	sodium intake, and during low	
			and 64 mmol/d in the	compared to intermediate sodium	
			usual U.S. diet group.	intake, with the decrement being	
				greater for the latter change.	
			Comparator: See	• In comparison to consumption of a	
			description above	usual U.S. diet at the high level of	

				sodium intake, the normotensive group consuming the DASH diet at the low level of sodium intake had a mean SBP difference of 7.1 mm Hg (p<0.001). <u>1° Safety endpoint:</u> Participants tended to report less symptoms during periods of reduced sodium intake, with a statistically significant reduction in reports of headache (p<0.05) consistent with prior experience in the TONE trial.	
PREMIER Appel LJ, et al., 2003 (83) 12709466	Aim: Study the effect of 2 behavioral interventions, aimed at dietary change, on BP Study type: • Multicenter RCT with 3 parallel arms: • Established • Established plus DASH diet • Advice only Size: 810 adults, with 62% (506) normotensive. At baseline, mean age, BMI and SBP/DBP were 50 y, 33 kg/m <sup>2</sup> , and 135/85 mm Hg, respectively. Duration: 6 mo, with observations at 3 and 6 mo.	Inclusion criteria: • Adults ≥25y • Average SBP between 120–159 mm Hg and average DBP between 80–95 mm Hg • No use of antihypertensive medication • BMI between 18.5 and 45 kg/m <sup>2</sup> Exclusion criteria: • Regular use of drugs that affect BP • Target organ damage or DM • Use of weight-loss meds • Hx CVD event • HF, angina, cancer, within 2 y • Consumption of >21 alcoholic drinks /wk • Pregnancy, planned pregnancy, lactation	Intervention: • Structured behavioral interventions that used an identical format (4 individual and 14 group sessions) to facilitate adoption of "established" dietary recommendations for reduction in BP or "established" plus the DASH diet. The "established" dietary recommendations used in PREMIER were a) weight loss in overweight participants, b) sodium reduction, increased physical activity, reduced alcohol intake in pts consuming alcohol. • Compared to experience in the advice only (control) group, there was only modest achievement of	<ul> <li><u>1° endpoint</u></li> <li>Compared to control (advice only), SBP and DBP were significantly reduced with both active interventions but there was no significant difference in the effect size between the 2 active intervention groups. This was true for both the normotensive and hypertensive pts, with the effect size being larger in the hypertensive group. In the normotensives, the MD for change in SBP was identical for the "established" compared to "established plus DASH Diet" groups: -3.1 (95% CI: -5.1– -1.1) mm Hg The corresponding changes for DBP were -1.6 (95% CI: -2.9– -0.2) for the "established" intervention group and -2.0 (95% CI: -3.4– -0.6) for the "established intervention plus DASH Diet) group.</li> <li>Overall, the incidence of HTN was lowest and the percent with optimal BP was highest in the "established plus DASH" diet but the incidence of</li> </ul>	<ul> <li>This was an interesting trial which employed a behavior change approach to implement both active interventions.</li> <li>The investigators goal was to determine the additive value of the DASH Diet in persons already following key elements of conventional (established) recommendations for nonpharmacologic intervention to lower BP.</li> <li>The intervention approach in this trial was less effective in achieving weight loss and reduction in dietary sodium compared to the corresponding experience in the TOHP and TONE trials and the DASH Diet effects on intermediate variables (such as fruit and vegetable consumption) was less than that achieved in the DASH Diet feeding studies.</li> <li>Despite the modest intervention effects, both SBP and DBP were significantly reduced with the conventional intervention approach (in normotensives as well as overall) and addition of the DASH diet did not have a</li> </ul>

			intervention goals in the "established" group, with a MDs of 3.8 kg (8.4 lbs) for body weight, 11.6 mmol (267 mg)/d) for urinary sodium excretion, no change in physical activity (but better fitness), and no change in alcohol consumption (but very low alcohol consumption at baseline). • Weight loss was somewhat greater in the "established" plus DASH diet group, with a MD of 4.8 kg (10.6 lbs) for body weight. This group also manifested expected effects of the DASH diet, with significantly higher urinary potassium and phosphorous levels, greater consumption of fruits and vegetables, dietary calcium, dairy products, and a lower consumption of total fat and saturated fat. <u>Comparator:</u> Advice only	HTN was significantly less and the percent with optimal BP was higher in both active intervention groups compared to advice only. The difference between the 2 active intervention groups was not significant. In the normotensives, there was a nonsignificant trend towards less HTN and a significantly higher percent with optimal BP in both active intervention groups compared to advice only, with no significant difference for percent with optimal BP in the 2 active intervention groups. <u>1° Safety endpoint</u> : N/A	significant effect on reduction of SBP or DBP. • There were some nonsignificant trends for slightly lower BP, less HTN, and more optimal BP in the "established plus DASH Diet" group compared to "established" group. The authors also cited use of the DASH Diet as a means to beneficially influence CVD risk factors in addition to BP.
Annall Latal	<b>A</b> <sup>1</sup>	la charten estherte	Only		This all shaded and a second set of the second set of the set
Appel LJ, et al., 2005 (84) <u>16287956</u>	<u>Aim:</u> Compare effects of 3 diets, each with a reduced intake of	Inclusion criteria: • Adults ≥30 y • Average SBP between	<ul> <li>Intervention:</li> <li>High protein with reduced fat/saturated fat</li> </ul>	<u>1° endpoint</u> Compared with the high carbohydrate diet, the high protein	Inis clinical trial demonstrated that substituting either protein or monounsaturated fat in place of
	saturated tats, on BP and serum lipids	120–159 mm Hg and	content	diet:	carbohydrate resulted in a small

	Study type: • 2 center RCT • 3 period crossover design • Each 8 wk period was separated by a 2– 4 wk wash-out phase Size: 161–164 included in analyses (191 pts randomized). 132 (80.5%) of the 164 included in the BP analyses were normotensive. Mean age and BMI were 54 y and 30.2 kg/m <sup>2</sup> , respectively.	average DBP between 80–95 mm Hg • No use of antihypertensive medication <u>Exclusion criteria:</u> DM, CVD (current or H/O), LDL cholesterol >220 mg/dL, fasting triglycerides >750 mg/dL, weight >350 lb., taking that effect BP or lipids, unwillingness to stop vitamin/mineral supplements, >14 alcoholic drinks/wk.	High unsaturated fats (predominantly monounsaturated fat) with low saturated fat content <u>Comparator:</u> High carbohydrate with reduced fat/saturated fat content	<ul> <li>Reduced SBP by -1.4 mm Hg (p=0.002) overall and by -0.9 mm Hg (p=0.047) in the normotensives</li> <li>Reduced LDL cholesterol by 3.3 mg/dL (p=0.01) overall and by -2.1 mg/dL (p=0.14) in the normotensives</li> <li>Reduced HDL-C by -1.3 mg/dL (p=0.02) overall</li> <li>Reduced serum Triglycerides by - 15.7 mg/dL (p&lt;0.001) overall</li> <li>Compared with the high carbohydrate diet, the high unsaturated fat diet:</li> <li>Reduced SBP by -1.3 mm Hg (p=0.005) overall and by -0.9 (p=0.06) in the normotensives</li> <li>Reduced LDL cholesterol by -1.5 mg/dL (p=0.01) and by -2.1 (p=0.14) in the normotensives</li> <li>Increased HDL-C by 1.1 mg/dL (p=0.03) overall</li> <li>Reduced serum Triglycerides by - 9.6 (p=0.02) overall</li> </ul>	reduction in SBP and improvement in lipid profile.
Bazzano LA, et al., 2014 (85) <u>25178568</u>	<u>Aim:</u> Compare the effects of a low- carbohydrate and a low-fat diet on body weight and CVD risk factors (including BP) <u>Study type</u> : Single center parallel arm RCT that compared the 2 diets over 12 mo of intervention. <u>Size:</u> 148 pts, with a mean age of 46.8 y at	Inclusion criteria: • 22–75 y • BMI: 30–45 kg/m <sup>2</sup> Exclusion criteria: • CVD • DM-2 • Kidney disease • Use of prescription weight loss meds/surgery • Weight loss >6.8 kg during prior 6 mo	Intervention: • Low-carbohydrate diet, with digestible carbohydrate (total carbohydrate minus total fiber) <40 g/d • Behavioral counselling that employed a mix of 20 individual and group meetings <u>Comparator:</u> • Low fat diet, with <30% of daily energy	<ul> <li><u>1° endpoint:</u></li> <li>Compared to the low-fat diet group, the low-carbohydrate diet group had a mean decrease at 12 mo of: Body weight: -3.5 (95% CI: -5.6 1.4) kg Fat mass: -1.5 (95% CI: -2.60.4) HDL-C: 7.0 (11.0-3.0) mg/dL Ratio total/HDL-C: -0.44 (95% CI: -0.710.16) Sr. triglyceride: -14.1 (95% CI: -27.40.8) mg/dL</li> </ul>	<ul> <li>This clinical trial provides 1 of the longest follow-up experiences related to the topic.</li> <li>It suggests low carbohydrate diets may be somewhat better than traditional low fat diets in achievement of weight loss, improvement of lipid profile, inflammation, and CHD risk.</li> <li>Although the BP differences were not significant, there was a consistent trend toward lower BPs in the low-carbohydrate diet group.</li> </ul>

	baseline. Mean SBP/DBP at baseline were 124.9/79.4 and 120.3/77.5 mm Hg in the low-fat and low- carbohydrate groups, respectively. The corresponding BMIs were 97.9 and 96.3 kg/m <sup>2</sup> . All 148 pts were included in the analysis (intention to treat)		intake from fat (<7% from saturated fat) • Behavioral counselling that used identical format to that employed in the low carbohydrate group	<ul> <li>At 3, 6, and 12 mo, BP tended to be lower in the low-carbohydrate group but none of the differences in SBP or DBP were significant.</li> <li>CRP was reduced in both diet groups but to a significantly greater extent in the low-carbohydrate group.</li> <li>At 6 and 12 mo pts in the low carbohydrate group experienced a significant improvement in their 10-y Framingham CHD risk score. In contrast, there was no change in Framingham CHD risk in the low-fat diet group.</li> <li><u>1° Safety endpoint:</u> No serious side effects noted</li> </ul>	
Nordmann AJ, et al., 2006 (86) <u>16476868</u>	Aim: Compare effects of low-carbohydrate and low-fat diets on weight loss and CVD risk factors Study type: • Systematic review and meta-analysis • Cochrane Collaboration strategy Size: 5 trials (447 pts)	Inclusion criteria: • RCT • Adults ≥16 y • Low-carbohydrate diet and low-fat diet interventions • BMI ≥25 kg/m <sup>2</sup> • Follow-up ≥6 m <u>Exclusion criteria:</u> • Cross-over or sequential design • Missing data	Intervention: Low- carbohydrate diet: maximum of 60 g/d carbohydrate <u>Comparator:</u> Low-fat diet: maximum of 30% energy from fat	<ul> <li><u>1° endpoint:</u> At 6 mo, the low-carbohydrate diet pts, compared to the low-fat diet participants, had a mean reduction in body weight that was greater by -3.3 (95% CI: -5.3 - 1.4) kg, and a more favorable profile for HDL-cholesterol and triglyceride levels. In contrast, the profile for total-cholesterol and HDL-cholesterol and HDL-cholesterol was more favorable in those assigned to a low-fat diet. The profile for SBP tended to be better in the low carbohydrate diet pts but the differences were not significant: MD at 6 mo: -2.4 (95% CI: -4.9–0.1) mm Hg.</li> <li><b>1° Safety endpoint:</b> N/A</li> </ul>	<ul> <li>This systematic review/meta-analysis tends to suggest low-carbohydrate diets are somewhat more effective in reducing body weight compared to the traditionally recommended low-fat diets.</li> <li>Although the BP differences were not significant they would probably have reached a conventional level of significance had subsequent clinical trials (including the Bazzano et al. trial) been included in the analysis.</li> </ul>

Nordmann AJ, et al., 2011 (87) <u>21854893</u>	Aim: Compare effects of Mediterranean and low-fat diets on weight loss and CVD risk factors Study type: • Systematic review and meta-analysis • Cochrane Collaboration strategy Size: 6 trials (2,650 pts)	Inclusion criteria: • RCT • Intent to treat analysis • Overweight/obese with at least 1 additional CVD risk factor • Follow-up ≥6 mo Exclusion criteria: N/A	Intervention: Mediterranean diet: moderate fat intake (main sources olive oil and nuts), rich in vegetables, and low in red meat. Comparator: Low fat diet: ≤30% of energy intake from fat	1° endpoint:       Compared to the low-fat diet, the Mediterranean diet resulted in MDs of:         • Body weight: -2.2 (95% Cl: -3.9 – -0.6) kg         • BMI: -0.6 (95% Cl: -1.0 – -0.1) kg/m²         • SBP: -1.7 (95% Cl: -3.3 – -0.05) mm Hg         • DBP: -1.5 (95% Cl: -2.1 – -0.8)         • Fasting Plasma Glucose: -3.8 (95% Cl: -7.0 – -0.6) mg/dL         • Total-Cholesterol.: -7.4 (95% Cl: -10.3 – -4.4)         • CRP: -1.0 (95% Cl: -1.5 – -0.5)         1° Safety endpoint: N/A	<ul> <li>Overall, this study suggests the Mediterranean diet compared to the traditional low fat diet results in greater weight loss, a better CVD risk factor profile (including better BP control), and less inflammation.</li> <li>The number of eligible trials was small and the study samples were heterogeneous (2 2° and 4 1° prevention trials).</li> </ul>
Yokoyama Y, et al., 2014 (88) <u>24566947</u>	Aim: Compare the effects of vegetarian and omnivorous diets on BP Study type: Systematic review and meta-analysis Size: • 7 trials (n=311). • 6 were RCT (n=198) • 4 parallel and 3 cross-over designs • All were open • Follow-up ≥6 wk (mean=15.7 wk) • Mean age=44.5 y	Inclusion criteria: • Adults ≥20 y • English language publications between Jan 1946-Nov 2013 Exclusion criteria: • Twin pt studies • Multiple interventions • Only categorical BP results	Intervention: • Lacto-ovo in 4 trials • Lacto in 1 trial • Vegan in 2 trials Comparator: Omnivorous diet in all trials	<ul> <li><u>1° endpoint:</u> Compared to the omnivorous diet, the vegetarian diet resulted in MDs of:</li> <li>SBP: -4.8 (95% CI: -6.6– -3.1) mm Hg</li> <li>DBP: -2.2 (95% CI: -3.5– -1.0)</li> <li>SBP was lower in the vegetarian diet group in 5 of the 7 trials (significant in 3) and DBP was lower in 6 of the 7 trials (significant in 2).</li> <li><u>1° Safety endpoint:</u> N/A</li> </ul>	<ul> <li>Overall, this meta-analysis of clinical trials suggested BP was lower in those who consumed a vegetarian diet compared to their counterparts who consumed an omnivorous diet.</li> <li>However, the trials were generally small, heterogeneous in their design and conduct, and of questionable quality.</li> <li>Even greater reductions in SBP and DBP were noted in a MA of 32 observational studies.</li> </ul>
PREDIMED Toledo E, et al., 2013 (89) <u>24050803</u>	<u>Aim:</u> Compare the effects of a Mediterranean and lower-fat diet on BP	Inclusion criteria: • Adults, men 5,580 y, women 60–80 y • Free from CVD	Intervention: Pts assigned to a control group or to 1 of 2 Mediterranean diets.	<u><b>1° endpoint:</b></u> The percentage of pts with controlled BP increased in all 3 intervention groups (p-value for within-group changes: p<0.001). Pts	• Both the traditional Mediterranean diet and a low-fat diet exerted beneficial effects on BP and could be part of advice to pts for controlling BP.

	DM or at least 3 major	The control group	allocated to either of the 2	However, lower values of DBP were
Study type: RCT,	CVD risk factors (smoking,	received education on	Mediterranean diet groups had	noted in the 2 groups following the
single-blinded, in	HTN, elevated LDL	following a low-fat diet,	significantly lower DBP than the pts	Mediterranean diet with extra virgin
Spanish primary	cholesterol, low HDL,	while the groups on	in the control group (-1.53 mm Hg	olive oil or with nuts than in the control
healthcare centers	overweight/obese, family	Mediterranean diets	(95% CI: -2.01– -1.04) for the	group.
	history of early CHD)	received nutritional	Mediterranean diet supplemented	
<u>Size</u> : 7,447 men (55–		education and also free	with extra virgin olive oil, and -0.65	
80 y) and women (60–	Exclusion criteria: Do	foods; either extra virgin	mm Hg (95% CI: -1.15– -0.15) mm	
80 y) at high risk for	not meet criteria listed	olive oil, or nuts.	Hg for the Mediterranean diet	
CVD.	above		supplemented with nuts). No	
		Comparator: Lower fat	between-group differences in	
		diet	changes of SBP were seen	

Data Supplement 16. RCTs and Meta-analysis RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Alcohol Reduction) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Xin X, et al., 2001 (90) <u>11711507</u>	Aim: Study the effect of alcohol reduction on BP Study type: Systematic review and meta-analysis Size: • 15 RCTs (25 comparisons) with 2,234 pts. • 6 trials were conducted in normotensives (269 pts with a mean age ranging from 26.5– 45.5 y). Average	Inclusion criteria: • RCT in humans • Publication between 1966-1999 • Duration ≥1 wk • Only pts regularly consuming alcohol • Only difference between the comparison groups was alcohol intake <u>Exclusion criteria</u> : Comparison of different doses of alcohol intake	Intervention: Reduction in alcohol consumption. In most trials this was achieved by randomization to "light" alcohol but some RCT were based on a behavioral intervention aimed at reducing the number of drinks consumed. <u>Comparator</u> : Usual consumption of alcohol	<ul> <li><u>1° endpoint</u>:</li> <li>Overall, alcohol reduction was associated with a significant reduction in mean SBP of -3.31 (95% Cl: -4.102.52) and DBP of -2.04 (95% Cl: -2.581.49).</li> <li>In the subgroup of 7 RCTs in persons with HTN, the mean changes in SBP and DBP were -3.9 (95% Cl: -5.042.76) and -2.41 (95% Cl: -3.021.57).</li> <li>In the subgroup of 6 RCTs in normotensives the corresponding changes in SBP and DBP and DBP were -3.5 (95% Cl: -4.612.51) and -1.80 (95% Cl: -3.030.58).</li> </ul>	<ul> <li>This is the most recent meta-analysis of this topic. Although this meta-analysis reports % reduction in alcohol intake, most trials aimed at reducing the number of alcoholic drinks consumed achieved a reduction of about 3 drinks/d.</li> <li>The intervention results were consistent with the relationship alcohol and BP in observational epidemiology – about a 1 mm Hg higher SBP per alcoholic drink consumed. In observational studies, type of alcohol does not seem to matter and at lower levels of alcohol consumption (&lt;1 standard size alcoholic drink per day in women and &lt;2 in men) there does not</li> </ul>

	consumption of alcohol at baseline was not reported. Follow-up varied from 1–18 wk			<ul> <li>In a meta-regression analysis, a dose-response was noted between % reduction in alcohol consumption and mean reduction in BP.</li> <li><u>1° Safety endpoint</u>: N/A</li> </ul>	<ul> <li>seem to be an important biological effect of alcohol on BP.</li> <li>The relationship between alcohol consumption and BP is predictable and consistent in observational and RCT studies. However, the relationship between alcohol consumption and CVD is more complex as alcohol is associated with an apparently beneficial effect on CVD risk, possibly mediated by an increase in HDL-cholesterol.</li> <li>Pregnant women, pts with HTN and those at risk of a drinking problem should not drink alcohol. Established light drinkers (&lt;2 standard drinks/d in men and &lt;1/d in women) who are normotensive are in a favorable risk category for CVD.</li> </ul>
Stewart SH, et al., 2008 (91) <u>18821872</u>	Aim: Study the effect of reduced alcohol intake on BP. Study type: Randomized, controlled factorial trial. Size: 1,383 pts.	Inclusion criteria: • Alcohol dependence. • 4—21 d of abstinence. • Men: >21 drinks/wk; Women >14 drinks/wk. • At least 2 heavy drinking days within a consecutive 30-d period during 90 d prior to baseline. Exclusion criteria: • Other substance abuse. • Psychiatric disorder requiring medication. • Unstable medical condition	Intervention: Pharmacotherapy (naltrexone, acamprosate, or both) and counseling strategies (behavioral and/or medical management). <u>Comparator</u> : Placebo.	<ul> <li>Change in BP:</li> <li>Based on up to 5 repeated measures of BP over 16 wk. Data modeled to estimate change in BP over time.</li> <li>For pts with higher than average baseline SBP (&gt;132 mm Hg), SBP declined by an average of 12 mm Hg (149—137) in the intervention arm compared to placebo, with a corresponding decline in DBP of 8 mm Hg. For those with a baseline SBP ≤132 mm Hg there was no change in SBP (120—121 mm Hg) or DBP.</li> <li>Safety endpoint: N/A</li> </ul>	<ul> <li>This trial was designed to evaluate interventions for treatment of alcohol dependence.</li> <li>BP measurements were not standardized.</li> <li>About 20% of the observations were missing and assumed to be random.</li> </ul>
Dickenson HO, et al., 2006 (92) <u>16508562</u>	<u>Aim</u> : Study effectiveness of lifestyle	Inclusion criteria: • Only parallel trials	Intervention: Lifestyle change aimed at reduced consumption of alcohol	1° endpoint: -Net reduction (95% CI): SBP -3.8 (-6.1— -1.4)	<ul><li> Relatively small number of trials</li><li> Limited details provided</li></ul>

	interventions, including reduced alcohol intake, for treatment of HTN. <u>Study type</u> : 1 of 10 meta-analyses. <u>Size</u> : 4 trials which collectively studied 305 pts	<ul> <li>SBP ≥140 mm Hg and/or DBP ≥85 mm Hg</li> <li>≥8 wk duration</li> <li>BP outcome</li> <li>Exclusion criteria:</li> <li>2° HTN or renal disease</li> <li>Pregnant women</li> <li>Change in BP meds during trial</li> </ul>	Comparator: Usual care	DBP -3.2 (-5.0— -1.4) <u>Safety endpoint</u> : N/A	
Wallace P, et al., 1988 (93) <u>3052668</u>	Aim: Study effectiveness of general practitioner advice to reduce heavy drinking. <u>Study type</u> : • RCT <u>Size</u> : 909 adults (641 men and 268 women)	Inclusion criteria: Heavy drinking during wk prior to screening interview. Exclusion criteria: None mentioned	Intervention: Physician counselling aimed at reduced consumption of alcohol. Comparator: Usual care	Endpoints: • 1° outcome was reduction in percent with heavy consumption of alcohol (mean net change=46%). Liver enzymes and BP also measured at 6 and 12 mo. • Pretreatment SBP/DBP=133.5/79.9 mm Hg. • Net reduction SBP=-2.12 (95% CI: -4.190.00) Safety endpoint: N/A	<ul> <li>The goal was to blind those conducting the outcome assessment to treatment assignment but by 6 mo assignment was known in 20-30% of the participants.</li> <li>A reduction in SBP was noted despite use of a modest intervention.</li> </ul>
Lang T, et al., 1995 (94) <u>8596098</u>	Aim: Worksite study of reduced alcohol intake effect on BP in heavy drinkers with HTN. Study type: RCT Size: 14 site physicians; 129 adults (95% men)	Inclusion criteria: • Heavy drinking (documented by history and liver enzyme elevation). • HTN (SBP/DBP >140/90 mm Hg) Exclusion criteria: • 2° HTN • Severe liver disease • Planned move/retirement.	Intervention: Physician and worker counselling aimed at reduced consumption of alcohol. Comparator: Usual care. Duration: Follow-up visits at 1, 3, 6, and 18 mo.	Endpoints: • Baseline SBP/DBP=162.5/98.0. Although all of the workers had HTN, only about 20% were being treated with antihypertensive medications at baseline. • At 1 y, the net change in SBP=-5.5 (p<0.05). When 5 sites with <5 workers/site were excluded, the net change in SBP=-7.3 mm Hg (p<0.01). • At 2 y, the net change in SBP=-6.6 (p<0.05).	<ul> <li>Behavioral intervention state of the art for its time</li> <li>Careful measurements of BP using Hawksley RZ sphygmomanometer.</li> <li>Main analyses do not seem to have accounted for cluster design.</li> </ul>

				Safety endpoint: N/A		
Roerecke M, et al., 2017 Lancet Public Health. 2017;2:e108-120.	Aim: Study the effect of reduced alcohol intake on BP. Systematic review and meta-analysis. Size: 36 RCT with 2865 participants. Design: • 15 parallel-arm trials • 21 crossover trials Setting: • 13 in hypertension • 13 in normotension • 12 HTN and NT • Only 3 trials presented data for women.	Inclusion criteria: • RCT in adult humans • Publication on or before July 13, 2016. • Full text articles. • Change in alcohol intake for ≥1 wk	Intervention: Reduction in alcohol consumption. Strategy varied from controlled inpatient administration to randomization to "light" alcohol to pragmatic primary care trials with counselling to reduce alcohol intake. Duration: Follow-up from 1 wk to 2 y (median 4 wk).	Safety endpoint: N/A 1° endpoint: • Overall, alcohol reduction was associated with a significant reduction in mean SBP of -3.31 (95% CI: -4.102.52) and DBP of -2.04 (95% CI: -2.581.49). • In the subgroup of 7 RCTs in persons with HTN, the mean changes in SBP and DBP were SBP: -3.13 (95% CI: -3.93 2.32) DBP: -2.00 (95% CI: -2.65 1.35). • In meta-regression analysis, there was a strong relationship between the extent of BP reduction and change in BP, with no reduction in BP for those consuming 2 or less drinks at baseline but increasing reductions in BP for those with progressively higher intakes of alcohol at baseline. For instance, in those consuming ≥6 drinks/day and reducing their alcohol intake by approximately 50%, the estimated reduction in SBP and DBP were: SBP: -5.5 (95% CI: -6.70 4.30) DBP: -3.97 (95% CI: -4.70 3.25). Similar patterns of the effect of baseline alcohol intake on treatment effect were noted for a variety of subgroups.	N/A	
				1° Safety endpoint: N/A		
Data Supplement 17.	RCTs and Meta-analysis F	RCTs Studying the Effec	t of Nonpharmacologic	Interventions on BP	(Calcium Suppleme	entation)
---------------------	--------------------------	-------------------------	-----------------------	---------------------	-------------------	-----------
(Section 6.2)						

Study	Aim of Study;	Patient Population	Study Intervention (#	Endpoint Results	Relevant 2° Endpoint (if any);
Acronym;	Study Type;		patients) /	(Absolute Event Rates,	Study Limitations;
Author;	Study Size (N)		Study Comparator (#	P value; OR or RR; & 95% CI)	Adverse Events
Year Published			patients)		
Van Mierlo LA,	Aim: Study the	Inclusion criteria:	Intervention: Increased	<u>1° endpoint</u> :	• This is the most recent SR/MA on this
et al.,	effect of calcium	<ul> <li>RCT in humans</li> </ul>	calcium intake, with a	<ul> <li>Overall, increased calcium</li> </ul>	topic to include RCT conducted in both
2006 (95)	supplementation on	<ul> <li>Publication between</li> </ul>	range from 355–2,000	intake was associated with a	normotensive and hypertensive pts. The
<u>166/3011</u>	ВЬ	1996 and 2003	mg/d (mean=1,200	significant reduction in mean SBP	authors interpreted their results as being
	o	<ul> <li>Nonpregnant</li> </ul>	mg/d; median=1,055	of -1.86 (95% CI: -2.91– -0.81)	consistent with a beneficial effect of
	Study type:	normotensive pts or	mg/d), primarily as a	and DBP of -0.99 (95% CI: -1.61–	calcium supplementation on BP, with about
	Systematic review	hypertensive pts	gluconate or carbonate	-0.37).	a 2 mm Hg reduction in SBP for a 1 g
	and meta-analysis	<ul> <li>Only difference</li> </ul>	sait.	• The reduction was slightly less	increase in calcium intake. This is slighter
	Sizo	between the	Comparator: Diacobo or	but still significant in the subset of	larger effect size than noted in several
	<u>SIZE</u> .	comparison groups was	usual intako 22	32 double-blind trials, with a	earlier meta-analyses.
	• 40 KCTS WIIN	magnesium intake	usual IIIlake - 52 doublo blind	mean SBP of -1.67 (95% CI: -	• A subsequent Cochrane Collaboration
	2,492 µls.	<ul> <li>Follow-up ≥2 wk</li> </ul>		2.87– -0.47) and DBP of -0.93	meta-analysis was confined to 13 RCT in
	• 27 KCTS III pis			(95% CIL - 1.64– -0.22).	405 adults ( $\geq$ 10 y) with HTN studied 101 $\geq$ 0
	<140/90 11111 Hy (n 1 720)	Exclusion criteria:		I here was no significant	WK (DICKINSOIT HO et al. Cochiane Database of Systematic Deviews, 2006)
	(II=1,720)	Study pts having renal		difference between the effect size	CD004620) The authors noted a
	• FUILOW-up valueu	disease or		In those with a baseline BP $\geq$	significant reduction in mean of 2.5 (05%
	(modian 9 E wk)	nyperparatnyroidism		UI<140/90 MM Hg.	Significant reduction in mean of -2.5 (75%) CI: $-1.5 = -0.6$ ) for SBP but a more modest
	(Ineulari=0.5 WK)			- The mean change in SBP and	insignificant change of -0.8 (95% CI: -2.1-
	• Age range $11-77$			DDF for those with a baseline $DD>140/00  mm Hg/23$	0.4) for DRP. Due to the poor quality of the
	y (mean=43.7 y)			DF = 140/90 mm rig (25 comparisons) was -2 17 (05% CI	RCT and heterogeneity of the results the
				-3 780 55) and -0 95 (95% CI:	authors concluded the reduction in SBP
				1 890.01) respectively	was likely an artifact due to bias.
				- The mean in SBP and DBP for	Although not included in most meta-
				those with a baseline BP $< 140/90$	analyses, calcium supplementation has
				mm Hg was -1.67 (95% CI: -3.01–	been effective as a treatment in pregnant
				-0.27) and -1.02 (95% CI: -1.85– -	women at risk for pre-eclampsia.
				0.19) mm Hg, respectively.	• Several of the meta-analyses (including
				The authors reported slightly	the 1 by van Mierlo et al) have suggested a
				larger effect sizes in those with a	bigger effect size in persons with a lower
				lower initial calcium intake, in	intake of calcium at baseline and in trials
				trials that employed a dietary	that utilized a dietary intervention.

	intervention (compared to a supplement), and in the 4 trials conducted in Asians.	• Most of the trials were of short duration and did not (have the capacity) report on potential adverse effects such renal stones.
	<u>1° Safety endpoint</u> : N/A	<ul> <li>In addition to being small, several trials were of uncertain quality.</li> <li>Overall, RCT experience provides limited and inconsistent evidence from trials of variable quality in support of calcium supplementation for prevention (or treatment) of HTN. Better evidence supports the role of calcium supplements, in conjunction with vitamin D, in strengthening hone density</li> </ul>

Data Supplement 18. RCTs and Meta-analyses RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Physical Activity) (Section 6.2)

Study Acronym;	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) /	Endpoint Results (Absolute Event Rates, Divelue: OB or DB: \$ 05% CI)	Relevant 2° Endpoint (if any); Study Limitations;
Year Published	Study Size (N)		patients)		Adverse Events
Whelton SP, et al., 2002 (96) <u>11926784</u>	Aim: Study the effect of aerobic exercise on BP Study type: Systematic review and meta-analysis Size: 38 reports (54 comparisons) with 2,419 pts; 27 of the comparisons were conducted in normotensive pts	Inclusion criteria: • English language publication between 1966–2001 • RCT in adults ≥18 y • Duration ≥2 wk • No concurrent interventions Exclusion criteria: Missing BP data	Intervention: Aerobic exercise Comparator: No exercise prescribed	<ul> <li><u>1° endpoint</u>:</li> <li>For the overall group, a pooled analysis of experience in 53 trials identified a mean net change in SBP of - 3.84 (95% CI: -4.972.72). In subgroup analysis, the effect was noted in different ethnic groups, in trials that employed different designs, durations, and sample sizes, in trials with obese, overweight or normal weight pts, and in trials that employed different types, intensity levels, and duration of aerobic exercise.</li> <li>In the subgroup of 15 trials in hypertensives, the mean net change in SBP was -4.94 (95% CI: -7.172.70).</li> </ul>	<ul> <li>This meta-analysis provides the most comprehensive analysis of the effect of aerobic exercise on BP and provides strong evidence in support of aerobic exercise as an intervention to lower BP in normotensives.</li> <li>Recognizing this, many of the trials were small and of short duration.</li> </ul>

				• In the subgroup of 27 trials conducted in normotensives, the mean net change in SBP was -4.04 (95% CI: -5.32– -2.75).	
				1° Safety endpoint: N/A	
Cornelissen VA, et al., 2013 (97) <u>23525435</u>	Aim: Study the effect of different types of physical activity on BP • Dynamic aerobic endurance • Resistance training • Dynamic • Static (Isometric) Study type: Systematic review and meta-analysis Size: Overall, 93 studies (>5,000 pts) • 59 Dynamic Aerobic Endurance studies • 13 Dynamic Resistance Training studies • 5 Combined Dynamic Aerobic and Resistance training • 4 Static (Isometric) Resistance • 12 Different interventions within 1	Inclusion criteria: • Parallel arm RCTs • Adults≥18 y • Peer reviewed journals up to February 2012 • Trial duration ≥4 wk Exclusion criteria: Inadequate reporting of the data	Intervention: Physical activity Comparator: No prescription of physical activity	<u>1° endpoint</u> : Overall (trials in hypertensives and normotensive), pooled experience identified a significant reduction in BP with all forms of physical activity (aerobic and both forms of resistance training), with mean reductions in SBP of -3.5 mm Hg following aerobic endurance training, - 1.8 mm Hg following dynamic resistance training, and -10.9 mm Hg following static (isometric) resistance training (p<0.001 for the difference between the effect size following static [isometric] and other forms of physical activity). In subgroup analysis, dynamic aerobic endurance and dynamic resistance training resulted in mean SBP changes of -2.1 (95% CI: -3.3 – 0.83) and -4.3 (95% CI: -7.7 – 0.90), respectively, in the pts with pre-HTN and smaller, nonsignificant reductions in the remaining pts with a normal BP. <u>Safety endpoint</u> : N/A	<ul> <li>Most recent in a series of progressively updated publications from Dr. Cornelissen and her colleagues.</li> <li>The findings suggest a beneficial effect of all forms of physical activity on BP, with a disproportionately large effect of resistance training on BP.</li> <li>Many of the available RCTs have been small, of short duration, and of uncertain quality.</li> </ul>
Rossi AM, et al., 2013 (98) <u>23541664</u>	Aim: Study the effect of resistance exercise on BP Study type:	Inclusion criteria: • RCTs in adults (≥18 y) • BP-lowering 1° outcome	Intervention: Dynamic resistance training but overall reporting of the details was poor.	<u><b>1°</b></u> endpoint: Pooled experience (hypertensive and normotensive pts) identified a small, nonsignificant reduction in mean SBP of -1.03 (95% CI: -3.44–0.39). The corresponding finding	• Suggests resistance training is effective in lowering BP and was the basis for recommending this intervention in the Canadian HTN Education Program
	Systematic review and meta-analysis				recommendations.

	Size: 9 RCTs (11 intervention groups and 14 comparisons) conducted in 452 pts. 10 (71%) of the 14 comparisons were conducted in normotensives	<ul> <li>Trial duration ≥4 wk</li> <li>Resistance training only intervention</li> <li><u>Exclusion criteria</u>: Handgrip/isometric exercise</li> </ul>	Comparator: No resistance training but not detailed in this article	for DBP was -2.19 (95% Cl: -3.87– - 0.51). <u>Safety endpoint</u> : N/A	• The discrepancy in effect size between this meta-analysis and the 1 conducted by Cornelisson et al may have been due to the more restrictive requirement by Rossi et al that change in BP be the 1° outcome.
Garcia-Hermosa A, et al., 2013 (99) <u>23786645</u>	Aim: Study the effect of exercise on BP in obese children. Systematic review and meta-analysis. Size: 9 RCTs (410 pts).	Inclusion criteria: • Children ≤14 y with obesity • RCT • Duration ≥8 wk • 1° outcome: change in BP Exclusion criteria: Concomitant intervention	Intervention: Physical activity, principally aerobic exercise. Comparator: No physical exercise, nutrition, education, or dietary restriction intervention	<u>1° endpoint</u> : Change in SBP: In pooled analysis, mean change in SBP was -0.4 (95% CI: -0.66– -0.24). <u>Safety endpoint</u> : N/A	<ul> <li>This meta-analysis focused specifically on the effect of physical activity on BP in children with obesity. Although it is not stated explicitly, it seems likely that all of the participants were normotensive and not receiving medication that could influence level of BP.</li> <li>The findings are consistent with other meta-analyses of the effect of physical activity on BP.</li> <li>Only limited information regarding study details is provided in this publication. The interventions were heterogeneous in type, duration, and quality.</li> </ul>
Carlson DJ, et al., 2014 (100) <u>24582191</u>	Aim:Study the effect of physical activity on BP in children with obesity.Study type:Systematic review and meta-analysis.Size:9 RCTs (223 pts: 127 intervention and 96 controls): 6 were conducted in normotensives.	Inclusion criteria: • Adults ≥18 y • RCT, including cross-over trials. • Duration ≥4 wk • Published in a peer reviewed journal between January 1, 1966 and July 31, 2013 Exclusion criteria: Studies that employed any intervention other	Intervention: Pure isometric exercise. Comparator: Use of a control group was a requirement but no additional specific information provided.	<ul> <li><u>1° endpoint</u>:</li> <li>In the overall pooled analysis (hypertensive and normotensive trials), mean change in SBP was -6.77 (95% CI: -7.935.62) mm Hg.</li> <li>In the subgroup of 3 trials with hypertensive pts (all on antihypertensive medication), the mean change in SBP was -4.31 (95% CI: -6.422.21) mm Hg.</li> <li>In the subgroup of 6 trials with normotensive pts, the mean change in SBP was -7.83 (95% CI: -9.216.45) mm Hg.</li> </ul>	<ul> <li>This study provides information regarding the effect of pure isometric exercise interventions on BP in adults.</li> <li>The BP reductions reported in this meta-analysis are surprisingly large but the overall effect pattern is quite consistent with other meta-analyses of isometric exercise.</li> </ul>

Cornelissen VA	Aim: Study the effect	than pure isometric exercise (e.g., dynamic resistance)	Intervention	Safety endpoint: N/A	This meta-analysis supports the
et al., 2011 (101) <u>21896934</u>	of resistance training on BP. <u>Study type</u> : Meta- analysis <u>Size</u> : 28 randomized, controlled trials, involving 33 study groups and 1,012 pts.	<ul> <li>Adults ≥18 y</li> <li>RCT, including cross-over trials.</li> <li>Duration ≥4 wk</li> <li>Published in a peer reviewed journal up to June 2010</li> <li>Exclusion criteria: Interventions other than pure isometric exercise (e.g. dynamic resistance)</li> </ul>	Resistance training, including isometric and dynamic modalities. <u>Comparator</u> : Use of a control group was a requirement but no additional specific information provided.	induced a significant SBP/DBP reduction in 28 normotensive or prehypertensive study groups of -3.9 (-6.4, -1.2)/-3.9 (- 5.6, -2.2] mm Hg). In the 5 hypertensive study groups, the change in mean SBP/DBP was -4.1 (95% CI: -0.63–1.4)/- 1.5 (95% CI: -3.4–0.40) mm Hg. When the study groups were divided according to the mode of training, isometric handgrip training in 3 groups resulted in a larger decrease in SBP/DBP (-13.5 [95% CI: -16.5– -10.5]/-6.1[95% CI: -8.3– -3.9] mm Hg) than dynamic resistance training in 30 groups (-2.8 [95% CI: -4.3– -1.3]/-2.7 [95% CI: -3.8– -1.7] mm Hg). <u>Safety endpoint</u> : N/A	<ul> <li>BP-lowering potential of dynamic resistance training and isometric handgrip training.</li> <li>Results further suggest that isometric handgrip training may be more effective for reducing BP than dynamic resistance training.</li> <li>However, given the small amount of isometric studies available, additional studies are warranted to confirm this finding.</li> </ul>

Data Supplement 19. RCTs and Meta-analysis RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Magnesium Supplementation) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% Cl)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Kass L, et al., 2012 (102) <u>22318649</u>	<u>Aim</u> : Study the effect of magnesium supplementation on BP <u>Study type</u> : Systematic review and meta-analysis	Inclusion criteria: • RCT in humans • Parallel or cross- over design • Publication before July 2010 • Adults >18 y • Only difference between the	Intervention: Increased magnesium intake, with a range in elemental magnesium of 120 to 973 mg/d and a mean of 410 mg/d. Comparator: Placebo or usual intake	<u>1° endpoint</u> : • Overall, increased magnesium intake was associated with a small nonsignificant reduction in mean SBP of -0.32 (95% CI: - 0.41– -0.23) and DBP of -0.36 (95% CI: -0.44– -0.27).	<ul> <li>This is the most recent systematic review/meta-analysis on this topic. The authors interpreted their results as being consistent with a beneficial effect of magnesium supplementation on BP. However, this interpretation seems at odds with the data.</li> <li>In an earlier meta-analysis of 20 RCT (6 in normotensives) by Jee Systolic</li> </ul>

<u>Size</u> : 22 RCTs (23	comparison groups	<ul> <li>Forest plots revealed</li> </ul>	HTN et al (Am J Hyperts. 2002;15:691-
comparisons) with	was magnesium	considerable heterogeneity in	696) magnesium supplementation
1,173 pts.	intake	effect size.	resulted in small mean NS reductions of
Data for RCTs		• The authors reported slightly	-0.6 (95% CI: -2.2–1.0) mm Hg in SBP
conducted in	Exclusion criteria:	larger effect sizes in subgroup	and -0.8 (95% CI: -1.9-0.4) in DBP. In
normotensive pts were	Comparison of	analysis of cross-over RCT	meta-regression analysis, there was an
not presented.	different doses of	and RCT that employed a	apparent dose-response with SBP and
However, most RCTs	alcohol intake	dose of magnesium >370	DBP reductions of -4.3 (95% CI: -6.3– -
were conducted in		ma/d	2.2) and -2.3 (95% CI: -4.9–0) mm Hg
normotensives and		ing/u.	for each 10 mmol/d higher level of
only 6 of the RCTs		19 Safaty and paint: N/A	magnesium intake
included some (or all)		<u>1 Salety enupoint</u> . WA	<ul> <li>Δ Cochrane systematic review/meta-</li> </ul>
nts who were being			analysis of magnesium supplementation
treated with			for treatment of HTN in adults (Dickinson
antihypertensive			HO et al. Cochrane Database
medication Overall			Systematic Review 2006: CD 004640)
mean age was ~50 v			included 12 PCT ( $n=545$ ) with follow-up
Follow-up varied from			of 8, 26 wk, Ovorall mean SRD and
$3_2/1$ wk with a mean			DRD woro roducod by 1.3 (05% Cl
of 11 2 wk			A = 15 and $22(05%  Cb 24 = 0.0)$
OF TT.5 WK.			4.0-1.3) and -2.2 (93% Ci3.40.9)
			the studies were of poor quality with
			the studies were of poor quality, with
			considerable neterogeneity, and reit the
			<ul> <li>Some authors have suggested there</li> </ul>
			may be a greater BP effect when the
			intervention is by means of diet change
			but there is insufficient RCT evidence to
			support this position.
			<ul> <li>Magnesium sulfate is the drug of</li> </ul>
			choice for prevention of seizures in the
			pre-eclamptic woman, or prevention of
			recurrence of seizures in the eclamptic
			woman, as demonstrated in RCT and a
			2010 Cochrane review (Duley L et al.
			Cochrane Database of Systematic
			Reviews. CD000127, 2010).
			Overall, RCT experience provides
			insufficient evidence to recommend oral

		magnesium supplementation as a means to prevent (or treat) HTN.

## Data Supplement 20. RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Weight Loss) (Section 6.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Neter JE, et al., 2003 (103) <u>12975389</u>	Aim: Study the effect of weight loss on BP Systematic review and meta-analysis Size: 25 RCTs (34 comparisons) with 4,874 pts; 17 of the comparisons were conducted in normotensive pts	Inclusion criteria: • RCT in humans • English language publication between 1966– 2002 • Nonpharmacologic intervention Exclusion criteria: • Duration <8 wk • Missing data • Objective not weight loss • Concomitant intervention(s)	Intervention: Weight loss (calorie reduction, physical activity, or combination of both) Comparator: No weight loss prescription	<ul> <li><u>1° endpoint</u>:</li> <li>For the overall group, mean baseline body weight was 88.3 kg and mean change in body weight following the application of the weight loss intervention was -5.1 (95% CI: -6.034.25) kg. This represents a mean percent change of -5.8%.</li> <li>There was strong evidence for a BP lowering effect of weight loss on BP, overall and in normotensive subgroup. In the normotensive group, the mean for change in SBP was 4.08 (95% CI: -6.012.16).</li> <li>Overall, a 1 kg reduction in body weight was associated with a mean change in SBP of -1.05 (95% CI: -1.430.66) mm Hg.</li> <li><u>1° Safety endpoint</u>: N/A</li> </ul>	<ul> <li>Substantial evidence for a reduction in BP, overall and in normotensives.</li> <li>With the exception of the mean (95% Cl) changes in BP, this paper provides limited data for the normotensive group</li> </ul>
Ho M, et al., 2012 (104) <u>23166346</u>	<u>Aim</u> : Study the effect of lifestyle weight loss interventions in obese/overweight children on weight	Inclusion criteria: • RCTs, in obese/overweight children and adolescents ≤18 y	Intervention: Lifestyle weight loss program with a dietary component <u>Comparator</u> : No treatment, usual care or	<u><b>1° endpoint</b></u> : Pooled experience in the 7 RCTs with BP experience identified a significant reduction in mean SBP of - 3.40 (95% CI: -5.19– -1.61). The pooled SBP MD was -3.72 (95% CI: -4.74– - 2.69) in the 3 RCTs with a duration >1 y	• Findings in children are consistent with experience in adult normotensives and with experience in hypertensive pts.

	change and cardio-	•English language	written education		Considerable
	metabolic risk factors	publications between 1975–	materials	Safety endpoint: N/A	heterogeneity in the data
	Study type:	• Trial duration >2 mo			
	Systematic review and				
	meta-analysis	Exclusion criteria:			
	Size	Studies that targeted			
	Overall, 38 studies	maintenance			
	33 included in	Drug trials			
	various meta-analyses	<ul> <li>Trials in persons with an</li> </ul>			
	Effect on SBP     studied in 7 PCTs that	eating disorder			
	included 554 pts	Inadequate reporting of the data			
Cai L, et al., 2014 (105) <u>24552832</u>	Aim: Study the effect of childhood obesity prevention programs on BP Study type: Systematic review and meta-analysis Size: Overall study included 23 studies (28 comparisons) conducted in 18,925 pts.	Inclusion criteria: • RCTs, quasi-experimental studies, and natural experiments in humans • Children and adolescents 2–18 y • Conducted in a developed country • English language publications • Trial duration ≥1 y (≥6 mo for school-based intervention studies) <u>Exclusion criteria</u> : • Studies that only targeted obese/overweight children or those with a medical condition	Intervention: • Weight loss • 15 school-based • 12 some combination of school, home and/or community-based • 1 child care <u>Comparator</u> : No weight loss	<u>1° endpoint</u> : Pooled experience in 19 studies (20 comparisons) identified a small but significant reduction in mean SBP of -1.65 (95% CI: -2.56– -0.71). The effect size was greater in studies that employed an intervention that combined diet and physical activity (mean change in SBP of -2.11 mm Hg). <u>Safety endpoint</u> : N/A	<ul> <li>Study included a mix of RCTs (13), quasi-experimental studies (9), and natural experiments (1).</li> <li>Included studies conducted over several decades (1985–2012). A significant reduction in BP was only noted in the studies conducted between 2000–2009: mean change in SBP of -3.73 (95% CI: -5.37– -2.09)</li> <li>Findings of a BP reduction in childhood consistent with evidence from the publications by</li> </ul>
		<ul> <li>Inadequate reporting of the data</li> </ul>			
TOHP, Phase II Hypertension Prevention Collaborative Research Group,	Aim: Study the effect of weight loss on BP and prevention of HTN.	Inclusion criteria: • Healthy community-dwelling adults 30–54 y	Intervention: Behavior change intervention (combination of diet change and physical activity) aimed at	<ul> <li><u>1° endpoint</u>: <u>Change in SBP</u></li> <li>Compared to usual care, the weight loss group experienced a significant mean reduction of -4.5 kg in body</li> </ul>	• Largest trial of weight loss in prevention of HTN and also provides the longest duration of follow-up

1997 (106) <u>9080920</u>	Study type: Randomized, controlled factorial trial. Size: 2,382 pts, of whom 1,192 were randomized to a weight loss intervention and 1,190 were randomized to a no weight loss intervention.	<ul> <li>BMI between 110% and 165% of desirable body weight</li> <li>Not taking BP-lowering medication</li> <li>Mean SBP &lt;140 mm Hg and DBP 83-89 mm Hg</li> <li><u>Exclusion criteria</u>:</li> <li>Taking antihypertensive medication</li> <li>Heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements</li> <li>&gt;14 drinks/wk</li> </ul>	studying the effects of a modest reduction in body weight during up to 48 mo (minimum 36 mo) of follow-up. <u>Comparator</u> : Usual care group	<ul> <li>weight and -3.7 (SD: 0.5; p&lt;0.001) mm Hg in SBP at 6 mo (-6.0 mm Hg in the weight loss group and -2.2 mm Hg in the usual care group).</li> <li>A progressive reduction in the effect sizes for body weight and BP was noted over time, with mean for SBP at 18, 36 mo and termination of -1.8 (SD: 0.5; p&lt;0.001), -1.3 (SD: 0.5; p=0.01), and - 1.1 (SD: 0.5; p=0.04).</li> <li><u>Prevention of HTN</u></li> <li>At 6 mo of follow-up the incidence of new onset HTN was 42% lower in the participants randomized to weight loss compared to the usual care group (p=0.02).</li> <li>During more prolonged follow-up, the effect size decreased but remained borderline significant after 48 mo of follow-up (13% reduction; p=0.06). Overall, the incidence of HTN was reduced by 21% (p=0.02).</li> <li><u>Safety endpoint</u>: N/A</li> </ul>	<ul> <li>The assumptions for a main effects factorial analysis (independence of the interventions) were not demonstrated. Given this finding, the most reliable analysis of this trial was comparison of the experience in each active intervention group with the usual care group. This results in a reduction in statistical power.</li> <li>Consistent with the pattern in the proceeding TOHP I trial weight loss reduced BP and the incidence of HTN but the effect sizes for weight loss and BP as well as the difficulty of maintaining the intervention in highly motivated and extensively counselled participants underscores the difficulty of achieving and maintaining ideal body weight in the general population by manns of lifestyle channe.</li> </ul>
TOHP, Phase I 1992 (79) <u>1586398</u>	Aim: Study the effect of weight loss on BP and prevention of HTN Study type: Randomized, controlled factorial trial. Size: Overall, 2,182 adults, with the 308	Inclusion criteria: • Community- dwelling adults 30–54 y • Not on antihypertensive medication • DBP 80-89 mm Hg • Healthy Exclusion criteria: • Disease	Intervention: Behavior change intervention (combination of diet change and physical activity) Comparator: Usual care	<u>1° endpoint</u> : Change in DBP <u>2° endpoint</u> : Change in SBP <u>Safety endpoint</u> : CVD events, symptoms and general and well being	<ul> <li>Significantly lower DBP (2.3 mm Hg; p&lt;0.01) and SBP (2.9 mm Hg; p&lt;0.01) in the weight loss group compared to usual care</li> <li>Few CVD events</li> <li>No difference in symptoms</li> <li>Significant improvement in general well-being at 6 and 18 mo (p&lt;0.05)</li> </ul>

	assigned to weight loss compared to 256 usual care controls	<ul> <li>Inability to comply with the protocol</li> </ul>			
TONE Whelton PK, et al., 1998 (107) <u>9515998</u>	Aim: Study the effect of weight loss on BP and need for antihypertensive drug therapy Study type: RCT, factorial design Size: 585 (obese) participants	Inclusion criteria: • Community-dwelling adults 60–80 y • SBP <145 mm Hg and DBP <85 mm Hg on 1 antihypertensive medication Exclusion criteria: • Heart attack or stroke within 6 mo • Current angina, HF, insulin- dependent DM • Inability to comply with protocol	Intervention: Behavior change intervention (combination of diet change and physical activity) Comparator: Usual care, with similar level of contact compared to active intervention group	<ul> <li><u>1° endpoint</u>: Recurrence of HTN following withdrawal of antihypertensive medication (or CVD event)</li> <li><u>2° endpoint</u>: BP (while still on antihypertensive medication prior to tapering of medication)</li> <li><u>Safety endpoint</u>: CVD events, symptoms (including headaches), dietary composition</li> </ul>	<ul> <li>Significant reduction in SBP prior to withdrawal of antihypertensive medication (mean±SE=-4.0±1.3 mm Hg)</li> <li>1° outcome significantly less common in weight loss group compared to usual care – Rel. HR: 0.70; 95% CI, 0.57–0.87; p&lt;0.001</li> <li>No overt evidence for adverse effects of intervention</li> </ul>

## Data Supplement 21. RCTs and Systematic Reviews for RCTs Studying the Effect of Nonpharmacologic Interventions on BP (Section 6.2)

Study	Aim of Study;	Patient Population	Study Intervention (#	Endpoint Results	Relevant 2° Endpoint (if any);
Acronym;	Study Type;		patients) /	(Absolute Event Rates,	Study Limitations;
Author;	Study Size (N)		Study Comparator (#	P value; OR or RR; & 95% CI)	Adverse Events
Year Published			patients)		
TOHP,	Aim: Study the	Inclusion criteria:	Intervention: Behavior	<u>1° endpoint</u> :	• This was the largest trial of weight loss in
Phase II	effect of weight	<ul> <li>Healthy community-</li> </ul>	change intervention	Change in SBP	prevention of HTN and also provides the
(Weight Loss	loss on BP and	dwelling adults 30–54 y	(combination of diet	<ul> <li>Compared to usual care, the</li> </ul>	longest duration of follow-up
component)	prevention of	<ul> <li>BMI between 110%</li> </ul>	change and physical	weight loss group experienced a	<ul> <li>The assumptions for a main effects</li> </ul>
1997 (1)	HTN.	and 165% of desirable	activity) aimed at	significant mean (standard error)	factorial analysis (independence of the
<u>9080920</u>		body weight	studying the effects of a	reduction of -4.5 kg in body weight	interventions) were not demonstrated. Given
	Study type:	<ul> <li>Not taking BP-lowering</li> </ul>	modest reduction in body	and -3.7 (0.5) (p<0.001) mm Hg in	this finding, the most reliable analysis of this
	Randomized,	medication	weight during up to 48	SBP at 6 mo (-6.0 mm Hg in the	trial was comparison of the experience in
	controlled	• Mean SBP <140 mm	mo (minimum 36 mo) of	weight loss group and -2.2 mm Hg	each active intervention group with the usual
	factorial trial.	Hg and DBP 83-89 mm	follow-up.	in the usual care group).	care group. This results in a reduction in
		Hq		• A progressive reduction in the	statistical power.
		5		effect sizes for body weight and BP	

	Size: 2,382 pts, of whom 1,192 were randomized to weight loss and 1,190 were randomized to no weight loss intervention	Exclusion criteria: • Taking antihypertensive medication • Heart disease, renal disease, poorly controlled hyperlipidemia or DM, DM requiring insulin, special dietary requirements • >14 drinks/wk.	Comparator: Usual care group	<ul> <li>was noted over time, with mean (SD) for SBP at 18, 36 mo and termination of -1.8 (0.5) (p&lt;0.001), - 1.3 (0.5) (p=0.01), and -1.1 (0.5) (p=0.04).</li> <li><u>Prevention of</u> HTN</li> <li>At 6 mo of follow-up the incidence of new onset HTN was 42% lower in the participants randomized to weight loss compared to the usual care group (p=0.02).</li> <li>During more prolonged follow-up, the effect size decreased but remained borderline significant after 48 mo of follow-up (13% reduction; p=0.06). Overall, the incidence of HTN was reduced by 21% (p=0.02).</li> </ul>	• Consistent with the pattern in the proceeding TOHP I trial weight loss reduced BP and the incidence of HTN but the effect sizes for weight loss and BP as well as the difficulty of maintaining the intervention in highly motivated and extensively counselled participants underscores the difficulty of achieving and maintaining ideal body weight in the general population by means of lifestyle change.
TONE (Weight Loss component) Whelton PK, et al., 1998 (3) <u>9515998</u>	Aim: Study the effect of weight loss on BP and need for antihypertensive drug therapy Study type: RCT, factorial design Size: 585 (obese) participants	Inclusion criteria: • Community-dwelling adults 60-80 y • SBP <145 mm Hg and DBP <85 mm Hg on 1 antihypertensive medication Exclusion criteria: • Heart attack or stroke within 6 mo • Current angina, HF, insulin-dependent DM • Inability to comply with protocol	Intervention: Behavior change intervention (combination of diet change and physical activity) Comparator: Usual care, with similar level of contact compared to active intervention group	Safety endpoint: N/A         1° endpoint: Recurrence of HTN         following withdrawal of         antihypertensive medication (or         CVD event)         2° endpoint: BP (while still on         antihypertensive medication prior to         tapering of medication)         Safety endpoint: CVD events,         symptoms (including headaches),         dietary composition	<ul> <li>Significant reduction in SBP prior to withdrawal of antihypertensive medication (mean±standard error=-4.0±1.3 mm Hg)</li> <li>1° outcome significantly less common in weight loss group compared to usual care – Rel. HR: 0.70; 95% CI: 0.57–0.87; p&lt;0.001</li> <li>No overt evidence for adverse effects of intervention</li> </ul>
TOHP, Phase I (Weight Loss component) 1992 (4) <u>1586398</u>	<u>Aim</u> : Study the effect of weight loss on BP and prevention of HTN	<ul> <li>Inclusion criteria:</li> <li>Community-dwelling adults 30–54 y</li> </ul>	Intervention: Behavior change intervention (combination of diet change and physical activity)	<u>1° endpoint</u> : Change in DBP <u>2° endpoint</u> : Change in SBP	<ul> <li>Significantly lower DBP (2.3 mm Hg; p&lt;0.01) and SBP (2.9 mm Hg; p&lt;0.01) in the weight loss group compared to usual care</li> <li>Few CVD events</li> </ul>

Stud Ranc contr facto	<u>dy type</u> : domized, rolled prial trial.	<ul> <li>Not on antihypertensive medication</li> <li>DBP 80-89 mm Hg</li> <li>Healthy</li> </ul>	Comparator: Usual care	Safety endpoint: CVD events, symptoms and general and well being	<ul> <li>No difference in symptoms</li> <li>Significant improvement in general well- being at 6 and 18 mo</li> </ul>
Size 2,182 the 3 to we comp usua contr	: Overall, 2 adults, with 308 assigned eight loss pared to 256 al care rols	Exclusion criteria: • Disease • Inability to comply with the protocol			

## Data Supplement 22. Observational Studies of CV Target Organ Damage Including LVH (Section 7.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
LIFE Devereux RB, et al., 2004 (108) <u>15547162</u>	Study type: Sub- study of pts with HTN and ECG LVH Size: 941	Inclusion criteria: • 55–80 y • BP 160–200/95–115 mm Hg • No MI or stroke within 6 mo • Had echo • Did not require treatment with BB, ACE or AT-1 antagonist for other reasons Intervention: Treatment to BP of 140/90 mm Hg beginning with pts randomized to losartan or atenolol	<ul> <li><u>1° endpoint</u>: Change in LV mass assessed by echo and change in BP in relation to CVD events</li> <li><u>Results:</u> <ul> <li>Composite endpoint of CV death, MI, or stroke reached in 104 in 4.8 y of follow-up</li> <li>Reduction in 1° endpoint per SD reduction in LV mass independent of BP change OR: 0.74 (95% CI: 0.6–0.91; p=0.003)</li> <li>Reductions for each composite endpoint component and total mortality were also significant; results independent of change in ECG LVH</li> </ul> </li> </ul>	Reduction in LV mass by echo independently related to CVD outcomes
CARDIA Armstrong AC, et al., 2014 (109) <u>24507735</u>	Study type: Observational study of population-based cohorts	Inclusion criteria: African American and white men and women stratified by education (above/below high school) 18– 30 y at study start and followed for over 20 y; previously healthy	<ul> <li><u>1° endpoint</u>: Composite of hard CVD events</li> <li><u>Results:</u></li> <li>LV mass indexed to body surface area or to height predicted CV events independently of the Framingham risk score (HR: 1.21; 95% CI: 1.05–1.39; p&lt;0.007)</li> </ul>	<ul> <li>LV mass measured at age 18– 30 y leads to modest risk reclassification later in life</li> <li>Low number of events limits generalizability</li> </ul>

	<u>Size</u> : 3,980		• Net reclassification improvement for LVM/height was 0.13 (p<0.01) and for LVM/BSA was 0.11 (p=0.02).	
ARIC Okwuosa TM, et al., 2015 (110) <u>25497261</u>	Study type: Observational study of population-based cohorts <u>Size</u> : 14,489	Inclusion criteria: African American and white men and women population-based cohort mean age 54.7 ± 5.7 y at study start and followed for over 25 y; previously healthy	<ul> <li><u>1º endpoint</u>: Pooled cohort CV events and 10-y Framingham CVD events</li> <li><u>Results:</u></li> <li>792 (5.5%) 10-y Pooled Cohort CV events and 690 (4.8%) 10-y Framingham CHD events.</li> <li>LVH was associated with CVD events (HR: 1.62; 95% CI: 1.38–1.90) and CHD events (HR: 1.56; 95% CIL 1.32–1.86.</li> <li>LVH by ECG did not significantly reclassify or improve C statistic compared with Framingham risk score (C statistics 0.767/0.719; net reclassification index =0.001 [p=not significant]), compared with (C statistics 0.770/0.718), respectively.</li> </ul>	ECG LVH does not improve risk reclassification
MESA Zalawadiya SK, et al., 2015 (111) <u>24699336</u>	Study type: Observational study of population-based cohorts Size: 4,921	Inclusion criteria: Multi-ethnic cohort of men and women followed for a mean follow-up of 4.5 y	<u>1° endpoint</u> : Hard CVD endpoints <u>Results:</u> MRI calculated LVH (indexed to BSA or height; >95 <sup>th</sup> percentile) predicted hard CVD events (LVH-BSA: HR: 2.36; 95% CI: 1.37–4.04; p=0.002; LVH-height [1.7]: HR: 1.95; 95% CI: 1.17– 3.26; p=0.01). but did not improve risk reclassification beyond conventional risk factors	Though LVH predicted events it did not improve risk reclassification

# Data Supplement 23. RCTs on Use of Risk Estimation to Guide Treatment of Hypertension (Section 8.1.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% Cl)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Sundstrom J,	Aim: We aimed to	Inclusion criteria: BPLTTC:	Intervention: BP-lowering	<u>1° endpoint</u> :	<u>Summary</u> :
et al., 2014	investigate whether	trials were eligible if they met the	meds	<ul> <li>Total major CV events,</li> </ul>	Lowering BP provides similar
(112)	the benefits of BP-	original inclusion criteria		consisting of stroke (nonfatal	relative protection at all levels
<u>25131978</u>	lowering drugs are	specified in the protocol, 11 and	Comparator: Placebo or	stroke or death from	of baseline CV risk, but
	proportional to	were part of the subset of	less intensive treatment	cerebrovascular disease), CHD	progressively greater absolute
	baseline CV risk, to	studies that randomly allocated		(nonfatal MI or death from CHD	risk reductions as baseline risk

	establish whether absolute risk could be used to inform treatment decisions for BP-lowering therapy, as is recommended for lipid-lowering therapy. <u>Study type</u> : Meta- analysis of RCTs <u>Size</u> : 11 trials and 26 randomized groups with 67,475 pts (51,917 pts data available for the calculation of the risk equations)	pts to either a BP-lowering drug or placebo, or to a more intensive or less intensive BP regimen. Trials had to have a minimum of 1,000 pt-y of planned follow-up in each randomized group, and should not have presented their main results before the protocol was finalized in July, 1995. <u>Exclusion criteria</u> : Not stated		<ul> <li>including sudden death), HF (resulting in death or admission to hospital), or CV morbidity.</li> <li>The mean estimated baseline levels of 5-y CV risk for each of the 4 risk groups were 6.0% (SD: 2–0), 12.1% (1–5), 17.7% (1–7), and 26.8% (5–4).</li> <li>In each consecutive higher risk group, BP-lowering treatment reduced the risk of CV events relatively by 18% (95% CI: 7–27), 15% (95% CI: 4–25), 13% (95% CI: 2–22), and 15% (95% CI: 5– 24), respectively (p=0·30 for trend) in each group with BP-lowering treatment for 5 y would prevent 14 (95% CI: 8–21), 20 (95% CI: 8–31),</li> </ul>	<ul> <li>increases. These results support the use of predicted baseline CVD risk equations to inform BP-lowering treatment decisions.</li> <li>Lowest risk group had &gt;83% with a risk that exceeds 4%.</li> </ul>
Sundstrom J, et al., 2015 (19) <u>25531552</u>	<u>Aim:</u> To investigate whether pharmacologic BP reduction prevents CV events and deaths in	Inclusion criteria: RCTs of at least 1 y duration; pts ≥18 y, at least 80% of whom had grade 1 HTN and no previous CVD (ML angina pectoris	Intervention: BP-lowering meds Comparator:	24 (95% CI: 8–40), and 38 (95% CI: 16–61) CV events, respectively (p=0.04 for trend). <u>1° endpoint</u> : Total major CV events, comprising stroke (nonfatal stroke or death from cerebrovascular disease), coronary events (nonfatal MI or death from	Summary: • BP-lowering therapy is likely to prevent stroke and death in pts with uncomplicated grade 1
	pts with grade 1 HTN. <u>Study type:</u> Meta- analysis of RCTs <u>Size:</u> 10 RTCs with 15,266 pts	CABG, PCI, stroke, TIA, carotid surgery, peripheral arterial surgery, intermittent claudication, or renal failure); and compared an antihypertensive drug provided as monotherapy or a stepped-care algorithm vs. placebo or another control regimen.	<ul> <li>Praceod of ress intensive treatment</li> <li>The difference in average achieved BP between the active and control groups was 3.6/2.4 mm Hg in the BPLTTC (Appendix Table 2, available at www.annals.org) but is unknown for the other contributing trial subgroups.</li> </ul>	CHD, including sudden death), HF (causing death or resulting in hospitalization), or CV death; OR: 0.86 (95% CI: 0.74–1.01) Other endpoints: Each of the above outcomes independently; and total deaths. • CHD 0.91 (95% CI: 0.74–1.12) • Stroke 0.72 (95% CI: 0.55–0.99) • HE 0.80 (05% CI: 0.57–1.12)	• 5 y risks in BPLTTC control groups CVD events 7.4% CVD deaths 3.1%
		Exclusion criteria: Excluded trials did not contribute an event		• CVD deaths 0.75 (95% Cl: 0.57– 0.98)	

Thompson AM, et al., 2011 (113)       Aim: To evaluate the effect of antitypertensive       Inclusion criteria: Studies were cligible for inclusion if they were RCTs of antitypertensive treatment anog pts with BP 2136/140       Inclusion criteria: Studies were cligible for inclusion if they were RCTs of antitypertensive treatment anog pts with BP 2136/140       Inclusion criteria: Studies were cligible for inclusion if they were RCTs of antitypertensive treatment anog pts with BP 2136/140       Inclusion criteria: Study type: Meta- analysis RCTs Study population did not include pts with previsiting CVD or CVD mortality).       Intervention: RB-Newrention: Propretod, Proposite CVD (Fight Or nonfalal Stroke, fatal or nonfatal Stroke,	r		T			
Intervention:       Aim: To evaluate the effect of anthypertensive treatment on 2° pervention of CVD anthypertensive treatment on 2° pervention of CVD events (fatal or nonfatal full cuscue)       Intervention::       BP-lowering two basis       Summary: Among pis with PP anthypertensive treatment anog pis with PP anthypertensive treatment on 2° pervention of CVD events (fatal or nonfatal full cuscue)       Intervention::       BP-lowering two basis       Intervention::       BP-lowering two basis       Summary: Among pis with PP anthypertensive treatment anog pis with PP anthypertensive treatment anog pis with PP anthypertensive treatment anog pis with PP anthysis       Intervention::       BP-lowering two basis       Intervention::       BP-lowering two basis       Summary: Among pis with PP anthypertensive treatment anog pis with PP anthypertensive treatment anog pis with PP anthysis       Intervention::       Intervention::<			for any of the outcomes of interest.		• Total deaths 0.78 (95% CI: 0.67– 0.92)	
Thompson AM, et al., 2011 (113)       Aim: To evaluate the effect of antihypertensive treatment anong pts with BP 21364140       Inclusion criteria: Studies were eligible for inclusion if they were RCTs of antihypertensive treatment among pts with BP <140 mm Hg systolic or <90 mm Hg diastolic for the prevention of CVD events and all-cause without clinically defined HTN.       Inclusion criteria: Studies were eligible for inclusion if they were RCTs of antihypertensive treatment among pts with BP <140 mm Hg systolic or <90 mm Hg diastolic for the prevention of CVD events (stal or nonfatal stroke, fatal or nonfatal stroke, fatal or nonfatal MI, CHF, or CVD mortality).       Intervention: BP-lowering meds, the majority were studies of ACE1, next most common were BBs.       Intervention: CVD events (stal or nonfatal stroke, fatal or nonfatal stroke, fatal or nonfatal stroke, fatal or nonfatal MI, CHF, or CVD mortality).       Intervention: CVD events kere analysis of RCTs       Intervention: CVD events kere excluded if CVD events were excluded if CVD events were not reported by HTN status in studies that included pts with and without HTN; the study population did not include pts with prevensive ranges; the study population did not include pts with prevensive treatment was not part of the intervention; treatment allocation was not random; a measure of wardpare (owalk end CO Mare per difficult intervention; treatment allocation was not random; a measure of wardpare (owalk end CO Mare pen					Only the first event for a pt was used for the analysis of each outcome, but a pt who had >1 outcome type could contribute to more than 1 analysis. They also	
Aim: To evaluate the AM, et al., 2011 (113)       Inclusion criteria: Studies were eligible for inclusion if they were antihypertensive treatment an 2° prevention of CVD events and all-cause mortality among pts without clinically defined HTN.       Intervention: BP-lowering mods, the majority were studies of ACEI, next most common were BBs.       Summary: Among pts wit clinical history of CVD but without HTN, antihyperten treatment ansociated decreased risk of stroke, ( 2 UD events, at all-cause mortality among pts without clinically defined HTN.       Summary: Among pts wit clinical history of CVD but without HTN, antihyperten treatment among pts with BP <140 mm Hg systolic or <90 mm Hg diastolic for the prevention of CVD events (fatal or nonfatal stroke, fatal or nonfatal MI, CHF, or CVD mortality).       Summary: Among pts wit clinical history of CVD but treatment was associated decreased risk of stroke, ( 2 Other endpoints:         Study type: Meta- analysis of RCTs       Exclusion criteria: Studies were excluded if CVD events were not reported by HTN status in studies that included pts with appulation did not include pts with prevensive ranges: the study population did not include pts with prevensive ranges: the study population did not include pts with prevensive treatment was not part of the intervention; reatment allocation was not random: a measure of was not random: a measure of w					tabulated overall withdrawals and withdrawals due to adverse events	
of pts with CAD vs. other, HF vs. reported or could not be calculated from the information provided: pts <18 v; or there	Thompson AM, et al., 2011 (113) <u>21364140</u>	Aim: To evaluate the effect of antihypertensive treatment on 2° prevention of CVD events and all-cause mortality among pts without clinically defined HTN. <u>Study type:</u> Meta- analysis of RCTs <u>Size:</u> 25 RCTs with 64,162 pts	Inclusion criteria:       Studies were eligible for inclusion if they were RCTs of antihypertensive treatment among pts with BP <140 mm Hg systolic or <90 mm Hg diastolic for the prevention of CVD events (fatal or nonfatal stroke, fatal or nonfatal MI, CHF, or CVD mortality).	Intervention: BP-lowering meds, the majority were studies of ACEI, next most common were BBs. Comparator: Placebo or active comparator	<ul> <li><u>I<sup>o</sup> endpoint</u>:</li> <li>Composite CVD (fatal or nonfatal stroke, fatal or nonfatal MI, CHF, or CVD mortality):</li> <li>CVD RR: 0.85 (95% CI: 0.80–0.90), absolute risk reduction: 27.1/1,000.</li> <li>This implies that a 2.7% absolute risk reduction reflects a 15% RR reduction, so the baseline risk for CVD would have been about 18%, but the follow-up interval is unclear.</li> <li><u>Other endpoints:</u></li> <li>Stroke RR: 0.77 (95% CI: 0.61, 0.98)</li> <li>MI RR: 0.80 (95% CI: 0.69, 0.93)</li> <li>HF RR: 0.71 (95% CI: 0.65, 0.77)</li> <li>CVD death RR: 0.83 (95% CI: 0.69, 0.93)</li> <li>HF RR: 0.71 (95% CI: 0.65, 0.77)</li> <li>CVD deaths RR: 0.87 (95% CI: 0.80, 0.95)</li> <li><u>Other results:</u> Table 4 shows similar results for CVD from studies of pts with CAD vs. other, HF vs. other, and DM vs. non-DM. Similar results from studies of ACEI vs.</li> </ul>	Summary: Among pts with clinical history of CVD but without HTN, antihypertensive treatment was associated with decreased risk of stroke, CHF, composite CVD events, and all-cause mortality. Limitations: • Difference in achieved BP was not reported. • Average baseline SBP not reported. No information on the entry levels of BP other than not hypertensive. Difficult to use to establish a treatment threshold or goal. • Many of these studies were designed to try to demonstrate specific drug benefits rather than BP-lowering benefits. Can we attribute the benefits to BP- lowering? We know these pts did not have HTN but we do not know the lower limit of the BP inclusion ranges or the treatment associated difference in SBP between

		intervention and control groups other than antihypertensive treatment.		conclusion that the effect is not a drug effect, but is a BP-lowering effect, and that the effect is seen in people with CVD broadly defined, not just in HF pts.	establish a treatment initiation threshold or goal.
Xie X, et al., 2015 (21) <u>26559744</u>	Aim: To assess the efficacy and safety of intensive BP-lowering strategies. Study type: Meta- analysis of RCTs Size: 19 RCTs with 44,989 pts	Inclusion criteria: RCTs with at least 6 mo follow-up that randomly assigned pts to more intensive vs. less intensive BP- lowering treatment, with different BP targets or different BP changes from baseline. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Exclusion criteria: N/A	Intervention: BP-lowering meds Comparator: • Less intensive treatment • BP difference 6.8/3.5 • The mean follow-up BP levels in the less intensive BP-lowering regimen group were 140/81 mm Hg, compared with 133/76 mm Hg in the more intensive treatment group.	<ul> <li><u>1º endpoint:</u> <ul> <li>CVD, other major CV events, defined as a MI, stroke, HF, or CV death, separately and combined; nonvascular and all-cause mortality; ESKD, and adverse events. Progression of albuminuria (defined as new onset of micro-albuminuria/macro-albuminuria or a change from micro-albuminuria) and retinopathy (retinopathy progression of 2 or more steps) were also recorded for trials that were done in pts with DM</li> <li>CVD RR: 0.86 (95% CI: 0.78–0.96)</li> </ul> </li> <li><u>Other endpoints:</u> MI RR: 0.87 (95% CI: 0.76–1.00; p=0.042) Stroke RR: 0.78 (95% CI: 0.68–0.90)</li> <li>HF RR: 0.85 (95% CI: 0.66–1.11) CVD death RR: 0.91 (95% CI: 0.74–1.11) Total deaths RR: 0.91 (95% CI: 0.81–1.03)</li> <li><u>Other results:</u></li> <li>Benefit for CVD not different by baseline SBP 120–139: 0.89 (95% CI: 0.68–1.00) &gt; 160: 0.83 (95% CI: 0.73–1.09)</li> </ul>	Summary: Intensive BP- lowering, including to <130 mm Hg, provided greater vascular protection than standard regimens. In high-risk pts, there are additional benefits from more intensive BP- lowering, including for those with SPB <140 mm Hg at baseline. The net absolute benefits of intensive BP- lowering in high-risk individuals are large. Limitations: • Lack of individual pt data, which would have allowed a more reliable assessment of treatment effects in different pt groups. • Interpretation: Supports treating pt with and without CVD at threshold of 130 to <130. Supports treating at threshold of about 130 even down to a CVD event rate of 0.9% per y.

				n hotorogonoity: 0.60	
				Ponofit for CVD not different for	
				Benefit for CVD not unreferit for more intensive and less intensive	
				targete in intensive and less intensive	
				140 or 150 mm Hay 0.76 (05%)	
				<140 01 <150 11111 Hy: 0.70 (95%	
				(1.0.00-0.97)	
				<120-<130 mm Hg: 0.91 (95% CI:	
				0.84 - 1.00	
				p-netero: 0.06	
				Absolute benefits were	
				proportional to absolute risk.	
				<ul> <li>For trials in which all pts had</li> </ul>	
				vascular disease, renal disease, or	
				DM at baseline, the average	
				control group rate of major	
				vascular events was 2.9% per y	
				compared with 0.9% per y in other	
				trials, and the numbers needed to	
				treat were 94 (95% CI: 44–782) in	
				these trials vs. 186 (95% CI: 107–	
				708) in all other trials.	
				<ul> <li>Increase in severe hypotension:</li> </ul>	
				0.3% vs. 0.1% per person y OR:	
				2.68 (95% CI: 1.21–5.89)	
Ettehad D, et	Aim: This systematic	Inclusion criteria:	Intervention: BP-lowering	<u>1° endpoint:</u>	<u>Summary:</u>
al., 2015 (17)	review and meta-	<ul> <li>RCTs of BP-lowering</li> </ul>	meds	• CVD.	<ul> <li>BP-lowering significantly</li> </ul>
<u>26724178</u>	analysis aims to	treatment that included a		<ul> <li>Major CVD events, CHD, stroke,</li> </ul>	reduces vascular risk across
	combine data from all	minimum of 1,000 pt-y of follow-	Comparator: Placebo,	HF, renal failure, and all-cause	various baseline BP levels and
	published large-scale	up in each study arm. No trials	active comparator or less	mortality.	comorbidities. Our results
	BP-lowering trials to	were excluded because of	intensive treatment	Standardized RR for 10 mm Hg	provide strong support for
	quantify the effects of	presence of baseline		difference in SBP	lowering BP to SBP <130 mm
	BP reduction on CV	comorbidities, and trials of		• CVD RR: 0.80 (95% CI: 0.77-	Hg and providing BP-lowering
	outcomes and death	antihypertensive drugs for		0.83)	treatment to individuals with a
	across various	indications other than HTN were			history of CVD, CHD, stroke,
	baseline BP levels,	eligible.		Other endpoints:	DM, HF, and CKD.
	major comorbidities,	<ul> <li>Eligible studies fell into 3</li> </ul>		• CHD RR: 0.83 (95% CI: 0.78–	<ul> <li>In stratified analyses, we saw</li> </ul>
	and different	categories: 1st, random		0.88)	no strong evidence that
	pharmacological	allocation of pts to a BP-lowering		• Stroke RR: 0.73 (95% CI: 0.68-	proportional effects were
	interventions.	drug or placebo; 2nd, random		0 77)	diminished in trials that
		allocation of pts to different BP-		0.77)	included people with lower

Study type: Meta-	lowering drugs; and third,	• HF RR: 0.72 (95% CI: 0.67–0.78)	baseline SBP (<130 mm Hg),
analysis of RCTs	random allocation of pts to	• Total deaths RR: 0.87 (95% CI	and major CV events were
,	different BP-lowering targets.	0.84–0.91)	clearly reduced in high-risk pts
Size: 123 studies with			with various baseline
613,815 pts	Exclusion criteria: <1,000 pt-y	Other results:	comorbidities. Both of these
	of follow-up in each treatment	Benefit for CVD and other	major findings—the efficacy of
	group.	endpoints not different hy baseline	BP-lowering below 130 mm Ha
		SBP including $<130$ mm Ha fig 4	and the similar proportional
		in paper	effects in high risk
		CVD: 0.63: 95% CI: 0.50–0.80	populations—are consistent
		p=0.22	with and extend the findings of
		CHD: 0.55; 95% CI: 0.42–0.72;	the SPRINT trial.
		p=0.93	
		Stroke: 0.65; 95% CI: 0.27–1.57;	Limitations:
		p=0.38	<ul> <li>Lack of individual pt data,</li> </ul>
		HF: 0.83; 95% CI: 0.41–1.70;	which would have allowed a
		p=0.27	more reliable assessment of
		Total deaths: 0.53; 95% CI: 0.37-	treatment effects in different pt
		0.76; p=0.79	groups.
		<ul> <li>More precision around estimates</li> </ul>	<ul> <li>Interpretation: Lowering of</li> </ul>
		of benefits in SBP 130–139 at	BP into what has been
		baseline, fig 4 in paper	regarded the normotensive
		<ul> <li>Results similar in trials of people</li> </ul>	range should therefore be
		with and without CVD at baseline	routinely considered for the
		figure 5	prevention of CVD among
		CVD+ 0.77 (95% CI: 0.71–0.81)	those deemed to be of
		CVD- 0.74 (95% CI: 0.67–0.83)	sufficient absolute risk.
		Total deaths	
		CVD+ 0.90 (95% CI: 0.83–0.98)	
		CVD- 0.84 (95% CI: 0.75–0.93)	
		Other outcomes similarly in figure 5	
		<ul> <li>In appendix, in general, benefits</li> </ul>	
		for CVD prevention seen in groups	
		with and without baseline CHD,	
		Stroke, DM, CKD and HF when	
		examined separately, but no	
		absolute risks provided to enable	
		estimation of how far down the	
		absolute risk curve these findings	
		have been demonstrated.	

					-
				<ul> <li>Some evidence of BB inferiority</li> </ul>	
				to other med classes in figure 6.	
				<ul> <li>Did not report absolute risks so</li> </ul>	
				do not know lower level of risk in	
				treated populations.	
SPRINT	Aim: To test the	Inclusion criteria: SBP≥130	Intervention: Intensive BP-	1° <u>endpoint:</u> CVD (MI, ACS,	Summary:
Wright JT Jr,	effectiveness of a goal	mm Hg, with upper limit varying	lowering treatment to goal	stroke, HF, CVD death)	<ul> <li>More intensive SBP lowering</li> </ul>
et al., 2015	SBP<120 mm Hg vs. a	as number of pre-trial BP-	SBP <120 mm Hg	HR: 0.75 (95% CI: 0.64, 0.89)	to a goal of <120 mm Hg with
(114)	goal SBP<140 mm Hg	lowering meds increased.			achieved mean of
26551272	for the prevention of	age ≥50 y	Comparison:	Other endpoints:	approximately 121 mm Hg
	CVD in pts with	Presence of at least 1 of the	Standard BP-lowering	• Total deaths HR: 0.73 (95% CI:	resulted in less CVD and lower
	SBP≥130 mm Hg at	following:	treatment to goal SBP<140	0.60-0.90)	total mortality over 3.26 v in
	baseline.	Clinical or subclinical CVD	mm Ha	• 1° or death HR: 0.78 (95% CI:	comparison with a goal SBP
		<ul> <li>CKD stage ≥3</li> </ul>	Net treatment difference	0.67-0.90)	<140 mm Hg and achieved
	Study type: RCT	• Age>75	$\sim$ 3 drugs (2.8) on average	Components of 1° composite	SBP of ~135 mm Ha.
		Framingham Conoral CVD	vs 2 drugs $(1.8)$ on	mostly consistent in direction other	• There were small increases
	Size: 9361 pts	risk>15% in 10 v	average	than $ACS = no difference$	in some expected SAEs
	followed median of	113R=1570 III 10 y	During the trial mean	indiff 105 no difference.	Perhans unexpected a sizable
	3.26 y.	Exclusion critoria: DM history	SBP was 121 5 vs 13/ 6	CKD outcomes:	increase in reduced eGER in
	,	of stroke ESPD (aGER < 20)	<b>3DI</b> Wu3 <b>121</b> . <b>3 v3</b> . <b>134</b> . <b>0</b> .	• 1° in CKD nts: reduction in GEP	the non-CKD group and
				of >50% or ESDD HD: 0.80 (05%)	AKI/ARF overall was observed
				C! = 0.72 + 1.87	in the intensive group. While of
				o Incident albuminuria HD: 0.72	uncertain etiology and
					significance there is
				(95% 0.40, 1.07)	speculation this could be an
				• In pis without CKD: reduction in	acute hemodynamic effect
				GFR 230% and 10 < 60	especially given the findings
				• HR: 3.49 (95% CI: 2.44–5.10)	regarding albuminuria
				Incident albuminuria HR: 0.81	
				(95% CI: 0.63–1.04)	Limitations: Few hts were
					untreated at baseline ~9% so
				Adverse events:	SPRINT provides little if any
				• SAEs: 1.04; p=0.25	insight at present regarding
				<ul> <li>Significant absolute increases</li> </ul>	BP-lowering medication
				seen in intensive group for	initiation for untreated people
				hypotension (1%), syncope (0.6%),	with SBP 130–139
				electrolyte abnormality (0.8%),	
				acute kidney injury/acute renal	
				failure (1.6%) over the study	
				period.	

				• 1 7% fewer nts had orthostatic	
				hypotension in intensive group	
				n=0.01	
Lawes MR_et	Aim	Inclusion criteria: The	Intervention: BP-lowering	1° endpoint:	Summary: The effect of RP-
al 2009 (115)	• To determine the	database search (by MRL) used	medications	CHD and stroke co-1°	lowering drugs in reducing the
16222626		Medline (1966 to December	medications	• Standardized to a 10/5 mm Hg	risk of disease is entirely or
10222020	different classes of	2007: any language) to identify	Comparison: Placebo or	BD reduction	largely due to RP reduction
	BP-lowering drugs in	randomized trials of BP-lowering	less intensive treatment	Overall	with 1 main excention a
	proventing CHD and	drugs in which CHD events or			special extra effect of BBs in
	stroke and who	strokes were recorded		Stroko: 0.50 (95% CI: 0.75-0.05)	people who have had a recent
	should receive	(irrespective of whether BP		<ul> <li>In absonce of vaccular disease</li> </ul>	MI The proportional reduction
	treatment	reduction was considered the			in CHD events and stroke for a
	• 5 questions	mechanism of action). Search		Stroko: 0.54 (95% CI: 0.72-0.00)	given reduction in BP. an
	encansulate this	terms were "antihypertensive		- History of CHD	approximate halving in risk for
	uncertainty 1st do	agents" or "HTN" or "diuretics.			each 10 mm Ha diastolic
	BBs have a special	thiazide" or "adrenergic beta-		Stroko: 0.65 (95% CI: 0.53_0.00)	reduction, is the same in
	effect over and above	antagonists" or "angiotensin-		History of stroko	people with and without a
	lowering BP in	converting enzyme inhibitors" or			history of vascular disease and
	preventing CHD	"receptors,		Stroko: 0.66 (05% CI: 0.02-1.00)	in people without high BP as
	events in people with a	angiotensin/antagonists &		• No big drug class offocts event	well as in those with high BP
	history of CHD? 2nd,	inhibitors" or "tetrazoles" or		more bonefit for BBs shortly after	There is benefit in lowering BP
	does the effect of BP-	"CCB s" or "vasodilator agents"			in anyone at sufficient CV risk
	lowering drugs in	or the names of all BP-lowering		Troatmont honofits soon down to	whatever their BP, so avoiding
	preventing CHD and	drugs listed in the British		• Treatment SRD of 110, 110 mm	the need to measure BP
	stroke differ in people	National Formulary as keywords		Ha for CHD events PP: 0.78 (05%	routinely.
	with and without a	or text words. Limits were		(10, 0.63, 0.06) and $(130, 130, 0.76)$	
	history of CVD (i.e., is	Medline publication type "clinical		Ha for stroke PP: 0.75 (05% CI:	Limitation:
	there a different effect	trial" or "controlled clinical trial"		0.63_0.80)	<ul> <li>Most of the pts without HTN</li> </ul>
	in 2° and 1°	or "RCT" or "meta-analysis". We		0.05-0.07	were in the trials of people with
	prevention)? 3 <sup>rd</sup> , does	also searched the Cochrane			pre-existing CVD; hence, most
	BP reduction alone	Collaboration and Web of			of the results of BP lowering in
	explain the effect of	Science databases and the			people with SBP<140 are in
	BP-lowering drugs in	citations in trials and previous			people with CVD.
	preventing CHD and	meta-analysis and review			<ul> <li>No absolute risks or benefits</li> </ul>
	stroke? 4th, should the	articles.			provided. Not possible to
	use of BP-lowering				estimate how far down the risk
	drugs be limited to	Exclusion criteria:			curve these results apply.
	people with high BP	We excluded nonrandomized			
	and not given to those	trials and trials in which treated			Interpretation: This MA
	at high risk of CVD	groups but not control groups			provides stronger support for

who have a lower BP?	had other interventions as well		treating at levels <140 for
A corollary is whether	as BP reduction, such as		people with CVD than for
BP should be reduced	cholesterol reduction. We		people without CVD.
to a limited extent	excluded trials in pts with		
only, a treat to target	chronic renal failure because		
approach. Although	these pts typically have high BP		
cohort	and high rates of CVD and their		
(prospective\observati	response to standard BP-		
onal) studies do not	lowering therapy may differ from		
show a lower BP limit	other people. We also excluded		
below which risk	trials in which fewer than 5 CHD		
ceases to decline ("the	events and strokes were		
lower the better"), this	recorded or the duration of		
has not been shown in	treatment was less than 6 mo.		
randomized trials	as these data would contribute		
across a wide range of	little to the overall results and		
BP.	substantially increase the		
Finally, what is the	complexity of the analyses.		
quantitative effect of	RCTs were otherwise included		
taking ≥1 BP-lowering	irrespective of pt age, disease		
drugs in lowering BP	status. BP before treatment, or		
and preventing CHD	use of other drugs.		
events and stroke	acc of other anager		
according to dose.			
pretreatment BP and			
age? To date no such			
quantitative summary			
of effect taking			
account of these			
determining factors			
has been made			
Study type: Meta-			
analysis of RCTs			
Size · 147 RCTs of RP-			
lowering meds and			
CHD events (22 000)			
and stroke (12 000)			

Lewington S,	Aim: To describe the	Inclusion criteria: Collaboration	Intervention: N/A	1° <u>endpoint:</u>	Summary: Throughout middle
et al., 2002	age-specific relevance	was sought from the		Not completely clear, but for our	and old age, usual BP is
(16)	of BP to cause-specific	investigators of all prospective	Comparator: N/A	purposes, stroke and IHD death	strongly and directly related to
<u>12493255</u>	mortality	observational studies in which		would be co-1°. Also looked at	vascular (and overall) mortality,
		data on BP, blood cholesterol,	• The exposures of interest	other vascular deaths.	without any evidence of a
	Study type: Meta-	date of birth (or age), and sex	were the level of SBP and	HRs for stroke mortality for a 20	threshold down to at least
	analysis of cohort	had been recorded at a baseline	DBP and age-group.	mm Hg lower SBP by age-group	115/75 mm Hg.
	studies	screening visit, and in which		40-49: 0.36 (95% CI: 0.32-0.40)	
		cause and date of death (or age		50–59: 0.38 (95% CI: 0.35–0.40)	
	Size: 61 prospective	at death) had been routinely		60–69: 0.43 (95% CI: 0.41–0.45)	
	studies with 12.7	sought for all screens during		70–79: 0.50 (95% CI: 0.48–0.52)	
	million person-y of	more than 5,000 person-y of		80–89: 0.67 (95% CI: 0.63–0.71)	
	observation, 56,000	follow-up (see appendix A;		HRs for IHD mortality for a 20	
	vascular deaths in 40–	http://image.thelancet.com/extra		mm Hg lower SBP by age-group	
	89 y.	s/01art8300webappendixA.pdf).		40–49: 0.49 (95% CI: 0.45–0.53)	
		Relevant studies were identified		50–59: 0.50 (95% CI: 0.49–0.52)	
		through computer searches of		60–69: 0.54 (95% CI: 0.53–0.55)	
		Medline and Embase, by hand-		70–79: 0.60 (95% CI: 0.58–0.61)	
		searches of meeting abstracts,		80–89: 0.67 (95% CI: 0.64–0.70)	
		and by extensive discussions		HRs for other vascular mortality	
		with investigators.		for a 20 mm Hg lower SBP by age-	
				group	
		Exclusion criteria: To minimize		40-49: 0.43 (95% CI: 0.38-0.48)	
		the effects of reverse causality		50–59: 0.50 (95% CI: 0.47–0.54)	
		(whereby established disease		60–69: 0.53 (95% CI: 0.51–0.56)	
		could change the usual BP),		70–79: 0.64 (95% CI: 0.61–0.67)	
		studies were excluded if they		80–89: 0.70 (95% CI: 0.65–0.75)	
		had selected pts on the basis of		<ul> <li>Similar results for DBP also in</li> </ul>	
		a positive history of stroke or		figure 1.	
		heart disease, and individuals		• Similar results for men and	
		from contributing studies were		women separately for stroke, figure	
	excluded from the present			3, and IHD, figure 5.	
		analyses if they had such a			
		history recorded at baseline.			
Inomopoulos	Aim: Investigating	Inclusion criteria: Intentional	Intervention/Comparator:	<u>1° endpoint</u> :	Summary: Meta-analyses
C, et al.,	whether all grades of	BP-lowering comparing active	Criteria of eligibility were	<ul> <li>As some trials were done on low-</li> </ul>	tavor BP-lowering treatment
2014 (20)	HIN benefit from BP-	drug treatment with placebo, or	Intentional BP-lowering	risk pts, others on higher risk pts,	even in grade 1 H I N at low-to-
<u>25259547</u>	iowering treatment and	less active treatment (intentional	comparing active drug	no evaluation of absolute risk-	moderate risk, and lowering
	which are the target	BP-lowering trials), or	treatment with placebo, or	reduction was made. However, a	SBP/DBP to <140/90 mm Hg.
		comparison of an active drug	less active treatment	2° analysis was done including	Achieving <130/80 mm Hg

	BP levels to maximize	with placebo over baseline	(intentional BP-lowering	trials or trial subgroups with mean	appears safe, but only adds
	outcome reduction.	antihypertensive treatment,	trials), or comparison of an	baseline SBP/DBP values in grade	further reduction in stroke.
		resulting in a BP difference of at	active drug with placebo	1 range and a low-to-moderate risk	
	Study type: Meta-	least 2 mm Hg in either SBP or	over baseline	(<5% CV deaths in 10 y in	
	analysis of RCTs	DBP (nonintentional BP-lowering	antihypertensive treatment,	controls): FEVER stratum with	
	5	trials); enrolling of hypertensive	resulting in a BP difference	baseline SBP below the median	
	Size: 32 RCTs with	individuals only or a high	of at least 2 mm Hg in	(<153 mm Hg) (e7); HTN Detection	
	104,359 pts	proportion (at least 40%) of	either SBP or DBP	and Follow-up Program stratum	
		them.	(nonintentional BP-lowering	with baseline DBP 90–94 mm Hg	
			trials); enrolling of	and no CVD (e9); OSLO (e17);	
		Exclusion criteria: N/A	hypertensive individuals	TOMHS (e28) and USPHS (e29).	
			only or a high proportion (at	Risks of stroke, CHD, the	
			least 40%) of them. Other	composite of stroke and CHD, and	
			inclusion criteria can be	all-cause death were significantly	
			found in the preceding	reduced by BP-lowering in these	
			paper. 51 trials were found	low-to-moderate risk pts (control	
			eligible either for assessing	group: average CV mortality 4.5%	
			BP-lowering effects in	in10 y) with a moderate BP	
			different HTN grades or for	elevation (average SBP/DBP	
			assessing the effects of	145.5/91 mm Hg) at randomization.	
			achieving different BP	Standardized risk ratio associated	
			levels	with 10/5 reduction in BP: stroke	
				0.33 (95% CI: 0.11–0.98)	
				CHD 0.68 (95% CI: 0.48–0.95)	
				CVD death 0.57 (95% CI: 0.32–	
				1.02) total death 0.53 (95% 0.35–	
				0.80)	
				Compared outcomes of achieved	
				on study SBP <130 vs. ≥130	
				Standardized Risk ratio associated	
				CVD 0.01 (95% CI: 0.07, 1.00) CVD doath 0.99 (05% CI: 0.77	
				1 01) total doath 0 00 (05% CI.	
				• Outcomes of achieved on study	
				Cultomes of achieved off sludy	
1	1		1	SBP 130-139 VS. 2140	

				Standardized Risk ratio associated with 10/5 reduction in BP: stroke 0.63 (95% CI: 0.52–0.77) CHD 0.77 (95% CI: 0.70–0.86) HF 0.76 (95% CI: 0.47–1.25) CVD 0.74 (95% CI: 0.62–0.88) CVD death 0.81 (95% CI: 0.67– 0.97) total death 0.87 (95% CI: 0.75–1.00) • Similar pattern of results for on treatment DBP.	
Lonn EM, et al., 2016 (116) <u>27041480</u>	Aim: To assess efficacy of fixed-dose antihypertensive therapy in adults with intermediate CVD risk. <u>Study type</u> : Double- blind, placebo- controlled RCT, factorial design <u>Size</u> : 12,705 pts	Inclusion criteria: Men ≥55 y and women ≥60 y at intermediate risk for CVD. No BP restrictions. Exclusion criteria: • Known CVD • Indications or contraindications to study meds • Mod/advanced CKD • Symptomatic hypotension	Intervention: FDC of ARB (candesartan 16 mg/d) and diuretic (hydrochlorothiazide 12.5 mg/d) or placebo Follow-up: Median=5.6 y	<u>1° endpoint</u> : 1 co-1° CVD composite outcomes • CVD mortality, nonfatal MI, nonfatal stroke • Above plus cardiac arrest, HF, revascularization	Summary: • SBP/DBP reduction of 6.0/3.0 mm Hg • No difference in treatment effect • 1st co-1° 0.93 (0.79–1.10) • 2nd co-1° 0.95 (0.81–1.11) • Suggestion of a subgroup effect in tertile with the highest baseline BP and increased CVD risk.
Neaton JD et al., 1993 (117) <u>8336373</u>	Aim: To compare 6 antihypertensive drugs (representing different drug classes) Study type: Double- blind, placebo- controlled RCT Size: 902 pts with stage 1 HTN	Inclusion criteria: • Men and women 45–69 y • Not taking antihypertensive medications, with DBP 90–99 mm Hg • Taking 1 antihypertensive medication, with DBP <95 mm Hg and between 85–99 mm Hg after withdrawal of BP medications	Intervention: Treatment (number): Once daily (AM): • Placebo (234) • Chlorthalidone 15 mg/d (136) • Acebutolol 400 mg/d (132) • Doxazosin 2 mg/d (134) • Amlodipine 5 mg/d (131) • Enalapril 5 mg/d (135) Follow-up: Median=4.4 y	<u>1° endpoint</u> : BP, QoL, side effects, chemistries, ECG, clinical events	Summary: • Drugs (plus diet) more effective compared to placebo (plus diet) for control of BP. • Minimal differences between drug regimens

Van Dieren S, et al., 2012 (118) <u>22677192</u>	Aim: To assess differences in treatment effects of a fixed combination of perindopril- indapamide on major clinical outcomes in pts with type 2 DM across subgroups of CV risk. Study type: RCT Size: 11,140 pts with DM-2, from the ADVANCE trial	Inclusion criteria: DM-2, aged ≥55 y, with a history of major macrovascular or microvascular disease, or at least 1 other risk factor for vascular disease Exclusion criteria: A definite indication for, or contraindication to, any of the study treatments, a definite indication for long-term insulin treatment or were participating in any other clinical trial.	Intervention: Perindopril- indapamide or matching placebo	<ul> <li><u>1° endpoint</u>:</li> <li>The Framingham equation was used to calculate 5-y CVD risk and to divide participants into 2 risk groups, moderate-to-high risk (&lt;25% and no history of macrovascular disease), very high risk (&gt;25% and/or history of macrovascular disease).</li> <li>Endpoints were macrovascular and microvascular events.</li> </ul>	Summary: Relative effects of BP-lowering with perindopril- indapamide on CV outcomes were similar across risk groups whilst absolute effects trended to be greater in the high-risk group.
Montgomery AA, et al., 2003 (119) <u>12923409</u>	Aim: To estimate the effectiveness and cost-effectiveness of BP-lowering treatment over a lifetime. Study type: Markov decision analysis model comparing treatment and nontreatment of HTN. Size: Hypothetical cohorts for 20 different strata of sex, age (30– 79 y, in 10-y bands), and CV risk (low and high)	Inclusion criteria: We created models for 20 different strata of sex, age (age 30–70 y in 10-y bands), and 2 risk profiles (designated as 'low' and 'high' risk). These example risk profiles represent the extremes of absolute CV risk, based on data from the Health Survey for England and using a Framingham risk function. We recognize that the risk of most individuals seen in primary care will be somewhere between the examples presented here. The data included were as follows: age- and sex-specific mean SBP of untreated individuals with SBP>0.160 mm Hg were used for both high-risk and low-risk profiles. In addition, low-risk profile was defined as nonsmoker, 10th percentile total cholesterol 90th percentile HDL	Intervention: Treatment and nontreatment of HTN.	<u>1º endpoint</u> : Life expectancy, and incremental cost: effectiveness ratios for treatment and nontreatment strategies	<ul> <li>Probabilities of clinical events were obtained from published literature.</li> <li><u>Summary</u>:         <ul> <li>Incremental cost per quality-adjusted life y among low-risk groups ranged from £1,030 to £3,304. Cost-effectiveness results for low-risk pts were sensitive to the utility of receiving antihypertensive treatment. Treatment of high-risk individuals was highly cost-effective, such that it was the dominant strategy in the oldest age group, and resulted in incremental costs per quality-adjusted life y ranging from £34–£265 in younger age groups.</li> <li>Policy decisions about which pts to treat depend on whether a life-expectancy or cost-</li> </ul> </li> </ul>

		cholesterol, no DM, and no LVH, and high-risk profile was defined as smoker, 90th percentile total cholesterol, 10th percentile HDL cholesterol, DM, and LVH. <u>Exclusion criteria</u> : N/A			effectiveness perspective is taken. Treatment increases life expectancy in all strata of age, sex, and CV risk. However, younger individuals stand to gain proportionately more from BP treatment than do the elderly. In terms of cost- effectiveness, pts at high risk of CVD are a highly cost- effective group to treat. In pts at lower risk of CVD, consideration should be given to issues of pt preference and cost.
Kassai B, et al., 2005 (120) <u>17315403</u>	Aim: Consideration of absolute risk has been recommended for making decisions concerning preventive treatment in HTN. Aim to estimate the benefit of antihypertensive therapy over a life- time. Study type: Meta- analysis on individual data in HTN and specific cause of death from national statistics. Disease-free survival curves until all pts have died were built using the "life-table" method. The treatment effect estimated from INDANA was applied to this curve to obtain the disease-free	Inclusion criteria: To estimate the rate of cv and non-CV deaths in a hypothetical U.S. population of untreated hypertensive pts, we used the following procedure: age-specific death rates in the U.S. general population were obtained from national vital statistics (1994), and in untreated hypertensive population they were obtained from the control groups of the INDANA database. This latter group represents a unique cohort of 14 942 untreated or placebo-treated hypertensive pts, 26–96 y with an average follow-up of 5 y Exclusion criteria: N/A	Intervention: The gain in life expectancy without stroke, CHD, and CV events was estimated from the area between the 2 survival curves of treated and control groups. The relative gain in life expectancy was defined as the ratio of gain in life expectancy to life expectancy.	1° endpoint:       Stroke and CHD co-1°         Results:       CHD         Age       ABb       RGLEe         Y       RRa (%) NNTc GLEd (%)         40       0.86       0.3       333       20       4.1         50       0.88       1.0       100       17       4.3         60       0.90       1.9       53       13       3.4         70       0.91       3.9       26       10       5.4         Stroke       Age       ABb       RGLEe       Y         Y       RRa (%) NNTc GLEd (%)       40       0.80       0.4       250       32       5.9         50       0.84       1.0       100       26       5.7       60       0.86       2.3       44       21       7.1         70       0.87       5.7       18       17       9.1       3       RR at 10 y       b       Absolute benefit at 10 y       c       NNT to avoid 1 event.       d       Gain in life expectancy in mo without events.	Summary: Absolute gains in life expectancy are likely to be greater for younger, lower risk people with HTN than for older, higher risk people with HTN. However, the NNT to prevent an event will likely be greater especially in the short term in younger, lower risk people. This modeling analysis provides support for treating younger, lower risk individuals with HTN, but relies on the assumption that the relative benefits of treatments observed in short-term trials of higher risk individuals applies over a longer term to lower risk individuals.

					-
	survival curve of the			e Relative gain in life expectancy	
	life-long treated			without events.	
	population. Gains in				
	event-free life				
	expectancy were				
	ostimated from				
	Survival curves. A				
	sensitivity analysis				
	was performed to				
	assess the impact of				
	possible death				
	misclassifications.				
	Size: 6 RCTs, ~30,000				
	pts				
Czernichow S	Aim: The objective of	Inclusion criteria: RCTs of BP-	Intervention: BP-lowering	1° endpoint:	Summary:
et al., 2011	this systematic review	lowering (drug vs. control or less	meds	Major CVD events (stroke CHD	• Effectiveness of BP-lowering
(121)	and meta-analysis was	intensive treatment) or different		and UE	regiments in reducing PR of
20881867	to compare the relative	classes of drug therapy that	Comparator: Placebo	All auideness of differences in the	major CVD overts does not
20001007	roductions in risk	included a minimum of 1 000 nt	activo comparator or loss	• No evidence of differences in the	soom to be influenced by
	achieved with different	v of follow up in each study arm	intensive treatment	ratio of risk across varying levels of	steriling level of DD
		y of tollow-up in each study ann.		baseline BP (with all classes of BP-	starting level of BP.
	starting levels of BP			lowering medications).	
	(and treatment	Exclusion criteria: <1,000 pt-y			Limitations:
	regimens).	of follow-up in each treatment			<ul> <li>The majority of the</li> </ul>
		group.			participants studied were at
	Study type: Meta-				high risk for CVD.
	analysis of RCTs				<ul> <li>Information pertaining to the</li> </ul>
					effect of treatment on absolute
	Size: 32 trials with				risk was not presented in this
	201,566 pts (20,079				manuscrint
	1° outcome events)				manasonpt.

## Data Supplement 24. Follow-Up After Initial BP Evaluation (Section 8.1.3)

Study Acronym;	Aim of Study;	Patient Population	Study Intervention	Endpoint Results	Relevant 2° Endpoint (if any);
Author;	Study Type;		(# patients) /	(Absolute Event Rates,	Study Limitations;
Year Published	Study Size (N)		Study Comparator	P value; OR or RR; & 95%	Adverse Events;
			(# patients)	CI)	Summary

Ambrosius WT, et al., 2014 (122) 24902920Aim: To describe the study design of the SPRINTStudy type: SPRINT RCT	Inclusion criteria: Adults ≥50 y, average SBP_≥130 mm Hg and evidence of CVD, CKD, or 10-y Framingham risk score ≥15%, or ≥75 y	Intervention: 9,361 pts randomized to 2 treatment groups: • Standard treatment group, SBP target <140 mm Hg • Intensive treatment group: SBP target <120 mm Hg.	<u>1° endpoint</u> : MI, ACS, stroke, HF, or CVD death.	Relevant 2° endpoint: All-cause mortality, decline in kidney function or development of ESRD, incident dementia, decline in cognitive function, and small-vessel cerebral ischemic disease         Summary:       This paper describes the protocol followed in the SPRINT trial that was successful in helping participants to attain and maintain BP targets in the study groups. Once treated, participants had follow-up visits to assessment BP control monthly until BP was at target. Medications were titrated and added as per protocol, when target BP was not attained.
Cushman WC, et al., 2007 (123) <u>17599425</u>	Inclusion criteria: Adults with a diagnosis of DM-2 for at least 3 mo and at high risk for CVD events, who meet the following BP criteria: (1) SBP 130–160 mm Hg and taking 0–3 antihypertensive medications; (2) SBP 161–170 and on 0–2 antihypertensive medications; or (3) SBP 171-180 and taking 0-1 antihypertensive medication. Other entry criteria included spot urine sample <2+, protein–Cr	Intervention: • Unmasked, open- label, factorial design, randomized trial with a sample size of 4,733 pts • Pts randomized to intensive SBP control (<120 mm Hg) or standard control (<140 mm Hg)	<u>1º endpoint</u> : Major CVD event (nonfatal MI or stroke, or CV death)	Relevant 2° endpoint:Expanded macrovascularoutcome (1° outcome plus coronaryrevascularization or HF hospitalization), totalmortality, each of the separate components of the1° outcome, HF death or hospitalization, andcomposite microvascular disease outcome (kidneyand eye disease).Summary:This paper describes the protocolfollowed in the ACCORD trial that was successfulin helping participants to attain and maintain BPtargets in the study groups. Once treated,participants had follow-up visits to assessment BPcontrol monthly until BP was at target. Medicationswere titrated and added as per protocol, whentarget BP was not attained.

Study Au Year F	Acronym; uthor; Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% Cl)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
VA NE Fried L 2013 (' <u>242064</u>	<b>PHRON-D</b> .F, et al., 124) <u>457</u>	<u>Aim</u> : Assess the efficacy of combination of an ACEI and an ARB vs. ARB monotherapy in reducing the progression of proteinuric diabetic nephropathy <u>Study type</u> : Multicenter, double- blind, RCT at 32 VA Medical Centers <u>Size</u> : 1448 pts	Inclusion criteria: Pts with type 2 DM, a urinary albumin-to-creatinine ratio of ≥300, and an eGFR 30.0–89.9 mL/min/1.73 m <sup>2</sup> Exclusion criteria: • Subjects with known nondiabetic kidney disease • Serum K+ >5.5 mmol/L • Current treatment with sodium polystyrene sulfonate • Inability to stop prescribed medication that increases the risk of hyperkalemia	Intervention: Losartan 100 mg daily plus lisinopril 10–40 mg daily (n=724) <u>Comparator</u> : Losartan 100 mg daily plus placebo (n=724)	1° endpoint:After a median follow-up of 2.2 y, the study was stopped early due to safety concerns.There was no difference in the 1° outcome of first occurrence of change in eGFR (decrease of ≥30 mL/min/1.73 m² if initial GFR was ≥60 mL/min/1.73 m² or a decline of ≥50% if initial eGFR was <60 mL/min/1.73 m²), ESRD, or death (HR with combination therapy: 0.88; 95% CI: 0.70–1.12; p=0.30).Safety endpoint: Combination therapy increased the risk of hyperkalemia (HR: 2.8; 95% CI: 1.8–4.2; p<0.001) and acute kidney injury (HR: 1.7; 95% CI: 1.3–2.2; p<0.001).	2° endpoint: There was no difference in the 2° endpoint of first occurrence of change in eGFR or ESRD (HR: 0.78; 95% CI: 0.58–1.05; p=0.10). There were no differences between combination therapy or losartan monotherapy for the endpoints of ESRD, death, composite of MI, HF, or stroke, MI, CHF, and stroke (p>0.05 for all). <u>Summary</u> : Combination therapy of losartan plus lisinopril did not improve renal outcomes compared to losartan alone, and was associated with greater risk of acute kidney injury and hyperkalemia.
ALTITI Parving al., 201 231213	UDE g HH, et 12 (125) <u>378</u>	<u>Aim</u> : Determine if addition of aliskiren as an adjunct to an ACEI or ARB reduces the risk of CV and renal events in pts with type 2 DM	Inclusion criteria: • ≥35 y with type 2 DM • On ACEI or ARB • At least 1 of the following: persistent macroalbuminuria (urine microalbumin to creatinine ratio ≥200 mg/g) and eGFR ≥30 mL/min/1.73 m <sup>2</sup> , persistent microalbuminuria (≥20 mg/g and <200 mg/g) and a mean eGFR ≥30 and <60	Intervention: Aliskiren 300 mg daily added to conventional treatment with an ACEI or ARB (n=4,274) <u>Comparator</u> : Placebo (n=4,287)	<u>1° endpoint</u> : After a median follow-up of 32.9 mo the study was stopped early. There was no difference in the 1° composite outcome death from CV causes or first occurrence of cardiac arrest with resuscitation; nonfatal MI; nonfatal stroke;	<ul> <li><u>2° endpoint</u>:</li> <li>There was no difference between aliskiren and placebo for the individual components of the composite 1° outcome (all p&gt;0.05) other than cardiac arrest with resuscitation, which was increased significantly with aliskiren (HR: 2.40; 95% CI: 1.05–5.48; p=0.04).</li> </ul>

## Data Supplement 25. RCTs for General Principles of Drug Therapy (Combination Therapies that Inhibit the RAAS) (Section 8.1.4)

	Study type	ml/min/1 73 m <sup>2</sup> or history of CVD (e.g.		unplanned hospitalization	• There was no differences in
	Doubled-blind	ML stroke HE or CAD) and a mean		for HE: ESRD: death	CV composite outcome repai
	multicenter RCT	eGFR $\geq$ 30 and <60 ml /min/1 73 m <sup>2</sup>		attributable to kidney failure	composite outcome, relia
				or need for renal-	from any cause $(n>0.05$ for all)
	Size: 8561	Exclusion criteria		replacement therapy with no	
		• Serum $K_{\pm} > 5.0 \text{ mmol/l}$		dialysis or transplantation	Summary: Aliskiren added to
		• Type 1 DM		available or initiated: or	background treatment of an
		• Type T Divi		doubling of the baseline	ACEL or ARB did not decrease
		• Officiable Seruin Ci		serum Cr between aliskiren	CV or renal outcomes and was
		• CV HISTORY (INTER CLASS III OF IV, SDP		or placebo (HR: 1.08: 95%	associated with increased risk of
		$\geq$ 170 IIIII FIG OF DDF $\geq$ 110 IIIII FIG OF SPD >125 and <170 mm Hg or DPD		CI: 0.98-1.20: p=0.12).	cardiac arrest with resuscitation
		$SBP \ge 135$ and $< 170$ mm Ha with at least 2		o	hyperkalemia and hypotension
		202 driu < 100 mm Hy with at least 5		Safety endpoint: The	hyperkalernia, and hypetension.
		ronal artory stonosis		combination of aliskiren	
		Surgical or modical conditions		added to an ACEI or an	
		• Surgical of medical conditions (malignancy in last $5 y < 2 y$ life		ARB was associated with	
		expectancy, repairing of the		greater risk of hyperkalemia	
		immunosuppressive therapy		and hypotension (11.2% vs.	
		drug/alcohol abuse		7.2% and 12.8% vs. 8.3%;	
		hypersensitivity/allergy/contraindication		p<0.001 for both,	
		to study drugs_pregnancy)		respectively).	
		Concomitant treatment with >2 agents			
		blocking RAAS or K+-sparing diuretics			
ONTARGET	Aim: Evaluate	Inclusion criteria:	Intervention: Ramipril	1º endpoint · After a	2° endpoint <sup>.</sup>
Yusuf S, et al.,	whether use of an	• ≥55 v	10 mg daily (n=8,576)	median follow-up of 56 mo.	• There was no difference in
2008 (126)	ARB was noninferior	• Coronary peripheral or	- <u>j</u> ,	there was no difference	composite of death from CV
18378520	to ACEI, and	cerebrovascular disease or DM with	Comparator:	between ramipril vs.	causes ML or stroke in the
	whether the	end-organ damage	Telmisartan 80 mg	telmisartan or combination	ramipril vs. telmisartan groups
	combination was		daily (n=8,542)	therapy vs. ramipril in the 1°	RR: 0.99: 95% CI: 0.9–1.07):
	superior to ACE	Exclusion criteria:	Combination of	composite outcome of death	p=0.001 or ramipril vs.
	alone in the	Inability to discontinue ACEI or ARB	telmisartan and	from CV causes, MI, stroke,	combination RR: 1.00; 95% CI:
	prevention of	Known hypersensitivity or intolerance	ramipril (n=8,502)	or hospitalization for HF	0.93–1.09
	vascular events in	to ACEI or ARB		(RR: 1.01; 95% CI: 0.94–	• There were no differences
	pts with CVD or DM	Selected CVDs (congestive HF		1.09 and RR: 0.99; 95% CI:	between ramipril vs. telmisartan
	but not HF.	hemodynamically significant valvular or		0.92–1.07, respectively)	or ramipril vs. combination
		outflow tract obstruction, constrictive			therapy in 2° outcomes including
	Study type: Multi-	pericarditis, complex congenital heart		Safety endpoint:	MI, stroke, hospitalization for HF,
	center, double-blind,	disease, syncopal episodes of unknown		<ul> <li>Combination therapy was</li> </ul>	death from CV causes, death
	RCT	etiology <3 mo, planned cardiac surgery		associated with greater risk	from non-CV causes, or death
				of hyperkalemia than	from any cause (p>0.05 for all).

<u>Size</u> : 25,620	or PTCA <3 mo, uncontrolled HTN on	ramipril monotherapy (480	
	treatment [e.g., BP >160/100 mm Hg],	pts vs. 283 pts; p<0.001)	Summary: Combination therapy
	heart transplant recipient, stroke due to	<ul> <li>Hypotensive symptoms</li> </ul>	with telmisartan and ramipril did
	subarachnoid hemorrhage)	were cited as reason for	not decrease the risk of CV
	<ul> <li>Other conditions (significant renal</li> </ul>	permanent discontinuing	events in pts at high risk
	artery disease, hepatic dysfunction,	more in telmisartan vs.	compared to monotherapy with
	uncorrected volume or sodium	ramipril (RR: 1.54; p<0.001)	ramipril. In addition, combination
	depletion, 1° hyperaldosteronism,	and combination therapy vs	therapy was associated with
	hereditary fructose intolerance, other	ramipril monotherapy (RR:	increased risk of hypotension,
	major noncardiac illness or expected to	2.75; p<0.001)	hyperkalemia, and renal
	reduce life expectancy or significant	<ul> <li>Renal impairment was</li> </ul>	impairment.
	disability interfere with study	more common in	
	participation, simultaneously taking	combination therapy vs.	
	another experimental drug, unable to	ramipril monotherapy RR:	
	provide written informed consent).	1.33; 95% CI: 1.2–1.44	

## Data Supplement 26. BP Goal for Patients with Hypertension (Section 8.1.5)

Study Acronym (if applicable) Author Year Published	Study Type/Design; Study Size (N)	Patient Population	Study Intervention (# patients) Study Comparator (# patients)	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lawes CM, et al., 2003 (50) <u>12658016</u>	Study type: Meta- analysis of RCTs of BP drugs recording CHD events and strokes Size: 464,000 pts	N/A	N/A	• CHD RR or 46% Stroke 64%	• All classes of BP meds confer benefit while BB confer greater benefit in those with CAD
LV J, et al., 2013 (127) <u>23798459</u>	Study type: MA of RTC that randomly assigned individuals to different target BP levels Size: 15 trials including a total of 37,348 pts	N/A	N/A	<ul> <li>7.5/4.5 mm Hg BP difference. Intensive BP lowering achieved.</li> <li><u>RR for</u></li> <li>Major CV events: 11%; 95% CI: 1%–21%)</li> <li>MI: 13%; 95% CI: 0%– 25%</li> </ul>	More intensive strategy for BP control reduced cardio- renal endpoint

				<ul> <li>Stroke: 24%; 95% CI: 8%–37%</li> <li>ESRD: 11%; 95% CI: 3%–18%</li> <li>Albuminuria: 10%; 95% CI: 4%–16%</li> <li>Retinopathy 19%; 95% CI: 0%–34% p=0.051</li> </ul>	
Xie X, et al., 2015 (21) <u>26559744</u>	Study type: MA of RTC that randomly assigned individuals to different target BP levels <u>Size</u> : 19 trials (n=44,989)	N/A	N/A	Achieved BP 133/76 mm Hg (intensive) 140/81 (less intense) • Major CV events: 14%; 95% Cl: 4%–22% • Ml: 13%; 95% Cl: 0%– 24% • Stroke: 22%; 95% Cl: 0%– 24% • Stroke: 22%; 95% Cl: 10%–32% • Albuminuria: 10%; 95% Cl: 3%–16% • Retinopathy progression: 19%; 95% Cl: 0%–34%. • More intensive had no effects on HF: 15%; 95% Cl: 0%–34%. • CV death: 9%; 95% Cl: - 11%–26% • Total mortality: 9%; 95% Cl: -3%–19% • ESKD: 10%; 95% Cl: - 6%–23%	More intensive approach reduced major CV events (stroke and MI) except heat failure, CVD, ESRD, and total mortality.

Verdecchia P et	Study type:	N/A	N/A	Stroke, ML HF, CVD	The results strongly
al., 2016	Cumulative meta-			mortality and all-cause	supported the benefit of
27456518	analysis of RCTs to			mortality	intensive BP reduction for
	study benefit of			Difference in achieved	prevention of stroke and MI
	more vs. less			SBP/DBP-7.6/4.5 mm Hg	and suggested benefit for
	intensive BP			• For stroke and MI the	prevention of CVD mortality
	lowering			cumulativo 7 scoro	and HF
	g			crossed the efficacy	
	Size: 18 trials			boundary after addition of	
	(n=53,405)			the SPRINT results	
				<ul> <li>For CVD mortality and</li> </ul>	
				HF, the cumulative Z	
				curve crossed the	
				conventional significance	
				boundary (but not the	
				sequential monitoring	
				boundary)	
				• For all-cause mortality,	
				the cumulative Z curve did	
				not reside in the futility are	
				but did not cross the	
				conventional significance	
				boundary	
Bangalore S, et	Study type:	N/A	N/A	There was a significant	Overall, the beneficial effects
al., 2017	Network meta-			reduction in stroke (RR:	of treatment were consistent
<u>28109971</u>	analysis in which			0.54) and MI (RR: 0.68)	with other reports. The cluster
	the authors			The point estimate	plots of treatment benefit vs.
	attempted to			favored all-cause	risk are difficult to interpret due
	compare the			mortality, CVD mortality	to limitations of the available
	benefits and			and HF but the results did	data base and the authors'
	adverse effects			not achieve significance	decision to weight treatment
	resulting from			<ul> <li>SBP targets &lt;120 and</li> </ul>	benefits and potential adverse
	intensive reduction			<130 mm Hg ranked #1	effects equally.
	in SBP			and #2 as the most	
				efficacious	
	Size: 17 trials			<ul> <li>Serious adverse effects</li> </ul>	
	(n=55,163)			were more common at a	
				lower SBP (120 vs. 150 or	
				140 mm Hg)	

				Cluster plots for combined efficacy and safety suggested a SBP <130 mm Hg as the optimal target for SBP reduction during treatment	
Bundy JD, et al., 2017 <u>28564682</u>	Systematic review and network meta- analysis to assess the benefits of intensive SBP reduction during treatment of hypertension Size: 42 trials (n=144,220)	N/A	N/A	• In general, there were linear associations between achieved SPB and risk of CVD and all- cause mortality, with the lowest risk at a SBP of 120–124 mm Hg.	• This was by far the largest and best powered meta- analysis to assess the relationship between SBP reduction and major outcomes during treatment of hypertension. The findings provided strong evidence for the "lower is better" approach to treatment in patients with a high SBP who are at high risk for CVD.
Lawes CMM, et al., 2002 <u>16222626</u>	Study type: Review of observational reports and randomized controlled trials	N/A	N/A	<ul> <li>The relative benefits of BP lowering for CHD prevention likely to be consistent across a wide range of different populations</li> <li>Likely to be considerable benefit for BP lowering beyond traditional thresholds, especially in those at high risk for CVD</li> <li>BP lowering is likely to be more important than choice of initial agent</li> <li>A large majority of patients being treated for</li> </ul>	• Strongly supports lower BPs during BP treatment, especially in those at high risk of CVD

	hypertension have suboptimal BPs. Initiatives to lower their BP further are essential	

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Xie X, et al., 2015 (21) <u>26559744</u>	<u>Aim:</u> To assess the efficacy and safety of intensive BP- lowering strategies. <u>Study type:</u> Meta- analysis of RCTs <u>Size:</u> 19 RCTs with 44,989 pts	Inclusion criteria: RCTs with at least 6 mo follow-up that randomly assigned pts to more intensive vs. less intensive BP-lowering treatment, with different BP targets or different BP changes from baseline. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Exclusion criteria: N/A	Intervention: BP-lowering meds Comparator: • Less intensive treatment • BP difference 6.8/3.5 • The mean follow-up BP levels in the less intensive BP- lowering regimen group were 140/81 mm Hg, compared with 133/76 mm Hg in the more intensive treatment group.	<ul> <li><u>1° endpoint</u>:</li> <li>CVD, other major CV events, defined as a MI, stroke, HF, or CV death, separately and combined; nonvascular and all-cause mortality; ESKD, and adverse events. Progression of albuminuria (defined as new onset of micro-albuminuria/macro-albuminuria or a change from micro-albuminuria to macro-albuminuria) and retinopathy (retinopathy progression of 2 or more steps) were also recorded for trials that were done in pts with DM</li> <li>CVD RR: 0.86 (95% CI: 0.78–0.96)</li> </ul>	Summary: Intensive BP- lowering, including to <130 mm Hg, provided greater vascular protection than standard regimens. In high- risk pts, there are additional benefits from more intensive BP-lowering, including for those with SPB <140 mm Hg at baseline. The net absolute benefits of intensive BP- lowering in high-risk individuals are large. Limitations: • Lack of individual pt data, which would have allowed a more reliable assessment of

			treatment effects in different		
		Other endpoints:	pt groups.		
		• MI RR: 0.87 (95% CI: 0.76–	Interpretation: Supports		
		1.00) p=0.042	treating pt with and without		
		• Stroke RR: 0.78 (95% CI:	CVD at threshold of 130 to		
		0.68-0.90)	<130. Supports treating at		
		• HE BB: 0.85 (95% CI: 0.66_	threshold of about 130 even		
		1 11)	down to a CVD event rate of		
		CVD death RP: 0.01 (05% CI:	0.9% per v.		
		0.74 + 1.11			
		• Total doaths DD: 0.01 (05%			
		• Total dealins KK. $0.91 (957)$			
		CI: 0.81 - 1.03)			
		Other results:			
		• Popofit for CVD pot different			
		• Deficit for CVD flot unreferit			
		120 120 0 80 (05% CI- 0 76			
		1 05)			
		1/0_160·0.83 (05% CI·0.68_			
		1 00)			
		1.00/ \160: 0.89 (95% CI: 0.73_1.09)			
		n-heterogeneity: 0.60			
		Benefit for CVD not different			
		for more intensive and less			
		intensive targets in intensive			
		aroup			
		<140  or  <150  mm Hg; 0.76			
		(95% CI: 0.60–0.97)			
		<120– <130 mm Hg: 0.91 (95%			
		Cl: 0.84–1.00; p-hetero: 0.06)			
		Absolute benefits were			
		proportional to absolute risk.			
		• For trials in which all pts had			
		vascular disease, renal disease.			
		or DM at baseline, the average			
		control group rate of major			
		vascular events was 2.9% per y			
		compared with 0.9% per y in			
		other trials, and the numbers			
		needed to treat were 94 (95%			
				CI: 44–782) in these trials vs. 186 (95% CI: 107–708) in all other trials. • Increase in severe hypotension: 0.3% vs. 0.1% per person y OR: 2.68 (95% CI: 1.21–5.89)	
---	--	---	--	--	---
Julius S, et al., 2006 (55) <u>16537662</u>	Study type: RCT in pre-HTN16 mg candesartan vs. placebo Size: 809 pts	• 58% men	N/A	• During the first 2 y, HTN developed in 154 (40.4%) pts in the placebo group compared with only 53 (13.6%) of those in the candesartan group, for a RR of 66.3% (p<0.0001). After 4 y, HTN developed in 240 (63.0%) in the placebo group vs. only 208 (53.2%) in the candesartan group RR 15.6% (p<0.0069).	• 2/3 of those with pre-HTN develop HTN within 4 y. Candesartan interrupts the onset and reduced by 15.6%
Lawes CM, et al., 2003 (50) <u>12658016</u>	Study type: Meta- analysis of RCTs of BP drugs recording CHD events and strokes Size: 464,000 pts	N/A	N/A	CHD RR or 46% Stroke 64%	• All classes of BP meds confer benefit while BB confer greater benefit in those with CAD
Lonn EM, et al., 2016 (116) <u>27041480</u>	Aim: To assess efficacy of fixed-dose antihypertensive therapy in adults with intermediate CVD risk. <u>Study type</u> : Double- blind, placebo- controlled RCT, factorial design	Inclusion criteria: Men ≥55 y and women ≥60 y at intermediate risk for CVD. No BP restrictions. Exclusion criteria: • Known CVD • Indications or contraindications to study meds • Mod/advanced CKD • Symptomatic hypotension	Intervention: FDC of ARB (candesartan 16 mg/d) and diuretic (hydrochlorothiazide 12.5 mg/d) or placebo Follow-up: Median=5.6 y	<ul> <li><u>1° endpoint</u>:</li> <li>1 co-1° CVD composite outcomes</li> <li>CVD mortality, nonfatal MI, nonfatal stroke</li> <li>Above plus cardiac arrest, HF, revascularization</li> </ul>	Summary: • SBP/DBP reduction of 6.0/3.0 mm Hg • No difference in treatment effect • 1st co-1° 0.93 (0.79–1.10) • 2nd co-1° 0.95 (0.81–1.11)

Siz	<u>ze</u> : 12,705 pts				• Suggestion of a subgroup effect in tertile with the highest baseline BP and increased CVD risk.
Neaton JD, et al., 1993 (117) <u>8336373</u> dru diff cla <u>Stu</u> blir cor	im: To compare 6 htihypertensive ugs (representing fferent drug asses) tudy type: Double- ind, placebo- ontrolled RCT ize: 902 pts with	<ul> <li>Inclusion criteria:</li> <li>Men and women 45–69 y</li> <li>Not taking antihypertensive medications, with DBP 90–99 mm Hg</li> <li>Taking 1 antihypertensive medication, with DBP &lt;95 mm Hg and between 85–99 mm Hg after withdrawal of BP medications</li> </ul>	Intervention: Treatment (number): Once daily (AM): • Placebo (234) • Chlorthalidone 15 mg/d (136) • Acebutolol 400 mg/d (132) • Doxazosin 2 mg/d (134) • Amlodipine 5 mg/d (131) • Enalapril 5 mg/d (135) Follow-up: Median=4.4 y	<u>1° endpoint</u> : BP, QoL, side effects, chemistries, ECG, clinical events	<ul> <li>Summary:</li> <li>Drugs (plus diet) more effective compared to placebo (plus diet) for control of BP.</li> <li>Minimal differences between drug regimens</li> </ul>

# Data Supplement 27. Choice of Initial Medication (Section 8.1.6)

Study Acronym Author Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Psaty BM, et al., 2003 <u>12759325</u>	Study type: Network meta- analysis to compare value of different first-line antihypertensive drugs in prevention of major CVD and all-cause mortality Size: 42 trials (n=192,478)	N/A	<ul> <li>For all outcomes, low-dose diuretics were better than placebo</li> <li>None of the other first-line agents (β-blockers, ACEI, CCBs, α-receptor blockers and ARBs) were superior to low-dose diuretics</li> <li>For several outcomes, low-dose diuretics were superior to other agents</li> </ul>	• Low-dose diuretics were identified as the most effective first-line treatment for prevention of CVD and all-cause mortality during treatment of hypertension	N/A

Brunström M, et al. 2016 (53)	Study type: Meta- analysis of levels of	• 49 trials (most pts with DM-2)	Baseline SBP >150 RR for	• BP lowering reduces major CV events in DM. Caution for	N/A
<u>26920333</u>	BP control in DM		• All death: 0.89; 95% CI:0.80-	initiating treatment in diabetics	
	hypertensives.		0.99	with SBP <140/90	
	<b>Size:</b> 73,738 pts		• CVD: 0.75; 95% CI: 0.57–		
	<u></u>		• MI: 0.74; 95% CI: 0.63–0.87		
			• Stroke: 0.77; 95% CI: 0.65-		
			0.91		
			• ESRD: 0.82; 95% CI: 0.71– 0.94		
			Baseline SBP140–150 <u>RR of</u>		
			• Dealin. 0.07, 95% Ci. 0.76– 0.98)		
			• MI: 0.84; 95% CI: 0.76–0.9		
			• HF: 0.80; 95% CI: 0.66–0.97		
			If baseline SBP, 140 mm Hg, however, further treatment		
			increased the risk of CV		
			mortality (1.15; 95% CI: 1.00–		
Ettehad D, et al.,	Study type: Meta-	N/A	Every 10 mm Ha reduction in	BP lowering reduces CV risk	N/A
2015 (17)	analysis of large		SBP RR:	across various baseline BP	
<u>26724178</u>	RTCs of		• Major CV events: 0.80; 95%	levels and comorbidities.	
	treatment			Suggest lowering SBP < 130 mm Ha and BP-lowering treatment to	
			0.88	pts with a history of CVD, CHD,	
	Size: 123 studies		• Stroke: 0.73; 95% CI: 0.68-	stroke, DM, HF, and CKD.	
	(613,815 pts)		0.77), HF (0.72, 0.67–0.78		
			• All-cause mortality: 0.87; 95% CI: 0.87: 0.84–0.91		
			• ESRD: 0.95; 0.84–1.07		
Thomopolous C,	Study type: Meta-	• 16 trials (52,235 pts)	More intense BP	Intensive BP reduction	N/A
et al., 2016 (54)	analysis of RTCs of	compared more vs. less	• Stroke RR: 0.71; 95% CI:	Improves CV outcomes	
20040774	intense BP control	34 (138,127 pts) active vs.	• CHD RR: 0.80: 95% CI:	<ul> <li>Achieved BP &lt;130/80 may be</li> </ul>	
		placebo	0.68–0.95)	associated with CV benefit.	

		-	-	-	
			Major CV events RR: 0.75; 95% CI: 0.68–0.85 CV mortality RR: 0.79; 95% CI: 0.63–0.97 Stratification of SBP cutoffs (150,140 and 130 mm Hg) showed that a SBP/DBP difference of 10/5 mm Hg across each cutoff reduced risk of all outcomes		
Julius S, et al., 2006 (55) <u>16537662</u>	<u>Study type:</u> RCT in pre-HTN 16 mg candesartan vs. placebo <u>Size</u> : 809 pts	• 58% men	• During the first 2 y, HTN developed in 154 (40.4%) pts in the placebo group compared with only 53 (13.6%) of those in the candesartan group, for a RR of 66.3% (p<0.0001). After 4 y, HTN developed in 240 (63.0%) in the placebo group vs. only 208 (53.2%) in the candesartan group RR 15.6% (p<0.0069).	• 2/3 of those with pre-HTN develop HTN within 4 y. Candesartan interrupts the onset and reduced by 15.6%	N/A
Ference BA, et al., 2014 (56) 24591335	Study type: Evaluated the effect of 12 polymorphisms (associated with BP) on the odds of CHD and compared it with the effect of lower SBP observed in both prospective cohort studies and BP-lowering randomized trials Size: 199,477 pts in 63 studies	N/A	•12 polymorphisms were associated with a $0.32 \text{ mm Hg}$ lower SBP (p=1.79×10 <sup>-7</sup> ) and a 0.093-mm Hg/decade slower age-related rise in SBP (p= $3.05 \times 10^{-5}$ ). The effect of long-term exposure to lower SBP on CHD mediated by these polymorphisms was 2- fold greater than that observed in prospective cohort studies (p= $0.006$ ) and 3-fold greater than that observed in short- term BP treatment trials (p= $0.001$ ).	• SBP may be causally associated with the rate of rise in SBP with age and has a cumulative effect on the risk of CHD.	N/A

Data Supplement 28.	Follow-Up After Ir	nitiating Antihypertensiv	ve Drug Therapy	(Section 8.3.1)
				(•••••••)

Study Acronym Author Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Ambrosius WT, et al., 2014 (122) 24902920	<u>Aim</u> : To describe the study design of the SPRINT trial <u>Study type</u> : description of study design and protocol for the SPRINT RCT	Inclusion criteria: Adults ≥50 y, average SBP ≥130 mm Hg and evidence of CVD, CKD, or 10-y Framingham risk score ≥15%, or age ≥75 y	Intervention: 9361 participants randomized to 2 treatment groups: (1) Standard treatment group, SBP target <140 mm Hg, and (2) Intensive treatment group: SBP target <120 mm Hg.	<u>1° endpoint</u> : MI, ACS, stroke, HF, or CVD death.	Relevant 2° endpoint: All- cause mortality, decline in kidney function or development of ESRD, incident dementia, decline in cognitive function, and small- vessel cerebral ischemic disease Summary: This paper describes the protocol followed in the SPRINT trial that was successful in helping participants to attain and maintain BP targets in the study groups. Once treated, participants had follow-up visits to assessment BP control monthly until BP was at target. Medications were titrated and added as per protocol, when target BP was not attained.
Cushman WC, et al., 2007 (123) <u>17599425</u>	Aim: To describe the study design of the BP trial of the ACCORD trial. Study type: description of study design and protocol	Inclusion criteria: Adults with a diagnosis of type 2 DM for at least 3 mo and at high risk for CVD events, who meet the following BP criteria: (1) SBP 130–160 mm Hg and taking 0–3 antihypertensive medications; (2) SBP 161–170 and on 0–2 antihypertensive	Intervention: • Unmasked, open-label, factorial design, randomized trial with a sample size of 4,733 pts • Patients were randomized to intensive SBP control (<120 mm Hg) or standard control (<140 mm Hg)	<u>1º endpoint</u> : Major CVD event (nonfatal MI or stroke, or CV death)	Relevant 2° endpoint: Expanded macrovascular outcome (1° outcome plus coronary revascularization or HF hospitalization), total mortality, each of the separate components of the 1° outcome, HF death or hospitalization, and

	for the ACCORD RCT	medications; or (3) SBP 171– 180 and taking 0–1 antihypertensive medication. Other entry criteria included spot urine sample <2+, protein–Cr ratio <700 mg protein/1 g creatinine, or 24-h protein excretion <1.0 g/24 h.			composite microvascular disease outcome (kidney and eye disease). <u>Summary:</u> This paper describes the protocol followed in the ACCORD trial that was successful in helping pts to attain and maintain BP targets in the study groups. Once treated, pts had follow-up visits to assessment BP control monthly until BP was at target. Medications were titrated and added as per protocol, when target BP was not attained.
Xu W, et al., 2015 (128) <u>25655523</u>	Aim: Retrospective assessment of the impact of follow-up intervals and treatment intensification thresholds on CVD events Study type: Retrospective cohort Size: 88,756 adult pts with HTN from The Health Improvement Network database	Inclusion criteria: Primary care practices in the U.K., 1986–2010.	N/A	<ul> <li>Median follow-up of 37.4 mo after the treatment strategy assessment period</li> <li>9,985 (11.3%) pts had an acute CV event or died.</li> <li>No difference in risk of the outcome with systolic intensification thresholds 130– 150 mm Hg, but HR: 1.21 for thresholds &gt;150 mm Hg</li> <li>Outcome risk increased progressively from the lowest (0–1.4 mo) to the highest 5<sup>th</sup> of time to medication intensification (HR: 1.12; 95% CI: 1.05–1.20; p=0.009) for intensification between 1.4 and 4.7 mo after detection of elevated BP). The highest fifth of time to follow-up (&gt;2.7 mo) was also associated with increased outcome risk HR:</li> </ul>	<ul> <li>Increased risk of acute CVD event or death with:</li> <li>Systolic intensification thresholds &gt;150 mm Hg</li> <li>Delays of &gt;1.4 mo before medication intensification after SBP elevation</li> <li>Delays of &gt;2.7 mo before BP follow-up after antihypertensive medication intensification</li> <li>Timely medical management and follow-up impacts outcomes in the treatment of pts with HTN.</li> <li>Retrospective study, but still sheds important light on the impact of follow-up actions</li> </ul>

				1.18; 95% CI: 1.11–1.25; p<0.001	
Birtwhistle RV, et al., 2004 (129) <u>14726370</u>	Aim: Assess impact of follow-up intervals on BP control in stable, treated pts with HTN Study type: RCT Size: 609 pts, 30– 74 y with essential HTN, on drug treatment, with HTN controlled for ≥3 mo prior to entry into study.	Inclusion criteria: 50 family practices in southeastern Ontario, Canada.	• 302 pts randomized to follow- up every 3 mo, 307 randomized to follow-up every 6 mo.	<ul> <li>Pts in both groups visited doctor more frequently than their assigned interval.</li> <li>Mean BP was similar in the groups, as was control of HTN.</li> <li>Pt satisfaction and adherence to treatment were similar in the groups.</li> <li>About 20% of pts in each group had BPs that were out of control during the study.</li> </ul>	<ul> <li>Study addresses follow-up interval for pts with treated, stable, and controlled HTN. No difference in BP control or pt satisfaction between 3 and 6 mo follow-up groups.</li> <li>May be helpful with recommendations for pts with treated, stable HTN.</li> </ul>

#### Data Supplement 29. Monitoring Strategies to Improve Control of BP in Patients on Drug Therapy for High BP (Section 8.3.2)

Study Acronym Author Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (include Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Brennan T, et al., 2010 (130) <u>20415618</u>	Aim: Assess impact of follow-up and monitoring system including home BP monitoring and telephonic nurse case management on BP control in pts treated for HTN Study type: RCT Size: 638 African American pts with high BP from a national health maintenance organization plan	Inclusion criteria: HTN	Intervention: Intervention group received telephonic nurse case management, pt education materials, lifestyle counseling, and a home BP monitor <u>Comparator</u> : Control group received a home BP monitor only	• Intervention group achieved lower SBP (123.6 vs. 126.7 mm Hg, p=0.03) and was 50% more likely than the control group to achieve BP control OR: 1.50; 95% CI: 0.997–2.27; p=0.052	Combination of home BP monitoring and nurse case management controlled HTN better than home BP alone

Bosworth, et al., 2009 (131) <u>19920269</u>	Aim: Assess impact of telephone follow-up intervention and/or home BP monitoring on BP control in pts with treated HTN <u>Study type:</u> RCT <u>Size</u> : 636 pts were randomized; 475 pts completed the trial, including 24-mo follow-up period.	Inclusion criteria: Pts with HTN, from 2 university- affiliated primary care clinics.	• 636 pts randomized to usual care or 1 of 3 intervention groups: (1) Nurse-administered telephone intervention targeting HTN -related behaviors, (2) home BP monitoring 3 times weekly, and (3) both interventions	<ul> <li>475 pts (75%) completed the 24-mo BP follow-up.</li> <li>At 24 mo, improvements in the proportion of pts with BP control relative to the usual care group were 4.3% (95% CI: -4.5%, 12.9%) in the behavioral intervention group, 7.6% (95% CI: -1.9%, 17.0%) in the home BP monitoring group, and 11.0% (95% CI: 1.9%, 19.8%) in the combined intervention group.</li> <li>Relative to usual care, the 24-mo difference in SBP was 0.6 mm Hg (95% CI: -2.2, 3.4 mm Hg) for the behavioral intervention group, -0.6 mm Hg (95% CI: -3.6, 2.3 mm Hg) for the BP monitoring group, and -3.9 mm Hg (95% CI: -6.9– -0.9 mm Hg) for the combined intervention group; patterns were similar for DBP</li> </ul>	• Home BP monitoring and tailored behavioral telephone intervention improved BP control, SBP, and DBP at 24 mo relative to usual care. Combined therapy was significantly better than either therapy alone.
Bosworth, et al., 2011 (132) <u>21747013</u>	Aim: Assess impact of telephone follow-up interventions on BP control in pts with treated HTN <u>Study type:</u> RCT <u>Size</u> : Of 1551 eligible pts, 593 randomized	Inclusion <u>criteria</u> : Primary care clinics at a VA Medical Center	• 593 pts randomized to either usual care or to 1 of 3 telephone follow-up groups: (1) nurse-administered behavioral management, (2) nurse- and physician- administered medication management, or (3) a combination of both	<ul> <li>1° endpoint: BP control measured every 6 mo for 18 mo</li> <li>Behavioral management and medication management alone showed significant improvements at 12 mo-12.8% (95% CI: 1.6%, 24.1%) and 12.5% (95% CI: 1.3%, 23.6%), respectively-but not at 18 mo.</li> <li>In subgroup analyses, among those with poor baseline BP control, SBP decreased in the combined intervention group by 14.8 mm Hg (95% CI: -21.87.8 mm Hg) at 12 mo and 8.0 mm Hg (95% CI: -15.50.5 mm Hg) at 18 mo, relative to usual care.</li> </ul>	<ul> <li>Telephone-based case management for high BP control effectively lowers BP for up to 1 y, but then BP control slackens.</li> <li>Interventions had the most impact on pts with worst BP control at study entry.</li> <li>Study carried out in the Veteran's Administration outpatient practice; unclear if results would apply to other practice settings.</li> </ul>

Green BB, et al., 2008 (133) <u>18577730</u>	Aim: Assess impact of follow-up and monitoring system including home BP monitoring, Internet-based BP management tool, and pharmacist care management on BP control in pts treated for HTN <u>Study type:</u> Cluster RCT <u>Size</u> : 778 pts from 16 clinics in integrated group practice in Washington state.	Inclusion criteria: Uncontrolled HTN and Internet access	<ul> <li>2 intervention groups: one with home BP monitoring and Internet tool, and the other with home BP monitoring, Internet tool, and pharmacist care management</li> <li>Compare to usual care</li> <li>1 y follow-up</li> </ul>	<ul> <li>Intervention group with all components achieved better BP control vs. usual care</li> <li>56% (95% Cl: 49%–62%) or combination intervention group achieved BP control vs. usual care (p&lt;0.001) and intervention with only home BP monitor and Internet tool (p&lt;0.001)</li> </ul>	• Combination of home BP monitoring, Internet-based BP management tools, and pharmacist case management helped control HTN better than usual care and better than BP monitoring and Internet-based tool alone.
Heisler M, et al., 2012 (134) <u>22570370</u>	Aim: Assess impact of follow-up pharmacist care management system on BP control in pts treated for HTN Study type: Cluster RCT Size: 1797 intervention and 2303 control pts from 16 primary care clinics at 5 medical centers (3 VA and 2 Kaiser Permanente)	Inclusion criteria: Uncontrolled HTN and Internet access	<ul> <li>14-mo intervention period</li> <li>BP 6 mo prior to and 6 mo after intervention period were compared in intervention and control groups</li> </ul>	• Mean SBP was 2.4 mm Hg lower (95% Cl: -3.4– -1.5), p<0.001 in the intervention group immediately after the intervention period, compared to the control group BP decrease was the same in the intervention and control groups (9 mm Hg).	<ul> <li>Pharmacist care management system in a "real world" setting was more effective than usual care in lowering BP in the short-term, but in the longer-term follow-up did not differ significantly from usual care.</li> <li>This study is one of very few studies to show no significant longer term impact of a care management system on BP control in pts with HTN.</li> </ul>
Margolis KL, et al., 2013 (25) <u>23821088</u>	Aim: Assess impact of follow-up and monitoring system including home BP tele-monitoring and pharmacist case management on BP control in pts treated for HTN <u>Study type:</u> Cluster RCT <u>Size</u> : 450 pts from 16 clinics in integrated health system in Minneapolis, MN	Inclusion criteria: Uncontrolled HTN	<ul> <li>222 pts randomized to 8 usual care clinics and 228 randomized to 8 intervention clinics</li> <li>Intervention included 12 mo of home BP tele- monitoring and pharmacist case management, with 6 mo of follow-up afterward</li> </ul>	<ul> <li>Intervention group achieved better BP control compared to usual care during 12 mo of intervention and persisting during 6 mo of follow-up</li> <li>SBP was &lt;140/90 in 57.2% (95% Cl: 44.8%, 68.7%) of intervention pts at 6 and 12 mo vs. 30% (95% Cl: 23.2%, 37.8%) in usual care (p=0.001)</li> </ul>	• Combination of home BP tele- monitoring and pharmacist case management helped control HTN better than usual care at 6, 12, and 18 mo

Data (				ا ماممهمام ا	least Diagona	$(C_{a} a t a = 0.1)$
Data 3	Supplement 3	). RUIS COM	paring Staple	e ischemic f	Heart Disease	(Section 9.1)
						···· /

Study Acronym;	Aim of Study; Study Type;	Patient Population	Study Intervention (# patients) /	Endpoint Results (Absolute Event Rates.	Relevant 2° Endpoint (if any); Study Limitations:
Author;	Study Size (N)		Study Comparator	P value; OR or RR; &	Adverse Events;
Year Published	5 . 7		(# patients)	95% CI)	Summary
INVEST Bangalore S, et al., 2014 (135) 25145522	Aim: To investigate optimal BP in pts ≥60 y with CAD and SBP >150 mm Hg treated with antihypertensive drugs Study type: Post- hoc analysis of PROBE trial (INVEST study— atenolol/HCTZ or verapamil- SR/trandolapril) Size: 8,354 pts	Inclusion criteria: Pts ≥60 y with CAD and SBP >150 mm Hg treated with antihypertensive therapy Exclusion criteria: N/A	Intervention: • 4,787 pts (57%) achieved SBP<140 mm Hg (group 1) • SBP achieved was <140 mm Hg (group 1) Comparator: • 1,747 pts (21%) achieved SBP of 140– 149 mm Hg (group 2); 1,820 pts (22%) achieved SBP ≥150 mm Hg (group 3) • SBP achieved was 140–149 mm Hg (group 2) and 150 mm Hg or higher (group 3)	<u>1° endpoint</u> : All-cause death, nonfatal MI, or nonfatal stroke. Multiple propensity score-adjusted 1° outcome showed that compared with group 1, the risk of 1° outcome adjusted HR: 1.12 (95% CI: 0.95– 1.32; p=0.19); for group 2 adjusted HR: 1.85 (95% CI: 1.59, 2.14), p<0.0001; for group 3 adjusted HR: 1.64 (95% CI: 1.40, 1.93), p<.0001 <u>1° Safety endpoint</u> : No significant difference between the 3 groups	Relevant 2° endpoint: Multiple propensity score- adjusted analysis:• Compared with group 1, no significant difference in all-cause mortality in group 2 but increased all-cause mortality in group 3 (HR: 1.64; 95% CI: 1.40–1.93; p<0.0001).

					from antihypertensive treatment. No adverse events
					were reported.
					Summary: The optimal SBP in $pts \ge 60$ v with CAD
					and SRP $>150$ mm Hg treated with antihypertensive
					therapy was $< 140$ mm Hg
Law MR_et al	Study type: Meta-	Inclusion criteria. The	N/A	1º endnoint: CAD events:	• With the exception of the extra protective effect of
2009 (18)	analysis of use of	database search used	1.1.7.	stroko	BBs given shortly after a MI and the minor additional
10/5/727	RD loworing drugs in	Modlino (1966 to Doc		SHOKE	offect of CCPs in proventing stroke, all the classes of
17434737	provention of CVD	2007 to identify		Decultor in 27 trials of nto	D lowering drugs have a similar effect in reducing
	from 147 randomized	randomized trials of PD		Results: III 37 IIIals of pls	CAD events and starks for a siver reduction in DD
		Idiluoinizeu (Ildis Ol DP-		with a history of CAD, BBS	CAD events and stroke for a given reduction in BP.
	lingis			reduced CAD events 29%	
	<b>C</b> : 06147	CAD events of strokes		(95% CI: 22%, 34%). In 27	
	<u>Size</u> : 01 147	were recorded. The		trials in which BBs were	
	randomized trials of	search also included		used after acute MI, BBs	
	464,000 pts, 37 trials	the Cochrane		reduced CAD events 31%	
	of BBs in CAD	Collaboration and Web		(95% CI: 24%–38%), and	
	included 38,892 pts,	of Science databases		in 11 trials in which BBs	
	and 37 trials of other	and the citations		were used after long-term	
	antihypertensive	in trials and previous		CAD, BBs insignificantly	
	drugs in CAD	meta-analyses and		reduced CAD events 13%.	
	included 85,395 pts	review articles.		In 7 trials, BBs reduced	
				stroke 17% (95% CI: 1%-	
		Exclusion criteria:		30%). CAD events were	
		Trials were excluded if		reduced 14% (95% CI:	
		there were <5 CAD		2%–25%) in 11 trials of	
		events and strokes or if		thiazide diuretics, 17%	
		treatment duration was		(95% CI: 11%–22%) in 21	
		<6 m0.		trials of ACEIs	
				insignificantly 14% in 4	
				trials of angiotensin	
				recentor blockers and	
				15% (05% Cl· 8%_22%) in	
				22  trials of  CCRs  Stroke	
				was reduced 38% (05%	
				Cl. 200/ 470/) in 10 trials	
				of this zide divertise 220/	
				(95% CI: 8%–34%) in 13	
	1			trials of ACEIs, and 34%	

				(95% CI: 25%–42%) in 9 trials of CCBs.	
HOPE Yusuf S, et al., 2000 (136) <u>10639539</u>	Aim: To investigate effect of ACE-I (Ramipril 10 mg) on CV events in high risk pts. over 5y with a mean entry BP of 139/79 mm Hg in both groups Study type: RCT, 2×2 factorial design Size: 9,297	Inclusion criteria: Pts ≥55 y with history of CAD, stroke, PVD or DM with either HTN, elevated total cholesterol, low LDL cholesterol, smoking, or micro albuminuria. Exclusion criteria: HF, <0.40 EF, on ACE-I or Vitamin E, uncontrolled HTN /overt nephropathy, Had MI or stroke <4 wk	Intervention: Ramipril (10 mg) (4,645) Comparator: Placebo (4,652)	<u>1º endpoint</u> : Composite of MI, stroke, or mortality from CV causes. <u>Results:</u> Endpoint reduction Ramipril group vs. Placebo (14% vs. 17.8%; RR: 0.78; CI: 0.70–0.86; p<0.001)	<ul> <li>Death from cardiac causes reduced (6.1% vs. 8.1%; p&lt;0.001)</li> <li>Death from MI reduced (9.9% vs. 12.3%; p&lt;0.001)</li> <li>Death from any cause (10.4 % vs. 12.2%; p=0.005)</li> </ul>
SAVE Pfeffer M., et al., 1992 (137) <u>1386652</u>	Aim: To assess if captopril decrease morbidity and mortality in pts with LV dysfunction after MI. Study type: RCT Size: 2,231	Inclusion criteria: Pts (21–80 y) surviving 3 d after MI, EF≤40%. Exclusion criteria: Pts not randomized within 16 d after MI, contra. to ACE-I use, Serum Cr. >2.5 mg/dL, severe comorbidities, unstable infarction, need for revascularization	Intervention: Captopril (titrated doses) (115) <u>Comparator</u> : Placebo (1116)	<u>1° endpoint and results</u> : All-cause mortality: 20% vs. 25%, RR: 19%; 95% Cl: 3%–32%; p=0.019 <u>Other endpoints</u> : Fatal and nonfatal major CV events were reduced in the captopril group.	<ul> <li>Captopril vs. Placebo group BP at 1 y (125±18 / 77±10 mm Hg for placebo vs. 119±18/74±10 mm Hg for captopril; p&lt;0.001)</li> <li>Dizziness, alteration in taste, cough and diarrhea were reported significantly more in the captopril group</li> <li>Ventricular size on Echo studies was independent predictor of adverse CV outcomes</li> </ul>
EUROPA Fox KM, et al., 2003 (138) <u>13678872</u>	Aim: To investigate efficacy of perindopril in CV events in pts with stable CAD. Study type: RCT	Inclusion criteria: Pts ≥18 y (women) with CAD >mo before screening, revascularization >6 mo before screening, ≥70% narrowing of major	Intervention: Perindopril (6,110) Comparator: Placebo (6,108)	<u>1º endpoint</u> : Composite of CV death, nonfatal MI, cardiac arrest with successful CPR <u>Results:</u> RR 20%; 95% CI: 9%–29; p=0.0003	• Perindopril resulted reduction in all these outcomes: composite of total mortality, nonfatal MI, hospital admission for UA, and cardiac arrest with successful CPR; CV mortality and nonfatal MI, the individual components these outcomes and revascularization, stroke, and admission for HF

MERIT-HF	<u>Size</u> : 12,218 pts <u>Aim</u> : To investigate if	coronary artery. Men with history of chest pain, positive ECG, echo or nuclear test <u>Exclusion criteria</u> : HF, planned revascularization, <110 mm Hg SBP, uncontrolled HTN, >100 mm Hg DBP, <i mo="" use<br="">of ACEI or ARB, Cr&gt;150 µmol/L, serum K&gt;5.5 mmol/L Inclusion criteria:</i>	Intervention:	<u>1° endpoint</u> : All-cause	Fewer sudden deaths in the metoprolol group
Goldstein S, et al., 1999 (139) <u>10526701</u>	metoprolol (CR/XL) once daily with std. treatment lowers mortality in pts with HF <i>r</i> EF <u>Study type</u> : RCT <u>Size</u> : 3,991 pts	Pts 40–80 y with NYHA class II-IV HF for 3 mo before randomization and on standard treatment 2 wk before entry, Stable clinical condition during 2 wk run-in phase, EF ≤0.40. Exclusion criteria: Acute MI, UA <28 d of entry, contra to beta blockade <6 mo, HF due to systemic disease/alcohol abuse, heart transplant candidate, ICD, planned revascularization in past 4 mo, decompensated heart, SBP <100 mm Hg, CCB treatment, amiodarone use within 6 mo	Metoprolol CR/XL (1,990) <u>Comparator</u> : Placebo (2,001)	mortality in the intent to treat <u>Results</u> : 145 vs. 217 deaths [11.0 %], RR: 0.66 (95% CI: 0.53–0.81; p=0.00009) or adjusted for interim analyses p=0.0062.	<ul> <li>(p=0.0002)</li> <li>Lesser deaths from HF<i>r</i>EF in the metoprolol group (p=0.002)</li> <li>Metoprolol improved survival and was well tolerated</li> </ul>

Packer M. et al.	Aim: To assess	Inclusion criteria: HF	Intervention:	1º endpoint:	• Study stopped early (1.3-y follow-up) due to benefit
2001 (140)	survival in severe	nts with	Carvedilol (1 156)	Death from any cause	on survival
11386263	chronic HF pts by the	dyspnea/exertion for 2		130 vs 190 deaths RR	• Long torm troatmont is yory valuable
	use of carvedilol	mo at least and left	Comparator: Placebo	35% 95% Cl· 19%-48%	• Not all the nts with source HE were allowed in the
		FE<25% despite	(1.133)	n=0.00013	• Not all the pts with severe HF were allowed in the
	Study type: RCT	treatment clinically	(1,100)	Combined risk of	sludy
	<u>otaaj tipo</u> i ito i	euvolemic: allowed on		death/hospitalization (24%	
	Size: 2,289 pts	digitalis, nitrates,		lower risk in the carvedilol	
	<u></u>	hydralazine		(95% CI: 13%-33%)	
		spironolactone. or		n<0.001	
		amiodarone.		p (0.001	
		Hospitalized pts with no		Safety endpoint: Lesser	
		acute illness.		nts in carvedilol group	
				required permanent	
		Exclusion criteria: HF		discontinuation because of	
		due to uncorrected prim.		adverse events or for	
		valvular disease or		reasons other than death	
		reversible		(p=0.02)	
		cardiomyopathy cardiac			
		transplant pts., coronary			
		revasc. <2 mo, acute MI			
		or stroke, ventricular			
		tachycardia, on alpha			
		blocker or CCB or on			
		antiarrythmics class I <4			
		wk, SBP <85 mm Hg,			
		serum Cr >2.8 mg/dL,			
		change in body weight			
		>1.5 kg during			
		screening.			
CAPRICORN	Aim: To investigate	Inclusion criteria: Pts	Intervention:	1° endpoint: All-cause	• CV mortality, nonfatal MI reduced in the carvedilol
Dargie HJ, et	outcomes after	≥18 y, MI within 3–21 d	Carvedilol (975)	mortality or hospital	group
al., 2001 (141)	carvedilol after MI in	of entry, LVEF≤40%,		admissions for CV issues	No difference between groups SCD and admission
<u>11356434</u>	pts with LV	concurrent ACEI stable	Comparator: Placebo		due to HF
	dysfunction.	dose for at least 24 h,	(984)	Results: 12% vs. 15%;	
		HF pts treated and		RR: 23%; 95% CI: 0.60-	
	Study type: RCT	controlled with ACEI		0.98; p=0.03	
		and diuretics but not		No difference between	
	<u>Size</u> : 1,959 pts	inotropes.		groups for death or CV	
				hospital admissions	

MERIT-HF HTN	Aim: To assess	Exclusion criteria: SBP<90 mm Hg, uncontrolled HTN, bradycardia, insulin- dependent DM, BBs not for HF, Beta-2 agonists and steroids Inclusion criteria:	Intervention:	1° endpoint: Total	Total mortality reduction was driven by reduction in
Herlitz J, et al., 2002 (142) <u>11862577</u>	metoprolol CR/XL influence on mortality and hospitalizations in HF and HTN pts. <u>Study type</u> : RCT Size: 1,747 pts	Same as above MERIT- HF, 1999 study (HTN subgroup) Exclusion criteria: Same as above MERIT- HF	Metoprolol CR/XL (871) <u>Comparator</u> : Placebo (876)	mortality <u>Results</u> : RR: 0.61; 95% Cl: 0.44–0.84; p=0.0022	the SCD and death from worsening HF • 12.5% pts had earlier discontinuation due to any cause. Lesser no. of pts in the metoprolol group (n=21) discontinued due to worsening HF The mean reduction in BP (adjusted) was 1.7 mm Hg in the metoprolol group vs. 4.8 mm Hg in placebo group (p=0.0001)
CIBIS-II 1999 (143) <u>10023943</u>	Aim: To determine efficacy of bisoprolol in reducing mortality in chronic HF. <u>Study type</u> : RCT <u>Size</u> : 2,647 pts	Inclusion criteria: 18– 80 y, LVEF<35%, dyspnea, orthopnea, fatigue, NYHA class III- IV Exclusion criteria: Uncontrolled HTN, MI, UA <3 mo revascularization. treatment, heart transplant, AV block <1 degree, SBP <100 mm Hg, renal failure, reversible obstructive lung disease	Intervention: Bisoprolol (1,327) Comparator: Placebo (1,320)	<u>1° endpoint</u> : All-cause mortality <u>Results</u> : 11.8% vs. 17.3% deaths with a RR: 0.66; 95% CI: 0.54–0.81; p<0.0001	<ul> <li>The trial stopped early due to benefit. Bisoprolol group had significantly fewer SCDs.</li> <li>Mean age was 61 y so more data on elderly pts is needed</li> </ul>
Elkayam U, et al., 1990 (144) <u>2242521</u>	<u>Aim</u> : To assess comparative efficacy and safety of nifedipine and ISDN alone and the combination for treating for chronic CHF.	Inclusion criteria: 18– 75 y HF pts, NYHA class II and III, LVEF<40%, clinically stable, maintenance dose of Digitalis and diuretics.	Intervention: Nifedipine (21), ISDN (20), Nifedipine+ISDN (23) Comparator: Placebo	Endpoints and Results: <u>HF-worsening</u> : 9 in Nifedipine group vs. 3 in ISDN group (p<0.09); and 21 in nifedipine-ISDN group (p<0.001 vs. nifedipine, p<0.0001 vs. ISDN)	<ul> <li>In clinical deterioration nifedipine pts (8) vs. rest of the pts (No difference in LVEF or VO<sup>2</sup> max)</li> <li>Although all the 3 drug regimens improved exercise capacity, nifedipine treatment alone or in combination resulted in clinical deterioration and worsening of CHF</li> </ul>

	Study type: RCT with a crossover design Size: 28 pts	Exclusion criteria: Pregnancy, nursing, history of MI <1 mo before entry, valvular disease, Angina, significant pulmonary, hepatic, renal and hematologic disease, unable to walk on the treadmill, noncompliance		Clinical deterioration discontinuation: Nifedipine 29% vs. ISDN group 5% (p<0.05) DBP: Nifedipine alone or combination with ISDN (reduction, p<0.05)	
The Multicenter Dilitiazem Postinfarction Research Group 1988 (145) <u>2899840</u>	<u>Aim</u> : To assess dilitiazem effect on recurrent infarction and death after acute MI <u>Study type</u> : RCT <u>Size</u> : 2,466 pts	Inclusion criteria: 25–75 y admitted to CCU, MI with enzyme confirmation. Exclusion criteria: • Cardiogenic shock, • Symptomatic hypotension, • PH with right HF, • 2nd/3rd degree heart block, • HR <50 bpm, • Contraceptives, • WPW syndrome, • CCBs, • Severe comorbidities or • Cardiac surgery	Intervention: Dilitiazem 240 mg (1,234) <u>Comparator</u> : Placebo (1,232)	<u>1° endpoints and</u> <u>results</u> : • Total mortality: identical in both groups • Cardiac death and nonfatal MI: 11% fewer in dilitiazem but difference was NS	No combined benefit from dilitiazem on mortality or cardiac events
MDPIT Goldstein RE, et al., 1991 (146) <u>1984898</u>	Aim: To determine if dilitiazem increases late onset CHF in post-MI pts with early decline in EF. Study type: RCT Size: 2,466 pts	Inclusion criteria: Same as above Exclusion criteria: Same as above	Intervention: Dilitiazem 240 mg (1,234) <u>Comparator</u> : Placebo (1,232)	1° endpoint and results:Same as aboveFollow-up Results:Pts with BL EF<0.40, late	<ul> <li>Life table analysis confirmed increased frequency of late CHF in pts taking dilitiazem (p=0.0017)</li> <li>Dilitiazem related CHF exclusively associated with systolic LVD with or without BBs</li> </ul>

Freemantle N, et al., 1999 (147) <u>10381708</u>	Aim: To evaluate BBs effectiveness for short-term treatment and long-term 2° prevention in acute MI. Study type: Meta- analysis of RCTs Size: 54,234 pts (82 RCTs)	Inclusion criteria: RCTs with treatment lasting >1 d and with follow-ups on clinical effectiveness in pts with MI Exclusion criteria: Cross-over RCTs	Intervention: BBs (mostly propranolol, timolol, metoprolol) Comparator: Controls (placebo/other treatment)	<u>1° endpoint</u> : All-cause mortality <u>Results</u> : • Long-term trials RR reduction: 23% (95% CI: 15%–31%) • Short-term trials RR reduction: 4%; 95% CI: - 8%–5%	<ul> <li>Meta-regression in long-term trials indicated a near significant trend for decreased benefit in drugs with ISA.</li> <li>NS in withdrawal between BBs of different cardio selectivity.</li> </ul>
de Peuter OR, et al., 2009 (148) <u>19841485</u>	Aim: To determine influence of beta-2 blockade in addition to beta-1 blockade for preventing vascular events in pts with ACS or HF. <u>Study type</u> : Meta- analysis of RCTs <u>Size</u> : 34,360 pts (33 RCTs)	Inclusion criteria: • RCTs comparing Beta-1 blockers vs. BBs 1 + 2 directly (5) • RCTs comparing Beta-1 blockers vs. Beta 1 + 2 blockers with a control group (28) <u>Exclusion criteria</u> : Studies not pre- specifying total mortality and vascular event as outcomes <3 mo follow- up, duplicate data, sub studies.	Intervention: Beta-1 blockers Comparator: BBs 1+2 with or without control group	<u>1° endpoint</u> : Total mortality, vascular events. <u>Results:</u> <u>ACS Population:</u> 1 study with different BBs underpowered to detect difference. Beta-1 vs. Placebo NS reduced mortality or vascular events <u>HF population:</u> Beta 1 + 2 blockers vs. Beta 1 blockers decreased mortality RR: 0.86; 95% Cl: 0.78–0.94 Beta 1 and Beta 1+2 decreased total mortality. Only Beta 1+2 blockers reduced vascular events.	<ul> <li>Supplementary beta 2 blockade may be more beneficial.</li> <li>Indirect comparisons and heterogeneity among studies</li> </ul>
Leon MB, et al., 1981 (149) <u>7246435</u>	<u>Aim</u> : To evaluate effectiveness of verapamil as a single agent and in combination with propranolol in pts with stable AP.	Inclusion criteria: Symptomatic angina pectoris pts, 1) not sufficiently controlled on BBs and nitrates and noncardiac	Intervention: Propranolol, verapamil, Combination of propranolol and verapamil	Results: Large dose verapamil significantly lowered BP. Propranolol and verapamil combined (at best dose) further lowered BP, improved	<ul> <li>HR and pressure-rate product lowered significantly on combination therapy</li> <li>PR interval increased on combination treatment Regarding antianginal properties, verapamil seemed to be more effective than propranolol.</li> </ul>

	1				
Staessen JA, et al., 1997 (150) 9297994	Study type: RCT (triple crossover) Size: 11 pts Aim: To determine if active treatment reduces complications from isolated systolic HTN in the elderly. Study type: RCT Size: 4,965 pts	effects from propranolol hindering treatment 2) who could stay 4 wk in hospital <u>Exclusion criteria</u> : LVD with CHF or LVEF<30% at rest and <25% for exercise, HR<50 b/min, ≥first degree heart block <u>Inclusion criteria</u> : Pts ≥60 y, sitting SPB 160– 219 mm Hg, sitting DBP 95 mm Hg, and standing SBP ≥140 mm Hg. <u>Exclusion criteria</u> : Systolic HTN 2nd to a disorder, retinal hemorrhages/papillede ma, CHF, aneurysms, serum Cr ≥180 µmol/L, history of nosebleed, stroke, MI <1 y, dementia, substance abuse, severe	<u>Comparator</u> : Placebo <u>Intervention</u> : Active treatment (2,398) <u>Comparator</u> : Placebo (2,297)	exercise time by 4.7 ± 0.7 min (p<0.001) <u>1° endpoint</u> : Fatal and nonfatal strokes combined. <u>Results</u> : 13.7 vs. 7.9 endpoints/ 1,000 pts-y (42% reduction; p=0.003)	<ul> <li>All fatal and nonfatal cardiac endpoints (with sudden death) decreased in the active treatment group (p=0.03)</li> <li>Cardiac mortality was lower in active treatment (-27%; p=0.07). All-cause mortality was not different.</li> <li>Nitrendipine used for active arm.</li> </ul>
Wright JT, et al., 2015 (114) <u>26551272</u>	Aim: To compare in pts with a SBP of 130–180 mm Hg and an increased CV risk but without DM the effect of a target SBP of <140 mm Hg vs. a target SBP of <120 mm Hg on the 1° composite outcome of MI, other ACSs,	ComorbiditiesInclusion criteria:9,361 pts, mean 67.9 y(28.2% ≥75 y; 35.6%women; 57.7% non-Hispanic white; 31.5%African American;10.5% Hispanic) with aSBP of 130–180 mm Hgand an increased CVrisk but without DM,history of stroke,symptomatic HF within	Intervention: 4,678 pts were randomized to intensive BP treatment Comparator: 4,683 pts were randomized to standard BP treatment	<u>1° endpoint</u> : • At 1 y, the mean SBP was 121.4 mm Hg with intensive treatment (mean number of antihypertensive drugs was 2.8) and 136.2 mm Hg with standard treatment (mean number of antihypertensive drugs was 1.8)	<ul> <li>At 3.26-y median follow-up, compared with standard BP treatment, intensive BP treatment reduced all-cause mortality 27% (p=0.003), HF 38% (p=0.002), CV mortality 43% (p=0.005), and the 1° composite outcome or death 22% (p&lt;0.001)</li> <li>Intensive BP treatment reduced the 1° composite endpoint 33% (14% to 49%) in pts aged 75 y and older and 20% (0% to 36%) in pts 50–74 y</li> <li>Serious adverse events were similar in both treatment groups. However, intensive BP treatment caused more hypotension (2.4% vs. 1.4%; p=0.001), more syncope (2.3% vs. 1.7%; p=0.05), more</li> </ul>

	stroke, HF, or CV death	past 6 mo, LVEF <35%, and eGFR <20 mL/min/1.73 mm <sup>2</sup> ; CVD was present in 20.1%, and the Framingham 10-y CVD risk score was ≥15% in 61.3% of pts		• At 3.26-y median follow- up, the 1° composite outcome was reduced 25% (p<0.001) by intensive BP treatment	electrolyte abnormality (3.1% vs. 2.3%; p=0.02), and more acute kidney injury or acute renal failure (4.1% vs. 2.5%; p<0.001). The incidence of bradycardia, injurious falls, and orthostatic hypotension with dizziness was similar in both treatment groups
ALLHAT Collaborative Research Group, 2003 <u>12925554</u>	<u>Aim</u> : In a follow-up analysis, to compare diuretic vs. alpha- blocker as first step treatment of hypertension.	Inclusion criteria: Men and women ≥ 55 y with BP ≥140/90 mm Hg or on medications for hypertension with at least one additional risk factor for coronary heart disease.	Intervention: 15,255 patients were randomized to chlorthalidone and 9,061 to doxazosin and followed for 3.2 y.	Primary endpoint: Combined fatal coronary heart disease or non-fatal MI, analyzed by intention to treat.	<ul> <li>There was no difference in primary outcome between the arms (RR: 1.02; 95% CI: 0.94–1.13).</li> <li>However, the doxazosin arm compared with the chlorthalidone arm had a higher risk for stroke (RR: 1.26; 95% CI: 1.10–1.46) and combined cardiovascular disease (RR: 1.20; 95% CI: 1.13– 1.27).</li> <li>The findings confirmed the superiority of diuretic- based over alpha blocker based antihypertensive treatment in the prevention of cardiovascular disease.</li> </ul>
Zanchetti A, et al., 2006 <u>17053536</u>	Aim: To provide additional analyses of the primary endpoint in the VALUE trial, including sex, age, race, geographic region, smoking status, type 2 diabetes, total cholesterol, left ventricular hypertrophy, proteinuria, serum creatinine, history of coronary heart disease, stroke or transient ischemic attack and history of peripheral artery disease.	Inclusion criteria: The 15,245 patients participating in VALUE were divided into subgroups according to baseline characteristics.	Statistical analysis: Subgroup interaction analyses were conducted by the Cox proportion hazard model. Within each subgroup, treatment effects were assessed by hazard ratios and 95% CIs.		<ul> <li>For cardiac morbidity and mortality, the only significant subgroup by treatment interaction was of sex (p=0.016) with HR indicating a relative excess of cardiac events in women but not in men, but SBP differences in favor of amlodipine were greater in women.</li> <li>In the VALUE cohort, in no subgroup of patients were there differences in the incidence of the composite cardiac endpoint with valsartan and amlodipine treatment despite greater BP reduction in the amlodipine group.</li> </ul>

Leenen FHH, et al., 2006 <u>16864749</u>	<u>Aim</u> : To compare the long-term relative safety and outcomes of ACE inhibitor- and CCB-based regimens in older hypertensive individuals in ALLHAT.	Inclusion criteria: men and women age ≥55 y with untreated (BP 140– 180/90–110 mm Hg) or treated hypertension (BP ≤160/100 mm Hg on ≤2 antihypertensive drugs) with ≥ 1 additional risk factor for coronary heart disease.	Intervention: Patients (were randomized to amlodipine (9,048) or Lisinopril (9,054).	Primary outcome: Combined fatal coronary heart disease or non-fatal MI, analyzed by intention to treat. Follow-up: 4.9 y	<ul> <li>Risk of coronary heart disease was similar between amlodipine and Lisinopril</li> <li>For stroke, combined cardiovascular disease, gastrointestinal bleeding and angioedema, risks are higher with Lisinopril compared to amlodipine.</li> <li>For heart failure, risks are higher with amlodipine compared to Lisinopril.</li> </ul>
--	---	---	---	---	--

#### Data Supplement 31. Meta-analyses of ischemic heart disease (Section 9.1)

Study Acronym;	Study	Patient Population	Primary Endpoint and Results	Summary/Conclusion
Autnor; Voar Publishod	Type/Design;		(Include P value; OR of RR; and CI)	Comment(s)
Year Published           Bundy JD, et al.,           2017           28564682	Study size Study type: Network meta- analysis <u>Size</u> : 144,220 patients in 42 RCTs.	Inclusion criteria:         • Random allocation into an antihypertensive medication, control or treatment target         • Allocation to antihypertensive Antihypertensive treatment was independent of other treatment regimens         • ≥100 patients in each treatment group         • Trial duration ≥ 6 mo         • One or more events for each treatment group reported         • Minimum 5 mm Hg difference in SBP level between the 2 treatment groups         • Outcomes included major CVD, stroke, CHD, CVD mortality or all-cause mortality	• There were linear associations between mean achieved SBP and risk of cardiovascular disease and mortality, with the lowest risk at 120 to 124 mm Hg. Randomized groups with a mean achieved SBP of 120 to 124 mm Hg had a hazard ratio (HR) for major cardiovascular disease of 0.71 (95% CI: 0.60–0.83) compared with randomized groups with a mean achieved SBP of 130 to 134 mm Hg, an HR of 0.58 (95% CI: 0.48–0.72) compared with those with a mean achieved SBP of 140 to 144 mm Hg, an HR of 0.46 (95% CI: 0.34–0.63) compared with those with a mean achieved SBP of 150 to 154 mm Hg, and an HR of 0.36 (95% CI: 0.26–0.51) compared with those with a mean achieved SBP of 160 mm Hg or more.	• This study suggests that reducing SBP to levels below currently recommended targets significantly reduces the risk of cardiovascular disease and all- cause mortality and strongly support more intensive control of SBP among adults with hypertension.

Data Cumulament 22 Nonvoudant	- ad Triala, Ohaamustianal	Chudian and/an Daniatrian	of look and a lloom Diacaaa	$(C_{a} a t a a 0 1)$
Data Supplement 32. Nonrandomi	zed Triais, Observational	Studies, and/or Registries	OF ISCHEMIC HEART DISEASE	(Section 9.1)
	1	, J		· /

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and 95% CI)	Summary/Conclusion Comment(s)
PROVE IT-TIMI 22 Bangalore S, et al., 2010 (151) 21060068	Study type: Nonrandomized trial of optimal BP after ACS Size: 4,162 pts	Inclusion criteria: Pts with acute MI or high-risk UA within 10 d randomized to pravastatin or atorvastatin and to gatifloxacin or placebo treated with standard medical and interventional treatment for ACS Exclusion criteria: N/A	<u>1° endpoint</u> : Composite of all-cause death, MI, UA requiring rehospitalization, revascularization after 30 d, and stroke with a mean follow-up of 24 mo <u>Results</u> : The relationship between SBP and DBP followed a J- or U-shaped curve association with the 1° outcome with increased events rates at both low and high BP values. A nonlinear Cox proportional hazards model showed a nadir of 136/85 mm Hg (range 130–140/80–90 mm Hg) at which the incidence of 1° outcome was lowest. There was a relatively flat curve for SBP of 110–130 mm Hg and for DBP of 70–90 mm Hg, suggesting a BP <110/70 mm Hg may be dangerous.	• After an ACS, a J- or U-shaped association existed between BP and the incidence of new CV events. The lowest incidence of CV events occurred with a BP of 130–140/80–90 mm Hg and a relatively flat curve for SBP of 110–130 mm Hg and of DBP of 70–90 mm Hg, suggesting a BP <110/70 mm Hg may be dangerous.
Law MR, et al., 2009 (18) <u>19454737</u>	Study type: Meta- analysis of use of BP-lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of other antihypertensive drugs in CAD included 85,395 pts	Inclusion criteria: The database search used Medline (1966 to Dec. 2007) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and Web of Science databases and the citations in trials and previous meta-analyses and review articles. Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment duration was <6 mo.	<u><b>1°</b> endpoint</u> : CAD events; stroke <u><b>Results:</b></u> In 37 trials of pts with a history of CAD, BBs reduced CAD events 29% (95% CI: 22%, 34%). In 27 trials in which BBs were used after acute MI, BBs reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which BBs were used after long-term CAD, BBs insignificantly reduced CAD events 13%. In 7 trials, BBs reduced stroke 17% (95% CI: 1%–30%). CAD events were reduced 14% (95% CI: 2%–25%) in 11 trials of thiazide diuretics, 17% (95% CI: 11%– 22%) in 21 trials of ACEIs, insignificantly 14% in 4 trials of angiotensin receptor blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCBs. Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEIs, and 34% (95% CI: 25%–42%) in 9 trials of CCBs.	• With the exception of the extra protective effect of BBs given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.

Study Acronym (if applicable) Author Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and 95% CI)	Summary/Conclusion Comment(s)
LV J, et al., 2013 (127) <u>23798459</u>	Study type: MA of RTC that randomly assigned individuals to different target BP levels Size: 37,348 pts	●15 trials	<ul> <li>7.5/4.5 mm Hg BP difference. Intensive BP lowering achieved. <u>RR for</u></li> <li>Major CV events: 11%; 95% CI: 1%–21%)</li> <li>MI: 13%; 95% CI: 0%–25%</li> <li>Stroke: 24%; 95% CI: 8%–37%</li> <li>ESRD: 11%; 95% CI: 3%–18%</li> <li>Albuminuria: 10%; 95% CI: 4%–16%</li> <li>Retinopathy 19%; 95% CI: 0%–34%</li> <li>p=0.051</li> </ul>	More intensive strategy for BP control reduced cardio-renal endpoint
Xie X, et al., 2015 (21) <u>26559744</u>	Study type: MA of RTC that randomly assigned individuals to different target BP levels Size: 44,989 pts	• 19 trials	Achieved BP 133/76 mm Hg (intensive) 140/81 (less intense) • Major CV events: 14%; 95% CI: 4%–22% • MI: 13%; 95% CI: 0%–24% • Stroke: 22%; 95% CI: 10%–32% • Albuminuria: 10%; 95% CI: 3%–16% • Retinopathy progression: 19%; 95% CI: 0%–34%. • More intensive had no effects on HF: 15%; 95% CI: -11%–34% • CV death: 9%; 95% CI: -11%–26% • Total mortality: 9%; 95% CI: -3%–19% • ESKD: 10%; 95% CI: -6%–23%	• More intensive approach reduced major CV events (stroke and MI) except heat failure, CVD, ESRD, and total mortality.
Thomopolous C, et al., 2016 (54) <u>26848994</u>	Study type: Meta- analysis of RTCs of more vs. less intense BP control	• 16 trials (52,235 pts) compared more vs. less intense treatment 34 (138,127 pts) active vs. placebo	More intense BP • Stroke RR: 0.71; 95% CI: 0.60–0.84) • CHD RR: 0.80; 95% CI: 0.68–0.95) • Major CV events RR: 0.75; 95% CI: 0.68–0.85 • CV mortality RR: 0.79; 95% CI: 0.63–0.97 Stratification of SBP cutoffs (150,140 and 130 mm Hg) showed that a SBP/DBP difference of 10/5 mm Hg across each cutoff reduced risk of all outcomes	• Intensive BP reduction improves CV outcomes compared to less intense Achieved BP <130/80 may be associated with CV benefit.

# Data Supplement 33. RCTs Comparing Heart Failure (Section 9.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Herlitz J, et al., 2002 (142) <u>11862577</u>	Aim: To see effect of metoprolol vs. placebo on mortality and hospitalizations among pts with history of HTN and HF with reduced LVEF Study type: RCT Size: 1,747 pts	Inclusion criteria: NYHA class II–IV HF with LVEF ≤40% within 3 mo of enrollment; supine resting HR ≥68 bpm; stable clinical condition Exclusion criteria: Acute MI or UA within 28 d of randomization; indication or contraindication for treatment with BBs or drugs with beta-blocking properties; poor compliance; CABG surgery or PTCA in past 4 mo	Intervention: • Administration of metoprolol • 871 pts randomized to metoprolol <u>Comparator</u> : • Administration of placebo • 876 pts randomized to placebo	1° endpoint: At 1-y follow-up, compared with placebo, metoprolol reduced all-cause mortality 39% (95% CI: 16%– 56%; p=0.002) and all-cause mortality or all-cause hospitalization 24% (95% CI: 11%–35%; p=0.0007) 1° Safety endpoint: Early permanent cessation of drug was 12.5% for metoprolol and 15.9% for placebo (p=0.048); 21 pts on metoprolol and 35 pts on placebo had early cessation because of worsening	Relevant 2° endpoint:At 1-y follow-up, compared with placebo, metoprolol reduced CV death 41% (95% CI: 17%–57%; p=0.002), death from HF: 51% (95% CI: 1%–75%; p=0.042), sudden cardiac death 49% (95% CI: 21%–67%; p=0.002), all- cause mortality or HF hospitalization 28% (95% CI: 11%–42%; p=0.002), and cardiac death or nonfatal acute MI 44% (95% CI: 23%–60%; p=0.0003)Study limitations and adverse events: Early permanent cessation of drug was 12.5% for metoprolol and 15.9% for placebo (p=0.048); 21 pts on M and 35 pts on placebo had early cessation because of worsening HF; all-cause withdrawals were 22% less with metoprolol; (p=0.048); adverse events were 28% less with metoprolol (p=0.026); worsening HF was 41% less with metoprolol (p=0.056)Summary: In an RCT of pts with HF with reduced EF and a history of HTN, compared with placebo, metoprolol succinate reduced all- cause mortality and all-cause mortality or all-cause hospitalization
Packer M, et al., 2001 (140) <u>11386263</u>	Aim: To assess survival in severe	Inclusion criteria: HF pts with dyspnea/exertion for 2 mo at least and left EF<25% despite	Intervention: Carvedilol (1,156)	<ul> <li><u>1° endpoint</u>:</li> <li>Death from any cause 130</li> <li>vs. 190 deaths (RR: 35%;</li> </ul>	• Study stopped early (1.3 y follow- up) due to benefit on survival

# Data Supplement 34. RCTs Comparing HF*r*EF (Section 9.2.1)

	chronic HF pts by the	treatment clinically euvolemic;	Comparator: Placebo	95% CI: 19%-48%;	Long-term treatment is very
	use of carvedilol.	allowed on digitalis, nitrates,	(1,133)	p=0.00013)	valuable.
		hydralazine, spironolactone, or		Combined risk of	<ul> <li>Not all the pts with severe HF were</li> </ul>
	Study type: RCT	amiodarone. Hospitalized pts		death/hospitalization (24%	allowed in the study
	<b>C'</b>	with no acute illness.		lower risk in the carvedilol;	
	<u>Size</u> : 2,289 pts	Fuchasian aritaria UE due te		95% CI: 13%–33%; p<0.001)	
		Exclusion criteria: HF due to		<b>Sofaty and point</b> , Lassar etc.	
		disease er reversible		<u>Salety enupoint</u> : Lessel pis	
		cardiomyonathy cardiac		nermanent discontinuation	
		transplant pts coronary revase		because of adverse events or	
		<2  mo acute MI or stroke		for reasons other than death	
		ventricular tachycardia on alpha		(p=0.02)	
		blocker or CCB or on		(p=0.02)	
		antiarrythmics class I <4 wk,			
		SBP <85 mm Hg, serum Cr >2.8			
		mg/dL, change in body weight			
		>1.5 kg during screening.			
CAPRICORN	Aim: To investigate	Inclusion criteria: Pts ≥18 y, MI	Intervention:	1° endpoint: All-cause	• CV mortality, nonfatal MI reduced in
Dargie HJ, et al.,	outcomes after	within 3–21 d of entry, LVEF	Carvedilol (975)	mortality or hospital	the carvedilol group
2001 (141)	carvedilol after MI in	≤40%, concurrent ACEI stable		admissions for CV issues	<ul> <li>No difference between groups</li> </ul>
<u>11356434</u>	pts with LV	dose for at least 24 h, HF pts	Comparator: Placebo		sudden death and admission due to
	dysfunction.	treated and controlled with ACEI	(984)	Results: 12% vs. 15%; RR:	HF
	Ctudu tumo. DCT	and diurelics but not inotropes.		23% (95% C1: 0.60–0.98;	
	Study type: RCT	Evaluation critoria: SPD <00		p=0.03)	
	<b>Sizo</b> : 1 050 nts	mm Ha, upcontrolled HTN		for death or CV bespital	
	<u>5126</u> . 1,757 pts	hradycardia insulin-dependent		admissions	
		DM BBs not for HF Beta-2		aumissions	
		agonists, and steroids			
Elkayam U, et al.,	Aim: To assess	Inclusion criteria: 18–75 y old	Intervention:	Endpoints and Results:	In clinical deterioration nifedipine
1990 (144)	comparative efficacy	HF pts, NYHA class II and III,	Nifedipine (21), ISDN	HF-worsening: 9 in	pts (8) vs. rest of the pts (No
2242521	and safety of	LVEF<40%, clinically stable,	(20), Nifedipine+ISDN	Nifedipine group vs. 3 in ISDN	difference in LVEF or VO <sup>2</sup> max.)
	nifedipine and ISDN	maintenance dose of Digitalis	(23)	group (p<0.09); and	Although all the 3 drug regimens
	alone and the	and diuretics.		21 in nifedipine-ISDN group	improved exercise capacity, nifedipine
	combination for		Comparator: Placebo	(p<0.001 vs. nifedipine,	treatment alone or in combination
	treating for chronic	Exclusion criteria: Pregnancy,		p<0.0001 vs. ISDN)	resulted in clinical deterioration and
	CHF.	nursing, history of MI <1 mo		<ul> <li>Clinical deterioration</li> </ul>	worsening of CHF
		before entry, valvular disease,		discontinuation:	
		angina, significant pulmonary,			

	Study type: Crossover RCT Size: 28 pts	hepatic, renal and hematologic disease., unable to walk on the treadmill, noncompliance		Nifedipine 29% vs. ISDN group 5% (p<0.05) • DBP: Nifedipine alone or combination with ISDN (reduction, p<0.05)	
MDPIT Goldstein RE, et al., 1991 (146) <u>1984898</u>	<u>Aim</u> : To determine if dilitiazem increases late onset CHF in post-MI pts with early decline in EF. <u>Study type</u> : RCT <u>Size</u> : 2,466 pts	Inclusion criteria: 18–75 y HF pts, NYHA class II and III, LVEF <40%, clinically stable, maintenance dose of digitalis and diuretics. Exclusion criteria: Pregnancy, nursing, history of MI <1 mo before entry, valvular disease, Angina, significant pulmonary, hepatic, renal and hematologic disease., unable to walk on the treadmill, noncompliance	Intervention: Dilitiazem 240 mg (1,234) <u>Comparator</u> : Placebo (1,232)	<ul> <li><u>1° endpoint and results</u>:         <ul> <li>HF-worsening: 9 in</li> <li>Nifedipine group vs. 3 in ISDN group (p&lt;0.09); and</li> <li>21 in nifedipine-ISDN group (p&lt;0.001 vs. nifedipine, p&lt;0.0001 vs. ISDN)</li> <li>Clinical deterioration discontinuation:</li> <li>Nifedipine 29% vs. ISDN group 5% (p&lt;0.05)</li> <li>DBP: Nifedipine alone or combination with ISDN (reduction, p&lt;0.05)</li> </ul> </li> <li>Eollow-up Results: Pts with BL EF&lt;0.40, late CHF in Dilitizam group (21%) vs. Placebe (12%) vs. Placebe (12%) vs. Placebe (12%)</li> </ul>	<ul> <li>Life table analysis confirmed increased frequency of late CHF in pts taking dilitiazem (p=0.0017)</li> <li>Dilitiazem related CHF exclusively associated with systolic LVD with or without BB s</li> </ul>
Cohn JN, et al., 2001 (152) <u>11759645</u>	<u>Aim</u> : To determine the effect of valsartan vs. placebo on mortality plus morbidity in pts with HF <i>r</i> EF	Inclusion criteria: 5,010 pts, mean age 63 y, with NYHA class II-IV HF <i>T</i> EF	Intervention/Compar ator: 5,010 pts on standard therapy for HF were randomized to valsartan or placebo	<ul> <li>Placebol (12%) p=0.004.</li> <li><u>1° endpoint and results</u>:</li> <li>At 23-mo follow-up, mortality was similar in pts treated with valsartan or placebo</li> <li>The combined endpoint of mortality plus morbidity was reduced 13.2% (p=0.009) by valsartan because of a lower rate of HF hospitalization for HF (13.8% vs. 18.2%; p&lt;0.001)</li> </ul>	• Treatment with valsartan resulted in improvements in NYHA class, LVEF, signs and symptoms of HF, and quality of life compared with placebo (p<0.01).
SOLVD Investigators, 1991 (153) 2057034	Aim: To determine the effect of enalapril vs. placebo on mortality and on mortality plus	Inclusion criteria: 2,569 pts, mean age 61 y, with HF <i>r</i> EF (90% with NYHA class II and III HF)	Intervention/Compar ator: 2,569 pts on standard therapy for	<u>1° endpoint and results</u> : At 41.4-mo follow-up, compared with placebo, enalapril	• At 41.4-mo follow-up, compared with placebo, enalapril reduced mortality by 16% (p=0.0036)

	hospitalization for HF in pts with HF <i>r</i> EF		HF were randomized to enalapril or placebo	reduced mortality or hospitalization for worsening HF by 26% (p<0.0001)	
1993 (154) <u>8104270</u>	<u>Aim</u> : To determine the effect of ramipril vs. placebo on mortality in pts with HF <i>r</i> EF	Inclusion criteria: 2,006 pts, mean age 65 y, with HFrEF after MI and without NYHA class0HF	Intervention/Compar ator: 2,006 pts were randomized to ramipril or placebo	<u>1° endpoint and results</u> : At 15-mo mean follow-up, compared with placebo, ramipril reduced all-cause mortality 27% (p=0.002)	• Analysis of prespecified 2° outcomes showed that ramipril reduced the first validated outcome (death, severe/resistant HF, MI, or stroke) by 19% (p=0.008).
Garg R, et al., 1995 (155) <u>7654275</u>	<u>Aim</u> : A meta-analysis was performed to determine the effect of ACEIs vs. placebo on mortality and on mortality plus hospitalization for HF in pts with HF <i>r</i> EF	Inclusion criteria: The meta- analysis included 32 trials of 7,105 pts with HF <i>r</i> EF treated with ACEIs vs. placebo	Intervention/Compar ator: In 25 trials, pts were treated with digoxin and/or diuretics, 4 trials only used diuretics, 1 trial used only digoxin, and 2 trials used no background therapy	<u>1° endpoint and results:</u> Compared with placebo, ACEIs reduced all-cause mortality 23% (p<0.001) and all-cause mortality or hospitalization for HF 35% (p<0.001).	• The reduction in mortality was primarily due to a 31% (17%–42%) reduction in death from progressive HF.
Pfeffer MA, et al., 2003 (156) <u>14610160</u>	<u>Aim</u> : To determine the effect of valsartan, captopril, or both on mortality in pts with MI complicated by HF, LV dysfunction, or both	Inclusion criteria: 14,703 pts, mean age 65 y, with MI complicated by HF, LV dysfunction, or both	Intervention: 4,909 pts were randomized to valsartan, 4,909 pts were randomized to captopril Comparator: 4,885 pts were randomized to valsartan plus captopril.	<u>1° endpoint and results</u> : At 24.7-mo median follow-up, mortality was similar in the 3 treatment groups.	• The incidence of adverse events causing discontinuation of drug was 5.8% with valsartan, 7.7% with captopril, and 9.0 % with valsartan plus captopril (p<0.05 comparing valsartan with captopril and valsartan plus captopril with captopril).
Maggioni AP, et al., 2002 (157) <u>12392830</u>	<u>Aim</u> : A subgroup analysis of the Val- HeFT study was performed to determine the effect of valsartan vs. placebo on mortality and on mortality plus morbidity in pts with HF <i>r</i> EF not receiving ACEIs	Inclusion criteria: 366 pts, mean age 67 y, with HF <i>r</i> EF not receiving ACEIs	Intervention/Compar ator: 185 pts were randomized to valsartan and 181 pts were randomized to placebo	<u><b>1° endpoint and results:</b></u> Compared with placebo, valsartan reduced mortality 33% (p=0.017) and mortality plus morbidity 44% (p<0.001).	• Compared with placebo, valsartan reduced first hospital admission for HF 53% (p=0.0006).

Granger CB, et al., 2003 (158) <u>13678870</u>	<u>Aim</u> : To determine the effect of candesartan vs. placebo on mortality in pts with HF <i>r</i> EF intolerant to ACEIs	Inclusion criteria: 2,028 pts, mean age 67 y, with HF <i>r</i> EF intolerant to ACEIs	Intervention/Compar ator: 1,013 pts were randomized to candesartan and 1,015 pts were randomized to placebo	<u>1° endpoint and results</u> : At 33.7-mo median follow-up, compared with placebo, the 1° endpoint of CV death or hospital admission for HF was reduced 30% by candesartan (p<0.0001).	• Compared with placebo, candesartan reduced CV death, hospital admission for HF, MI, stroke, or coronary revascularization 24% (p<0.0001).
Pitt B, et al., 2003 (159) <u>12668699</u>	Aim: To determine the effect of eplerenone vs. placebo on mortality and on CV death or hospitalization for CV events in pts with MI complicated by HF <i>r</i> EF	Inclusion criteria: 6,632 pts, mean age 64 y, with HF <i>r</i> EF after MI	Intervention/Compar ator: 3,313 pts were randomized to eplerenone and 3,319 pts were randomized to placebo	<u>1° endpoint and results:</u> At 16-mo mean follow-up, eplerenone reduced mortality 15% (p=0.008) and CV death or hospitalization for CV events 17% (p=0.005).	• Compared with placebo, eplerenone reduced death from any cause or any hospitalization 8% (p=0.02) and sudden cardiac death 21% (p=0.03), reduced hypokalemia from 13.1% to 8.4% (p<0.001), and increased serious hyperkalemia from 3.9%–5.5% (p=0.002).
Taylor AL, et al., 2004 (160) <u>15533851</u>	<u>Aim</u> : To determine the effect of ISDN plus hydralazine vs. placebo on mortality, first hospitalization for HF, and change in quality of life in black pts with HF <i>r</i> EF	Inclusion criteria: 1,050 African American pts, mean age 57 y, with HF <i>r</i> EF and NYHA class III or IV HF.	Intervention/Compar ator: 518 pts were randomized to ISDN plus hydralazine and 532 pts were randomized to placebo	<u>1° endpoint and results:</u> At 10-mo mean follow-up, compared with placebo, the mean 1° endpoint of mortality, first hospitalization for HF, and change in quality of life was reduced by ISDN plus hydralazine (p=0.01).	<ul> <li>Compared with placebo, ISDN plus hydralazine reduced mortality from 10.2%–6.2% (p=0.02) causing cessation of the study.</li> <li>Compared with placebo, ISDN plus hydralazine reduced all-cause mortality 43% (first hospitalization for HF 33% (p=0.001), and improved quality of life (p=0.02).</li> </ul>
The Multicenter Dilitiazem Postinfarction Research Group, 1988 (145) <u>2899840</u>	Aim: To assess dilitiazem effect on recurrent infarction and death after acute MI <u>Study type</u> : RCT <u>Size</u> : 2,466 pts	Inclusion criteria: 25–75 y admitted to CCU, MI with enzyme confirmation. Exclusion criteria: Cardiogenic shock, symptomatic hypotension, PH with right HF, 2nd/3rd degree heart block, HR <50 bpm, contraceptives, WPW syndrome, CCBs, severe comorbidities or cardiac surgery	Intervention: Dilitiazem 240 mg (1,234) Comparator: Placebo (1,232)	<ul> <li><u>1° endpoints and results</u>:</li> <li>Total mortality: identical in both groups</li> <li>Cardiac death and nonfatal MI: 11% fewer in dilitiazem but difference was NS</li> </ul>	• No combined benefit from dilitiazem on mortality or cardiac events
ONTARGET Investigators, et al., 2008 (126) <u>18378520</u>	<u>Aim</u> : Evaluate whether use of an ARB was noninferior to ACEI, and whether the combination was	Inclusion criteria: • ≥55 y • Coronary, peripheral, or cerebrovascular disease or DM	Intervention: Ramipril 10 mg daily (n=8,576) Comparator:	<u>1° endpoint</u> : After a median follow-up of 56 mo, there was no difference between ramipril vs. telmisartan or combination therapy vs. ramipril in the 1°	• Telmisartan was equivalent to ramipril in pts with vascular disease or high-risk DM and was associated with less angioedema. The combination of the 2 drugs was associated with more

superior to ACE alone	with end-organ damage	Telmisartan 80 mg	composite outcome of death	adverse events without an increase in
in the prevention of		daily (n=8,542)	from CV causes, MI, stroke,	benefit
vascular events in pts	Exclusion criteria:	<ul> <li>Combination of</li> </ul>	or hospitalization for HF (RR:	
with CVD or DM but	<ul> <li>Inability to discontinue ACEI or</li> </ul>	telmisartan and	1.01; 95% CI: 0.94–1.09 and	
not HF.	ARB	ramipril (n=8,502)	RR: 0.99; 95% CI: 0.92–1.07,	
	<ul> <li>Known hypersensitivity or</li> </ul>		respectively)	
Study type: Multi-	intolerance to ACEI or ARB			
center, double-blind,	<ul> <li>Selected CVDs (congestive</li> </ul>		Safety endpoint:	
RCT	HF, hemodynamically significant		<ul> <li>Combination therapy was</li> </ul>	
	valvular or outflow tract		associated with greater risk of	
<u>Size</u> : 25,620 pts	obstruction, constrictive		hyperkalemia than ramipril	
	pericarditis, complex congenital		monotherapy (480 pts vs. 283	
	heart disease, syncopal		pts; p<0.001)	
	episodes of unknown etiology <3		<ul> <li>Hypotensive symptoms</li> </ul>	
	mo, planned cardiac surgery or		were cited as reason for	
	PTCA <3 mo, uncontrolled HTN		permanent discontinuing more	
	on treatment [e.g., BP >160/100		in telmisartan vs. ramipril (RR:	
	mm Hg], heart transplant		1.54; p<0.001) and	
	recipient, stroke due to		combination therapy vs.	
	subarachnoid hemorrhage)		ramipril monotherapy (RR:	
	<ul> <li>Other conditions (significant</li> </ul>		2.75; p<0.001)	
	renal artery disease, hepatic		Renal impairment was more	
	dysfunction, uncorrected volume		common in combination	
	or sodium depletion, 1°		therapy vs. ramipril	
	hyperaldosteronism, hereditary		monotherapy (RR: 1.33; 95%	
	fructose intolerance, other major		CI: 1.22–1.44)	
	noncardiac illness or expected to			
	reduce life expectancy or			
	significant disability interfere with			
	study participation,			
	simultaneously taking another			
	experimental drug, unable to			
	provide written informed			
	consent).			

Study	Aim of Study;	Patient Population	Study Intervention	Endpoint Results	Relevant 2° Endpoint (if any);
Acronym;	Study Type;		(# patients) /	(Absolute Event Rates,	Study Limitations;
Author;	Study Size (N)		Study Comparator	P value; OR or RR; &	Adverse Events;
Year Published			(# patients)	95% CI)	Summary
TOPCAT Pfeffer MA, et al., 2015 (161) 25406305	<u>Aim</u> : To investigate variation in pts and outcome in TOPCAT between pts from the Americas vs. Russia/Georgia <u>Study type</u> : Post- hoc analysis of prospective, double- blind, RCT <u>Size</u> : 3,445 pts	Inclusion criteria: NYHA class II–IV HF with LVEF ≤40% within 3 mo of enrollment; supine resting heart rate ≥68 bpm; stable clinical condition Exclusion criteria: Acute MI or UA within 28 d of randomization; indication or contraindication for treatment with BBs or drugs with beta- blocking properties; poor compliance; CABG surgery or PTCA in past 4 mo	Intervention: • Americas 886 on spironolactone • Russia/Georgia 836 on spironolactone • Spironolactone 15–45 mg daily <u>Comparator</u> : • Americas 881 on placebo • Russia/Georgia 842 on placebo • Placebo	<u>1° endpoint</u> : Composite of CV death, aborted cardiac arrest, or HF hospitalization at 3.3 y follow-up was: Americas: 27.3% for spironolactone and 31.8% for placebo HR: 0.82; 95% CI: 0.69– 0.98; p=0.026; Russia/Georgia 9.3% for spironolactone and 8.4% for placebo HR: 1.10; 95% CI: 0.79– 1.51; p=0.58 <u>1° Safety endpoint:</u> • Doubling of serum creatinine: Americas: 17.8% for spironolactone and 11.6% for placebo HR: 1.60; 95% CI: 1.25–2.05; p<0.001 • Russia/Georgia 2.0% for S and 2.1% for p HR: 0.95; 95% CI: 0.49– 1.85; p=0.89 • Creatinine >3.0 mg/dL • Americas 9.8% for spironolactone and 9.1% for placebo HR: 1.10; 95% CI: 0.81–1.49; p=0.55 • Russia/Georgia 0.2% for spironolactone and 0.4% for placebo HR: 0.5; 95% CI: 0.09–2.75; p=0.43 • Hyperkalemia (potassium >5.5 mmol/L) • Americas 25.2% for spironolactone and 8.9% for placebo OR: 3.46; 95% CI: 2.62–4.56; p<0.001	Relevant 2° endpoint:CV mortality:Americas 10.8% for spironolactoneand 14.4% for placebo HR: 0.74; 95%CI 0.57–0.97; p=0.027;Russia/Georgia 7.7% forspironolactone and 5.8% for placeboHR: 1.31; 95% CI: 0.91–1.90; p=0.15.Aborted cardiac arrest: NS betweengroups. HF hospitalization: 20.8% forspironolactone and 24.5% for placeboHR: 0.82; 95% CI: 0.67–0.99;p=0.042; Russia/Georgia 2.6% forspironolactone and 3.4% for placeboHR: 0.76; 95% CI: 0.44–1.32;p=0.327; Recurrent HF: 361 events forplacebo (IRR: 0.75; 95% CI: 0.58–0.96; p=0.024) Russia/Georgia 33events for spironolactone and 37events for placebo (IRR: 0.83; 95% CI:0.42–1.62; p=0.58) All-cause mortality:NS between groups in Americas andRussia/Georgia. All-causehospitalization: NS between groups inAmericas and Russia/Georgia. MI: NSbetween groups; Stroke: NS betweengroupsStudy limitations and adverseevents:The pts enrolled inRussia/Georgia in the TOPCAT trialdid not demonstrate either theexpected morbidity and mortalityassociated with symptomatic HE or

Data Supplement 35. RCTs Comparing HF*p*EF (Section 9.2.2)

				<ul> <li>Russia/Georgia 11.8% for spironolactone and 9.4% for placebo OR: 1.30; 95% CI: 0.95–1.77; p=0.10</li> <li>Hypokalemia (potassium &lt;3.5 mmol/L) Americas 15.2% for spironolactone and 26.2% for placebo) 0.51 (95% CI: 0.40–0.64; p&lt;0.001)</li> <li>Russia/Georgia 17.2% for S and 19.4% for p OR: 0.87 (95% CI: 0.68–1.11; p=0.26)</li> </ul>	most pharmacological responses to spironolactone <u>Summary</u> : In pts with HF with preserved EF, spironolactone reduced the 1° endpoint of composite of CV death, aborted cardiac arrest, or HF hospitalization in the Americas group but not in the Russia/Georgia group. The pts enrolled in the Russia/Georgia group did not demonstrate either the expected morbidity and mortality associated with symptomatic HF with preserved EF or most pharmacological responses to spironolactone
Aronow WS, et al., 1997 (162) <u>9230162</u>	<u>Aim</u> : To determine effect of propranolol vs. no propranolol on mortality plus nonfatal MI in pts with prior MI and HF <i>p</i> EF	Inclusion criteria: Pts ≥62 y with MI and LVEF ≥40% and HF NYHA class II or III treated with diuretics and ACEIs for 2 mo	<ul> <li>Intervention: 79 pts were randomized to treatment with propranolol</li> <li><u>Comparator</u>: 79 pts were randomized to no propranolol.</li> <li>All pts continued diuretic and ACEI therapy.</li> </ul>	<u>1° endpoint</u> : At 32-mo mean follow- up, multivariate Cox regression analysis showed that compared with no propranolol, propranolol reduced mortality 35% (p=0.03) and mortality plus nonfatal MI 37% (p=0.018)	Relevant 2° endpoint: At 1-y follow- up, LVEF was increased by propranolol from 57% to 63% (p<0.001) and LV mass was decreased by propranolol from 312 grams to 278 grams (p=0.001) Propranolol was stopped because of adverse effects in 11 of 79 pts (14%)
Kostis JB, et al., 1997 (163) <u>9218667</u>	Aim: To determine the effect of antihypertensive drug therapy vs. placebo in prevention of HF in pts with isolated systolic HTN	Inclusion criteria: Pts ≥60 y with isolated systolic HTN in the SHEP program	Intervention/Comparator: 4,736 pts were randomized to antihypertensive drug therapy or placebo	<u>1° endpoint</u> : At 4.5-y follow-up, fatal or nonfatal HF was reduced 49% (p<0.001) by antihypertensive drug therapy (NNT to prevent 1 event =48)	<u>Relevant 2° endpoint:</u> CV mortality and nonfatal hospitalized HF was reduced 30% (p=0.002) by antihypertensive drug therapy
Beckett NS, et al., 2008 (164) <u>18378519</u>	<u>Aim</u> : To determine the effect of antihypertensive drug therapy on fatal or nonfatal stroke in pts ≥80 y	Inclusion criteria: Pts ≥80 y with a SBP≥160 mm Hg	Intervention/Comparator: 3,845 pts were randomized to antihypertensive drug therapy or placebo	<u><b>1° endpoint</b></u> : The 1° endpoint of fatal or nonfatal stroke was reduced 30% (p=0.06) by antihypertensive drug therapy	Relevant 2° endpoint: Antihypertensive drug therapy reduced HF 64% (p<0.001) all-cause mortality 21% (p=0.02), and CV death 23% (p=0.06)

Van Veldhuisen DJ, et al., 2009 (165) <u>19497441</u>	Aim: To determine the effect of nebivolol vs. placebo in pts with HF <i>r</i> EF and HF <i>p</i> EF	Inclusion criteria: Pts ≥70 y, history of HF, and HF <i>r</i> EF or HF <i>p</i> EF	Intervention/Comparator: 1,359 pts with a history of HF <i>r</i> EF and 752 pts with a history of HF <i>p</i> EF were randomized to nebivolol or to placebo	<u>1° endpoint</u> : At 21-mo follow-up, the 1° endpoint of all-cause mortality or CV hospitalization was reduced by nebivolol 14% (95% CI: 0.72– 1.04) in pts with HF <i>r</i> EF and 19% (95% CI: 0.63, 1.04) in pts with HF <i>p</i> EF	Relevant 2° endpoint: HR for reduction of all-cause mortality by nebivolol: 0.84 (95% Cl: 0.86–1.08) for HF <i>r</i> EF and 0.91 (95% Cl: 0.62–1.33) for HF <i>p</i> EF
Yusef S, et al., 2003 (166) <u>13678871</u>	Aim: To determine the effects of candesartan vs. placebo in pts with HF <i>p</i> EF	Inclusion criteria: 3,032 pts, mean age 67 y, with HF <i>p</i> EF and NYHA class II-IV HF	Intervention/Comparator: 3,032 pts were randomized to candesartan or placebo	<u>1° endpoint</u> : At 36.6 m follow-up, the 1° outcome of CV death or hospitalization for HF was reduced 11% (p=0.118) by candesartan	Relevant 2° endpoint: Hospitalization was reduced 16% (p=0.047) by candesartan
Massie BM, et al., 2008 (167) <u>19001508</u>	<u>Aim</u> : To determine the effect of irbesartan vs. placebo on all- cause mortality or hospitalization for a CV cause in pts with HF <i>p</i> EF	Inclusion criteria: Pts 60 y and older with HF <i>p</i> EF and NYHA class II, III, or IV HF	Intervention/Comparator 4,128 pts were randomized to irbesartan or placebo	<u>1° endpoint</u> : At 49.5-mo follow-up, the 1° outcome of all-cause mortality or hospitalization for CV cause was reduced 5% by irbesartan (p=0.35)	Relevant 2° endpoint: Irbesartan did not significantly reduce the 2° outcomes of death from HF or hospitalization for HF, death from any cause and from CV causes, and quality of life
Piller LB, et al., 2011 (168) <u>21969009</u>	<u>Aim</u> : To determine mortality rates in pts who developed HF in ALLHAT	Inclusion criteria: 1,761 pts, mean age 70 y, developed HF during ALLHAT	Intervention/Comparator At 8.9-y mean follow-up, 1,348 of 1,761 pts (77%) with HF died	<u>1° endpoint</u> : Post-HF all-cause mortality was similar for pts treated with chlorthalidone, amlodipine, and lisinopril. 10-y adjusted rates for mortality were 86% for amlodipine, 87% for lisinopril, and 83% for chlorthalidone	<b><u>Relevant 2° endpoint:</u></b> All-cause mortality rates were similar for those with HF <i>r</i> EF (84%) and for those with HF <i>p</i> EF (81%) with no significant differences by randomized treatment arm
Law MR, et al., 2009 (18) <u>19454737</u>	Study type: Meta- analysis of use of BP-lowering drugs in prevention of CVD from 147 randomized trials Size: Of 147 randomized trials of 464,000 pts, 37 trials of BBs in CAD included 38,892 pts, and 37 trials of	Inclusion criteria: The database search used Medline (1966- Dec. 2007 in any language) to identify randomized trials of BP-lowering drugs in which CAD events or strokes were recorded. The search also included the Cochrane Collaboration and	<u>1° endpoint</u> : CAD events; stroke <u>Results:</u> In 37 trials of pts with a history of CAD, BBs reduced CAD events 29% (95% CI: 22%–34%). In 27 trials in which BBs were used after acute MI, BBs reduced CAD events 31% (95% CI: 24%–38%), and in 11 trials in which BBs were used after long-term CAD, BBs	• With the exception of the extra protective effect of BBs given shortly after a MI and the minor additional effect of CCBs in preventing stroke, all the classes of BP-lowering drugs have a similar effect in reducing CAD events and stroke for a given reduction in BP.	N/A

other	Web of Science	insignificantly reduced CAD	
antihypertensive	databases and the	events 13%. In 7 trials, BBs	
drugs in CAD	citations in trials and	reduced stroke 17% (95% CI:	
included 85,395 pts	previous meta-	1%–30%). CAD events were	
	analyses and review	reduced 14% (95% CI: 2%-	
	articles.	25%) in 11 trials of thiazide	
		diuretics, 17% (95% CI:	
	Exclusion criteria:	11%–22%) in 21 trials of	
	Trials were excluded	ACEIs, insignificantly 14% in	
	if there were <5 CAD	4 trials of angiotensin	
	events and strokes	receptor blockers, and 15%	
	or if treatment	(95% CI: 8%–22%) in 22	
	duration was <6 mo.	trials of CCBs. Stroke was	
		reduced 38% (95% CI: 28%-	
		47%) in 10 trials of thiazide	
		diuretics, 22% (95% CI: 8%-	
		34%) in 13 trials of ACEIs,	
		and 34% (95% CI: 25%-	
		42%) in 9 trials of CCBs.	

#### Data Supplement 36. Nonrandomized Trials, Observational Studies, and/or Registries of HFpEF (Section 9.2.2)

Study Acronym;	Study Type/Design;	Patient Population	Primary Endpoint and Results	Summary/Conclusion
Author;	Study Size (N)		(include P value; OR or RR; & 95% CI)	Comment(s)
Year Published				
Law MR, et al.,	Study type: Meta-	Inclusion criteria: The database	<u>1° endpoint</u> : CAD events; stroke	<ul> <li>With the exception of</li> </ul>
2009 (18)	analysis of use of BP-	search used Medline (1966–Dec.		the extra protective
<u>19454737</u>	lowering drugs in	2007 in any language) to identify	Results: In 37 trials of pts with a history of CAD, BBs reduced	effect of BBs given
	prevention of CVD from	randomized trials of BP-lowering	CAD events 29% (95% CI: 22%, 34%). In 27 trials in which BBs	shortly after a MI and
	147 randomized trials	drugs in which CAD events or	were used after acute MI, BBs reduced CAD events 31% (95%	the minor additional
		strokes were recorded. The	CI: 24%, 38%), and in 11 trials in which BBs were used after	effect of CCBs in
	Size: Of 147 randomized	search also included the	long-term CAD, BBs insignificantly reduced CAD events 13%.	preventing stroke, all
	trials of 464,000 pts, 37	Cochrane Collaboration and Web	In 7 trials, BBs reduced stroke 17% (95% CI: 1%–30%). CAD	the classes of BP-
	trials of BBs in CAD	of Science databases and the	events were reduced 14% (95% CI: 2%–25%) in 11 trials of	lowering drugs have a
	included 38,892 pts, and	citations in trials and previous	thiazide diuretics, 17% (95% CI: 11%–22%) in 21 trials of	similar effect in
	37 trials of other	meta-analyses and review	ACEIs, insignificantly 14% in 4 trials of angiotensin receptor	reducing CAD events
	antihypertensive drugs in	articles.	blockers, and 15% (95% CI: 8%–22%) in 22 trials of CCBs.	and stroke for a given
	CAD included 85,395 pts		Stroke was reduced 38% (95% CI: 28%–47%) in 10 trials of	reduction in BP.

	Exclusion criteria: Trials were excluded if there were <5 CAD events and strokes or if treatment	thiazide diuretics, 22% (95% CI: 8%–34%) in 13 trials of ACEIs, and 34% (95% CI: 25%–42%) in 9 trials of CCBs.	
	duration was <6 mo.		

# Data Supplement 37. RCTs Comparing CKD (Section 9.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
MDRD Klahr S, et al., 1994 (169) <u>8114857</u>	Aim: To determine whether restricted protein intake or tighter HTN control would delay progression of CKD Study type: Randomized management to low or usual BP goal and usual, low or very low protein intake Size: • Total n=840 Study 1 n=585 Study 2 n=255 • Mean follow-up 2.2 y • Mean MAP, mm Hg (SD): Study 1: 98 (11) Study 2: 98 (11) • Mean SBP, mm Hg (SD): Study 1: 131 (18) Study 2: 133 (18)	Inclusion criteria: Adults 18–70 y, with renal insufficiency (serum Cr 1.2–7.0 mg/dL in women and 1.4–7.0 mg/dL in men or CrCl <70 mL/min per 1.73 m <sup>2</sup> ) and MAP≤125 mm Hg (normotensives included) Exclusion criteria: Pregnancy, body weight <80% or >160% of standard, DM requiring insulin, urine protein >10 g/d, history of renal transplant, chronic medical conditions, doubts regarding compliance.	Intervention:• Study 1 includedsubjects with GFR 25–55mL/min 1.73 m² (n=585);• Study 2 includedsubjects with GFR 13–24mL/min 1.73 m² (n=255)• Low MAP goal ≤92 mmHg for those 18–60 y;≤98 for those ≥61 y• Usual: MAP goal ≤107m Hg for those 18–60;MAP ≤113 for subjects≥61• 2 studies:Study 1: above BP goalsplus usual or low proteindiet (1.3 or 0.58 g proteinper kg of body weight/d)Study 2: above BP goalsplus low or very lowprotein diet (0.58 or 0.28g per kg/d)• Between groupdifference in MAP, mmHg 4.7; p<0.001	1° endpoint: Rate of decline in GFR, mL/min (95% Cl) • Study 1 From baseline to 4 mo Low: 3.4; 95% Cl: 2.6–4.1 Usual: 1.9; 95% Cl: 1.1–2.7 p=0.010 4 mo to study end, Low: 2.8; 95% Cl: 2.2–3.3 Usual: 3.9; 95% Cl: 3.3–4.5 p=0.006 Baseline to 3 y, Low: 10.7; 95% Cl: 9.1–12.4 Usual: 12.3; 95% Cl: 9.1–12.4 Usual: 12.3; 95% Cl: 10.6–14.0 p=0.18 • Study 2 From baseline to end of study, Low: 3.7; 95% Cl: 3.1–4.3 Usual: 4.2; 95% Cl: 3.6–4.9 p=0.28 ESRD or death: • Study 2 RR for low vs. usual: 0.85; 95% Cl: 0.60– 1.22 p=NR	<ul> <li>Limitations:</li> <li>Drug therapy was not randomized. Recommended ACEI ± diuretic then CCB and others. More subjects in the low BP goal groups received ACEIs (48%, 51% also reported elsewhere) compared to the usual BP goal group (28%, 32% also reported e/w) (not noted in 1° manuscript but reported in Peterson JC, et al., 1995 (170)).</li> <li>1.9% study 1, 1.2% study 2 lost to follow-up.</li> <li>Rate of GFR decline was slower than expected in the control groups and was not constant.</li> <li>Summary: No significant benefits overall from either low protein or lower BP target. There was a significant interaction between baseline urinary protein excretion and BP interventions (p=0.01) indicating that low BP was of benefit to subjects with &gt;1 g proteinuria with slower progression of loss of GFR</li> </ul>

DEIN 2	• Mean DBP, mm Hg (SD): Study 1: 81 (10) Study 2: 81 (10)		Comparator: By BP and protein intake goals	18 and a sint	Limitations: The study was
Ruggeneti P, et al., 2005 (171) <u>15766995</u>	whether intensive BP control will achieve further renoprotection (delayed progression to ESRD) compared to standard BP control in pts with chronic nephropathies <u>Study type</u> : Multicenter RCT of pts all placed on ACEI (ramipril) at maximum dose tolerated to achieve DBP <90 then assigned to conventional or intensified BP control. Add-on drug was dihydropyridine felodipine 5–10 mg/d <u>Size</u> : 335 (median time 19 mo)	<ul> <li>Adults, age 18–70 y, with nondiabetic nephropathy, persistent proteinuria (urinary protein excretion &gt;1 g/24 h for ≥3 mo) and not on ACEIs in previous 6 wk</li> <li>Pts with proteinuria 1–3 g/24 h included if CrCl &lt;70 mL/min/1.73 m<sup>2</sup></li> <li>For overall population, mean SBP, mm Hg (SD): Intensive: 137.0 (16.7) Conventional: 136.4 (17.0)</li> <li>For overall population, mean DBP, mm Hg (SD): Intensive: 84.3 (9.0) Conventional: 83.9 (10.4)</li> <li>Exclusion criteria: Urinary tract infection, CHF class III–IV, treatment with corticosteroids, NSAIDs, immunosuppression, acute MI or stroke in prior 6 mo, severe uncontrolled HTN,</li> </ul>	<ul> <li>Intervention:</li> <li>Intensive: BP goal &lt;130/80 mm Hg</li> <li>Conventional: DBP goal &lt;90 mm Hg, irrespective of SBP</li> <li>For baseline proteinuria subgroups, result BP values NR</li> <li>For the overall population, achieved BP, mm Hg (SD) Intensive: 129.6/79.5 (10.9/5.3) Conventional: 133.7/82.3 (12.6/7.1) p=0.0019/&lt;0.0001</li> <li>For the overall population, change in BP, mm Hg Intensive: -7.4/-4.8 Conventional: -2.7/-1.6 p=NR</li> <li>For the overall population, BP difference between groups, mm Hg 4.1/2.8 p=NR</li> </ul>	• Time to ESRD; over 36 mo follow-up, median 19 mo 1° outcome: ESRD in pts with baseline proteinuria 1–3 g/24 h HR (95% CI): 1.06 (95% CI: 0.51–2.20) p=0.89 • ESRD in pts with baseline proteinuria >3 g/24 h HR (95% CI): 1.09 (95% CI: 0.55–2.19) p=0.81 • 23% of intensive and 20% of conventional control groups progressed to ESRD. • Median rate of GFR decline, mL/min/1.73 m <sup>2</sup> /mo (IQR) in pts with baseline proteinuria <3 g/24: Intensive: 0.18 (95% CI: 0.03–0.49) Conventional: 0.21 (95% CI: -0.03–0.40) p=0.89 • Median rate of GFR decline, mL/min/1.73 m/mo (IQR) in pts with baseline proteinuria $\geq$ 3 g/24: Intensive: 0.51; 95% CI: 0.16–1.05 Conventional: 0.39; 95% CI: 0.030.98 p=0.39	Stopped at the 1st interim analysis for futility. Median time 19 mo Summary: In pts with non-DM proteinuric nephropathies receiving background ACEI therapy, no additional benefits from further BP reduction by felodipine could be shown. Dihydropyridine CCBs do not offer additional renoprotection to ACEIs or ARBs.

		suspicion for	Comparator: By BP		
		renovascular disease,	goais		
		obstructive uropatny,			
		DIVI- I, collagen vascular			
		disease, cancer, elevated			
		aspartate transaminase,			
		chronic cough, history of			
		allergy or poor tolerance			
		to study meds, alcohol			
		abuse, pregnancy,			
		breastfeeding, ineffective			
		contraception.			
AASK	Aim: To compare the	Inclusion criteria:	Intervention:	<u>1° endpoint:</u>	Limitations:
Wright JI, et al.,	effects of 2 levels of	<ul> <li>Adult African-</li> </ul>	<ul> <li>Low: MAP goal ≤92</li> </ul>	• 1° outcome: difference in mean slopes,	Based on DSMD
	BP and 3	Americans,18–70 y, with	mm Hg	acute GFR slope, mL/min/1.73 m <sup>2</sup> /3 mo	recommendation, amlodipine arm
12430200	classos on CEP	HTN (DBP ≥95) and	Usual: MAP goal 102–	(SE):	halted early and those pts
	decline in HTN	GFR of 20–65	107 mm Hg	• 1.82 (0.54) in low BP group	switched to open label Rx,
		mL/min/1.73 m <sup>2</sup> , no DM	<ul> <li>Initial treatment with a</li> </ul>	p<0.001	continued study schedule and
	Study type:	<ul> <li>At entry: mean MAP,</li> </ul>	B Blocker (metoprolol),	• 1° outcome: difference in mean slopes.	same BP goals
	Randomized 3x2	mm Hg:	and ACEI (ramipril) or a	chronic GFR slope, mL/min/1.73 m <sup>2</sup> /v	5
	factorial trial	Low: 115 (27)	dihydropyridine	(SF): 0.21 (0.22)	Summary:
	Measured GER with	Usual: 113 (15)	(amlodipine) with open	p=0.33 NS	No difference in GER decline
	iothalamato	Mean SBP, mm Hg	label agents added to	• Difference in mean slopes total GER	with lower BP goal and no
	Iotrialamate	(SD):	achieve BP goals	slope ml/min/1 73 m <sup>2</sup> /y (SF):	difference in composite clinical
	Sizo: 1 00/	Low:152 (25)	<ul> <li>Study duration:</li> </ul>	-0 25 (0 22)	endnoints
	<u>5126</u> . 1,074	Usual: 149 (23)	3–6.4 у	n=0.24	• Average rate of GER decline 2
		• Mean DBP, mm Hg:	<ul> <li>BP similar across drug</li> </ul>	Main 2º clinical composite outcome	ml /min/v is similar or slower than
		Low: 96 (15)	groups except 2 mm Hg	GER event ESRD or death	nevious reports
		Usual: 95 (14)	lower in amlodipine	% risk roduction (05% CI): 2 (05% CI)	• There was a trend favoring the
			group	22 21)	• There was a trend lavoring the
		Exclusion criteria:	• Mean from 3 mo to	$p_{-0.95}$	lower BP goal in subjects with
		DBP<95, history of DM.	study end	p=0.00	the ennesite trend for these
		Urinary protein/creatinine	• MAP, mm Hg (SD)	• GFR evenil of ESRD,	une opposite trend for those
		ratio $>2.5$ , accelerated or	Low: 95.8 (8)	% KISK KEUUCIIUT: -2; 95% CT: -31-20;	
		malignant HTN, non-BP	Usual: 104 (7)		Kamiprii treatment group had
		related cause of CKD	• SBP/DBP, mm Hg (SD)	• ESRU OF death,	slower progression compared
		serious systemic disease	Low: 128/78 (12/8)	% risk reduction: 12; 95% CI: -13–32;	with metoproiol and amiodipine
		clinical CHF specific	Usual: 141/85 (12/7)	p=0.31	complined, less evident between
		indication or	<ul> <li>MAP change, mm Hg</li> </ul>	• ESRD alone,	ramipril and metoproloi
		contraindication for a	Low: -20	% risk reduction: 6; 95% CI: -29–31;	
				p=0.72	

		study drug or procedure	0 deual	- 20 outcomo, urino protoin overetica	
		study drug or procedure	CDD/DDD change mm	• 2° outcome: unne protein excretion	
			• SDP/DDP Change, mm	Cofety and points	
				Salety endpoint:	
			LOW: -24/-8	Acute and chronic rate of change in	
				GFR (Slope):	
			Achieved mean BP	NS for chronic and total slope in	
			difference between	subgroup analyses by baseline	
			groups, mm Hg	proteinuria strata	
			MAP: 11	<ul> <li>Acute slope: p=0.08 for interaction</li> </ul>	
			SBP: 16	<ul> <li>Total slope: p=0.04 for interaction</li> </ul>	
			DBP: 8	<ul> <li>Chronic slope: p=0.16 for interaction</li> </ul>	
				Clinical composite outcome: includes	
			Comparator: N/A	reduction in GFR by 50% or by 25	
				mL/min/m <sup>2</sup> , ESRD, death, NS in	
				subgroup analyses by baseline	
				proteinuria strata; p=0.007 for interaction	
				<ul> <li>For above outcomes, trends favored</li> </ul>	
				the lower BP goal over the usual goal in	
				participants with higher baseline	
				proteinuria and opposite trends in	
				participants with little or no proteinuria	
				Within each drug group, risk reductions	
				for any 2° clinical outcome of the low vs.	
				usual BP goal were not significantly	
				different between pts with baseline urine	
				protein to creatinine ratio ≤0.22 and	
				>0.22 (p=NS)	
Contreras G, et al.,	Aim: Within AASK to	Inclusion criteria:	Intervention:	<u>1° endpoint:</u>	Limitations: Post-hoc analysis,
2005 (173)	examine the effect of	<ul> <li>Adult African</li> </ul>	<ul> <li>Analysis by initial drug</li> </ul>	<ul> <li>GFR event, ESRD, or death prior to</li> </ul>	effects on GFR may have been
<u>15897360</u>	BP intervention	Americans, ages 18–70,	treatment group	dialysis, Amlodipine, Low vs. Usual Goal	obscured by early rise and later
	separately in the 3	with HTN (DBP ≥95) and	<ul> <li>Low, Amlodipine: MAP</li> </ul>	RR: 32%; 95% CI: -14–60; p=0.14	fall with amlodipine, follow-up
	drug treatment groups	GFR of 20–65	goal ≤92 mm Hg,	<ul> <li>Metoprolol, Low vs. Usual Goal RR:</li> </ul>	only 3–6.4 y, many comparisons
		mL/min/1.73 m <sup>2</sup> , no DM	Amlodipine (5–10 mg/d)	4%; 95% CI: -39–33; p=0.84	so risk for type I error, unable to
	Study type:	Mean MAP, mm Hg:	Usual, Amlodipine: MAP	• Ramipril, Low vs. Usual Goal RR: -8%;	test ACEI – DHP CCB
	<ul> <li>Randomized 3×2</li> </ul>	Low, Amlodipine: 115.3	goal 102–107 mm Hg,	95% CI: -93–15; p=0.24	combination.
	factorial trial	(18.3)	Amlodipine (5–10 mg/d)	p for interaction=0.17	
	<ul> <li>Measured GFR with</li> </ul>	Usual, Amlodipine: 112.7	<ul> <li>Low, Metoprolol: MAP</li> </ul>	<ul> <li>GFR event or ESRD,</li> </ul>	Summary:
	iothalamate	(14.7)	goal ≤92 mm Hg,	Amlodipine, Low vs. Usual Goal RR:	<ul> <li>BP effect was similar among</li> </ul>
		Low, Metoprolol: 114.5	Metoprolol (50–200	26%; 95% CI: -33–58; p=0.32	drug groups for GFR slope and
	<u>Size</u> : 1,094	(17.5)	mg/d)	· · ·	main clinical composite.
	Usual Metoprolol <sup>,</sup> 112.4	Usual Metoprolol MAP	<ul> <li>Metoprolol Low vs. Usual Goal RR<sup>1</sup></li> </ul>	BP effect differed among drug	
--	---	-----------------------------------	--	---------------------------------	
	(14 1)	anal 102–107 mm Ha	7% 95% Cl <sup>-</sup> -42–39 n=0.74	arouns for composite of ESRD or	
	Low Ramipril 115.2	Metoprolol (50–200	• Ramipril Low vs. Usual Goal RR.	death and FSRD alone	
	(15.2)	ma/d)	-42%; 95% CI: -126–11' n=0.14	Higher event rates for	
	Usual Raminril <sup>,</sup> 114.0	● Low Ramipril MAP	n for interaction=0.20	amlodipine and usual BP goal	
	(16.7)	$a_{0}a_{1} < 92 \text{ mm Hg}$	<ul> <li>ESRD or death prior to dialysis</li> </ul>	compared with other groups	
	Mean SBP mm Ha	Raminril (2 5 $-10$ mg/d)	Amlodinine Low vs. Usual Goal RR	• Low BP goal associated with	
	Low Amlodinine: 152.2	Usual Raminril MAP	51% 95% CI $13-73$ n=0.016	reduced risk of ESRD or death	
	(28.2)	aoal 102–107 mm Ha	Metoprolol Low vs. Usual Goal RR:	and ESRD for amlodinine but not	
	Usual Amlodinine: 1/17.7	Raminril $(2.5-10 \text{ mg/d})$	11%: 95% CI: -40-44: n-0.61	for other drug groups (in the	
	(21.9)	• Note: Amlodinine arms	• Raminril Low vs. Usual Goal RR:	absence of ACEL treatment)	
	Low Metoprolol: 152.0	terminated 1 v early	-32% 95% CI: -11/-18 n-0.26	absence of NoEr redimenty.	
	(25.7)	Achieved MAP	n for interaction=0.035		
	Usual Metoprolol: 1/7 7	difference between	<ul> <li>Death alone (prior to dialysis)</li> </ul>		
	$(21 \ A)$	arouns mm Ha	Amlodining Low vs. Usual Goal RP:		
	(21.4) Low Raminril 151.0	Amlodinine Low vs	Altioupine, Low VS. Osual Obal KK.		
	(22.5)	Ligual:12.80	• Metoprolol Low vs. Usual Coal PD: 1:		
	(22.5) Usual Paminril 150.0	Metonrolal Low vs	● Metoproloi, Low VS. Osual Goal KK1, 95% CI: _110_5: n=0.97		
	(24.1)	Heual: 11 11	Pamipril Low vs. Usual Coal PD:		
	• Moon DPD mm Ha	Dominril Low ve Heude	• Rampin, Low VS. Usual Goal KK. 21%: 05% CI: 02.67: $p=0.61$ : p for		
	■ Mean DDF, mini Fig. Low_Amlodinino: 96 55	Rahliphi, Low vs. Osuai. 10.12	21%, 95% CI. $-92-07$ , $p=0.01$ , $p101$		
	(15 1)	n_ND			
	(13.1) Usual Amlodinino: 04.87	Achieved SBP	Safaty and point:		
	(12 0)	● Achieved Sbi	• ESPD along Amledining Low VS		
	(12.7)		• ESRD alone, Annoulpine, Low vs.		
	(15 4)	Amladinina Law va	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		
	(10.4) Usual Motoprolol: 04.47	Annoupine, Low vs.	P=0.020		
		USUAL 18.4	• Melopioloi, Low VS. Usual Goal RR: $11\%$ , 05% CL, 40, 50, p, 0.70		
	(12.3) Low Dominrily 04.00	Netopioloi, Low VS.	11%; 95% CI: -00-50; μ=0.70		
	LOW, Ramphi: 90.90	USUAI: 15.4	• Ramphi, Low VS. Usual Goal RR: $(E_{1}^{0}) = 0.00$ m for		
	(13.0)	Ramiphi, Low VS. Usual:	-05%; 95% CI: -195–8; p=0.09; p 101		
	USUAI, RAMIPHI: 95.12	12.0 m ND	Interaction=0.021		
	(15.3)	p=NR	• Death alone (prior to dialysis),		
	Fucharian aritaria		Amlodipine, Low vs. Usual Goal: RR:		
	Exclusion criteria:	Achieved DBP	48%; 95% CI: -59–83; p=0.25		
	DBP<95, NISTORY OF DM,	difference between	Metoprolol, Low vs. Usual Goal: RR: -		
	Urinary protein/creatinine	groups, mm Hg	1; 95% CI: -110–5; p=0.97		
	ratio >2.5, accelerated or	Amioaipine, Low vs.	<ul> <li>Ramipril, Low vs. Usual Goal RR:</li> </ul>		
	malignant HTN, non-BP	Usual: 10.14	21%; 95% CI: -92–67; p=0.61; p for		
	related cause of CKD,	Metoprolol, Low vs.	interaction=0.61		
	serious systemic	Usual: 8.86			

		disease, clinical CHF,	Ramipril, Low vs. Usual:	<ul> <li>Proteinuria within each drug group,</li> </ul>	
		specific indication or	8.96	risk reductions for any 2° clinical	
		contraindication for a	p=NR	outcome of the low vs. usual BP goal	
		study drug or procedure		were not significantly different between	
			Comparator: N/A	pts with baseline urine protein to	
				creatinine ratio ≤0.22 and >0.22 (p=NS)	
Norris K, et al.,	Aim: Compared effect	Inclusion criteria:	Intervention:	<u>1° endpoint:</u>	Limitations:
2006 (174)	of treatment on CV	Adult African	<ul> <li>Achieved SBP/DBP,</li> </ul>	Number of deaths before ESRD, n of	Limited power, only 202 CV
17059993	event rate during mean	Americans, 18–70 y, with	mm Hg (SD)	events	events - low incidence. CV
	follow-up of 4.1 y by	HTN (DBP ≥95) and	Low: 128/78	Low: 38	outcomes were 2° endpoints of
	drug class and level of	GFR of 20–65	Usual: 141/85	Usual: 47; p=NR	high priority (prespecified).
	BP control.	mL/min/1.73 m <sup>2</sup> , no DM	p=NR	Major CAD events, n of events (rate	<ul> <li>&gt;50% had a history of heart</li> </ul>
	Determined baseline	Mean MAP. mm Hq:	• SBP/DBP change, mm	per person-v)	disease at entry, 40% with LVH
	factors that predict CV	114 (16)	На	Low: 19 (0.008)	by ECG, 1/3 smokers, almost
	outcomes	Mean SBP. mm Hg:	Low: -23/-19	Usual: 23 (0.010); p=NS	50% had income <15K.
		150 (24)	Usual: -8/-9	• Stroke events, number of events (rate	
	Study type:	Mean DBP.	p=NR	per person-v)	Summary:
	Randomized 3×2	mm Ha: 96	• Achieved mean BP	Low: 26 (0.011)	CV outcome rate was not
	factorial trial	(14)	difference between	Usual: 29 (0.013): $p=NS$	related to randomized
	Measured GFR with	()	aroups, mm Ha	• HE events, n of events (rate per	interventions, either drug or BP
	iothalamate	Exclusion criteria: N/A	SBP: 15	person-v)	target
			DBP: 10	Low: 27 (0.012)	• 7 baseline risk factors were
	Size:		n=NR	$U_{SUAL} 23 (0.012)$	independently associated with
	1.094		p	n=NS	increased risk for CV composite
			Comparator: N/A	CV composite outcome in of events	outcome in multivariable analyses
				(rate per person-v)	after controlling for age sex
				$L_{OW}$ : 71 (0.032)	haseline GER haseline
				1  [sual: 71 (0.032)]	proteinuria: PP_duration of HTN
				Composite outcome or ESRD, n of	protein/creatinine ratio urine
				• composite outcome of EORD, if of	sodium-potassium ratio and
				Low: $142 (0.064)$	annual incomo <15 000
				1000.143(0.004)	
				DSuai. 139 (0.072)	
				• Overall rate of CV events in of events	
				• Overall rate of Overents, if of events	
				(100 + 100	
				LUW. $100(0.040)$	
				USual: $94 (0.042); p=NS$	
				• Uv death, n of events (rate per	
				person-y)	
				LOW: 16 (0.007)	

				Usual: 15 (0.006); p=NS	
Amlodipine Versus	<u>Aim</u> :	Inclusion criteria:	Intervention:	1° endpoint: Change in GFR from	Summary:
Enalapril in Renal	To compare GFR	• 18–80 y	<ul> <li>Amlodipine: 5–10 mg/d</li> </ul>	baseline to final assessment	<ul> <li>No difference in GFR change</li> </ul>
Failure (AVER trial)	decline in nondiabetic,	• CrCl 20–60	<ul> <li>Enalapril: 5–20 mg/d</li> </ul>		or serum creatinine at trial end
Esnault VL, et al.,	nonnephrotic adults	mL/min/1.73 m <sup>2</sup>	Therapy initiated with	2° Outcome: Clinical composite of renal	Last observation: mean change in
2008 (175)	with HTN and	(Cockcroft-Gault)	amlodipine 5 mg/d or	replacement therapy, discontinuation	GFR, mL/min/1.73 m <sup>2</sup>
<u>18405787</u>	estimated CrCl 20–60	Nondiabetic	enalapril 5 mg/d. Drugs	due to deterioration of renal function,	Amlodipine -4.92, Enalapril -3.98;
	mL/min/1.73 m <sup>2</sup> when	<ul> <li>Enrollment confirmed</li> </ul>	up-titrated to amlodipine	50% decrease in GFR, doubling of	p=NS
	randomized to a CCB	at end of 4-wk placebo	10 mg/d or enalapril 20	serum Cr, hospitalization for transient	• Last observation: mean change
	(amlodipine, 5–10	run-in if sitting DBP	mg/d at wk 8 and 12 if	renal failure. "Other 2º outcome	in Serum Cr from baseline (mg/d)
	mg/d) or an ACEI	between 90 and 119 mm	DBP >90 mm Hg.	measures" included: changes in serum	Amlodipine +0.57, Enalapril
	(enalapril, 5–20 mg/d).	Hg	After 18 wk, if maximal	Cr, sitting DBP and SBP, heart rate,	+0.47; p=NS
		<ul> <li>Mean SBP, mm Hg</li> </ul>	tolerated dose of study	total and HDL cholesterol, 24-h urinary	• No difference in composite 2°
	Study type: RCT	(SD):	drug did not decrease BP	protein excretion, ambulatory BP	endpoints.
		Amlodipine: 165.1 (15.4)	to target, add on anti-	monitoring, and safety measures.	• Mean BP (mm Hg): baseline to
	<u>Size</u> :	Enalapril: 165.2 (16.6)	HTN treatments were the	Composite Outcomes: 2º clinical	last observation
	Amlodipine: 132	<ul> <li>Mean DBP, mm Hg</li> </ul>	following: atenolol (50-	composite	Amlodipine 164.8/101.8 to
	Enalapril: 131	(SD):	100 mg/d), loop diuretics		140.1/85.4, delta -24.7/16.4
		Amlodipine: 102.0 (6.7)	(furosemide 20–500	Safety endpoint: Proteinuria subgroup,	Enalapril 165.0/102.5 to
		Enalapril: 102.5 (7.1)	mg/d or torsemide, 5-	$>1 \alpha/d$ : protein excretion rate decreased	140.3/86.4, delta -24.7/16.1
		<ul> <li>Mean serum Cr, mg/dL</li> </ul>	200 mg/d), alpha	significantly in pts taking enalapril plus	
		(SD):	blockers (prazosin, 2.4–5	diuretic (median -270 mg/d; p<0.001)	
		Amlodipine: 2.00 (0.8)	mg/d or doxazosin, 1–16	but not in pts taking amlodipine plus	
		Enalapril: 2.05 (0.7)	mg/d) and centrally	diuretic (-25 mg/d) at last obs	
			acting drugs (rilmenidine		
		Exclusion criteria:	(1–2 mg/d or		
		<ul> <li>Nephrotic proteinuria</li> </ul>	methyldopa, 250-500		
		<ul> <li>2° or malignant HTN</li> </ul>	mg/d).		
		(DBP >120 mm Hg)			
		A major CV event	BP goal:		
		within 3 mo	Amlodipine: <130/85 mm		
		<ul> <li>Angina pectoris</li> </ul>	Hg		
		<ul> <li>Congestive heart</li> </ul>	Enalapril: <130/85 mm		
		disease (NYHA II-IV)	Hg		
		Uncontrolled	Duration of treatment:		
		arrhythmias	Median follow-up 2.93 y		
		II-III AV block	in amlodipine group; 2.95		
		<ul> <li>Need for serious</li> </ul>	y in enalapril group		
		steroids, NSAIDS or			
		cytotoxic drugs			

		Alexander of the			
		women or child-     boaring notontial not			
		contracontivos			
		contraceptives			
		• Any disease that could			
		infill the ability of pis to			
		requirements			
ESPIRAL	<u>Aim</u> : To investigate in	Inclusion criteria:	Intervention:	<u>1° endpoint:</u>	Limitations:
Marin R, et al.,	a random comparison	• 18–75 y	Nifedipine GHS: 30–	• 1° Outcome: Time elapsed until serum	• SBP was 4–6 mm Hg lower
2001 (176)	the capacity of an	• Serum Cr between 1.5	60 mg QD	Cr values doubled, or the need to enter a	with ACEI which may have
<u>11593109</u>	angiotensin converting	and 5 mg/dL (133–442	• Fosinopril: 10–30 mg	dialysis program	impacted improved outcomes.
	enzyme inhibitor	µmol/l)	QD	<ul> <li>2º Outcome: CV events (including MI,</li> </ul>	Still positive effects remained
	(fosinopril), and that of	<ul> <li>HTN defined as BP</li> </ul>	<ul> <li>Drugs added in step-</li> </ul>	stroke, angina, and death), proteinuria	from fosinopril after adjusted for
	a long-acting	>140/90 mm Hg or by	wise fashion to achieve	evolution and serum Cr	BP levels.
	dihydropiridine	the use of	BP goal.		<ul> <li>Sodium restriction may have</li> </ul>
	(nifedipine GITS) to	antihypertensive agent(s)	<ul> <li>Step 1: Randomized</li> </ul>	Safety endpoint: N/A	favored the ACEI group.
	modify the decay in	<ul> <li>Proven progression of</li> </ul>	drug		
	renal function in pts	chronic renal failure in	Step 2: Furosemide		Summary:
	with primary renal	the previous 2 y, defined	(up to 100 mg)		<ul> <li>Renal survival was significantly</li> </ul>
	disease, exhibiting a	by increase by >25% or	• Step 3: Atenolol (up to		better if fosinopril used as first
	progressive increase in	>0.5 mg/dL (44.2 µmol/l)	100 ma)		agent, unrelated to the primary
	serum Cr during the	in serum Cr	• Step 4: Doxazosin (up		renal disease.
	previous 2 y.	<ul> <li>Mean SBP, mm Hg</li> </ul>	to 12 mg)		<ul> <li>Proteinuria decreased by 57%</li> </ul>
		(SD):	• BP goal:		in the fosinopril group and
	Study type:	Nifedipine GITS: 157.5	Nifedinine GITS: $< 140/90$		increased by 7% in the nifedipine
	Randomized open	(20)	mm Ha		GITS group while BP control did
	label trial	Fosinopril: 155 (17)	Fosinopril: $< 140/90$ mm		not differ between treatment
		Mean DBP, mm Ha	На		groups for DBP.
	Size: 241	(SD):	<ul> <li>Duration of treatment:</li> </ul>		• 3-v follow-up
	Nifedipine GITS: 112	Nifedipine GITS: 96 (11)	mean follow.un NP.		Doubling of serum Cr or entering
	Fosinopril <sup>,</sup> 129	Fosinopril: 96 (8)	authors roport minimum		dialysis N (%)
			follow up of 3 y and this		Nifedinine GITS 40 (36%)
		Exclusion criteria	is when most outcome		Fosinopril 27 (21%)
		• DM	is when most outcome		$OR \cdot 0.47 (0.26 - 0.84) \cdot n = 0.01$
		Previous recent history	measures reported		• Decrease in SBP mm Hg (SD)
		of CVD (stroke ML or			Nifedinine GITS $1/10$ (22.5)
					Fosinonril 10 8 (10 6) n ND
		Taking concomitant			$\frac{1}{2} = \frac{1}{2} = \frac{1}$
		- raking conconniant			Nifodipipo CITS 14.0 (11.0)
	l	medications that could	1		witeupine 013 14.9 (11.8)

ACCOMPLISH Bakris GL, et al., 2010 (177) 20170948	Aim: To examine the effect of initial antihypertensive therapy with benazepril plus amlodipine compared to benazepril plus hydrochlorothiazide on progression of CKD <u>Study type:</u> RCT, forced drug titration <u>Size:</u> • Overall benazepril plus amlodipine n=5,744 benazepril plus hydrochlorothiazide n=5,762 • Pts with CKD benazepril plus amlodipine n=561 benazepril plus amlodipine n=561 benazepril plus hydrochlorothiazide n=532 • Pts without CKD benazepril plus amlodipine n=5,171 benazepril plus amlodipine n=5,171 benazepril plus hydrochlorothiazide n=5,218 <u>Aim:</u> Compare effects	interfere with study results (steroids, immunosuppressant drugs, or NSAIDS) ● Presenting intolerance to fosinopril or nifedipine Inclusion criteria: ● Males or females ≥55 y, with HTN, high CV risk (history of coronary events, MI, revascularization, stroke, CKD, PAD, LVH, DM) ● Entry BP for pts with CKD benazepril plus amlodipine: 145.1/78.6 (20.2/11.2) benazepril plus hydrochlorothiazide: 145.0/78.1 (20.5/10.7) ● Rate of DM same in CKD and non-CKD pts (58.9% vs. 60.5%; p=0.302 Exclusion criteria: N/A	Intervention:         • Initial antihypertensive therapy with benazepril plus amlodipine compared to benazepril plus hydrochlorothiazide         • BP after dose adjustment benazepril plus amlodipine: 131.6/73.3 (18.2/10.3 SD), 4119 (75%) controlled         • Benazepril plus amlodipine: 131.6/73.3 (18.2/10.3 SD), 4119 (75%) controlled         • Benazepril plus hydrochlorothiazide: 132.5/74.4 (17.9/11.2 SD), 3963 (72%) controlled p<0.0013 Target <140/90 and <130/80 for DM or CKD         Comparator: N/A	1° endpoint:         • Overall: time to first event of composite CV morbidity and mortality         • Progression of CKD, a prespecified endpoint, was defined as doubling of serum creatinine concentration or ESRD (estimated glomerular filtration rate <15 mL/min/1·73 m² or need for dialysis).         • All randomized pts were included in the intention-to-treat analysis. There were 113 (2.0% x 0%) events of CKD progression in the benazepril plus amlodipine group compared with 215 (3.7% x 7%) in the benazepril plus hydrochlorothiazide group HR: 0.52, (95% CI: 0.41–0.65), p<0.0001         • 2° endpoints:       CKD plus death, change in albuminuria, change in eGFR         • Subset with more advanced CKD analyzed for rate of progression         Safety endpoint: N/A	Fosinopril 12.7 (11.6); p=NS         Limitations:         • Trial terminated early (mean follow-up 2.9 y [SD 0.4]) because of superior efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide with 20% lower CV risk.         • Very small proportion of study population had albuminuria above 33.9 mg/mmol combined with early trial termination to reduce renal events.         • Funded by Novartis.         Summary:         • Initial antihypertensive treatment with benazepril plus amlodipine slowed progression of nephropathy to a greater extent compared to benazepril plus hydrochlorothiazide.         Limitations: No renal endpoints
Parving HH, et al.,	of dual blockade of	Pts with HTN, 18–85 y,	losartan then aliskiren or	<ul> <li>Ratio of albumin to creatinine at 6 mo</li> </ul>	regarding function, survival, CV

2008 (178) <u>18525041</u>	RAAS by aliskiren 300 mg/d added to maximal dose losartan 100 mg/d and optimal HTN therapy <u>Study type</u> : RCT, double-blinded, duration was 6 mo <u>Size</u> : 805 entered open label, 599 randomized, 524 completed.	and DM-2 and nephropathy (early morning alb/creat >300 mg/g or >200 mg/g in on RAAS blocker already <u>Exclusion criteria:</u> Non-DM kidney disease, >3,500 mg/g alb/ Cr ratio, eGFR, 30 mL/min/BSA, chronic urinary tract infections, baseline serum potassium >5.1, severe HTN, major CVD in prior 6 mo	placebo added <u>Comparator</u> : All on losartan, aliskiren or placebo added	<ul> <li>2°: decline in eGFR, development of renal dysfunction (serum creatinine &gt;176.8 micromol/I (2.0 mg/dL)</li> <li><u>Safety endpoint</u>: Hyperkalemia 5% in aliskiren group, 5.7% in placebo group but more frequent individual elevations &gt;5.5 in aliskiren group</li> </ul>	events, BP 2/1 mm Hg lower in aliskiren group; supported by Novartis • Outcome was degree of albuminuria. Aliskiren reduced urinary alb/creat ratio by 20% (95% Cl 9–30; p<0.001) • From post hoc analysis: Antiproteinuric effects consistent across CKD stages (19%, 22%, and 18% for stages 3, 2, and 1). For CKD 3, renal dysfunction more frequent in placebo group (29.3 vs. 13.6%; p=0.032) • No differences in deaths or acute renal failure by treatment group (0.7% in both)
VA NEPHRON-D Fried LF, et al., 2010 (124) 20728887	<u>Aim</u> : To test the efficacy of the combination of losartan with lisinopril as compared with standard treatment with losartan alone in slowing the progression of proteinuric diabetic kidney disease <u>Study type:</u> RCT, multi-center, double- blind <u>Size</u> : 1448 were randomized	Inclusion criteria: Pts without adverse events on full dose losartan DM-2, eGFR 30–89.9 mL/min/1.73 m <sup>2</sup> by 4 variable MDRD formula, urinary albumin/creatinine ratio of ≥300 in a random sample Exclusion criteria: Known non-DM kidney disease, serum potassium >5.5 mmol/L, current treatment with sodium polystyrene sulfonate or inability to stop prescribed medications increasing risk of hyperkalemia.	Intervention:● Pts with DM-2 alreadytaking losartan 100 mg/dwith albumin to creatinineratio of ≥300 wererandomized to eitherlisinopril 10–40 mg/d orplacebo.• 132 1° endpoints inthe combination therapygroup; No benefit tomortality or CV events.Combination therapyincrease risk ofhyperkalemia 6.3events/100 person-y vs.2.6 events/100 person-y(p<0.001) and acute	<u>1° endpoint</u> : First occurrence of a change in eGFR (a decline of ≥30 mL/min/1.73 m² if initial GFR ≥60 or a decline of ≥50% if initial eGFR <60, ESRD or death 2° endpoint: First occurrence of decline in eGFR or ESRD <u>Safety endpoint</u> : mortality, hyperkalemia, acute kidney injury	Summary: Study stopped early due to safety concerns. Combination of ACEI and ARB was associated with increased risk of adverse events among pts with diabetic nephropathy

	Comparator: 152	
	primary endpoints in	
	monotherapy group	

#### Data Supplement 38. Nonrandomized Trials, Observational Studies, and/or Registries of CKD (Section 9.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Upadhyay A, et al., 2011 (179) <u>21403055</u>	<u>Aim:</u> To summarize trials comparing lower vs. higher BP targets in pts with CKD; focus on proteinuria as an effect modifier <u>Study type:</u> Systematic review <u>Size:</u> 2,272	Inclusion criteria: >50 pts/group, 1 y follow-up, outcomes of death, kidney failure, CV events, change in kidney function, number of antihypertensive agents, adverse events. 3 trials (MDRD, AASK, REIN-2; 8 reports)	<b><u>Results:</u></b> Overall trials did not show that BP target of <125/75–130/80 is more beneficial than a target of <140/90. Lower quality evidence suggests a low target may be beneficial in subgroups with proteinuria >300–1,000/d	<u>Limitations</u> : No pts with DM-1 included. Duration (mean follow- up 2–4 y) may be too short to detect differences in clinically important outcomes. Reporting of adverse events not uniform. <u>Summary</u> : Available evidence is inconclusive but does not prove a BP target <130/80 improves clinical outcomes more than a target of <140/90 in adults with CKD.
Lv, et al., 2013 (127) <u>23798459</u>	Aim: To assess the renal and CV effects of intensive BP lowering in people with CKD Study type: Systematic review Size: 9,287 pts with CKD and 1,264 kidney failure events	<ul> <li>Inclusion criteria:</li> <li>Randomized trials of pts with CKD assigned to different target BP that reported kidney failure and CV events.</li> <li>11 trials on 9,287 pts with CKD and 1,264 kidney failure events (doubling of serum creatinine, 50% decline in GFR or ESKD)</li> <li>Included AASK, REIN-2, MDRD, Wuhl (children), Toto, Schrier plus 5 trials with CKD subgroups, also included the late nonrandomized follow-up studies for AASK and MDRD</li> <li>BP targets varied substantially between trials. 2 trials targeted mean BP &lt;92 mm Hg for the intensive treatment arm, and 107 mm Hg in the standard treatment arm. 1 trial aimed for BP&lt;130/80 mm Hg vs. a DBP of 90 mm Hg, 1 study targeted &lt;120/80 mm Hg vs.</li> </ul>	<b><u>Results:</u></b> Compared with standard regimens, more intensive BP lowering reduced risk of composite endpoint HR: 0.82; 95% CI: 0.68–0.98, and ESKD HR: 0.79; 95% CI: 0.67–0.93. Effect was modified by proteinuria (p=0.006) and markers of trial quality. Intensive BP lowering reduced the risk of kidney failure HR: 0.73; 95% CI: 0.62–0.86 but not in pts without proteinuria at baseline HR: 1.12; 95% CI: 0.67–1.87. No clear effect on CV events or death.	<ul> <li>Limitations: All trials used open label, in 2 pts were blinded, substantial variability in design quality. There was substantial variability in BP targets by MAP, systolic and DBP or only DBP. Most trials did not include pts with diabetic kidney disease</li> <li>Summary: <ul> <li>Renal outcomes: 7 trials (N=5,308) recorded a total of 1,264 kidney failure events. A -7.7 mm Hg difference in SBP and a -4.9 mm Hg difference in DBP seen between treatment arms. Overall, a more intensive regimen reduced risk of composite kidney failure events by 17% HR: 0.82; 95% CI: 0.68–0.98, reduced the risk of ESKD alone by 18% (pooled HR for composite outcomes: 0.79; 95% CI: 0.67–0.93).</li> <li>Intensive BP lowering had no effect on kidney failure in pts who did not have proteinuria (3 trials involving 1,218 pts HR: 1.12; 95% CI: 0.67–1.87), but it did reduce the risk of progressive kidney failure by 27% (5 trials involving 1,703 pts HR: 0.73; 95% CI: 0.62–0.86 in people who did have proteinuria at baseline.</li> </ul> </li> </ul>

		135–140/85–90 mm Hg, and 4 studies had DBP<75–80 mm Hg vs. from 80–90 mm Hg. A trial involving pediatric pts targeted a 24-h mean BP <the 50th<br="">percentile, compared with the 50th to 95th percentiles in the control group. 2 trials had more liberal targets for intensive treatment (&lt;140–150 mm Hg systolic, 85 mm Hg diastolic)</the>		<ul> <li>CV outcomes: major CV events reported in 5 trials (472 CV events in 5,308 pts with CKD). Intensive BP lowering did not reduce risk of CV events in pts with CKD, but the CIs remained wide RR: 1.09; 95% CI: 0.83–1.42. 6 trials reported stroke outcomes (197 events in 5,411 pts), 5 trials reported MI (138 events in 4,317 pts), and 5 trials reported HF (118 events in 5,308 pts). They saw no clear effect of intensive treatment on any of these vascular outcomes.</li> <li>Death: 10 trials involving 6,788 participants reported 846 deaths. There was no clear effect of intensive BP lowering on risk of all-cause death RR: 0.94; 95% CI: 0.84–1.05) or CV death RR: 1.20; 95% CI: 0.82–1.75</li> </ul>
Jafar TH, et al., 2003 (180) <u>12965979</u>	Aim: To determine the levels of BP and urine protein excretion associated with lowest risk for progression of CKD during antihypertensive therapy with and without ACEIs. <u>Study type:</u> 11 RCTs in pts with predominantly nondiabetic kidney disease <u>Size:</u> 1,860 pooled in pt level meta- analysis; mean duration of follow-up 2.2 y	<ul> <li>Inclusion criteria:         <ul> <li>Pt-level meta-analysis using data from the AIPRD Study Group database to assess relationships among pts with nondiabetic kidney disease across a wide range of urine protein excretion values during antihypertensive therapy with and without ACEIs.</li> <li>The AIPRD Study Group database included 1,860 pts with nondiabetic kidney disease enrolled in 11 RCTs of ACEIs to slow the progression of kidney disease. The database contained information on BP, urine protein excretion, serum creatinine, and onset of kidney failure during 22,610 visits.</li> <li>Included only randomized trials (with a minimum 1 y follow-up) that compared the effects of antihypertensive regimens that included ACEIs with the effects of regimens that did not include ACEIs. HTN or decreased kidney function was required for entry into all studies.</li> </ul> </li> <li>Exclusion criteria: Common to all studies: acute kidney failure, treatment with immunosuppressive meds, clinically significant chronic HF, obstructive uropathy, renal artery stenosis, active systemic disease, DM-1, history of transplantation, history of allergy to</li> </ul>	<u>1° endpoint</u> : Progression of CKD defined as doubling of serum creatinine or onset of kidney failure <u>Results</u> : Kidney disease progression documented in 311 pts, 124 (13.2%) in the ACEI group and 187 (20.5%) in the control group (p=0.001). 176 (9.5%) developed kidney failure: 70 (7.4%) in the ACEI group and 106 (11.6%) in the control group (p=0.002). SBP of 110–129 mm Hg and urine protein excretion <2.0 g/d were associated with lowest risk for kidney disease progression. ACEI beneficial after adjustment for BP and urine protein excretion (RR: 0.67; 95% CI: 0.53–0.84). The increased risk for kidney progression at higher SBP levels was greater in pts with urine protein excretion >1.0 g/d (p<0.006).	Limitations: Studies included were not designed to assess the effect of lowering BP and urine protein excretion on kidney disease progression. Conclusions: Although reverse causation cannot be excluded with certainty, SBP goal between 110 and 129 mm Hg may be beneficial in pts with urine protein excretion >1.0 g/d. SBP <110 mm Hg may be associated with higher risk for kidney disease progression.

		ACEIs, and pregnancy.		
Giatras I, et al., 1997 (181) <u>9273824</u>	Aim: To use meta- analysis to assess effects if ACEIs on development of ESRD in nondiabetic pts Study type: Meta- analysis Size: 1,594 pts from 10 studies	Inclusion criteria: All randomized studies comparing ACEIs with other antihypertensive agents, with at least 1 y of follow-up Exclusion criteria: Studies of diabetic renal disease and renal transplants were excluded.	Results:• Among 806 pts receiving ACEIs, 52 (6.4%) developed ESRD and 17 (2.1%) died.• In 788 controls, 72 (9.1%) developed ESRD and 12 (1.5%) died. The pooled RR were 0.70; 95% CI: 0.51–0.97 for ESRD and 1.24; CI: 0.55– 2.83 for death.• The decreases in weighted mean systolic and DBPs during follow-up were 4.9 and 1.2 mm Hg greater, received ACEIs	Limitations: Included studies through 5/1996, published (7) and nonpublished (3) study results. Did not require that pts have HTN or renal insufficiency at baseline. Did not report results by severity of proteinuria related to the diseases included many of which are not characterized by proteinuria. Summary: ACEIs are more effective than other antihypertensive agents in reducing the development of end-stage nondiabetic renal disease, and they do not increase mortality. It could not be determined whether this beneficial effect is due to the greater decline in BP or to other effects of ACE inhibition.
ONTARGET Investigators, et al., 2008 (126) <u>18378520</u>	Aim: Evaluate whether use of an ARB was noninferior to ACEI, and whether the combination was superior to ACE alone in the prevention of vascular events in pts with CVD or DM but not HF. Study type: Multi- center, double-blind, RCT Size: 25,620 pts	Inclusion criteria:         ≥55 y         • Coronary, peripheral, or cerebrovascular disease or DM with endorgan damage         Exclusion criteria:         • Inability to discontinue ACEI or ARB         • Known hypersensitivity or intolerance to ACEI or ARB         • Selected CVDs (congestive HF, hemodynamically significant valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes of unknown etiology <3 mo, planned cardiac surgery or PTCA <3 mo, uncontrolled HTN on treatment [e.g., BP >160/100 mm Hg], heart transplant recipient, stroke due to subarachnoid hemorrhage)         • Other conditions (significant renal artery disease, hepatic dysfunction, uncorrected volume or sodium depletion,	Intervention: Ramipril 10 mg daily (n=8,576) Comparator: • Telmisartan 80 mg daily (n=8,542) • Combination of telmisartan and ramipril (n=8,502)	<ul> <li><u>1° endpoint</u>: After a median follow-up of 56 mo, there was no difference between ramipril vs. telmisartan or combination therapy vs. ramipril in the 1° composite outcome of death from CV causes, MI, stroke, or hospitalization for HF RR: 1.01; 95% CI: 0.94–1.09 and RR: 0.99; 95% CI: 0.92–1.07, respectively</li> <li><u>Safety endpoint</u>:         <ul> <li>Combination therapy was associated with greater risk of hyperkalemia than ramipril monotherapy (480 pts vs. 283 pts; p&lt;0.001)</li> <li>Hypotensive symptoms were cited as reason for permanent discontinuing more in telmisartan vs. ramipril RR: 1.54; p&lt;0.001 and combination therapy vs. ramipril monotherapy RR: 2.75; p&lt;0.001</li> <li>Renal impairment was more common in combination therapy vs. ramipril monotherapy RR: 1.33; 95% CI: 1.22–1.44).</li> </ul> </li> </ul>

		1° hyperaldosteronism, hereditary fructose intolerance, other major noncardiac illness or expected to reduce life expectancy or significant disability interfere with study participation, simultaneously taking another experimental drug, unable to provide written informed consent).		
VALIANT White HD, et al., 2005 (182) <u>16301343</u>	Aim: Evaluate whether use of an ARB or the combination of an ACEI and an ARB was superior to a proven effective dose of an ACEI after AMI in pts with HF and/or LVEF <40%. Study type: Multi- center, double-blind, RCT Size: 14,703 pts	Inclusion criteria: • ≥18 y • Between 12 h and 10 d after AMI • Clinical or radiological signs of HF and/or evidence of depressed LV systolic function with EF<40% or reduced echo wall motion index Exclusion criteria: • Cardiogenic shock • Serum creatinine >2.5 mg/dL • Known hypersensitivity or intolerance to ACEI or ARB • SBP<100 mm Hg • Known or suspected bilateral renal artery stenosis • Stroke or TIA within previous 3 mo • Refractory ventricular arrhythmia • Refractory angina • Right ventricular MI • Mitral stenosis, aortic regurgitation, aortic stenosis, aortic regurgitation of hemodynamic significance • Obstructive cardiomyopathy • Previous major organ transplant • Conditions likely to lead to poor adherence	Intervention: Valsartan 160 mg bid Comparator: • Captopril 50 mg tid • Combination of captopril 50 mg tid and valsartan 160 mg bid • Analyzed by prespecified age groups of <65 y (n=6988) 65–74 y (n=4555) 75–84 y (n=2777) ≥85 y (n=383)	<ul> <li><u>1° endpoint</u>: All-cause mortality</li> <li><u>2º endpoint</u>: <ul> <li>Composite of CV mortality or emergency treatment or hospitalization for new or worsening HF, reinfarction, stroke, and resuscitated cardiac arrest</li> <li>On 3-y multivariable analysis, each 10-y age increase was associated with HR: 1.49; 95% CI: 1.43–1.56); p&lt;0.0001 for mortality and an OR: 1.38; 95% CI: 1.31–1.46; p&lt;0.0001 for readmission with HF.</li> <li>Similar but slightly smaller trend for composite endpoint, higher mainly in the oldest group.</li> </ul> </li> <li>Valsartan was at least as effective as captopril in reducing mortality and other adverse outcomes in all age groups and combination therapy with both agents added no incremental benefit.</li> <li>Combination therapy increased the incidence of adverse effects leading to discontinuation in all age groups</li> </ul> Safety endpoint: <ul> <li>Adverse events associated with captopril and valsartan were more common in the elderly and in pts receiving combination therapy.</li> <li>Renal dysfunction was more common with older age and combination therapy.</li> </ul>

# Data Supplement 39. RCTs Comparing Hypertension after Renal Transplantation (Section 9.3.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% Cl)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Midtvedt K, et al., 2001 (183) <u>11468543</u>	Aim: To compare the effect of an ACEI (lisinopril) with a CCB (controlled release nifedipine) in the treatment of post- transplant HTN focusing on changes in LVH. Study type: prospective RCT Size:154 pts 123 completed 1 y good quality echo data for 116 at 2 and 12 mo post treatment	Inclusion criteria: All RTx pts with HTN by DBP ≥95 in first 3 wk after transplant Exclusion criteria: Normotensive, isolated systolic HTN, refusal, requirement of ACEI for HF.	Intervention: Renal transplant recipients with HTN (DBP ≥95 mm Hg) in the first 3 wk after Transplant were randomized to double-blind nifedipine CR 30 mg or lisinopril 10 mg daily. <u>Comparator</u> : 2 treatment arms	<u>1° endpoint</u> : BP controlled in both groups (mean 140 $\pm$ 16/87 $\pm$ 8 with nifedipine, 136 $\pm$ 17/85 $\pm$ 8 with lisinopril, NS). LV mass reduced by 15% (p<0.001) in both groups (from 153 $\pm$ 43 to 131 $\pm$ 38 g/m <sup>2</sup> with nifedipine and from 142 $\pm$ 35 to 121 $\pm$ 34 g/m <sup>2</sup> with lisinopril) with no difference between groups at baseline or at follow-up.	Summary: In renal transplant pts with HTN with well-controlled BP, there is regression of LV mass after renal transplantation which is observed to be similar in pts treated with lisinopril or nifedipine.
Midtvedt K, et al., 2001 (184) <u>11740389</u>	Aim: To examine whether graft function as determined by GFR was better maintained with a CCB (controlled release nifedipine) as compared to an ACEI (lisinopril) in hypertensive renal transplant recipients treated with cyclosporine. Study type: Prospective RCT Size:154 pts 123 completed 1 y good quality echo data for 116 at 2 and 12 mo post-Transplant 64 recruited to complete a 2nd y	Inclusion criteria: All renal transplant pts with HTN by DBP ≥95 in first 3 wk after transplant Exclusion criteria: Normotensive, isolated systolic HTN, refusal, requirement of ACEI for HF.	Intervention: Renal transplant pts with HTN (DBP ≥95 mm Hg) in the first 3 wk after transplant were randomized to double-blind nifedipine CR 30 mg or lisinopril 10 mg daily. <u>Comparator</u> : 2 treatment arms	<ul> <li><u>1° endpoint</u>:</li> <li>GFR baseline at 3–5 wk after entry, and at 1 and 2 y</li> <li>Nifedipine: baseline GFR 46 mL/min, at 1 y 56</li> <li>Lisinopril: baseline GFR 43, at 1 y 44</li> <li>delta N vs. L: 9.6 at 1 y (95% CI: 5.5–13.7 mL/min; p=0.0001), 10.3 at 2 y (95% CI: 4.0–16.6 mL/min; p=0.0017)</li> <li>Baseline GFR similar, change in GFR significant after 1 y and remained statistically significant after 2 y</li> </ul>	Summary: Both nifedipine and lisinopril were safe and effective in treatment of HTN in renal transplant pts treated with cyclosporine. Pts receiving nifedipine but not lisinopril had improved renal function over 2 y.

Suwelack B, et al., 2000 (185) <u>11009288</u>	Aim: To compare the structural and functional cardiac changes of quinapril vs. atenolol administered to hypertensive kidney transplant recipients Study type: Prospective RCT Size: 31 cyclosporine treated stable function recipients with HTN 6–12 wk after transplant	Inclusion criteria: Cyclosporine-based immunosuppression, stable graft function with serum creatinine <2.5 mg/dL. Exclusion criteria: Pts with severe aortic or mitral regurgitation or with heart rates >100 beats/min	Intervention: • Cyclosporine treated stable function pts with HTN 6–12 wk after transplant randomized to double-blinded quinapril or atenolol to target DBP<90. • Echo within 24 h of first dose and at 24 mo • Stepwise increase in dose, could then add furosemide 40–80 mg/d, third-line CCB <u>Comparator</u> : 2 treatment arms	<ul> <li><u>1° endpoint</u>:</li> <li>BP was lower in the atenolol group, delta 10.7 ± 3.4 mm Hg vs. 4.5 ± 2.9 mm Hg with quinapril</li> <li>E/A ratio (impaired relaxation) increased (improved) only in quinapril group (+0.11; p&lt;0.05) and decreased by 0.03 (p&gt;0.05 vs. start of treatment) in the atenolol group. Difference in E/A ratio alterations was significant (p&lt;0.05).</li> <li>LV mass index decreased only in quinapril group (p&lt;0.05) from entry to 24 mo.</li> </ul>	<ul> <li>Summary:         <ul> <li>In hypertensive renal allograft recipients, quinapril in contrast to atenolol provided a sufficient reduction in LVH and a concomitant improvement in LV diastolic cardiac relaxation and these effects occurred independently from BP reduction.</li> <li>While the conclusion was that quinapril showed a benefit not seen with atenolol, the actual numbers are very close (14.1 ± 10.1 atenolol, 15.8 ± 7.7 quinapril).</li> <li>BP reduction was twice as great in the atenolol group as in the quinapril group. Arterial BP did not correlate with cardiac mass</li> </ul> </li> </ul>
Paoletti E, et al., 2007 (186) <u>17591533</u>	Aim: To assess the effectiveness of ACEIs in regressing LVH persisting after renal transplantation during an 18-mo observation period. To assess the impact of cyclosporine vs. tacrolimus in affecting LVH outcome. Study type: Prospective RCT Size: 70 renal transplant recipients at 3–6 mo after transplant.	Inclusion criteria: • Renal transplant pts with serum creatinine <2.5 mg/dL, urine protein excretion not exceeding 1 g/d and with persistent LVH at 3–6 mo after transplant. • Previously randomized to either cyclosporine or tacrolimus immunosuppression. • All were pts of deceased donor transplants. Exclusion criteria:	Intervention: • RCT Lisinopril (n=36) vs. placebo (n=34), also used other agents to treat HTN • Endpoint LVMI at 18 mo • Echo at 3–6 mo and at 18 mo <u>Comparator</u> : Treatment vs. placebo	<ul> <li><u>1° endpoint</u>:</li> <li>Change in LV mass index at 18 mo.</li> <li>BP decreased in both groups (p=NS, between group differences SBP -1.7 ± 3.3 mm Hg; 95% Cl: -4.8–8.2; and DBP 0.3 ± 2.2 mm Hg; 95% Cl: -4.8–4.1).</li> <li>LVMI regressed more in ACEI group (-9.1 ± 13.3 g/m 2.7; p&lt;0.001) but only in those on cyclosporine immunosuppression. Interaction of LVMI effect and</li> </ul>	summary: LVMI regressed more in ACEI group but only in those on cyclosporine immunosuppression. Interaction of LVMI effect and cyclosporine in post hoc analysis.

		<ul> <li>No DM, HF, severe valvular disease, previous renal artery stenosis blocking agents, acute rejections in prior 3 mo or significant renal artery stenosis.</li> <li>Pts receiving a preemptive 2nd transplant or a living donor transplant were excluded.</li> </ul>		cyclosporine in post hoc analysis. • 74/104 had LVMI above normal. • Change in LVMI ACEIs vs. controls p<0.001 Number of meds comparable • Number using CCB/BBs/diuretic/others was 17/21/2/9 for ACEI, 24/26/3/15	
VA NEPHRON-D Fried LF, et al., 2010 (124) 20728887	Aim: To test the efficacy of the combination of losartan with lisinopril as compared with standard treatment with losartan alone in slowing the progression of proteinuric diabetic kidney disease Study type: RCT, multi-center, double-blind Size: 1,448 were randomized	Inclusion criteria: Pts without adverse events on full dose losartan DM-2, eGFR 30–89.9 mL/min/1.73 m <sup>2</sup> by 4 variable MDRD formula, urinary albumin/creatinine ratio of ≥300 in a random sample Exclusion criteria: Known nondiabetic kidney disease, serum potassium >5.5 mmol/L, current treatment with sodium polystyrene sulfonate or inability to stop prescribed medications increasing risk of hyperkalemia.	Intervention:         ● Pts with DM-2 already         taking losartan 100 mg/d with         albumin to creatinine ratio of         ≥300 were randomized to         either lisinopril 10–40 mg/d or         placebo.         • 132 1° endpoints in the         combination therapy group         No benefit to mortality or CV         events.         • Combination therapy         increase risk of hyperkalemia         6.3 events/100 person-y vs.         2.6 events/100 person-y         (p<0.001) and acute kidney         injury 12.2 vs. 6.7 events/100         person-y (p<0.001)         Comparator:       152 1°         endpoints in monotherapy         group	controls         1° endpoint: First occurrence         of a change in eGFR (a         decline of ≥30 mL/min/1.73 m²         if initial GFR ≥60 or a decline         of ≥50% if initial eGFR <60,         ESRD or death         2° endpoint: First occurrence         of decline in eGFR or ESRD         Safety endpoint: Mortality,         hyperkalemia, acute kidney         injury	Summary: Study stopped early due to safety concerns. Combination of ACEI and ARB was associated with increased risk of adverse events among pts with diabetic nephropathy

Data Supplement 40. Nonrandomized Trials, Observational Studies, and/or Registries for Hypertension after Renal Transplantation (Section 9.3.1)

Study Acronym;	Study Type/Design;	Patient Population	Primary Endpoint and Results	Summary/Conclusion
Author; Year Published	Study Size (N)		(Include P value; OR or RR; & 95% Cl)	Comment(s)
Cross NB, et al., 2009 (187) <u>19588343</u>	Study type:Comparativeassessment by drugclass using RCTs andquasi-RCTs lasting atleast 2 wk in kidneytransplant ptsSize:• 60 studies, 3,802 pts,most takingcyclosporine basedimmunosuppression• 29 studies (n=2,262)compared CCB toplacebo, 10 (n=445)ACEI to placebo, 7(n=405) CCB to ACEI	Inclusion criteria: 21 studies for HTN, 6 for erythrocytosis, 2 CAN, 2 LVH, 30 not specified Exclusion criteria: N/A	<u>1° endpoint</u> : To assess comparative effects of antihypertensive agents in kidney transplant pts <u>Results:</u> Used random effects meta- analysis, risk ratios for dichotomous outcomes and MD for continuous outcomes, both with 95% Cl. Stratified analyses and meta- regression to investigate heterogeneity.	<ul> <li>CCBs vs. placebo or no treatment had strongest results: improved GFR MD: 4.45 mL min (95% CI: 2.22–6.68), reduced graft loss RR: 0.75, (95% CI: 0.57–0.99).</li> <li>ACEI vs. placebo inconclusive for GFR MD: - 8.07 mL/min (95% CI: -18.57–2.43) and variable for graft loss.</li> <li>Compared to CCB, ACEI decreased GFR MD: -11.48 mL/min; 95% CI: -5.75– -7.21), proteinuria MD: -0.28 g/24 h (95% CI: -0.47– -0.10), also reduced hemoglobin MD: -12.96 g/L (95% CI: -5.72– -10.21) and increased hyperkalemia RR: 3.74 (95% CI: 1.89– 7.43). Graft loss data were inconclusive.</li> <li>CCB may be preferred as first line for HTN after kidney transplant. ACEI may have some detrimental effects. There were not enough studies with other agents.</li> </ul>
Jennings DL, et al., 2008 (188) <u>18094340</u>	Study type: Literature review Size: 5 studies with 3 reporting safety endpoints and 2 reporting clinical efficacy endpoints	Inclusion criteria: Studies using either ACEI or ARB initiated within the first 12 wk after renal transplant	<ul> <li><u>1° endpoint</u>: Safety or efficacy</li> <li><u>Results:</u></li> <li>No significant increase in serum creatinine or potassium after up to 9 mo Rx</li> <li>Early initiation of ACEI may be more effective than BB in reducing LVH and proteinuria after 24 mo treatment</li> </ul>	<u>Conclusion</u> : Reasonable to consider RAAS inhibitors as first-line treatment in pts with HTN and compelling indications i.e., DM, HF in first 12 wk after renal transplant.
Ninomiya T, et al., 2013 (189) <u>24092942</u>	Aim: To define CV effects of lowering BP in pts with CKD Study type:	Inclusion criteria: Had to meet 1 of the following criteria: Pts randomized to a BP-lowering drug/regimen or a control group (placebo or less intensive BP lowering regimen) or pts randomized	<u>Results:</u> Compared with placebo, BP lowering regimens reduced the risk of major CV events by about a sixth per 5 mm Hg reduction in SBP in individuals with (HR: 0.83; 95% CI	Limitations: • Limited numbers with CKD and most were stage 3a: • There were 121,995 pts (80%) with eGFR ≥60 mL/min/1.73 m <sup>2</sup> (mean eGFR 81 (SD 17)

	<ul> <li>Meta-analysis of RCTs</li> <li>Individual pt data available for 23 trials, with summary data from another 3. Meta- analysis was performed according to baseline kidney function.</li> <li><u>Size:</u> 26 trials (152,290 pts), including 30,295 pts with reduced eGFR, defined as eGFR &lt;60 mL/min/1.73 m<sup>2</sup>.</li> </ul>	between regimens based on different classes of drugs to lower BP. Trials required to have at least 1,000 pt-y of planned follow-up in each randomized arm and not to have presented or published their main results before finalization of the overview protocol in July 1995. <u>Exclusion criteria:</u> Trials prior to July 1995.	0.76–0.90) and without reduced eGFR (HR: 0.83; 95% CI: 0.79– 0.88), with no evidence for any difference in effect (p=1.00 for homogeneity). The results were similar irrespective of whether BP was reduced by regimens based on ACEIs, calcium antagonists, or diuretics/BBs. There was no evidence that the effects of different drug classes on major CV events varied between pts with different eGFR (all p>0.60 for homogeneity).	<ul> <li>mL/min/1.73 m<sup>2</sup>) and 30,295 pts (20%) with eGFR</li> <li>&lt;60 mL/min/1.73 m<sup>2</sup> (mean 52 (SD 7) mL/min/1.73 m<sup>2</sup>) at baseline (table 4<sup>1</sup>U). Only 439 pts (0.3%) had eGFR &lt;30 mL/min/1.73 m<sup>2</sup> at baseline.</li> <li>Limited numbers had proteinuria, present in 2,500 (7%) of 37161 pts with data available.</li> <li>Summary: <ul> <li>These analyses provided compelling evidence for the CV benefits of reduction in BP in pts with stage 1–3 CKD. The proportional reductions in risk of major CV events were similar in pts with and without evidence of CKD, however those with CKD stood to gain larger absolute benefits because their baseline risk was much higher.</li> <li>BP-lowering is an effective strategy for preventing CV events among pts with moderately reduced eGFR. There is little evidence from these overviews to support the preferential choice of particular drug classes for the prevention of CV events in CKD.</li> </ul> </li> </ul>
ONTARGET Investigators, et al., 2008 (126) <u>18378520</u>	Aim: Evaluate whether use of an ARB was noninferior to ACEI, and whether the combination was superior to ACE alone in the prevention of vascular events in pts with CVD or DM but not HF. Study type: Multi- center, double-blind, RCT Size: 25,620	Inclusion criteria: • ≥55 y • Coronary, peripheral, or cerebrovascular disease or DM with end-organ damage Exclusion criteria: • Inability to discontinue ACEI or ARB • Known hypersensitivity or intolerance to ACEI or ARB • Selected CVDs (congestive HF, hemodynamically significant valvular or outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, syncopal episodes of unknown etiology <3 mo, planned cardiac surgery or PTCA <3 mo, uncontrolled HTN on treatment [e.g., BP >160/100 mm Hg], heart transplant recipient,	Intervention: Ramipril 10 mg daily (n=8,576) Comparator: • Telmisartan 80 mg daily (n=8,542) • Combination of telmisartan and ramipril (n=8,502)	<ul> <li><u>1° endpoint</u>: After a median follow-up of 56 mo, no difference between ramipril vs. telmisartan or combination therapy vs. ramipril in the 1° composite outcome of death from CV causes, MI, stroke, or hospitalization for HF RR: 1.01 (95% CI: 0.94–1.09) and RR: 0.99 (95% CI: 0.92–1.07), respectively.</li> <li><u>Safety endpoint</u>:</li> <li>Combination therapy was associated with greater risk of hyperkalemia than ramipril monotherapy (480 pts vs. 283 pts; p&lt;0.001)</li> <li>Hypotensive symptoms were cited as reason for permanent discontinuing more in telmisartan vs. ramipril RR: 1.54, p&lt;0.001; and combination therapy RR: 2.75, p&lt;0.001</li> <li>Renal impairment was more common in combination therapy vs. ramipril monotherapy RR: 1.33: 95% CI: 1.22–1.44</li> </ul>

VALIANT	<u>Aim</u> : Evaluate whether	stroke due to subarachnoid hemorrhage) • Other conditions (significant renal artery disease, hepatic dysfunction, uncorrected volume or sodium depletion, 1° hyperaldosteronism, hereditary fructose intolerance, other major noncardiac illness or expected to reduce life expectancy or significant disability interfere with study participation, simultaneously taking another experimental drug, unable to provide written informed consent). Inclusion criteria:	Intervention: Valsartan 160 mg bid	<u>1° endpoint</u> : All-cause mortality
While HD, et al.,	use of an ARB of the	• ≥18 y	Commenter	
2005 (182)	complination of an ACEI	Between 12 h and 10 d after AMI	Captopril 50 mg tid	<u>2º endpoint</u> :
10301343	superior to a proven	Clinical or radiological signs of HF and/or ovidence of depressed LV	Captophi 50 mg tid     Combination of cantonril 50 mg tid	Composite of CV mortality or emergency     treatment or bespitalization for new or worsening
	effective dose of an	systolic function with $EE < 10\%$ or	and valsartan 160 mg bid	HE reinfarction stroke and resuscitated cardiac
	ACEI after AMI in pts	reduced echo wall motion index	Analyzed by prespecified age	arrest
	with HF and/or LVEF		aroups of	• On 3-v multivariable analysis, each 10-v increase
	<40%.	Exclusion criteria:	<65 (n=6,988)	was associated with HR: 1.49 (95% CI: 1.43–1.56),
		Cardiogenic shock	65 to 74 (n=4,555)	p<0.0001 for mortality and OR: 1.38 (95% CI:
	<u>Study type</u> : Multi-	<ul> <li>Serum creatinine &gt;2.5 mg/dL</li> </ul>	75 to 84 (n=2,777)	1.31–1.46; p<0.0001) for readmission with HF.
	center, aouble-blina,	Known hypersensitivity or intolerance	≥85 y (n=383)	<ul> <li>Similar but slightly smaller trend for composite</li> </ul>
	KUI	to ACEI or ARB		endpoint, higher mainly in the oldest group.
	Size: 14,703	• SBP<100 mm Hg		Valsartan was at least as effective as captopril in
	<u>0.20</u> . 1.1,7.00	Known or suspected bilateral renal		all age groups and combination therapy with both
		allery stenosis		agents added no incremental benefit.
		Shoke of TIA within previous 5 mo     Pofractory vontricular arrhythmia		Combination therapy increased the incidence of
		Refractory angina		adverse effects leading to discontinuation in all age
		Right ventricular MI		groups
		Mitral stenosis, mitral regurgitation.		Cafata andraint
		aortic stenosis, aortic regurgitation of		Salety enapoint:
		hemodynamic significance		Auverse events associated with Captophi and     valsartan were more common in the elderly and in
		<ul> <li>Obstructive cardiomyopathy</li> </ul>		pts receiving combination therapy.
		<ul> <li>Previous major organ transplant</li> </ul>		Renal dysfunction was more common with older
				age and combination therapy.

		Conditions likely to I	and to poor		
		- Contaitions likely to I			
		aunerence			
SPRINT Senior	Aim: Intensive SBP	Inclusion criteria:	Intervention:	<u>1° endpoint</u> : Composite CVD	Limitations: Does not apply to nursing home pts or
Williamson JD, et	goal <120 mm Hg) vs.	Men and women	Medications	outcome (AMI, non-MI ACS, Stroke,	those with dementia or advance
al., 2016	standard (SBP goal	age 75+; mean age	and dietary	HF, CVD death.	
(190)	<140)	79.8 y; 38% women;	advice to		<b>Conclusions:</b> Intensive SBP is safe and effective
27195814	,	17% black, 74%	achieve SBP of	Results:	for lowering CVD events and total mortality in
	Study type: RCT	Caucasian	<120 mm Hg	• 102 events in the intensive	adults ≥75 v
			5	treatment group vs 148 events in	,
	Size: 2,636: 30% met	Exclusion criteria:	Comparator:	the standard treatment group: HR:	
	criteria for being	Nursing home	Medications	0.66: 95% CI: 0.51_0.85 and all-	
	classified as	residents: prevalent	and dietary	0.00, 7570 CI: $0.51-0.05$ and all cause mortality (72 deaths vs. 107	
	ambulatory frail	DM stroke Class	advice to	deaths, respectively, LID: 0.47, 0E9/	
	ambulatory frail	III/IV/ UE domontio	achiovo SPD of	Chi 0,40, 0,01, No difference in falle	
	Moon follow up 2.1 v		achieve SDP U	CI: 0.49–0.91. No difference in fails,	
	iviean ronow-up:3.1 y		<140 mm Hg	orthostatic hypotension, or overall	
				SAEs.	
			Achieved SBP:	<ul> <li>NNT for 1° outcome=27 and NNT</li> </ul>	
			Intensive=	for all-cause mortality=41	
			123.4 mm Hg		
			Standard=		
			134.8 mm Hg		

### Data Supplement 41. RCTs Comparing Acute Intracerebral Hemorrhage Outcomes (Section 9.4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
INTERACT2	<u>Aim</u> : To assess	Inclusion	Design: Intensive treatment	1° outcome: Death or major disability	<u>Summary</u> :
Anderson CS, et al.,	whether rapid lowering	<u>criteria</u> :	to lower BP (with a target	(score of 3 to 6 on the modified Rankin	<ul> <li>In pts with ICH, intensive lowering</li> </ul>
2013 (191)	of elevated BP would	Pts with	systolic level of <140 mm	scale) at 90 d.	of BP did not result in a significant
<u>23713578</u>	improve the outcome	spontaneous	Hg within 1 h) vs. guideline-		reduction in the rate of death or
	in pts with ICH.	ICH within the	recommended treatment	Pre-specified 2° outcome: Ordinal	severe disability.
		previous 6 h	(with a target SBP <180 mm	analysis of the modified Rankin score.	<ul> <li>However, there may be improved</li> </ul>
	Study type: Phase III	with elevated	Hg) among pts with SBP		functional outcomes with intensive
	RCT	SBP	between 150 and 220 mm	Key findings:	lowering of BP.
			using agents of the	• Among the 2,794 pts for whom the 1°	<ul> <li>INTERACT-2 is so far the largest</li> </ul>
	Study size: 2,839 pts		physician's choosing.	outcome could be determined, 719 of	(and only phase 3) RCT evaluating
	-			1,382 participants (52.0%) receiving	efficacy of intensive BP lowering.

ATACH-1 2010 (192) 19770736	Aim: To determine the feasibility and acute (i.e., within 72 h) safety of 3 levels of SBP reduction in subjects with supratentorial ICH treated within 6 h after symptom onset. Study type: Phase I, dose- escalation, multicenter prospective study. Study size: 60	Inclusion criteria: Pts with ICH with elevated SBP ≥170 mm Hg who presented to the ED within 6 h of symptom onset.	Design: • IV nicardipine to reduce SBP to a target of: <u>#1</u> : 170–200 mm Hg in the first cohort of pts <u>#2</u> : 140–170 mm Hg in the 2nd cohort <u>#3</u> : 110–140 mm Hg in the third cohort. • Each subject was followed-up for 3 mo to preliminarily assess mortality and the clinical outcomes. A total of 18, 20, and 22 pts were enrolled in the respective 3 tiers of SBP treatment goals.	<ul> <li>intensive treatment, vs. 785 of 1,412</li> <li>(55.6%) receiving guideline-recommended treatment, had a 1° outcome event; intensive treatment OR: 0.87; 95% CI: 0.75–1.01; p=0.06.</li> <li>The ordinal analysis showed significantly lower modified Rankin scores with intensive treatment. OR for greater disability: 0.87; 95% CI: 0.77–1.00; p=0.04.</li> <li>Mortality was 11.9% in the group receiving intensive treatment and 12.0% in the group receiving guideline-recommended treatment.</li> <li>Nonfatal serious adverse events occurred in 23.3% and 23.6% of the pts in the 2 groups, respectively.</li> <li><u>1° outcome</u>: Treatment feasibility (achieving and maintaining the SBP goals for 18–24 h)</li> <li><u>2° outcomes</u>: #1: Neurologic deterioration within 24 h; #2: Serious adverse events within 72 h.</li> <li><u>Key findings</u>:</li> <li>Overall, 9 of 60 pts had treatment failures (all in the last tier). A total of 7 subjects with neurologic deterioration were observed: 1 (6%), 2 (10%), and 4 (18%) in tier 1, 2, and 3, respectively.</li> <li>Serious adverse events were observed in1 subject (5%) in tier 2 and in 3 subjects (14%) in tier 3. However, the safety stopping rule was not activated in any of the tiers.</li> <li>3 (17%), 2 (10%), and 5 (23%) subjects in tiers1, 2, and 3, respectively, died within 3 mo</li> </ul>	<ul> <li>No clear relationship between outcome and time from onset of ICH to commencing treatment and no significant effect of intensive BP-lowering treatment on hematoma growth.</li> <li>Of note, only1 third of pts achieved the target SBP level within 1 h (half achieved the target by 6 h), and most (75%) presented with mild to moderate size (&lt;20 mL) hematomas.</li> </ul> Summary: <ul> <li>Observed proportions of neurologic deterioration and serious adverse events were below the prespecified safety thresholds, and the 3-mo mortality rate was lower than expected in all SBP tiers. Summary: Early intensive BP-</li></ul>
	safety and efficiency of	criteria: Pts with	lowering of BP (target SBP	hematoma volume at 24 h.	lowering treatment is clinically

Anderson CS, et al.,	this treatment, as a	acute	140 mm Hg; n=203) vs.		feasible, well tolerated, and might
2008 (193)	run-in phase to a larger	spontaneous	standard guideline-based	2° outcomes: Measurements of	reduce hematoma growth in ICH.
<u>18396107</u>	trial.	ICH diagnosed	management of BP (target	hematoma volume.	5
		by CT within 6 h	SBP 180 mm Hg; n=201).		
	Study type:	of onset,		Safety and clinical outcomes: Assessed	
	Randomized pilot trial	elevated SBP		for up to 90 d.	
		(150–220 mm			
	<u>Study size</u> : 404	Hg), and no		Key findings:	
		definite		<ul> <li>Mean hematoma volumes were smaller</li> </ul>	
		indication or		in the guideline group (12.7 mL, SD 11.6)	
		contraindication to treatment		than in the intensive group (14.2 mL, SD	
		to treatment		• From randomization to 1 h. mean SBP	
				was 153 mm Hg in the intensive group and	
				167 mm Ha in the auideline group	
				(difference 13.3 mm Hg (95% CI: 8.9–17.6)	
				mm Hg; p<0.0001); from 1 h to 24 h, BP	
				was 146 mm Hg in the intensive group and	
				157 mm Hg in the guideline group (10.8	
				mm Hg; 95% CI: 7.7–13.9 mm Hg;	
				p<0.0001).	
				<ul> <li>Mean proportional hematoma growth</li> </ul>	
				was 36.3% in the guideline group and	
				13.7% in the intensive group (difference	
				22.6%; 95% CI: 0.6%–44.5%; p=0.04) at	
				24 N.	
				• After adjustment for initial nematoma	
				bomatema growth differed between the	
				aroups with $p=0.06$ ; the absolute	
				difference in volume between arouns was	
				1.7  m (95% Cl <sup>·</sup> -0.5–3.9 <sup>·</sup> n=0.13) RR of	
				hematoma growth $\geq$ 33% or $\geq$ 12.5 mL was	
				36% lower (95% CI: 0%–59%; p=0.05) in	
				the intensive group than in the guideline	
				group. Adjusted RR: 8% (95% CI: -1.0%-	
				17%; p=0.05).	
				<ul> <li>Intensive BP-lowering treatment did not</li> </ul>	
				alter the risks of adverse events or 2°	
				clinical outcomes at 90 d.	

Tsivgoulis G, et al., 2014 (194) <u>25239836</u>	Aim: To evaluate the safety and efficacy of intensive BP reduction in pts with acute-onset ICH Systematic review and meta-analysis of RCTs. Study size: 4 eligible studies, including a total of 3,315 pts	Inclusion criteria: Pts with acute ICH randomized to either intensive or guideline BP- reduction protocols.	• Intensive early BP lowering after acute ICH onset compared with guideline-based treatment	<ul> <li>Key findings:</li> <li>Death rates similar between pts randomized to intensive BP-lowering treatment and those receiving guideline BP-lowering treatment OR: 1.01; 95% CI: 0.83–1.23; p=0.914</li> <li>Intensive BP-lowering treatment associated with strong trend towards lower 3-mo death or dependency vs. guideline treatment OR: 0.87; 95% CI: 0.76–1.01; p=0.062.</li> <li>Intensive BP reduction was also associated with a greater attenuation of absolute hematoma growth at 24 h (standardized MD± standard error: -0.110 ± 0.053; p=0.038).</li> </ul>	<ul> <li>Summary:</li> <li>Intensive BP management in pts with acute ICH is safe.</li> <li>Intensively treated ICH pts tended to have more favorable 3-mo functional outcome.</li> <li>Intensive BP reduction associated with a greater attenuation of absolute hematoma growth at 24 h.</li> <li>Starting antihypertensive treatment in the initial 5–10 d after ICH may have a different outcome from that seen after an ischemic stroke because of 2° edema formation and hemodynamic changes</li> </ul>
ATACH2 Qureshi AI, et al., 2016 27276234	Aim: To determine the relative efficacy of intensive vs. standard antihypertensive treatment that was initiated within 4.5 H after symptom onset and continued for the next 24 H in patients with spontaneous supratentorial intracerebral hemorrhage Study type: Phase III RCT Study size: 1,000 pts	Inclusion criteria: Pts with spontaneous ICH (volume, <60 cm3) and a Glasgow Coma Scale (GCS) score of 5 or more	Design: Intravenous nicardipine administered within 4.5 H after symptom onset and continued for the next 24 H to lower BP	<ul> <li><u>1° outcome</u>: Moderately severe or severe disability or who had died (modified Rankin scale score, 4 to 6) at 3 months</li> <li><u>Key findings</u>: <ul> <li>Among 1,000 participants with a mean (±SD) systolic BP of 200.6±27.0 mm Hg at baseline, 500 were assigned to intensive treatment and 500 to standard treatment. Enrollment was stopped because of futility</li> <li>Death or disability occurred in 38.7% of patients in the intensive-treatment group and 37.7% in the standard-treatment group. RR: 1.04; 95%CI: 0.85–1.27.</li> <li>Serious adverse events occurring within 72 H after randomization were reported in 1.6% of the patients in the intensive-treatment group.</li> <li>Renal adverse events within 7 d after randomization were significantly higher in the intensive-treatment group than in the</li> </ul> </li> </ul>	<u>Summary</u> : Treatment of patients with spontaneous ICH to achieve a target systolic BP of 110 to 139 mm Hg did not result in a lower rate of death or disability compared to conventional reduction to a target of 140–179 mm Hg. Furthermore, there was more than twice the frequency of renal adverse events in the more intensively treated arm within a week of treatment initiation.

	standard-treatment group (9.0% vs. 4.0%, p=0.002).
--	--

## Data Supplement 42. RCTs Comparing Acute Ischemic Stroke Outcomes (Section 9.4.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
COSSACS Robinson TG, et al., 2010 20621562	Aim: Assess the efficacy and safety of continuing or stopping pre- existing antihypertensive drugs in patients with acute stroke Study type: RCT Size: 763	Inclusion criteria: Acute ischemic stroke (or ICH) within previous 48 h Exclusion criteria: • Impaired level of consciousness • Unable to swallow • Hypertensive emergency • BP >200/120 mm Hg • Premorbid disability • Intravenous alteplase	Intervention: Continue previous antihypertensive medication/s (n=379) <u>Comparator</u> : Stop previous antihypertensive medication/s (n=384)	<u>1° endpoint</u> : Death or major disability (mRS 3–6) at 14 d: RR: 0.86 (95% CI: 0.65–1.14; p=0.3) <u>Safety endpoint</u> : Adverse events, minor and serious: p>0.05 for all	Relevant 2° endpoint• 2-wk NIHSS: p=0.46 and 2-wkBarthel Index: p=0.30• 2-wk BP: significantly lower in thecontinue arm (mean difference of -13 mm Hg in SBP and -8 mm Hg inDBP) p<0.0001

CATIS He J, et al., 2014 24240777	Aim: Evaluate whether immediate blood pressure reduction in patients with acute ischemic stroke would reduce death and major disability at 14 d or hospital discharge Study type: RCT Size: 4071	Inclusion criteria: • Age >22 y • Acute ischemic stroke within previous 24 h Exclusion criteria: • Impaired level of consciousness • Hypertensive emergency • BP >220/120 • Atrial fibrillation • Intravenous alteplase	Intervention: Antihypertensive medication to maintain BP <140/90 for the first wk (n=2038) <u>Comparator</u> : No antihypertensive medication for the first wk (n=2033)	<ul> <li><u>1° endpoint</u>: Death or major disability (mRS 3–6) at 14 d: OR: 1.0 (95% CI: 0.88–1.14; p=0.98)</li> <li><u>Safety endpoint</u>:</li> <li>Vascular disease events p=0.28</li> <li>Recurrent stroke p=0.07</li> </ul>	Relevant 2° endpoint• Death or major disability (mRS 3- 5) at 90 d: OR: 0.99 (95% CI: 0.86- 1.15; p=0.93)• Lower blood pressure at 14 d (mean difference of -8.6 mm Hg in SBP and -3.9 mm Hg in DBP; p<0.001) and at 90 d (mean difference of -2.9 mm Hg in SBP and -1.4 mm Hg in DBP; p<0.001) in the active armStudy limitations Antihypertensive regimen was not standardized
					Summary/conclusions • Early treatment of hypertension was safe but ineffective to prevent death or dependency • Early initiation of anti- hypertensives was associated with better BP control at 2 wk
Wang H, et al., 2014 (195) <u>24853087</u>	Aim: To assess the effects of early BP lowering on early and long-term outcomes after acute stroke. Systematic review and meta-analysis of RCTs. Study size: 17 trials (n=13,236 pts)	Inclusion criteria: Prospective RCTs of pts ≥18 y with acute ischemic or hemorrhagic stroke; intervention compared with placebo was initiated within 7 d of stroke onset; intervention aimed to lower BP or intervention achieved BP reduction;1 or more functional outcomes reported, such as death or dependency.	• Early BP lowering after acute stroke onset compared with placebo	<ul> <li><u>1° outcomes</u>: Early (within 30 d) and long-term (from 3–12 mo).</li> <li><u>Key findings</u>: <ul> <li>Early BP lowering after acute stroke onset associated with more death within 30 d compared with placebo RR: 1.34; 95% CI: 1.02–1.74; p=0.03.</li> <li>Early BP lowering after acute stroke onset not associated with early neurological deterioration, early death within 7 d, long-term death, early and long-term dependency, early and long-term stroke recurrence, long-term MI and long-term CVE.</li> </ul> </li> </ul>	Summary: Results do not support early BP lowering after acute stroke. Early BP lowering may be associated with greater risk of death within 30 d after acute stroke.

		Exclusion criteria: Studies with the pts of subarachnoid hemorrhage, studies without available full- text or relevant data, studies about ongoing trials and those written in languages other than English.			
Znao R, et al.,	AIM: 10 determine	inclusion criteria: Pts	Early BP lowering	<u>1° outcomes</u> : Change in SBP and DBP	<u>Summary</u> : Antinypertensive agents
26061309	BP during the	(ischemic or	compared with placebo	dependency and mortality rates	acute phase of an ischemic stroke.
	acute phase of an	hemorrhagic) treated		aspendency and mortality rates.	but seem to confer no benefit with
	ischemic stroke	with an		Key findings:	regard to short- and long-term
	improves short-	antihypertensive agent		• Treatment groups had a greater decrease	dependency and mortality.
		or placebo.		In BP than control groups, and this effect	
	outcomes.	Groups: Treatment		antihypertensive drugs	
	Study type:	groups were n=5,672		<ul> <li>Short-term and long-term dependency</li> </ul>	
	Systematic review	(range, 6–2,308), and		rates were similar between treatment and	
	and meta-analysis	in the control groups		control groups (short-term dependency:	
	OFRETS.	was 5,416 (range, 6– 2033)		pooled UR: 1.041; 95% CI: 0.936–1.159; n=0.457; long-term dependency; pooled	
	Study size: 22	2000).		OR:1.013; 95% CI: 0.915–1.120; p=0.806).	
	RCTs	Follow-up: Ranged		<ul> <li>Short-term or long-term mortality was</li> </ul>	
		from 5 d–12 mo		similar between the treatment and control	
				groups (short-term mortality: pooled OR: 1 020 (05% CI: 0 740, 1 289; $p=0.002$ );	
				1.020 (95% Cl. 0.749 - 1.366, p=0.902),	
				Cl: 0.883–1.222; p=0.644).	
Ahmed N, et al.,	Aim: To	Inclusion criteria: Pts	Interventions:	<u>1° outcomes</u> : Neurological outcome per the	Summary:
2000 (197)	investigate	with a diagnosis of	Nimodipine as IV     Infusion of 1 mg/h for 5	Orgogozo scale and functional outcome per	<ul> <li>DBP, but not SBP, reduction was associated with pourological</li> </ul>
10030440	INWEST	carotid artery territory	d followed by oral dose	The Barthel Scale at 0.21	worsening after the IV high-dose
	subgroups with	within 24 h.	of 120 mg daily for a	Key findings:	nimodipine after acute stroke.
	increasing levels of		total treatment period of	Nimodipine treatment resulted in a	• For low-dose nimodipine, the
	BP reduction.		21 d (n=101)	significant reduction in BP from baseline vs.	results were inconclusive.
				placebo during the first few d.	

	Study type: Post- hoc analysis of RCT Size: 265		<ul> <li>Nimodipine as IV infusion of 2 mg/h for 5 d followed by oral dose of 120 mg daily for a total treatment period of 21 d (n=94)</li> <li><u>Comparator</u>: Placebo (n=100)</li> </ul>	<ul> <li>A significant correlation between DBP reduction and worsening of the neurological score was found for the high-dose group (beta=0.49; p=0.048).</li> <li>Pts with a DBP reduction of ≥20% in the high-dose group had a significantly increased adjusted OR for death or dependency (n/N=25/26, OR: 10.16; 95% CI: 1.02–101.74) and death alone (n/N=9/26, OR: 4.336; 95% CI: 1.131–16.619) vs. all placebo pts (n/N=62/92 and 14/92, respectively). No correlation between SBP change and outcome.</li> </ul>	
Bath PM, et al., 2014 (198) <u>25353321</u>	Aim: To assess the clinical effectiveness of altering BP in pts with acute stroke, and the effect of different vasoactive drugs on BP in acute stroke. Update of previously published Cochrane reviews (1997, 2001, and 2008). Study type: Meta- analysis of RCTs of interventions that aimed to alter BP vs. control in pts within 1 wk of acute ischemic or hemorrhagic stroke.	Inclusion criteria: RCTs of interventions that aimed to alter BP compared with control in pts with 1 wk of acute ischemic or hemorrhagic stroke	BP lowering after acute stroke onset compared with placebo	<ul> <li><u>1° outcome</u>: Functional outcome</li> <li><u>Key findings</u>: <ul> <li>At 24 h after randomization #1: Oral</li> <li>ACEIs reduced SBP MD: -8 mm Hg (95% CI: -17-1) and DBP MD: -3 mm Hg (95% CI: -9-2), sublingual ACEIs reduced SBP MD: -</li> <li>12.00 mm Hg (95% CI: -26-2) and DBP MD: -</li> <li>2 (95% CI: -10-6).</li> <li>Oral angiotensin receptor antagonists reduced SBP MD: -1 mm Hg (95% CI: -3-2) and DBP MD: -1 mm Hg (95% CI: -3-2) and DBP MD: -1 mm Hg (95% CI: -3-1).</li> <li>Oral BBs reduced SBP MD: -14 mm Hg (95% CI: -271) and DBP MD: -1 mm Hg (95% CI: -9-7), IV BBs reduced SBP MD: -5 mm Hg (95% CI: -18-8) and DBP MD: -5 mm Hg (95% CI: -13-3).</li> <li>Oral CCBs reduced SBP MD: -13 mm Hg (95% CI: -14-2), IV CCBs reduced SBP MD: -13 (95% CI: -31-6).</li> <li>Nitric oxide donors reduced SBP MD: -12 mm Hg (95% CI: -195) and DBP MD: -3 (95% CI: -42).</li> </ul> </li> </ul>	<ul> <li>Summary:</li> <li>No current evidence showing that lowering BP during the acute phase of stroke improves functional outcome.</li> <li>It seems reasonable to withhold BP-lowering drugs until pts are medically and neurologically stable, after which drugs can then be reintroduced.</li> <li>CCBs, ACEI, angiotensin receptor antagonists, BBs and nitric oxide donors each lower BP in acute stroke while phenylephrine appears to increase BP.</li> </ul>

	Size: 26 trials			<ul> <li>Phenylephrine, nonsignificantly increased</li> </ul>	
	involving 17,011			SBP MD: 21 mm Hg (95% CI: -13–55) and	
	pts (8,497 pts were			DBP MD: 1 mm Hg (95% CI: -15–16).	
	assigned active			<ul> <li>BP lowering did not reduce death or</li> </ul>	
	therapy and 8,514			dependency either by drug class OR: 0.98	
	pts received			(95% CI: 0.92–1.05), stroke type OR: 0.98	
	placebo/control)			$(95\% \text{ Cl} \cdot 0.92-1.05)$ or time to treatment OR	
	Not all trials			$0.98 (95\% \text{ C}) \cdot 0.92 - 1.05)$	
	contributed to each			Troatmont within 6 h of stroke appeared	
				• frequinent within of of stoke appeared	
	oucome.			OD: 0.96 (05% CI: 0.76, 0.00) but not death	
				OR: 0.80 (95% CI: 0.70–0.99) but hot death	
				OR: 0.70 (95% CI: 0.38–1.26) by trial end.	
				• while death or dependency did not diller	
				between pts who continued pre-stroke	
				antihypertensive treatment vs. those who	
				stopped it temporarily (worse outcome with	
				continuing treatment OR: 1.06; 95% CI:	
				0.91–1.24), disability scores at the end of the	
				trial were worse in pts randomized to	
				continue treatment (Barthel Index MD: -3.2	
				(95% CI: -5.8– -0.6).	
SITS-ISTR	Aim: To determine	Inclusion criteria:	<ul> <li>Various categories of</li> </ul>	1° outcomes: Symptomatic (National	Summary:
Ahmed N. et al.	the association of	Pts with acute	HTN treatments	Institutes of Health Stroke Scale score	Strong association of high SBP
2009 (199)	BP and	ischemic stroke		deterioration $\geq 4$ ) ICH Type 2 mortality and	after thrombolysis with poor
19461022	antihypertensive	treated with IV rtPA		independence at (modified Rankin Score 0	outcome
	therapy with	<ul> <li>BP values were</li> </ul>		to 2) 3 mo	Higher BPs during the initial 24 h
	clinical outcomes	recorded at baseline 2			were associated with greater risk of
	after thrombolysis	h and 24 h after		Key findings:	ICH in a linear fashion
	for acute ischemic	thrombolysis		• High SBP 2_24 h after thromholysis as a	U-shaped relation found between
	stroke	an ornoorysis.		continuous variable was associated with	BP during initial 24 h and death or
	50 010	Categories		worse outcome ( $p < 0.001$ ) and as a	dependency at 3 mo with best
	Study type:	By history of HTN and		catogorical variable had a linear accordation	outcomes associated with SRD of
	Dotrospoctivo	antibuportonsivo		with symptomatic homorrhage and a U	1/1 150 mm Hg
	analysis of	thorapy within 7 d after		with symptomatic nemonage and a U-	141–150 mini rig.
	analysis Ul	thrombolycic		shaped association with SDD 141, 150 mm Ltr	
	prospectivery			independence with <u>SBP 141-150 mm Hg</u>	
	thrombolysis	• Gloup I, HIN		associated with most ravorable outcomes.	
				• INO difference in symptomatic nemorrhage	
	registry.			UR: 1.09 (95% CI: 0.83–1.51; p=0.58) and	
		(N=5,612)		independence OR: 1.03 (95% CI: 0.93–1.10;	
				p=0.80 but lower mortality OR: 0.82 (95%)	

 $^{\odot}$  2017 American College of Cardiology Foundation and American Heart Association, Inc.

	Study size:	<ul> <li>Group 2, HTN</li> </ul>		CI: 0.73–0.92; p=0.0007) for Group 1 vs.	
	11.080 pts from	withholding		Group 4.	
	2002-2006.	antihypertensives		<ul> <li>Group 2 had a higher symptomatic</li> </ul>	
		(n=1.573)		hemorrhage (OR: 1.86; 95% CI: 1.34–2.68;	
		Group 3. without		p=0.0004) and mortality (OR: 1.62: 95% CI:	
		history of HTN treated		1.41–1.85; p<0.0001) and lower	
		with antihypertensives		independence (OR: 0.89: 95% CI: 0.80–	
		(n=995)		0.99; p=0.04) vs. with Group 4. Group 3 had	
		Group 4. without		similar results as Group 1.	
		history of HTN not			
		treated with			
		antihypertensives			
		(n=2,632).			
ACCESS	Aim: To assess	Inclusion criteria:	Design: 4 mg	1° outcome: Trial was stopped prematurely	Summary: Early antihypertensive
Schrader J, et al.,	safety of modest	Motor deficit, a	candesartan daily or	when 342 pts (339 valid) had been	therapy with candesartan might be a
2003 (200)	BP reduction by	cerebral CT scan	placebo on d 1. On d 2,	randomized because of an imbalance in	safe therapeutic option in acute
<u>12817109</u>	candesartan in	excluding ICH, and	dosage was increased	endpoints.	stroke, but study sample size very
	early treatment of	necessity to treat HTN	to 8 or 16 mg		small.
	stroke; and provide	per prevailing	candesartan or placebo	Key findings: Cumulative 12 mo mortality	
	an estimate of the	recommendation	if BP >60 mm Hg SPB	and the number of vascular events differed	
	number of cases		or 100 mm Hg DBP.	significantly in favor of the candesartan	
	required to perform	Exclusion criteria:	Treatment was targeted	cilexetil group (OR: 0.475; 95% CI: 0.252–	
	a larger phase III	>85 y, disorders in	to a 10%–15% BP	0.895).	
	efficacy study.	consciousness	reduction within 24 h.		
		preventing acquisition			
	Study type:	of consent, occlusion			
	Prospective,	or >70% stenosis of			
	double-blind, RCT;	the internal carotid			
	multicenter phase	artery, malignant HTN,			
	II study.	manifest cardiac			
		failure, high-grade			
	<u>Size</u> : 342 pts	aortic or mitral			
		stenosis, UA pectoris,			
		or contraindications			
		against candesartan.			
SCAST	Aim: To examine	Inclusion criteria: Pts	Design: Pts	<u>1° effect variables</u> : Composite of vascular	Relevant 2° endpoint:
Sandset EC, et al.,	whether careful	>18 y with acute	randomized to	death, MI, or stroke during the first 6 mo; and	• Similar effects for all prespecified
2011 (201)	BP-lowering	stroke (ischemic or	candesartan (n=1,017)	tunctional outcome at 6 mo, as measured by	2º endpoints.
21316/52	treatment with the	hemorrhagic) and SBP	or placebo (1,012) (1:1)	the modified Rankin Scale.	• During follow-up, 9 (1%) pts on
	candesartan is	ot $\geq$ 140 mm Hg were	for / d, with doses		candesartan and 5 (<1%) on

	beneficial in pts with acute stroke and raised BP. <u>Study type</u> : Double-blind RCT <u>Study size</u> : 2,029 pts	included within 30 h of symptom onset.	increasing from 4 mg on d 1–16 mg on d 3–7.	<ul> <li>Data for status at 6 mo were available for 2,004 pts (99%; 1,000 candesartan, 1,004 placebo).</li> <li><u>Key findings</u>: <ul> <li>BPs significantly lower in pts allocated candesartan vs. placebo (mean 147/82 mm Hg [SD 23/14] in the candesartan group on d 7 vs. 152/84 mm Hg [22/14] in the placebo group; p&lt;0.0001).</li> <li>Risk of the composite vascular endpoint did not differ between treatment groups (candesartan, 120 events, vs. placebo, 111 events; adjusted HR: 1.09; 95% CI: 0.84–1.41; p=0.52.</li> <li>Analysis of functional outcome suggested a higher risk of poor outcome in the candesartan group (adjusted OR: 1.17; 95% CI: 1.00–1.38; p=0.048.</li> </ul> </li> </ul>	placebo had symptomatic hypotension, and renal failure was reported for 18 (2%) pts taking candesartan and 13 (1%) allocated placebo. <u>Summary</u> : Careful BP-lowering treatment with candesartan was not beneficial in pts with acute stroke and raised BP. Indeed, there was the suggestion of a harmful effect.
CATIS He J, et al., 2014 (202) <u>24240777</u>	Aim: To evaluate whether immediate BP reduction in pts with acute ischemic stroke would reduce death and major disability at 14 d or hospital discharge. Single-blind, blinded end-points RCT. Study size: 4,071 pts	Inclusion criteria: Pts with nonthrombolysed ischemic stroke within 48 h of onset and elevated SBP	Design: Pts (n=2,038) randomized to antihypertensive treatment (aimed at lowering SBP by 10% to 25% within first 24 h, achieving BP <140/90 mm Hg within 7 d, and maintaining this level during hospitalization) vs. to discontinue all antihypertensive medications (control) during hospitalization (n=2,033).	<ul> <li><u>1° outcome</u>: Combination of death and major disability (modified Rankin Scale score ≥3) at 14 d or hospital discharge.</li> <li><u>Key findings</u>:</li> <li>Mean SBP was reduced from 166.7 mm Hg to 144.7 mm Hg (-12.7%) within 24 h in the antihypertensive treatment group and from 165.6 mm Hg to 152.9 mm Hg (-7.2%) in the control group within 24 h after randomization (difference, -5.5% (95% CI: -4.96.1%); absolute difference, -9.1 mm Hg (95% CI: -10.28.1), p&lt;0.001).</li> <li>1° outcome did not differ between treatment groups (OR: 1.00; 95% CI: 0.88-1.14; p=0.98) at 14 d or hospital discharge.</li> <li>BP at 14 d and 90 d: significantly lower in the active arm (mean difference of -2.9 mm Hg in systolic BP and -1.4 mm Hg in diastolic BP)</li> </ul>	<ul> <li><u>Relevant 2° endpoint:</u> Death and major disability at 3-mo posttreatment follow-up did not differ between treatment groups (500 events [antihypertensive treatment] vs. 502 events [control]; OR: 0.99; 95% CI: 0.86–1.15; p=0.93).</li> <li><u>Summary</u>: Among pts with acute ischemic stroke, BP reduction with antihypertensive medications, vs. absence of hypertensive medication, did not reduce the likelihood of death and major disability at 14 d or hospital discharge.</li> <li>Early initiation of antihypertensives was associated with better BP control at 2 wk</li> </ul>

COSSACS Robinson TG, et al., 2010 (203) 20621562	Aim: To assess the efficacy and safety of continuing or stopping pre- existing antihypertensive drugs in pts who recently had a stroke. Study type: Multicenter, prospective, randomized, open, blinded-endpoint trial. Study size: 763 pts	Inclusion criteria: Pts >18 y taking antihypertensive drugs enrolled within 48 h of stroke and last dose of antihypertensive drug.	Design: Continue (n=379) or stop (n=384) pre-existing antihypertensive drugs for 2 wk.	<ul> <li><u>1° outcome</u>: Death or dependency at 2 wk.</li> <li><u>Key findings</u>: <ul> <li>72 of 379 pts in the continue group and 82 of 384 pts in the stop group reached the 1° endpoint RR: 0.86; 95% CI: 0.65–1.14; p=0.3.</li> <li>Difference in SBP at 2 wk between the continue group and the stop group was 13 mm Hg (95% CI: 10–17) and the difference in DBP was 8 mm Hg (6–10; difference between groups; p&lt;0.0001).</li> <li>No substantial differences were observed between groups in rates of serious adverse events, 6-mo mortality, or major CV events.</li> </ul> </li> </ul>	Summary: • Continuation of antihypertensive drugs did not reduce 2-wk death or dependency, CV event rate, or mortality at 6 mo • Early reinitiation of antihypertensives was associated with better BP control at 2 wk • Lower BP levels in those who continued antihypertensive treatment after acute mild stroke were not associated with an increase in adverse events. • Of note, COSSACS was likely underpowered due to early termination of the trial.
CHHIPS Potter JF, et al., 2009 (204)	<u>Aim</u> : To assess feasibility, safety, and effects of 2	Inclusion criteria: Pts with cerebral infarction or cerebral	Design: ● Within 36 h of symptom onset:	<u>1° outcome:</u> Death or dependency at 2 wk. Key findings:	Summary: • Labetalol and lisinopril are effective antihypertensive drugs in
<u>19058760</u>	regimens for lowering BP in pts	hemorrhage who were hypertensive SBP	<u>#1</u> : Oral labetalol, lisinopril vs. placebo if	• 1° outcome occurred in 61% (69) of the active vs. 59% (35) of the placebo group	acute stroke that do not raise risk of serious adverse events.
	who with acute stroke.	>160 mm Hg)	they were nondysphagic;	(RR: 1.03; 95% CI: 0.80–1.33; p=0.82) • No evidence of early neurological	• Early lowering of BP with lisinopril and labetalol after acute stroke may
	Study type:		<u>#2</u> : IV labetalol, sublingual lisinopril, or	deterioration with active treatment (RR: 1.22; 95% CI: 0.33–4.54; p=0.76) despite greater	be a promising approach to lower mortality and disability.
	Double-blind pilot trial.		placebo if they had dysphagia.	drop in SBP within the first 24 h in this group vs. placebo (21 [17–25] mm Hg vs. 11 [5–17]	However, pilot nature and very small sample size limit
	Study size: 179		• Labetaioi ( $n=58$ ), lisinopril ( $n=58$ ), or	<ul> <li>Mm Hg; p=0.004).</li> <li>No rise in serious adverse events with a structure to a first order of the series of the seri</li></ul>	generalizability.
	pis		<ul> <li>Doses were titrated</li> </ul>	1.12; p=0.50) but 3-mo mortality was halved	
			up it target BP was not reached.	(9.7% vs. 20.3%; HR: 0.40; 95% CI: 0.2–1.0; p=0.05).	
Bath PM, et al.,	Aim: To assess	Inclusion criteria: Pts	Design:	<u>1° outcome</u> : Function, assessed with the	Summary:
2015 (205)	outcomes after	aumilieu lo nospital	• / 0 of transdermal	modified Rankin Scale at 90 d	In pis with acute stroke and high     BP transdermal divicervit trinitrate

	drugs to lower their BP. <u>Study type:</u> Multicenter, randomized partial- factorial trial <u>Study size</u> : 4,011 pts	or hemorrhagic stroke and raised SBP (140– 220 mm Hg)	per d), started within 48 h of stroke onset vs. No glyceryl trinitrate (control group). • Pts taking antihypertensive drugs before index stroke randomly assigned to continue vs. stop taking these drugs.	<ul> <li>Key findings:</li> <li>Mean BP was 167 (SD: 19) mm Hg/90</li> <li>(13) mm Hg at baseline (median 26 h (16– 37) after stroke onset), and was significantly reduced on d 1 in 2,000 pts allocated to glyceryl trinitrate vs. 2,011 controls</li> <li>(difference -7.0 (95% CI: -8.5– -5.6) mm Hg/- 3.5 [-4.4– -2.6] mm Hg; both p&lt;0.0001), and on d 7 in 1,053 pts allocated to continue antihypertensive drugs compared with 1,044 pts randomized to stop them (difference: -9.5 (95% CI: -11.8– -7.2) mm Hg/-5.0 [-6.4– -3.7] mm Hg; both p&lt;0.0001).</li> <li>D-90 functional outcome did not differ in either treatment comparison-glyceryl trinitrate vs. no glyceryl trinitrate (OR: 1.01; 95% CI 0.91–1.13; p=0.83), and with continue vs. stop antihypertensive drugs (OR: 1.05; 95% CI: 0.90–1.22; p=0.55).</li> </ul>	<ul> <li>lowered BP with acceptable safety but did not improve functional outcome.</li> <li>Continuing prestroke antihypertensive drugs in acute stroke pts in the first few d did not confer benefit.</li> </ul>
ATACH-1 2010 (192) <u>19770736</u>	Aim: To determine the feasibility and acute (i.e., within 72 h) safety of 3 levels of SBP reduction in subjects with supratentorial ICH treated within 6 h after symptom onset. Study type: Phase I, dose- escalation, multicenter prospective study. Study size: 60	Inclusion criteria: Pts with ICH with elevated SBP ≥170 mm Hg who presented to the ED within 6 h of symptom onset.	<ul> <li>Design:</li> <li>IV nicardipine to reduce SBP to a target of:</li> <li>#1: 170-200 mm Hg in the first cohort of pts</li> <li>#2: 140-170 mm Hg in the 2nd cohort</li> <li>#3: 110-140 mm Hg in the third cohort.</li> <li>Each subject was followed-up for 3 mo to preliminarily assess mortality and the clinical outcomes. A total of 18, 20, and 22 pts were enrolled in the respective 3 tiers of SBP treatment goals.</li> </ul>	<ul> <li><u>1° outcome</u>: Treatment feasibility (achieving and maintaining the SBP goals for 18–24 h)</li> <li><u>2° outcomes</u>: <u>#1</u>: Neurologic deterioration within 24 h; <u>#2</u>: Serious adverse events within 72 h.</li> <li><u>Key findings</u>:</li> <li>Overall, 9 of 60 pts had treatment failures (all in the last tier). A total of 7 subjects with neurologic deterioration were observed: 1 (6%), 2 (10%), and 4 (18%) in tier 1, 2, and 3, respectively.</li> <li>Serious adverse events were observed in1 subject (5%) in tier 2 and in 3 subjects (14%) in tier 3. However, the safety stopping rule was not activated in any of the tiers.</li> <li>3 (17%), 2 (10%), and 5 (23%) subjects in tiers1, 2, and 3, respectively, died within 3 mo</li> </ul>	<ul> <li>Summary:</li> <li>Observed proportions of neurologic deterioration and serious adverse events were below the prespecified safety thresholds, and the 3-mo mortality rate was lower than expected in all SBP tiers.</li> <li>Results formed the basis of an ongoing larger randomized trial (ATACH-2) addressing the efficacy of SBP reduction in pts with ICH.</li> </ul>

INTERACT-1 Anderson CS, et al., 2008 (193) <u>18396107</u>	Aim: To assess the safety and efficiency of this treatment, as a run-in phase to a larger trial. Study type: Randomized pilot trial Study size: 404	Inclusion criteria: Pts with acute spontaneous ICH diagnosed by CT within 6 h of onset, elevated SBP (150– 220 mm Hg), and no definite indication or contraindication to treatment	Design: Early intensive lowering of BP (target SBP 140 mm Hg; n=203) vs. standard guideline-based management of BP (target SBP 180 mm Hg; n=201).	<ul> <li><u>1° outcome</u>: Proportional change in hematoma volume at 24 h.</li> <li><u>2° outcomes</u>: Measurements of hematoma volume.</li> <li><u>Safety and clinical outcomes</u>: Assessed for up to 90 d.</li> <li><u>Key findings</u>: <ul> <li>Mean hematoma volumes were smaller in the guideline group (12.7 mL, SD 11.6) than in the intensive group (14.2 mL, SD 14.5).</li> <li>From randomization to 1 h, mean SBP was 153 mm Hg in the intensive group and 167 mm Hg in the guideline group (difference 13.3 mm Hg (95% Cl: 8.9–17.6) mm Hg; p&lt;0.0001); from 1 h to 24 h, BP was 146 mm Hg in the intensive group and 157 mm Hg in the guideline group (10.8 mm Hg; 95% Cl: 7.7–13.9 mm Hg; p&lt;0.0001).</li> <li>Mean proportional hematoma growth was 36.3% in the guideline group and 13.7% in the intensive group (difference 22.6%; 95% Cl: 0.6%–44.5%; p=0.04) at 24 h.</li> <li>After adjustment for initial hematoma volume and time from onset to CT, median</li> </ul> </li> </ul>	Summary: Early intensive BP- lowering treatment is clinically feasible, well tolerated, and appears to reduce hematoma growth in ICH.
				<ul> <li>36.3% in the guideline group and 13.7% in the intensive group (difference 22.6%; 95% CI: 0.6%–44.5%; p=0.04) at 24 h.</li> <li>After adjustment for initial hematoma volume and time from onset to CT, median hematoma growth differed between the groups with p=0.06; the absolute difference</li> </ul>	
				in volume between groups was 1.7 mL (95% CI: -0.5–3.9; p=0.13). RR of hematoma growth $\geq$ 33% or $\geq$ 12.5 mL was 36% lower (95% CI: 0%–59%; p=0.05) in the intensive group than in the guideline group. Adjusted RR: 8% (95% CI: -1.0%–17%; p=0.05). • Intensive BP-lowering treatment did not alter the risks of adverse events or 2° clinical	
Hack W, et al., 2008 (206)	Aim: To assess the efficacy and	Inclusion criteria: Pts 18–80 y, who had	Design:	outcomes at 90 d. <u>1° outcome</u> : Disability at 90 d, dichotomized as a favorable outcome (a score of 0 or 1 on	Summary: Compared with placebo, IV alteplase administered between 3

<u>18815396</u>	safety of alteplase administered between 3 and 4.5 h after the onset of a stroke. <u>Study type</u> : RCT <u>Study size</u> : 821 pts	received a clinical diagnosis of acute ischemic stroke, and were able to receive the study drug within 3–4 h after the onset of symptoms. Exclusion criteria: SBP >185 mm Hg or DBP >110 mm Hg or aggressive treatment (IV medication) necessary to reduce BP to these limits	<ul> <li>Eligible pts were randomly assigned 1:1 to receive 0.9 mg of alteplase per kg, administered IV (with an upper limit of 90 mg), or placebo.</li> <li>418 pts were assigned to receive alteplase and 403 pts were assigned to receive placebo</li> </ul>	<ul> <li>the modified Rankin scale, which has a range of 0–6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2–6 on the modified Rankin scale).</li> <li><u>2° outcome:</u> global outcome analysis of 4 neurologic and disability scores combined.</li> <li><u>Safety outcomes:</u> death, symptomatic intracranial hemorrhage, and other serious adverse events.</li> <li><u>Key findings:</u> <ul> <li>More pts had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; OR: 1.34; 95% CI: 1.02–1.76; p=0.04.</li> <li>Incidence of ICH was higher with alteplase than with placebo (for any ICH, 27.0% vs. 17.6%; p=0.001; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; p=0.008).</li> <li>Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; p=0.68).</li> </ul> </li> </ul>	and 4.5 h after the onset of symptoms significantly improved clinical outcomes in pts with acute ischemic stroke; alteplase was more frequently associated with symptomatic ICH.
				<ul> <li>No significant difference in the rate of other serious adverse events</li> </ul>	
NINDS rt-PA Stroke Study Group, 1995 (207) <u>7477192</u>	Aim: To assess the difference in clinical efficacy between IV t-PA and placebo among pts with an acute ischemic stroke Study type: Double-blind RCT	Inclusion criteria: Pts with an ischemic stroke with a clearly defined time of onset (<3 h), a deficit measurable on the NIH stroke scale, and a base-line CT scan of the brain that showed no evidence of ICH. Exclusion criteria:	Design: RCT with acute ischemic stroke pts randomized to t-PA vs. placebo	<ul> <li><u>1° outcome</u>: Clinical outcome at 3 mo, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIH stroke scale:</li> <li><u>Key findings</u>:         <ul> <li>As compared with pts given placebo, pts treated with t-PA were at least 30% more likely to have minimal or no disability at 3 mo on the assessment scales.</li> <li>Symptomatic ICH within 36 h after the onset of stroke occurred in 6.4% of pts given</li> </ul> </li> </ul>	<u>Summary</u> : Despite an increased incidence of symptomatic ICH, treatment with IV t-PA within 3 h of the onset of ischemic stroke improved clinical outcome at 3 mo

Study si	ize: 624 SBP >185 mm Hg c	t-PA but only 0.6% of pts given placebo	
pts	DBP >110 mm Hg	(p<0.001).	
		<ul> <li>Mortality at 3 mo was 17% in the t-PA</li> </ul>	
		group and 2% in the placebo group (p=0.30)	

Data Supplement 43. RCTs Comparing Secondary Stroke Prevention (Section 9.4.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Post-stroke Antihypertensive Treatment Study (PATS) 1995 (208) <u>8575241</u>	Aim: To assess whether lowering BP prevents the recurrence of stroke in Chinese pts with history of cerebrovascular disease Study type: Double- blind RCT Size: 5,665 pts	Inclusion criteria: Pts with history of stroke or TIA <u>Exclusion</u> criteria: N/A	Intervention: Indapamide 2.5 mg daily (n=2,840 pts) <u>Comparator</u> : Placebo (n=2,825 pts)	<u>1° outcome</u> : Recurrence of fatal or nonfatal stroke. <u>Key findings</u> : Average SBP/DBP at randomization was 153.8/92.8 mm Hg. At median follow-up (2 y), BP was 6.8/3.3 mm Hg lower in pts on active treatment. 143 pts on indapamide vs. 219 pts on placebo had recurrent strokes (HR: 0.69; 95% Cl: 0.54–0.89; p<0.001).	<ul> <li><u>2° outcome</u>:</li> <li>Major fatal and nonfatal CV events In addition, 199 pts on indapamide and 258 pts on placebo had a CV event (HR: 0.75; 95% CI: 0.89–0.62; p=0.002).</li> <li>2,825 pts received a placebo and 2,840 pts received.</li> <li><u>Summary</u>: For pts with a history of stroke or TIA, BP reduction of 5/2 mm Hg with 2.5 mg of indapamide lowered the first incidence of fatal and nonfatal stroke by 29%, with 3-y absolute benefit of 29 events per 1,000 pts.</li> </ul>
PROGRESS 2001 (209) <u>11589932</u>	<u>Aim</u> : To determine effects of a BP- lowering regimen in hypertensive and nonhypertensive pts with a history of stroke or TIA. <u>Study type</u> : Double- blind, placebo- controlled trial <u>Size</u> : 6,105	Inclusion criteria: Pts with history of stroke (evidence of an acute disturbance of focal neurological function with symptoms lasting more than 24 h and	Intervention: Active treatment comprised a flexible regimen based on the ACEI perindopril (4 mg daily), with addition of diuretic indapamide at discretion of treating physicians (n=3,051) <u>Comparator</u> : Placebo (n=3,054)	<ul> <li><u>1° outcome</u>: Total stroke (fatal or nonfatal)</li> <li><u>Key findings</u>: <ul> <li>Over 4 y of follow-up, active treatment reduced BP by 9/4 mm Hg. 307 (10%) pts assigned active treatment suffered a stroke, vs. 420 (14%) assigned placebo (RR reduction: 28% (95% CI: 17, 38), p&lt;0.0001).</li> <li>Combination therapy with perindopril plus indapamide reduced BP by 12/5 mm Hg and stroke risk by 43% (95% CI: 30%–54%). Single-drug therapy reduced</li> </ul> </li> </ul>	Relevant 2° endpoint:Active treatment also reduced the risk of total major vascular events (26% [16–34]).There were similar reductions in the risk of stroke in hypertensive and nonhypertensive subgroups (all p<0.01).

 $^{\odot}$  2017 American College of Cardiology Foundation and American Heart Association, Inc.

		thought to be due to ICH or ischemia) or TIA within the previous 5 y. <u>Exclusion</u> <u>criteria</u> : N/A • Pts clinically stable for at least 2 wk after their most recent vascular event before entry to the study.		BP by 5/3 mm Hg and produced no discernable reduction in the risk of stroke.	reductions and larger risk reductions than single drug therapy with perindopril alone. • This trial showed the benefits of BP lowering in both hypertensive pts. However, based on older definitions, presence of baseline HTN in the trial was defined as ≥160/90 mm Hg.
MOSES Schrader J, et al., 2005 (210) <u>15879332</u>	Aim: To assess among hypertensive stroke pts, whether for the same level of BP control, eprosartan would be more effective than nitrendipine in reducing cerebrovascular and CV morbidity and mortality. Study type: PROBE design Size: 1,405	Inclusion criteria: High- risk hypertensives with cerebral event during the last 24 mo (proven by cerebral CT scan or nuclear magnetic resonance) Exclusion criteria: Internal carotid artery occlusion or stenosis >70%, manifest HF (NYHA grade III–IV), age >85 y at the time of	Intervention: Eprosartan 600 mg (n=681) Comparator: Nitrendipine 10 mg (n=671)	<ul> <li><u>1° endpoint</u>: Composite of total mortality and all CV and cerebrovascular events, including all recurrent events.</li> <li><u>Key findings</u>: BP reduced to comparable extent without significant differences between 2 groups during study period (150.7/84 mm Hg vs. 152.0/87.2 mm Hg with eprosartan and nitrendipine therapy to 137.5/80.8 mm Hg and 136.0/80.2 mm Hg, respectively). 75.5% reached values &lt;140/90 mm Hg with eprosartan regimen and 77.7% with nitrendipine. During follow-up, 461 1° events occurred: 206 eprosartan and 255 nitrendipine (IDR: 0.79; 95% CI: 0.66– 0.96; p=0.014.</li> </ul>	<ul> <li><u>Relevant 2° endpoint:</u> CV events were: 77 eprosartan and 101 nitrendipine (IDR: 0.75; 95% CI: 0.55–1.02; p=0.06); cerebrovascular events: 102 eprosartan and134 nitrendipine (IDR: 0.75; 95% CI: 0.58–0.97; p=0.03).</li> <li><u>Summary</u>:</li> <li>The combined 1° endpoint was significantly lower in the eprosartan group.</li> <li>However, it was a reduction in TIAs that accounted for most of the benefit in cerebrovascular events, with no significant difference in ischemic strokes.</li> <li>Also a more traditional analysis of time to first cerebrovascular event did not show a benefit of eprosartan.</li> </ul>

		the cerebrovascula r event, pts treated with anticoagulants for a cardiac arrhythmia, high-grade aortic or mitral valve stenosis, or UA pectoris.			
PROFESS Yusuf S, et al., 2008 (211) <u>18753639</u>	<u>Aim</u> : To evaluate the effects of therapy with an ARB, telmisartan, initiated early after a stroke <u>Study type</u> : Double- blind RCT <u>Size</u> : 20,332 pts	Inclusion <u>criteria</u> : Pts ≥55 y with an ischemic stroke <90 d before randomization <u>Exclusion</u> <u>criteria</u> : 1° hemorrhagic stroke, severe disability after the qualifying stroke	Intervention: Telmisartan 80 mg daily (n=10,146) <u>Comparator</u> : Placebo (n=10,186)	<u><b>1° endpoint</b></u> : Recurrent stroke <u><b>Key findings</b></u> : During mean follow-up of 2.5 y, mean BP was 3.8/2.0 mm Hg lower in telmisartan group vs. placebo group. 880 pts (8.7%) in telmisartan group vs. 934 pts (9.2%) in placebo group had a subsequent stroke (HR: 0.95; 95% CI: 0.86–1.04; p=0.23).	<ul> <li><u>Relevant 2° endpoint</u>: Major CV events (death from CV causes, recurrent stroke, MI, or new or worsening HF) occurred in 1,367 pts (13.5%) in telmisartan group vs. 1,463 pts (14.4%) in placebo group (HR: 0.94; 95% CI: 0.87–1.01; p=0.11).</li> <li><u>Summary</u>:</li> <li>Therapy with telmisartan initiated soon after ischemic stroke and continued for 2.5 y did not significantly lower Rate of recurrent stroke, or major CV events.</li> <li>Impact of treatment with telmisartan may have been affected by the high rate of discontinuation of treatment medication because of hypotensive symptoms, syncope, diarrhea, and nausea experienced in the telmisartan arm and the more aggressive treatment with other standard antihypertensive therapies in the placebo arm. Thus, adverse side effects from treatment medications may affect quality of life and thus medication adherence after stroke.</li> </ul>
SPS-3 Benavente OR, et al., 2013 (212) <u>23726159</u>	<u>Aim</u> : To investigate effects of different BP targets on rate of recurrent stroke in pts	Inclusion criteria: Pts with recent, MRI-defined symptomatic	Intervention: SBP target of 130–149 mm Hg (n=1,519)	<u>1° outcome</u> : All stroke (including ischemic strokes and intracranial hemorrhages). <u>Key findings</u> :	<u>2° outcomes</u> : No difference between target groups in disabling or fatal stroke 0.81, (95% CI: 0.53–1.23; p=0.32) or composite outcome of MI or vascular death 0.84 (95% CI: 0.68–1.04; p=0.32). However,

with recent lacunar stroke.	lacunar infarctions.	Comparator: SBP target of <130 mm Hg (n=1.501)	• After 1 y, mean SBP was 138 mm Hg (95% CI: 137–139) in the higher-target group and 127 mm Hg (95% CI: 126–	hemorrhagic stroke occurred in 16 pts assigned to the higher-target group (0.29% per v) vs. 6 assigned to the lower-target
Study type: Randomized open- label trial Size: 3,020 pts	Exclusion criteria: Pts with cortical strokes, cardioembolic		<ul> <li>128) in the lower-target group.</li> <li>Recurrent stroke was observed in 152 pts assigned to higher-target group (2.8% per y) vs. 125 assigned to the lower-target group (2.3% per y; HR: 0.81; 95%</li> </ul>	group (0.11% per y; HR: 0.37 (95% CI: 0.15– 0.95). Serious complications of hypotension were observed in 15 pts assigned to the higher-target group (0.26% per y) and 23 assigned to the lower-target group (0.40%
	disease, or carotid stenosis were excluded.		CI: 0.64–1.03).	per y; HR: 1.53; 95% CI: 0.80–2.93). <u>Summary</u> : Use of a SBP target of less than 130 mm Hg was not significantly better than a target of 130–149 mm Hg for preventing any recurrent stroke. However, the lower target appeared to confer benefit for prevention of hemorrhagic stroke.

### Data Supplement 44. Nonrandomized Trials, Observational Studies, and/or Registries of Secondary Stroke Prevention (Section 9.4.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Rashid P, et al., 2003 (213) <u>14576382</u>	<u>Study type</u> : Meta- analysis of RCTs <u>Size</u> : 7 RCTs	Inclusion criteria: Pts with a history of ischemic stroke, TIA, or ICH Exclusion criteria: N/A	<u>1° outcome</u> : Recurrent stroke <u>Key findings</u> : Antihypertensive drug therapy associated with a 24% reduction in recurrent stroke risk (RR: 0.76; 95% CI: 0.63–0.92) Recurrent stroke risk reduction seen in both hypertensive and normotensive (as defined by the respective trials) pts and linked to magnitude of reduction in SBP	2° outcomes: Nonfatal stroke OR: 0.79 (95% CI: 0.65–0.95), MI OR: 0.79 (95% CI: 0.63, 0.98), and total vascular events OR: 0.79 (95% CI: 0.66– 0.95). No effect seen on vascular or all-cause mortality. ACEIs and diuretics separately, and particularly together, reduced vascular events, while beta-receptor antagonists had no discernable effect. Summary: Use of antihypertensive agents to lower BP for the prevention of vascular events in pts with previous stroke or TIA is efficacious.
Lakhan SE, et al., 2009 (214) <u>19843330</u>	<u>Aim</u> : To examine the role of BP reduction using antihypertensive	Inclusion criteria: Pts with a history of ischemic stroke, TIA, or ICH Exclusion criteria: N/A	<u>1° outcome</u> : Recurrent stroke BP-lowering agents reduced recurrent stroke OR: 0.71 (95% CI: 0.59–0.86; p=0.0004) and	<u>2°outcomes</u> : BP-lowering agents did not affect the rate of MI or all-cause mortality.

	agents to prevent recurrent stroke. Systematic review and meta-analysis Size: 10 RCTs		CV events OR: 0.69 (95% CI: 0.57–0.85; p=0.0004) in pts with a prior stroke or TIA.	Summary: BP lowering agents reduced the occurrence of subsequent stroke and CV events. Rate of MI and all-cause mortality was unchanged.	
Liu L, et al., 2009 (215) <u>19798097</u>	Aim: To examine role of BP reduction using antihypertensive agents to prevent recurrent stroke. Study type: Systematic review and meta-analysis Size: 10 RCTs	Inclusion criteria: Pts with a history of ischemic stroke, TIA, or ICH Followed up 2 to 5 y. Exclusion criteria: N/A	<u>1° outcome</u> : Recurrent stroke <u>Key findings</u> : Antihypertensive drugs associated with significant reduction in recurrent strokes (RR: 0.78; 95% CI: 0.68– 0.90). Impact of antihypertensive treatment after ischemic stroke was similar in a restricted group of subjects with HTN and when all subjects, including those with and without HTN, were included. Pooled OR: 0.63 (95% CI: 0.54–0.73; p<0.0001) for trials involving diuretics as a component of therapy and 0.93 (95% CI: 0.87– 1.01; p=0.086) for trials in which treatment included renin system inhibitors (p<0.0001 for heterogeneity).	<ul> <li><u>2° outcomes</u>: Significant reduction in recurrent stroke seen with diuretics (alone or in combination with ACEIs) but not with renal artery stenosis inhibitors, BBs, or CCBs used alone; however, statistical power was limited, particularly for the assessment of BBs and CCBs.</li> <li><u>Summary</u>: In conclusion, BP lowering by indapamide treatment reduced the recurrence of stroke and the incidence of CV events in Chinese pts with cerebrovascular disease. Whether prevention of stroke recurrence depends on drug class, degree of BP lowering or both requires further investigation.</li> </ul>	
Lee M, et al., 2012 (216) <u>21796663</u>	Aim: To compare impact of achieving tight vs. usual SBP control on stroke prevention <u>Study size</u> : 11 studies with 42,572 pts and 794 stroke events.	Inclusion criteria: (1) Achieved SBP<130 mm Hg in an active treatment group and SBP 130 to 39 mm Hg in a comparator group by trial; (2) trial duration at least 6 mo; (3) total pts and number of stroke events reported separately for active treatment and comparator groups. Exclusion criteria: (1) Nonrandomized trials; (2) trials in which either the	<ul> <li><u>1° outcome</u>: Association of future stroke risk and achieved level of different SBP (intensive vs. usual)</li> <li><u>Key findings</u>:         <ul> <li>Final SBPs, weighted for trial size, were a mean of 126.5 mm Hg in the intensive treatment arms and 132.6 mm Hg in the conventional arms (mean SBP reduction, 6.1 mm Hg).</li> <li>In subgroup analyses, those with established (symptomatic) CVD at entry did not experience stroke risk reduction with tight control (0.92; 95% CI: 0.83–1.03).</li> </ul> </li> </ul>	Summary: Achieving an SBP <130 mm Hg vs. 130–139 mm Hg appears to provide additional stroke protection only among pts with risk factors but no established CVD.	
-					
---	---	---	---	---	---
			comparator or the active therapy group received additional treatment that other group did not; (3) majority of participants had ESRD; (4) <10 stroke events in a trial, because stroke was not a major endpoint; (5) SBP not significantly different between active and comparator groups at trial end; (6) Achieved SBP<130 mm Hg in a comparator group.		
	Lee M, et al., 2012 (217) <u>22052520</u>	<u>Aim:</u> To_evaluate whether use of ACEIs or ARB reduces future vascular events in persons with prior stroke. <u>Size</u> : 8 RCTs with 29,667 pts	Inclusion criteria: (1) RCT design; (2) pts had a history of stroke or TIA; (3) active treatment consisted of ACEIs or ARBs; (4) follow-up duration at least 6 mo; (5) total pts and number of future major vascular events and/or recurrent stroke were reported separately for active treatment and comparator groups.	<u>1° outcome</u> : Major vascular event (nonfatal stroke, nonfatal MI, or death from CV causes) or stroke (ischemic or hemorrhagic) <u>Key findings</u> : Use of ACEIs or ARBs in persons with prior stroke was associated with lower risks of future major vascular events RR: 0.91 (95% CI: 0.87–0.97; p=0.001); NNT=71 and recurrent stroke RR: 0.93 (95% CI: 0.86– 0.99; p=0.03); NNT=143.	Summary: Treatment with an ACEI or ARB has a clear but rather modest effect on reducing vascular risk in persons with prior stroke.
			Exclusion criteria: (1) mandatory ACEI or ARB use in control groups; (2) study purpose was to examine efficacy of ACEIs or ARBs in pts with acute stroke		
	Arima H, et al., 2006 (218) <u>16685221</u>	Aims: <u>#1</u> : To investigate the effects of randomized treatment on recurrent stroke by baseline BP levels <u>#2</u> : To investigate association	Inclusion criteria: Pts with history of cerebrovascular event (stroke or TIA) within the previous 5 y Groups: Defined by baseline BP of <120, 120–139, 140–159, and 160 mm Hg or greater	<u>1° outcome</u> : Total stroke (fatal or nonfatal) <u>Key findings</u> : • Smaller BP differences between active vs. placebo groups (p<0.0001) and corresponding lesser risk reductions (p trend=0.05) with lower baseline BPs Association of stroke incidence with achieved	Summary: • These analyses provide no evidence of a J-curve relationship between BP level and stroke risk among pts with cerebrovascular disease. However, ischemic stroke, TIA, and hemorrhagic pts were all enrolled and within 5 y of the index event suggesting that these pts were generally neurologically stable and not acknowledging the

	between achieved		follow-up SBP level was strong and continuous	differences in pathophysiologic mechanism
	follow-up BP levels		with no	between stroke types.
	and recurrent stroke		evidence of a 1-curve in the range of achieved	• First analysis showed that the effectiveness of
	risk		follow-up	antihypertensive treatment for 2° stroke prevention
	115K.		SBD from 112, 168 mm Hg (n trond $< 0.0001$	diminished as baseline RD declined (relative DDs
	Study type:		DD of study treatment on the discontinuation	were 20% 21% 14% and 0% respectively in the
	<u>Study type</u> .		RR of study field ment of the use of a	were 59%, 51%, 14%, and 0%, respectively, in the
	Post-noc analysis of		oi randomized treatment increased	groups defined previously). This trend of
	PROGRESS trial.		progressively	decreasing effect was despite successful reduction
			across the subgroups with lower baseline SBP	of mean SBP in each active-treatment group
	<u>Size</u> : 6,105 pts		levels	compared with placebo (11.1, 9.2, 7.6, and 7.4 mm
			at entry (p trend=0.04), but there was no	Hg reductions, respectively, in the groups defined
			corresponding difference in effects of	previously). Also of note, 40% of pts with a
			randomized treatment on the risks of death or	baseline BP<140 mm Hg were taking
			hospital admission (both p trend >0.2) or	antihypertensive therapy at baseline.
			hypotension, renal dysfunction, electrolyte	
			disturbance, hip fracture, or depression	
			between pts with different levels of baseline BP	
			at haseline (all n trend $>0.1$ )	
			• Minor side effects were progressively more	
			common at lower PD lovels	
			(n homogonoity 0.04)	
	Alua Ta datamaina	Inclusion eniteric Discuith		
	Aim: To determine	Inclusion criteria: Pis with	<u>1° outcome</u> : Rates of side effects related to	<u>Summary</u> : PIS $\geq$ 75 y with a recent facunar stroke
2015 (219)	safety and	lacunar stroke ≥75 y	Iowering SBP	who achieved a lower SBP target (<130 mm Hg)
25850462	tolerability of			were significantly more likely to report
	lowering BP in older		<u>2° outcome</u> : Stroke recurrence and death from	unsteadiness on standing than their younger
	adults with lacunar		vascular causes	counterparts. Lower SBP was not related to a
	stroke			decrease in recurrent stroke risk in elderly pts with
			Key findings:	lacunar stroke but there was a potential protective
	Study type: Post-		Older pts achieved SBP levels similar to	advantage from vascular death.
	hoc analysis of		younger pts (mean SBP of 125 mm Hg in lower	
	randomized trial		SBP target group and 137 mm Hg in higher	
			target group)	
	Study Size: 494 pts		• 3.5 v of follow-up	
			21% reported dizziness and 15% reported	
			lightheadedness when standing: only significant	
			difference between vounder and older groups	
			was unstaadingss when standing (22% vs	
			220/ n (0.001) No difference in requirement	
			52 %, p<0.001). No unierence in recultent	
			stroke by target SBP level among the older	
1			subjects (HR: 1.01; 95% CI: 0.59–1.73), but the	

			lower target SBP group in older pts was linked to a significant reduction in vascular death (HR:	
			0.42; 95% CI: 0.18–0.98; p=0.049).	
Ovbiagele B, et al., 2011 (220) <u>22089721</u>	Aim: To assess the association of maintaining low- normal vs. high- normal SBP levels with risk of recurrent stroke. Study type: Post hoc analysis of a multicenter trial involving 20,330 pts (age ≥50 y) with recent noncardioembolic ischemic stroke followed up for 2.5 y Study Size: 20,330 pts	Inclusion criteria: Pts 55 y or older with an ischemic stroke <90 d before randomization Categories: Based on mean SBP level was very low-normal (<120 mm Hg), low-normal (120≤130 mm Hg), high-normal (130≤140 mm Hg), high (140≤150 mm Hg), and very high (≥150 mm Hg). • 1° outcome was recurrent stroke and the 2° outcome was a composite of recurrent stroke, MI, and death due to vascular causes	<u>1° outcome</u> : First recurrence of stroke of any type <u>2° outcome</u> : Composite of stroke, MI, or death from vascular causes. <u>Key findings</u> : Recurrent stroke rates were 8.0% (95% CI: 6.8%–9.2%) for the very low- normal SBP level group, 7.2% (95% CI: 6.4%– 8.0%) for the low-normal SBP group, 6.8% (95% CI: 6.1%–7.4%) for the high-normal SBP group, 8.7% (95% CI: 7.9%–9.5%) for the high SBP group, and 14.1% (95% CI: 13.0%–15.2%) for the very high SBP group. Compared with pts in the high-normal SBP group, the risk of 1° outcome was higher for pts in the very low- normal SBP group AHR: 1.29 (95% CI: 1.07– 1.56), in the high SBP group AHR: 1.23 (95% CI: 1.07–1.41), and in the very high SBP group AHR: 2.08 (95% CI: 1.83–2.37).	Relevant 2° endpoint: Compared with pts in the high-normal SBP group, the risk of 2° outcome was higher for pts in the very low-normal SBP group AHR: 1.31 (95% CI: 1.13–1.52), in the low-normal SBP group AHR: 1.16 (95% CI: 1.03–1.31), in the high SBP group AHR: 1.24 (95% CI: 1.11–1.39), and in the very high SBP group AHR: 1.94 (95% CI: 1.74–2.16).Summary: Among pts with recent noncardioembolic ischemic stroke, SBP levels during follow-up in the very low-normal (<120 mm Hg), high (140–≤150 mm Hg), or very high (≥150 mm Hg) range were associated with increased risk of recurrent stroke.
Ovbiagele B, et al., 2013 (221) <u>22244715</u>	Aim: To assess association of maintaining low- normal vs. high- normal SBP levels with risk of recurrent stroke. Study type: Post hoc analysis of a multicenter trial involving 3,680 pts with recent noncardioembolic ischemic stroke followed up for 2 y	Inclusion criteria: Pts with an ischemic stroke <120 d before randomization <u>Categories</u> : • Based on mean in-trial SBP value was low-normal (<120 mm Hg), high-normal (120 to <140 mm Hg), or high (>140 mm Hg). • 1° outcome was stroke	<u>1° outcome</u> : First recurrence of stroke of any type <u>Key findings</u> : Rate of recurrent stroke was 9.1% in the low- normal group, 6.7% in the high-normal group, and 10% in the high group. Difference in recurrent stroke rate between low-normal and high-normal groups was more prominent within the first 6 mo (low-normal, 4.5%; high-normal, 2.5%; high, 3.4%) vs. after 6 mo (low-normal, 4.6%; high-normal, 4.2%; high, 6.6%). Over study period, compared with the high-normal group, risk of the 1° outcome trended higher in the low-normal group AHR: 1.47 (95% CI: 0.94–2.29; p=0.09) and was higher in the high group AHR: 1.39 (95% CI: 1.08–1.79; p=0.01).	Summary: Results support a possible pattern of increased risk of recurrent stroke in pts with low- normal SBP levels, especially within the first 6 mo after first stroke. However, this study likely was not sufficiently powered to detect more than a strong statistical trend underlying this relationship.

Lin MP, et al., 2015 (222) <u>25765723</u>	Aim: To assess link between SBP and mortality after stroke. Study type: Analyses of nationally representative survey data (NHANES) Study Size: 455 pts	Inclusion criteria: Adults ≥20 y with self-reported stroke. Categories: Baseline SBP was as low to normal (<120 mm Hg), normal (120–140 mm Hg), and high (≥140 mm Hg).	<u><b>1° outcomes</b></u> : All-cause and vascular mortality <u><b>Key findings</b></u> : 2 y after assessment, the low to normal SBP group tended to have the highest cumulative all-cause mortality (11.5%), compared with mortality rates of 8.5% and 7.5% in the normal and high SBP groups, respectively. Similar patterns were seen with vascular mortality. After adjusting for covariates, compared with the high SBP group, the low to normal group had higher all-cause mortality AHR: 1.96 (95% CI: 1.13–3.39; p=0.017) and trended toward higher vascular mortality AHR: 2.08 (95% CI: 0.93–4.6; p=0.075). Compared with the normal BP group, the risk of all-cause and vascular mortality trended higher in low to normal BP group but did not achieve statistical significance.	Summary: After stroke, compared with SBP in the high range, low to normal SBP may be associated with poorer mortality outcomes. Study limited by self-reported nature and retrospective design.
Kim J, et al., 2014 (223) <u>24509123</u>	<u>Aim</u> : To investigate the association between BP and vascular events up to 10 y after stroke. <u>Study type</u> : Analysis of population based study (North East Melbourne Stroke Incidence Study (NEMESIS)	Inclusion criteria: 5-y survivors of stroke Categories: Stratification by quartiles of SBP Follow-up: Annually by telephone at 6, 8, and 9 y and face-to-face interview at 7 and 10 y after stroke.	<u>1° outcomes</u> : Composite of all-cause death or nonfatal vascular event (stroke or AMI); and all- cause death alone. <u>Key findings</u> : In 5-y survivors of stroke, compared to a SBP of 131–141 mm Hg, SBP of 120 mm Hg or less was associated with a 61% greater risk of stroke, acute MI and death (HR: 1.61; 95% CI: 1.08–2.41; p=0.019). Compared to the reference category of SBP 131–141 mm Hg, there were no differences in outcome in the pts with SBP 121–130 mm Hg (p=0.491) or 142–210 mm Hg (p=0.313). Findings were not modified after adjusting for antihypertensive drug prescriptions.	Summary: There appears to be a greater risk of poor outcome in long-term survivors of stroke with low SBP. This is further evidence that low SBP may result in poor prognosis.
Wang WT, et al., 2016 (224) <u>27082571</u>	Aim: To investigate the relative effects of BP-lowering therapies [ACEI, ARB, BB, CCBs, diuretics, and	Inclusion criteria: • RCTs comparing the effects of any of the 6 most commonly used BP-lowering drug classes [ACEI, ARB, alpha-blocker, BB, diuretics, and CCB] vs. placebo	<u>1° outcome</u> : Recurrent stroke <u>2° outcome</u> : CHD, and MACCE <u>Key findings</u> : • Compared with placebo, ACEI plus diuretic	<ul> <li>Virtually all BP-lowering medication classes reduced vascular events including recurrent stroke.</li> <li>The higher the average BP reduction between the treatment vs. control groups the larger the risk reduction in recurrent stroke events and MACCE.</li> </ul>

	combinations of 3 drugs] in pts with a prior stroke history <u>Study size</u> : 15 RCTs composed of 39,329 participants previous stroke	or comparing 1 type of antihypertensive agent with another type on pts who have suffered from stroke or TIA s • RCTs reporting outcomes of interest with a follow-up of more than a month.	<ul> <li>reduced recurrent stroke (OR: 0.54; 95% CI: 0.33–0.90).</li> <li>ACEI plus diuretic had a higher probability of being at the best ranking position (31%).</li> <li>Compared with regimens not including diuretics, diuretics-based treatments resulted in a significantly larger reduction in BP (12.0mm Hg; 95% CI: 7.0–16.9),</li> <li>Treatment regimens including diuretics had a RR of 0.619 (95% CI: 0.515–0.743) for recurrent stroke, which was significantly lower than treatments that did not include diuretics (RR=0.882; 95% CI: 0.800–0.973) with a p value for interaction of 0.0008.</li> <li>None of the between-drug comparisons showed significant differences in effect on outcomes</li> </ul>	<ul> <li>Diuretic-based treatments lowered the risk of recurrent stroke more than treatments that did not include diuretics.</li> <li>There were no significant differences in effect on 2° stroke reduction between the various individual antihypertensive medication classes.</li> </ul>
Katsanos AH, et al., 2017 (225) <u>27802419</u>	Aim: To assess the association of BP reduction with recurrent stroke and CV events using available RCT data on 2° stroke prevention <u>Study size</u> : 14 studies with 42,736 pts	Inclusion criteria: RCTs of antihypertensives for 2° stroke prevention pts that reported achieved BP values during the follow-up period. Exclusion criteria: Observational studies, case series, case reports, RCTs in non-IS/TIA population, and studies not reporting data on finally achieved BP values	<ul> <li><u>1° outcome</u>: Recurrent stroke</li> <li><u>2° outcome</u>: MI, death from any cause, and risk of CV death</li> <li><u>Key findings</u>: <ul> <li>SBP reduction linearly associated with lower risk of recurrent stroke (regression slope, 0.02; 95% CI: 0.01–0.04; p=0.049), MI (regression slope, 0.022; 95% CI: 0.002–0.041; p=0.024), death from any cause (regression slope, 0.02; 95% CI: 0.01–0.03; p=0.001), and CV death (regression slope, 0.05; 95% CI: 0.03–0.07; p&lt;0.001).</li> <li>No relation was observed between the degree of SBP reduction and the risk of disabling or fatal stroke (regression slope, 0.001; 95% CI: -0.024–0.022; p=0.944).</li> <li>Relation of SBP reduction with ischemic or hemorrhagic stroke was not assessed due to the small number of studies with available data (&lt;10).</li> </ul> </li> </ul>	Summary: BP reduction is linearly associated with the magnitude of risk reduction in recurrent cerebrovascular and CV events, but optimal BP target not evaluated.

# Data Supplement 45. RCTs and Meta-analysis Comparing PAD (Section 9.5)

Stud Yea	ły Acronym; Author; r Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% Cl)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Öster 2004 <u>14683</u>	<sup>⊥</sup> (226) <u>3738</u>	<ul> <li><u>Aim</u>. To assess the impact of ramipril compared to placebo on the prevention of major CV events in PAD pts in the HOPE study.</li> <li><u>Study type</u>: Multicenter, double-blind RCT</li> <li><u>Size</u>: 9,541 randomized in HOPE (1,725 randomized who had baseline PAD, defined by ABI with pulse detection by either Doppler or palpation)</li> </ul>	<ul> <li>≥55 y</li> <li>Existing CVD (CAD, stroke, PAD) or DM with an additional CVD risk factor (smoking, HTN, hypercholesterolemia, low HDL, microalbuminuria)</li> <li>Exclusion criteria:         <ul> <li>Received ACEI or vitamin E or had uncontrolled HTN</li> <li>HF or LV dysfunction</li> <li>*All eligible pts had 7- to 10-d run-in period, received 2.5 mg ramipril daily; those who tolerated were then assigned placebo for 10–14 d and then were randomized to1 of intervention arms or control</li> </ul> </li> </ul>	(10 mg/d): 4,645 randomized Intervention: Placebo: 4,652 randomized	<ul> <li>Combined CV death, nonfatal MI, nonfatal stroke</li> <li>In pts with history of symptomatic PAD, comparing ramipril to placebo: RR: 0.75; 95% CI: 0.61–0.92</li> <li>In pts with no history of symptomatic PAD, but severe subclinical disease defined as ABI &lt;0.6, comparing ramipril to placebo: RR: 0.77; 95% CI: 0.55–1.09</li> <li>In pts with no history of symptomatic PAD, but moderate subclinical disease defined as ABI 0.6–0.9, comparing ramipril to placebo: RR: 0.72; 95% CI: 0.56–0.92</li> <li>Safety endpoint: N/A</li> <li>Summary: Ramipril prevented clinical evidence of PAD as well as in those without PAD. The relative benefit was similar in pts classified by levels of ABI, even though event rates were higher in pts with subclinical and clinical ABI.</li> </ul>	<ul> <li>Individual components of composite endpoint, all-cause mortality, hospitalizations for HF, DM complications</li> <li>In pts with history of symptomatic PAD, comparing ramipril to placebo: for MI, RR: 0.75 (95% CI: 0.58–0.98); for stroke, RR: 0.72 (95% CI: 0.50–1.05); for CVD mortality, RR: 0.75 (95% CI: 0.56–0.99); for total mortality, RR: 0.85 (95% CI: 0.68–1.07); for DM complications, RR: 0.87 (95% CI: 0.74–1.09); for HF, RR: 0.81 (95% CI: 0.53–1.24)</li> <li>In pts with no history of symptomatic PAD, but severe subclinical disease defined as ABI &lt;0.6, comparing ramipril to placebo: for MI, RR: 0.73 (95% CI: 0.48–1.11); for stroke, RR: 0.99 (95% CI: 0.52–1.89); for CVD mortality, RR: 0.76 (95% CI: 0.46–1.25); for total mortality, RR: 0.81 (95% CI: 0.55–1.19); for DM, RR: 0.83 (95% CI: 0.55–1.19); for DM, RR: 0.83 (95% CI: 0.34–1.28)</li> <li>In pts with no history of symptomatic PAD, but moderate subclinical disease defined as ABI 0.6–0.9, comparing ramipril to placebo: for MI, RR: 0.81 (95% CI: 0.60–1.09); for stroke, RR: 0.44 (95% CI: 0.60–1.09); for stroke, RR: 0.44 (95% CI: 0.26–0.77); for CVD mortality, RR: 0.62 (95% CI: 0.42–0.90); for total mortality, RR: 0.58 (95% CI: 0.42–0.79); for diabetic complications, RR: 0.80 (95% CI: 0.53–1.21); for HF, RR: 0.69 (95% CI: 0.38–1.23)</li> </ul>

					Study limitations and adverse events: ABI not measured by Doppler gold standard
Overlack A, et al., 1994 (227) <u>8059778</u>	Aim: To determine the effect of perindopril compared to placebo on various clinical outcomes in pt subgroups. Study type: Multicenter, double-blinded RCT (3 wk placebo run-in period, 6 wk double-blind phase) Size: 490 (54 with PAD)	Inclusion criteria: • Mild newly diagnosed essential HTN in addition to 1 concomitant diseases or therapies: hyperlipidemia, DM-2, IHD, cardiac arrhythmias, PAD, nephropathy with proteinuria, COPD, or degenerative join disease with NSAIDs • 40–75 y *Antihypertensive treatment was stopped 1 wk prior to randomization, required DBP 95–104 mm Hg <u>Exclusion criteria</u> : N/A	Intervention: Perindopril (4 mg/d): 253 randomized Comparator: Placebo: 237 randomized	<ul> <li><u>1° endpoint</u>:         <ul> <li>ABI measured by Doppler</li> <li>In pts with baseline PAD, there was no difference in post-treatment Doppler Index between perindopril (0.75) vs. placebo (0.75); p&gt;0.05</li> </ul> </li> <li><u>1° Safety endpoint</u>:         <ul> <li>Spontaneously reported side effects: 5.5% of pts in perindopril, 3.8% of pts in placebo</li> <li><u>Summary</u>: In pts with PAD, Doppler index at baseline was not different between the 2 groups and remained unchanged during treatment. Pain-free and maximal walking distances increased from baseline but there were no significant between group differences.</li> </ul></li></ul>	Relevant 2° endpoint:• Pain-free walking distance (m), maximal walking distance• In pts with baseline PAD, there was no difference in change in pain-free walking distance (m) between perindopril (+11 m) vs. placebo (+11 m); p>0.05• In pts with baseline PAD, there was no difference in change in maximal walking distance between perindopril (pre-trial: 318 m (SD: 45), post-trial: 323 m (SD: 43) vs. placebo (pre-trial: 333 m (SD: 43), post-trial: 369 m (SD: 46)Study limitations and adverse events: Short follow-up, unable to assess hard clinical outcomes
Schweizer J, et al., 1998 (228) <u>9581724</u>	Aim: To determine whether treatment with high dose verapamil prevents restenosis in pts with PAD at high risk for reoccurrence after successful PTCA. Study type: Double- blind RCT (6 mo duration)	Inclusion criteria: • PAD (based on arterial angiography and color- coded duplex ultrasound) present for >6 mo • Primary success of PTCA treatment (≥30% reduction of initial lumen constriction) • Stable angina pectoris, mild HTN and at least1	Intervention: Verapamil (240 mg/twice/d): 49 randomized Comparator: Placebo: 49 randomized	<ul> <li><u>1° endpoint</u>:</li> <li>Percentage of diameter stenosis</li> <li>At 6 wk, mean % diameter stenosis in verapamil group was 46.8 (SD: 14.1) vs. placebo was 55.5 (SD: 10.0)</li> <li>At 6 mo, mean % diameter stenosis in verapamil group was 48.0 (SD: 11.5) vs.</li> </ul>	Relevant 2° endpoint:• Intima/media thickness was 1.2 mm(SD: 0.31) in verapamil vs. 1.9 mm (SD:0.47), p<0.001

					-
	<u>Size</u> : 98 pts	additional risk factor: DM, hyperlipoproteinemia, total or subtotal vascular occlusion of dilated segmented, eccentric stenosis, residual stenosis of at least 30%, or stenosis localized in the distal superficial femoral artery <u>Exclusion criteria</u> : • History of pelvic stenosis • Previous adjuvant therapy with calcium antagonists or beta- adrenergic blocking agents • Age >75 y • Prior revascularization of same area • 1st, 2nd, or 3rd AV block, sinoatrial block, diseases of supporting or connective tissues, moderate arterial HTN with SBP >170 mm Hg and DBP >95 mm Hg • Pts requiring stent for large anatomic segments or alactic stanascia		placebo was 69.6 (SD: 12.2), p<0.01 <u>1° Safety endpoint</u> : N/A <u>Summary:</u> In pts with PAD at increased risk for restenosis, the administration of high dose verapamil prevented recurrent stenosis for 6 mo after successful peripheral angioplasty and was well tolerated.	<ul> <li>Crurobrachial ratio tibial artery was 0.76 (SD: 0.09) in verapamil vs. placebo was 0.70 (SD: 0.10)</li> <li>Arterial pressure was 134/87 mm Hg (SD: 5.2/4.2) in verapamil vs. placebo was 165/97 mm Hg (6.5/4.4), p&lt;0.001</li> <li>Total vessel diameter was 8.3 mm (SD: 0.3) in verapamil vs. 7.5 mm (SD: 0.3), p&lt;0.001</li> <li><u>Study limitations and adverse events:</u> Short follow-up, unable to assess hard clinical outcomes</li> </ul>
NORMA Espinola-Klein C, et al., 2011 (229) 21646599	<u>Aim</u> : Evaluate the effects of treatment with the endothelium-dependent vasodilating beta 1- selective blocker nebivolol, as compared with the nonvasodilating beta 1-selective blocker metoprolol, on clinical parameters of PAD and endothelial function, and to compare the	Inclusion criteria: • Stable intermittent claudication for ≥6 mo and an ABI of <0.9 • Stage 1 arterial HTN (SBP: 140–159 mm Hg, DBP: 90–99 mm Hg untreated, or treated stage 1 arterial HTN) • SBP at time of enrollment 100–160 mm Hg	Intervention arms: • Nebivolol (5 mg/d): 65 randomized • Metoprolol (95 mg/d): 63 randomized	<u>1° endpoint:</u> • Change in ABI measured by Doppler • In nebivolol: initial ABI 0.62 (SD: 0.16), post-treatment ABI 0.68 (SD: 0.20), p-value for change: 0.002 • In metoprolol: initial ABI 0.63 (SD: 0.17), post- treatment ABI 0.67 (SD:	<ul> <li><u>Relevant 2° endpoint:</u></li> <li>Change in absolute claudication distance were 32.7 m in nebivolol (p-value 0.03) vs. 39.7 m in metoprolol (p-value 0.01), but no difference between 2 groups (p-value 0.54)</li> <li>Changes in SBP were -5.2 mm Hg in nebivolol (p=0.001) and -3.9 mm Hg in metoprolol (p=0.01), no difference between groups</li> </ul>

	tolerability of both drugs in pts with PAD <u>Study type</u> : Double- blinded RCT (48 wk) <u>Size</u> : 128	<ul> <li>DBP at time of enrollment &lt;100 mm Hg</li> <li><u>Exclusion criteria</u>:</li> <li>Premenopausal women</li> <li>Critical limb ischemia with rest pain, leg ulcer, gangrene, severe angina pectoris that limits exercise capacity, severe HF that limits exercise capacity, hyperthyroidism, poorly controlled DM (HbA1c&gt;10%)</li> <li>Contraindications for BBs</li> <li>Acute MI within 6 mo before screening</li> <li>Previous treatment with nebivolol or carvedilol</li> <li>*Concomitant treatment with calcium antagonists, ACEIs, angiotensin II type 1 receptor antagonists, aspirin, clopidogrel, statins, estrogens was permitted if no change in dosage had been made in the previous 3 mo before screening</li> </ul>		0.21), p-value for change: 0.04 • Comparing ABI change in nebivolol to metoprolol: 0.02 (p=0.69). <u>1st safety endpoint</u> : N/A <u>Summary:</u> BB therapy was well tolerated in pts with intermittent claudication and HTN during a treatment period of 1 y. In the direct comparison, there was no significant difference between nebivolol and metoprolol.	<ul> <li>No change in flow-mediated dilatation in either group (p=0.16)</li> <li><u>Study limitations and adverse events:</u></li> <li>Absence of placebo group</li> <li>21 total adverse events, 10 in nebivolol, 11 in metoprolol (adverse events: bradycardia, tachycardia, blurred vision, worsening HTN, edema, worsening claudication, blurred vision, erectile dysfunction, edema, vertigo, temporary dysesthesia of the hands, dyspnea, skin irritation, headache, moderate diarrhea)</li> </ul>
INVEST Bavry AA, et al., 2010 (230) <u>19996066</u>	<u>Aim</u> : To examine the effect of average treated BP on adverse outcomes in PAD pts with CAD and to compare 2 antihypertensive medications <u>Study type</u> : Post hoc analysis of international	Inclusion criteria: • ≥50 y • HTN, clinically stable CAD • Pt reported PAD Exclusion criteria: Contraindications to the treatment groups	Interventions: • Calcium antagonist- based strategy: verapamil with or without trandolapril • BB-based strategy: atenolol with or without hydrochlorothiazide *2° medications only given to achieve BP of	<ul> <li><u>1° endpoint</u>:</li> <li>Composite outcome: all-cause death, nonfatal MI, nonfatal stroke</li> <li>No statistically significant difference in composite 1° outcome OR: 0.90 (95% CI: 0.76, 1.07) comparing calcium antagonist based group to BB based group in fully adjusted model</li> </ul>	Relevant 2° endpoint: N/A• This trial also notes the J-shaped relationship between BP achieved and clinical outcomes• Risk of 1° outcome was reduced most when SBP was treated to 130–140 mm Hg and DBP 60–90, as opposed to <130/80 as 2005 guidelines suggest in PAD ptsStudy limitations and adverse events:

	randomized, blinded- endpoint trial (48 wk) <u>Size</u> : 22,576 in total trial (2,699 with PAD in this analysis)		<140/90 mm Hg in all participants except for those with renal impairment or DM, BP<130/85 mm Hg	<ul> <li>Kaplan–Meier curve for 1° outcome shows slightly lower cumulative incidence in calcium antagonist group (log rank p=0.26)</li> <li><u>1st safety endpoint</u>: N/A</li> <li><u>Summary:</u> Among PAD pts, the incidence of the 1° outcome was not significantly different between treatment groups.</li> </ul>	<ul> <li>PAD was not uniformly measured or adjudicated (only based on pt report)</li> <li>Asymptomatic PAD was not captured</li> </ul>
VALUE Zanchetti A, et al., 2006 (231) <u>17053536</u>	Aim: To examine the effect of valsartan vs. amlodipine on cardiac morbidity and mortality in hypertensive pts at high CV risk Study type: Prespecified additional analyses of international randomized, double-blind, parallel- group trial Size: 15,245 in total trial (2,114 with PAD)	Inclusion criteria: • ≥50 y • HTN (untreated: 160– 210/<115 mm Hg, treated: <210/<115 mm Hg) • High risk for cardiac events (male sex, verified DM, current smoking, high cholesterol, LV hypertrophy by ECG, proteinuria on dipstick, serum creatinine 150–265 micromol/L, coronary disease diagnosis, cerebrovascular disease diagnosis, or PAD diagnosis) Exclusion criteria: • Renal artery stenosis • Pregnancy • AMI, coronary angioplasty or CABG in last 3 mo • Severe hepatic disease • Severe chronic renal failure	Interventions: • Valsartan: 7,649 total • Amlodipine: 7,596 total *No PAD-specific numbers available	<ul> <li><u>1° endpoint</u>:</li> <li>Composite of sudden cardiac death, fatal MI, death during/after percutaneous coronary intervention or CABG, HF requiring hospitalization, nonfatal MI, or emergency procedure to prevent MI</li> <li>There was no significant difference in the 1° outcome by treatment group among all pts and by PAD status. Among pts with PAD, the 1° outcome occurred in 13.4% of valsartan vs. 13.6% of amlodipine pts. Among pts without PAD, the corresponding % were 10.1% and 9.9%.</li> <li><u>1st safety endpoint</u>:</li> <li><u>Summary:</u> The effects of treatments on occurrence of the 1° outcome did not different by PAD status.</li> </ul>	Relevant 2° endpoint: N/A <u>Study limitations and adverse events:</u> • Limited subgroup analyses, only 1° outcome reported • High-risk population limits generalizability

Piller LB, et al., 2014 (232) 25002161	Aim: To compare, by randomized treatment groups (amlodipine, lisinopril, chlorthalidone) hospitalized or revascularized PAD rates and subsequent morbidity and mortality. Study type: Post-hoc analysis of prospective, randomized, double- blinded active-control trial (ALLHAT study— amlodipine, lisinopril compared to chlorthalidone control arm)	<ul> <li>Congestive HF requiring ACEI therapy</li> <li>Pts on monotherapy with 3 blockers for both CAD and HTN</li> <li>Inclusion criteria:</li> <li>BP of 140–180/90–110 for untreated, 160/100 for treated pts</li> <li>Age ≥55 y</li> <li>Have at least1 CV risk factor (risk factors: old myocardial injury or stroke, history of coronary revascularization procedure, other documented atherosclerotic CVD PAD, history of intermittent claudication, peripheral artery revascularization or peripheral artery angioplasty, DM-2, current cigarette smoking, HDL</li> </ul>	Intervention arms: • Amlodipine: 8,898 randomized • Lisinopril: 8,904 randomized <u>Comparator:</u> Chlorthalidone: 15,002 randomized *Goal BP was <140/90 in each randomized group (achieved using study drug but adding open-label agents at physician discretion when necessary)	<ul> <li><u>1° endpoint:</u></li> <li>PAD requiring hospitalization or outpatient revascularization procedure</li> <li>830 cases of PAD over 8.8 y follow-up; no significant difference between treatment groups after adjustment</li> <li>HR comparing amlodipine to chlorthalidone: 0.86 (95% Cl: 0.72, 1.03) after full adjustment, p-value: 0.099</li> <li>HR comparing lisinopril to chlorthalidone: 0.98 (95% Cl: 0.83, 1.17) after full adjustment, p-value: 0.847</li> <li>Kaplan Meier: Y-to-PAD was longer amlodipine vs. chlorthalidone (no difference</li> </ul>	Relevant 2° endpoint:• Post-PAD morbidity and mortality• Comparing amlodipine tochlorthalidone, no difference in post-PADmorbidity or mortality: MI, HR: 0.82 (95%Cl: 0.48, 1.40); Stroke, HR: 0.86 (95% Cl:0.41, 1.79); Cardiac Revascularization,HR: 1.39 (95% Cl: 0.81, 2.39); HF, HR1.32 (95% Cl: 0.79, 2.18); Total Mortality,HR: 0.92 (95% Cl: 0.74, 1.15)• Comparing lisinopril to chlorthalidone,no difference in post-PAD morbidity ormortality: MI, HR: 0.74 (95% Cl: 0.44,1.25); Stroke, HR: 0.94 (95% Cl: 0.48,1.86); Cardiac Revascularization, HR:1.25 (95% Cl: 0.73, 2.13); HF, HR: 1.08(95% Cl: 0.65, 1.80); Total Mortality, HR:0.95 (95% Cl: 0.77, 1.18)
	arm) <u>Size</u> : 33,357 pts	angioplasty, DM-2, current cigarette smoking, HDL <0.90 mmol/L, LVH, major ST depression, T-wave inversion) <u>Exclusion criteria</u> : • Canadian pts for whom outcome measures could not be assessed (n=533)		<ul> <li>Kapian Meet. 1-10-FAD was longer amlodipine vs. chlorthalidone (no difference between lisinopril and chlorthalidone)</li> <li><u>1º Safety endpoint</u>: N/A</li> </ul>	<ul> <li>0.95 (95% CI: 0.77, 1.18)</li> <li><u>Study limitations and adverse events:</u></li> <li>PAD not specifically collected at baseline, thus cannot detect actual incidence (however, randomization presumably resulted in equal number of baseline PAD cases in each group)</li> <li>Asymptomatic PAD likely missed (definition used in this study based on hospitalization, likely only capturing very severe cases)</li> </ul>
Thompson AM, et al., 2011 (113) <u>21364140</u>	<u>Aim:</u> To evaluate the effect of antihypertensive treatment on 2° prevention of CVD events and all-cause mortality among pts	Inclusion criteria: RCTs of antihypertensive treatment among pts with BP <140/90 mm Hg for the prevention of CVD events.	Interventions: Any antihypertensive agent compared with placebo or no treatment.	Results: Compared with controls, pts receiving antihypertensive medications had a pooled RR of 0.77 (95% CI: 0.61, 0.77) for stroke: 0.80 (95% CI: 0.69,	<ul> <li>Study limitations and adverse events:</li> <li>PAD not specifically collected at baseline, thus cannot detect actual incidence (however, randomization presumably resulted in equal number of baseline PAD cases in each group)</li> </ul>

without clinically defined	Exclusion criteria: CVD	0.93) for	r MI: 0.71 (95% CI:	Asymptomatic PAD likely missed
HTN.	events were not reported	0.65, 0.7	77) for CHF: 0.85	(definition used in this study based on
	by HTN status that	(95% CI	I: 0.80, 0.90) for	hospitalization, likely only capturing very
Study type: Meta-	included participants with	composi	ite CVD events: 0.83	severe cases)
analysis including 25	and without HTN; study	(95% CI	I: 0.69, 0.99) for CVD	,
RCTs	population did not include	mortality	y and 0.87 (95% CI:	
	persons with BP in the	0.80, 0.9	95) for all-cause	
Size: 64,162 pts without	normal or prehypertensive	mortality	y from random effect	
HTN.	ranges; study population	models.	Results did not differ	
	did not include persons	accordin	ng to trial	
	with preexisting CVD or	characte	eristics or subgroups	
	CVD equivalents, such as	defined	by clinical history,	
	DM; antihypertensive	although	h no specific PAD	
	medication was not a part	subgrou	ip was defined.	
	of the intervention;	, i i i i i i i i i i i i i i i i i i i		
	treatment allocation was	Summa	ary: Among pts with	
	not random; measure of	clinical h	history of CVD,	
	variance not reported;	including	g PAD, but without	
	participants were <18 y;	HTN, an	ntihypertensive	
	there were differences	treatmer	nt was associated	
	between intervention and	with redu	luced risk of stroke,	
	control groups other than	CHF, co	omposite CVD events	
	antihypertensive treatment.	and all-c	cause mortality.	
	Preexisting CVD included		-	
	PAD.			

# Data Supplement 46. RCTs and Meta-analyses Comparing BP Targets in DM (Section 9.6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# pts) / Study Comparator (# pts)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
ADVANCE Kaplan NM, et al., 2007 (233) <u>17765962</u>	<u>Aim:</u> To assess the effects of an ACEI perindopril and a diuretic indapamide combination on serious vascular events in pts with	DM-2 pts 30–55 y. <u>Inclusion criteria</u> : At least 1 of the following: history of major CVD, (stroke, MI, admission for TIA, UA, coronary	• Fixed combination of perindopril and indapamide compared with perindopril and placebo.	<u>1° endpoints</u> : Composite of CV death, nonfatal MI, nonfatal stroke, new or worsening nephropathy, or retinopathy. <u>Results</u> : After 4.3 y follow-up, pts assigned to active therapy had a reduction of SBP of 5.6 mm Hg. RR of major macro- or micro-	Summary: • This large RCT provides evidence that routine administration of fixed combination ACEI and thiazide-type diuretic therapy reduces risk of major CV events in those with at least 1 risk factor.

	DM irrespective of initial BP levels or the use of other BP- lowering drugs. <u>Study type</u> : RCT <u>Size:</u> 11,140 pts, 4.3 y follow-up	revascularization, or amputation for PVD) or at least 1 other risk factor (history of microvascular disease, microalbuminuria, proliferative diabetic retinopathy, retinal photocoagulation therapy, macular edema, blindness, cigarette smoking, high cholesterol, low HDL cholesterol, low HDL cholesterol, diagnosis of DM at least 10 y before enrollment or ≥65 y at entry <u>Exclusion criteria</u> : HbA1c target ≤6.5% or indication for insulin.		vascular events decreased by 9% (HR: 0.91; (95% CI: 0.83, 1.00), p<0.04). Death from CVD decreased by 18%; RR: 0.82 (95% CI: 0.68, 0.98) and death from any cause decreased by 14%; RR: 0.86 (95% CI: 0.75, 0.98). The effects of study treatment did not differ by initial BP or concomitant use of other treatments at baseline. The pts had at least 1 CV risk factor.	• The ADVANCE trial included DM pts both with and without HTN. In this RCT, pts were randomized to active treatment or placebo rather than to a different BP goal, so that it is impossible to determine whether the benefit was due to the treatment of HTN <i>per se</i> .
ACCORD Cushman WC, et al., 2010 (234) <u>20228401</u>	<u>Aim</u> : To assess whether therapy targeting normal SBP (<120 mm Hg) reduces major CV events in DM-2 at high risk for CV events. <u>Study type</u> : RCT <u>Size</u> : 4,733 pts, 4.7 y follow-up	Inclusion criteria: DM-2 with HgbA1c ≥7.5%;≥40 y with CVD or ≥55y with anatomicalevidence ofatherosclerosis,albuminuria, LVH, or≥2 additional riskfactors for CVD.Exclusion criteria:BMI ≥45, serumcreatinine >1.5, andother serious illness.	• Pts were randomly assigned to intensive therapy SBP <120 mm Hg or standard therapy SBP <140 mm Hg.	<u><b>1° outcomes:</b></u> Nonfatal MI, nonfatal stroke, or CV death. <u><b>Results:</b></u> Mean SBP in the intensive therapy group was 119.3 mm Hg and in the standard therapy group was 133.5 mm Hg. The annual 1° outcome 1.87% in the intensive therapy group and 2.09% in the standard therapy group HR: 0.88; 95% CI: 0.073–1.06; p=0.20. The annual rates of death from any cause were 1.28% and 1.19% in the 2 groups, respectively (HR: 0.59; 95% CI: 0.39–0.89; p=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive therapy group and 1.3% of the standard therapy group (p<0.001).	Limitations: This trial had an open label design. The rate of adverse events in the standard therapy group was less than expected. Pts younger than 40 y or older than 79 y were not included. Summary: In pts with DM-2 and high risk for CV events, targeting SBP of <120 as compared with <140 mm Hg did not reduce the rate of composite outcome of fatal and nonfatal major CV events and was associated with greater risk for adverse events.

Margolis KL et al., 2014 (235) <u>24595629</u>	Aim: To compare effects of combinations of standard and intensive treatment of glycemia and BP in the ACCORD trial. Study type: RCT Size: 4,733 pts, 4.7 y follow-up	Inclusion criteria:Type 2 DM withHgbA1c $\geq$ 7.5%; $\geq$ 40 ywith CVD or $\geq$ 55 y withanatomical evidence ofatherosclerosis,albuminuria, LVH, or atleast 2 additional riskfactors for CVD.Exclusion criteria:BMI $\geq$ 45, serumcreatinine >1.5, andother serious illness.	• Pts were randomly assigned to intensive therapy SBP<120 mm Hg or standard therapy SBP<140 mm Hg.	<ul> <li><u>1° outcomes:</u> Nonfatal MI, nonfatal stroke, or CV death.</li> <li><u>Results</u>: In the BP trial, risk of the 1° outcome was lower in the groups intensively treated for glycemia HR: 0.67 (95% CI: 0.50, 0.91), BP HR: 0.74 (95% CI: 0.55, 1.00), or both HR: 0.71 (95% CI: 0.52, 0.96) compared with combined standard BP and glycemia treatment. For 2° outcomes, MI was significantly reduced by intensive glycemia treatment and stroke by intensive BP treatment; most other HRs were neutral or favored intensive treatment groups.</li> </ul>	Limitations: 2° analysis; results analyzed across individual cells of a factorial design with shorter follow- up than originally intended reducing power to detect meaningful differences and interactions; results may not apply to younger, healthier diabetics. Conclusions: Either intensive BP or glycemia control reduced major CVD compared with combined standard treatment, but the combination was no better than the individual intensive interventions.
Soliman EZ et al., 2015 (236) 26459421	Aim: To compare effects of combinations of standard and intensive control of BP on the risk of LVH in the ACCORD trial. Study type: RCT <u>Size</u> : 4,331 pts, 4.7 y follow-up	Inclusion criteria: DM- 2 with HgbA1c ≥7.5%; ≥40 y with CVD or ≥55 y with anatomical evidence of atherosclerosis, albuminuria, LVH, or at least 2 additional risk factors for CVD. Exclusion criteria: BMI ≥45, serum creatinine >1.5, and other serious illness.	• Pts were randomly assigned to intensive therapy SBP<120 mm Hg or standard therapy SBP<140 mm Hg.	<u><b>1° outcomes:</b></u> Nonfatal MI, nonfatal stroke, or CV death. <u><b>Results</b></u> : The outcome measures were electrocardiographic LVH defined by Cornell voltage (binary variable) and mean Cornell index (continuous variable). The baseline prevalence of LVH (5.3% vs. 5.4%; p=0.91) and the mean Cornell index (1,456 vs. 1,470 $\mu$ V; p=0.45) were similar in the intensive (n=2,154) and standard (n=2,177) BP- lowering arms, respectively. However, after median follow-up of 4.4 y, intensive, compared with standard, BP lowering was associated with a 39% lower risk of LVH (OR: 0.61; 95% CI: 0.43–0.88; p=0.008) and a significantly lower adjusted mean Cornell index (1,352 vs. 1,447 μV; p<0.001). The lower risk of LVH associated with intensive BP lowering during follow-up was because of more regression of baseline LVH and lower rate of developing new LVH, compared with standard BP lowering. No interactions by age, sex, or race were observed.	Limitations: 2° analysis; open-label design; LVH defined by EKG and not by echo or cardiac MRI; results may not apply to younger, healthier diabetics. Conclusions: Targeting a SBP of <120 mm Hg when compared with <140 mm Hg in pts with HTN and DM produces a greater reduction in LVH

Xie X, et al.,	Aim: To assess the	Inclusion criteria:	• 5 RCTs (6,960	1º outcomes: Major CV events, defined as	Study limitations: Only 6,960 pts
2015 (21)	efficacy and safety	RCTs with different BP	pts) enrolled only	MI, stroke, HF or CV death, separately and	with DM were included in the total
20009/44	OF INTENSIVE BP	changes between more	pts with DIVI and 6	combined; nonvascular and all-cause	Sludy Size of 44,989 pls.
	iowening strategies.	vs loss intonso thorany	lials (2,809 pls)	monality; ESKD; and adverse events; new onsot microalbuminuria.	Conclusions: The absolute CV
	Study type	with at least 6 mo	specifically recruited	change from micro, to macroalbuminuria and	benefits were greatest in trials in
	Systematic review	follow-up	pts with OKD.	retinonathy in nts with DM	which all enrolled pts had vascular
	and meta-analysis				disease, renal disease or DM.
	, , , , , , , , , , , , , , , , , , ,	Exclusion criteria:		Results: Pts in the more intensive BP-	However, only 6,960 of the 44,989
	Size: 19 trials with	Trials that did not		lowering treatment group had mean BP	pts had DM and no sub-analysis for
	44,989 pts; 3.8 y of	assess a different		133/76 mm Hg compared with 140/81 mm	DM was provided; however, the
	follow-up.	target or relevant		Hg in the less intensive group. Intensive BP-	outcome benefits were qualitatively
		outcome.		lowering treatment achieved RR reductions	most striking for pts with DM, CKD
				for major CV events: 14% (95% CI: 4–22),	and/or vascular disease.
				MI: 13% (95% CI: 0–24), stroke: 22% (95%	
				CI: 10–32), albuminuria: 10% (95% CI: 3–	
				16), and relinopatiny progression: 19% (95%	
				CI. 0-34). HOWEVEL, HILLE INTENSIVE	
				15% (05% CI: 11-34) CV death: 0% (11-	
				$(95\% \text{ Cl}^{-11})$ , $(95\% \text{ Cl}^{-11})$ , $(95\% \text{ Cl}^{-11})$ , $(95\% \text{ Cl}^{-11})$ , or	
				ESKD: 10% (95% CI: -6–23). The reduction	
				in major CV events was consistent across pt	
				groups, and additional BP lowering had a	
				clear benefit even in pts with SBP <140 mm	
				Hg. The absolute benefits were greatest in	
				trials in which all enrolled pts had vascular	
				disease, renal disease, or DM. Serious	
				adverse events associated with BP lowering	
				were only reported by 6 trials and had an	
				event rate of 1%–2% per y in intensive BP	
				lowering group pts, compared with 0.9% in	
				The less intensive treatment group (RR: 1.35;	
				75% CI. 0.73-1.77). Severe hypotension Was	
				treatment regimen (RR· 2.48· 05% CI· 1.21	
				5.89: $n=0.015$ ) but the absolute excess was	
				small ( $0.3\%$ vs. $0.1\%$ per pt-v for the duration	
				of follow-up).	

ACCOMPLISH Weber MA, et al., 2010 (237) 20620720	Aim: To determine which combination therapy in pts with HTN and DM most effectively decreases CV events. Study type: RCT Size: 2,842 pts with DM from the ACCOMPLISH study of 6,946 pts; 30 mo follow-up	Inclusion criteria: HTN and DM with high risk for CV events. Exclusion criteria: BMI >45; serum Cr >1.5; other serious illness	• Pts were randomly assigned to benazepril plus amlodipine or benazepril plus hydrochlorothiazide. BPs were 145/79 at baseline.	<u>1° outcomes</u> : Composite of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. <u>Results</u> : The mean achieved BP was 131.5/72.6 and 132.7/73.7 in the B + A and B + H groups, respectively, during the 30 mo of follow-up. There were 8.8% and 11% 1° events, respectively (HR: 0.79; 95% CI: 0.684–0.92; p=0.003). In the pts with DM there were clear coronary benefits with B + A, including both acute clinical events (p=0.013 and revascularizations (p=0.024). There were no unexpected adverse events.	Summary: In pts with DM and HTN, combining an ACEI with a CCB, compared with hydrochlorothiazide, was superior in reducing CV events.
ASCOT Ostergren J, et al., 2008 (238) <u>18854748</u>	Aim: To compare the effects of an amlodipine-based regimen vs. and atenolol-based regimen on CV outcomes in pts with DM Study type: RCT (BP lowering arm of ASCOT) Size: 5,137 pts with DM, minimum 4 y follow-up	Inclusion criteria: Pts 40–65 y with HTN (>160/100 mm Hg) or treated HTN and DM plus 2 additional CV risk factors: PAD, previous stroke or TIA, male sex, ≥55 y, microalbuminuria, smoking, total cholesterol to HDL ratio ≥6, or family history of CHD.	• Pts were randomly assigned to an amlodipine- based regimen with addition of perindopril as required or an atenolol-based regimen with addition of a thiazide as required and therapy titrated as required to achieve target BP of 130/80 mm Hg.	<u><b>1° outcomes:</b></u> Fatal CHD and nonfatal MI. <u><b>Results</b></u> : BPs were 136/75 (amlodipine and 137/76 (atenolol) at the end of study. There was a 3/1.9 mm Hg lower BP in pts on amlodipine. The amlodipine-based regimen reduced CV events and procedures compared to the atenolol-based regimen (HR 0.86; 0.76-0.98; p=0.026). Fatal and nonfatal strokes were reduced by 25% (p=0.017), PAD by 48% (p=0.004) and noncoronary vascularization procedures by 57% (p=0.001).	Summary: In the large DM subgroup of the BP-lowering arm of ASCOT, the benefits of an amlodipine-based treatment compared with an atenolol-based treatment on the incidence of total CV events and procedures was significant.
SHEP Kostis JB, et al., 2005 (239) <u>15619390</u>	<u>Aim:</u> To assess the long-term mortality rate of pts with DM pts in the SHEP trial randomly assigned to stepped care with chlorthalidone or placebo.	Inclusion criteria: Isolated systolic HTN (SBP 160–219 mm Hg) with DBP <90 mm Hg. Exclusion criteria: Pts with insulin–dependent DM and those who	• Pts were randomly assigned to chlorthalidone or placebo. If BP remained above goal, atenolol or placebo was added.	<u><b>1° outcomes:</b></u> CV mortality rate <u><b>Results</b></u> : BP was 11.1/3.4 mm Hg lower in the active treatment group at the end of the study. Diuretic treatment in pts with DM was strongly associated with long-term CV mortality rate (AHR: 0.668 (95% CI: 0.526,	Summary: Chlorthalidone-based treatment improved long-term outcomes in pts with DM.

	Study type: RCT Size: 4,732 pts; follow-up 14.3 y	required diuretic therapy.		0.848) and total mortality rate: 0.805 (95% CI: 0.680, 0.952).	
ROADMAP Menne J, et al., 2012 (240) <u>22418908</u>	Aim: To assess whether olmesartan compared to placebo delays the onset of albuminuria in pts with DM and HTN. Study type: RCT Size: 4,020 pts; follow-up 3.2 y	Inclusion criteria: Pts with HTN defined as BP ≥130/80 mm Hg and at least 1 CV risk factor.	• Pts were randomly assigned to olmesartan or placebo. Additional antihypertensive therapy except for ACEs and ARBs to lower BP.	<u>1° outcome:</u> Time to onset of microalbuminuria. <u>Results</u> : Average BP was 126.3/74.7 and 129.5/76.6, respectively (significant not stated). Olmesartan delayed the onset of microalbuminuria by 25% (0.75; 95% CI: 0.61–0.92; p=0.007). CV events were comparable in the 2 groups.	<u>Summary:</u> Pts with better BP reduction are less likely to develop microalbuminuria. Treatment with an ARB delayed the onset of microalbuminuria independently of baseline BP and degree of BP reduction.
ABCD Estacio RO, et al., 1998 (241) <u>9486993</u>	Aim: To compare the effects of "intensive" compared with "moderate" BP treatment on 24-h creatinine clearance (GFR) in pts with DM and HTN. <u>Study type</u> : RCT – open label <u>Size:</u> 472 pts; follow- up 5 y	Inclusion criteria: Pts with HTN defined as DBP ≥90 mm Hg and DM-2	Pts were randomly assigned to "intensive" treatment (DBP<75 mm Hg and "moderate" treatment (DBP 80– 89 mm Hg) with a combination of nisoldipine and enalapril as the initial antihypertensive medication.	<ul> <li><u>1° outcome</u>: Change in 24-h creatinine clearance.</li> <li><u>Results</u>:         <ul> <li>The mean BP achieved was 132/78 in the intensive group and 138/86 in the moderate control group. During the 5-y follow-up period, there was no difference in GFR between the groups. After the first y of antihypertensive treatment, GFR stabilized in both the intensive and moderate groups with normal albumin excretion or microalbuminuria. In contrast, pts with overt albuminuria demonstrated steady decline in GFR whether on intensive or moderate therapy. Neither was there a significant difference in the progression from normal to micro- or micro-to overt albuminuria.</li> <li>Intensive therapy demonstrated a lower overall incidence of deaths, 5.5% vs. 10.7%; p=0.037 (2° endpoint).</li> </ul> </li> </ul>	Limitations: Open-label design; the definition of DM was 2 fasting blood glucose measurements >140 mg/dL as opposed to >126 today; serious side effects were not reported. Risk of bias due to a greater proportion of pts with established CVD at baseline assigned to the standard BP target. Summary: BP control of 138/86 or 132/78 with either nisoldipine or enalapril as the initial antihypertensive agent appeared to stabilize renal function in HTN pts with type 2 DM without overt albuminuria over a 5-y period. For the ABCD trials, only ABDC (H) included strictly pts with HTN and DM. The quality of evidence is low due to imprecision and risk of bias.
Hypertension Optimal Treatment (HOT trial)	Aim: To assess the optimum target DBP	Inclusion criteria: Pts with HTN defined as	<ul> <li>Pts were randomly assigned to 1 of 3 DBP target</li> </ul>	<u><b>1° outcomes:</b></u> Major CV events, MI, stroke, CV mortality and total mortality.	Limitations: Open-label design; the definition of DM-2 fasting blood glucose measurements >140 mg/dL

Hansson L, et al.,	in the treatment of	DBP 100–115 mm Hg	groups: ≤90, ≤85,	<u>Results:</u> In the group randomized to $\leq 80$	as opposed to >126 today; serious
1998 (242) 9635947	HIN.		or ≤80 mm Hg.	halved in comparison to the target <90 CV	side effects were not reported;
1000711	Study type: RCT			mortality was lower in the $\leq 80$ group	analysis.
				compared to the other groups.	5
	Size: 1,501 pts in				Summary: In pts with DM and HTN,
	the DM subgroup;				Intensive lowering of BP was
	ioliow-up s.o y				events. The quality of evidence is
					low to very low due to imprecision
					and risk of bias.
UKPDS	Aim: To determine	Inclusion criteria:	Pts were	<u>1° outcomes:</u>	Limitations: DBP targets were high
1998 (243)	whether tight control	Fasting plasma glucose	randomized to tight	1) First clinical endpoint related to DM	(85 mm Hg in the tight control group
9732337	of BP prevents	concentration >6	BP control (target	(sudden death, death from hyperglycemia or	and 105 mm Hg in the less tight
	macrovascular and	mmoi/i in 2 mornings.	BP<150/85 mm Hg)	hypoglycemia, fatal or nonfatal MI, angina,	control group) and similar to the
	complications in pts	Exclusion criteria	on tess light BP	hemorrhage, retinal photocoagulation	in trials comparing treatment with no
	with DM-2.	Ketonuria >3 mmol/l:	<180/105  mm Ha	blindness in 1 eve or cataract extraction)	treatment. UKPDS evaluated
		history of MI in the	(Too, Too IIIII Tig),	2) Death related to DM.	lowering both SBP and DBP so it is
	Study type: RCT	previous y; current		3) Death from all causes.	impossible to separate the outcomes
		angina or HF; >1 major			effects of DBP. Therefore, the
	<u>Size:</u> 1,148	vascular episode;		<u>Results</u> : BP in the tight BP control group	evidence is of low quality.
	hypertensive pts with	serum creatinine		was 144/82 compared with the group	Summary: Tight PD control in ptc
	type z Divi	LUNCENII alion > 175		assigned less light control (154/87), $p_{c0} = 0.0001$ . Reductions in risk in the group	<u>Summary.</u> Fight BP control in pts with HTN and DM-2 achieved a
	Follow-up: 8.4 v	requiring laser		assigned tight BP control compared with	clinically important reduction in the
	<u>_</u> ,	treatment; malignant		those of the less tight control group were	risk of death related to DM,
		HTN; an uncorrected		24% (95% CI: 8%–38%; p=0.0046) in DM	complications related to DM,
		endocrine abnormality;		related endpoints; 32% in deaths related to	progression of DM retinopathy and
		an occupation that		DM (95% CI: 6%–51%; p<0.019; 44% in	deterioration of visual acuity, but the
		would preclude insulin		strokes (95% CI: 11%–65%; p<0.013; and	quality of evidence is low.
				37% (95% CI: 11%–36%; p<0.0092 In	
		inadequate		to risk of retinal photocoagulation	
		understanding or			
		unwillingness to enter			
		the study.			
Arguedas JA, et al.,	Aim: To determine if	Inclusion criteria:	Pts with HTN and	<u>1° outcomes:</u> Total mortality, total serious	Conclusions: Evidence from RCTs
2013 (244)	"Iower" BP targets	RCIS IN Which	DM were randomly	adverse events, MI, stroke, CHF, and ESRD.	does not support BP targets lower
<u>24170009</u>	(any larget < 130/85	inuividuais were	assigned to the		

	mm Hg) are	randomized to a "lower"	intensive or	Results: Only 1 trial (ACCORD) compared	than standard targets in pts with
	associated with	compared with a	standard BP control	outcomes associated with 'lower' (<120 mm	HTN and DM.
	reduction in mortality	"standard" BP target.	aroup.	Ha) or 'standard' (<140 mm Ha) SBP targets	
	and morbidity	Jan 1997	5	in 4734 pts. Despite achieving a significantly	
	compared to	Exclusion criteria:		lower BP (119.3/64.4 mm Ha vs. 133.5/70.5	
	"standard" BP	Studies that did not		mm Hg, p<0.0001), and using more	
	targets (<140-	meet the inclusion		antihypertensive medications, the only	
	160/90–100 mm Ha)	criteria. Excluded		significant benefit in the group assigned to	
	in pts with DM.	studies were UKPDS		'lower' SBP was a reduction in the incidence	
	1	1998, HTN in Diabetes		of stroke: RR: 0.58; (95% CI: 0.39–0.88;	
	Study type: Meta-	Study IV 1996, SANDS		p=0.009), absolute risk reduction 1.1%. The	
	analysis of RCTs.	2008, Lewis 1999 and		effect of SBP targets on mortality was	
	5	the Steno-2 study.		compatible with both a reduction and	
	Size: 5 RCTs			increase in risk: RR: 1.05 (95% CI: 0.84,	
	recruiting a total of			1.30), low quality evidence. Trying to achieve	
	7,314 ps.			the 'lower' SBP target was associated with a	
				significant increase in the number of other	
	Mean follow-up: 4.5			serious adverse events: RR: 2.58, (95% CI:	
	у			1.70–3.91; p<0.00001, absolute risk increase	
				2.0%. 4 trials (ABCD-H, ABCD-N, ABCD-2V,	
				and a subgroup of HTN Optimal Treatment)	
				specifically compared clinical outcomes	
				associated with 'lower' vs. 'standard' targets	
				for DBP in pts with DM. The total number of	
				pts included in the DBP target analysis was	
				2580. Pts assigned to 'lower' DBP had a	
				significantly lower achieved BP: 128/76 mm	
				Hg vs. 135/83 mm Hg; p<0.0001. There was	
				a trend towards reduction in total mortality in	
				the group assigned to the 'lower' DBP target:	
				RR: 0.73 (95% CI: 0.53–1.01), mainly due to	
				a trend to lower non-CV mortality. There was	
				no difference in stroke: RR: 0.67, (95% CI:	
				0.42–1.05), In MI: RR: 0.95 (95% CI: 0.64–	
				1.40) OF IN CHF: RR: 1.06 (95% CI: 0.58–	
				1.92), low-quality evidence. End-stage renal	
				ratione and total serious adverse events were	
				not reported in any of the trials. A sensitivity	
				analysis of thats comparing DBP targets <80	
1	1			I mm Hg (as suggested in clinical guidelines)	

				vs. <90 mm Hg showed similar results. There was a high risk of selection bias for every outcome analyzed in favor of the 'lower'	
				target in the trials included for the analysis of DBP targets.	
Palmer SC, et al., 2015 (245) <u>26009228</u>	Aim: To investigate the benefits and harms of BP- lowering drugs in adults with DM Study type: Network meta-analysis of RCTs. Size: 157 studies in 43,256 pts mostly with DM and CKD. Mean follow-up: 4.5 y	Inclusion criteria: Pts ≥18 y with DM and CKD and were treated in clinical trials that compared any orally administered antihypertensive agent alone or in combination with a 2nd antihypertensive agent or combination, placebo, or control. Exclusion criteria: Pts who underwent kidney transplantation or dialysis.	N/A	<u>1° outcomes</u> : All-cause mortality and ESKD (need for dialysis or transplantation). <u>Results:</u> No drug regimen was more effective than placebo for reducing all-cause mortality. However, compared with placebo, ESRD was significantly less likely after dual treatment with an ARB and an ACEI: OR: 0.62 (95% CI: 0.43–0.90) and after ARB monotherapy: OR: 0.77 (95% CI: 0.65–0.92). No regimen significantly increased hyperkalemia or acute kidney injury, although combined ACEI and ARB treatment had the lowest rank among all interventions because of borderline increases in estimated risks of these harms; OR: 2.69 (95% CI: 0.97–7.47) for hyperkalemia; OR: 2.69 (95% CI: 0.98– 7.38) for acute kidney injury.	Limitations: Effects of BP treatment on CV events and related mortality were uncertain. Data for the outcome of ESKD were restricted largely to pts with macroalbuminuria. Acute kidney injury was poorly defined with low quality of evidence. Conclusions: No BP-lowering strategy prolonged survival in adults with DM and CKD. ACEIs and ARBs, alone or in combination, were the most effective strategies against ESKD. Any benefits of combined ACEI and ARB treatment need to be balanced against potential harms of hyperkalemia and acute kidney injury.
Turnbull F, et al., 2005 (246) <u>15983291</u>	Aim: To determine the benefits associated with different treatment regimens in pts with and without DM and whether there are important differences in the effects of different BP-lowering regimens in these 2 pt groups. Study type: Meta- analysis of RCTs.	Inclusion criteria: Randomization of pts between a BP-lowering agent and a control (placebo or less intensive BP-lowering regimen) or randomization of pts between regimens based on different classes of BP-lowering drugs. Exclusion criteria: Studies not meeting the above criteria.	N/A	<u>1° outcomes</u> : Nonfatal stroke or death from cerebrovascular disease; nonfatal MI or death from CAD; HF causing death or requiring hospitalization; total CV events; total CV deaths; and total mortality. <u>Results</u> : Total major CV events were reduced to a comparable extent in individuals with and without DM by regimens based on ACEIs, calcium antagonists, ARBs and diuretics/ BBs (p<0.19 for all). There was limited evidence that lower BP goals produced larger reductions in total major CV events in pts with vs. without DM (p<0.03).	Limitations: No analysis of renal outcomes, risk of new DM or progression of existing DM; combined comparison of persons taking diuretics and BB s; some studies selected pts on the basis of the presence or absence of DM. Summary: Effects of BP-lowering agents on major CV events were broadly comparable for pts with and without DM.

	Size: 27 RCTs including 158,709 pts (33,395 with DM and 125,314 without DM). Follow-up: Minimum 1,000 pt-y				
ALLHAI Whelton PK, et al., 2005 (247) <u>15983290</u>	Aim: I o determine the optimal first step antihypertensive drug therapy in DM- 2 or impaired fasting blood glucose levels and specifically whether treatment with a CCB or ACEI decreases clinical complications compared to treatment with a thiazide type diuretic. Study type: RCT <u>Size</u> : 31,512 pts stratified into type 2 DM (13,101), IFG (1,399) and normoglycemia (17,012)	Inclusion criteria: Pts ≥55 y with HTN and at least 1 other risk factor for CHD. Exclusion criteria: No history of DM or no fasting glucose measurement or nonfasting glucose level ≥110 mg/dL.	• Pts were randomly assigned to double-blind first- step treatment with chlorthalidone 12.525 mg/d, amlodipine 2.5–10 mg/d or Lisinopril 10–40 mg/d.	<u>1° outcomes:</u> Fatal CHD and nonfatal MI <u>Results</u> : There was no significant difference in RR (RR) for the 1° outcome in DM or NG pts assigned to amlodipine or lisinopril vs. chlorthalidone or in IFG pts assigned to lisinopril vs. chlorthalidone RR: 1.73 (95% CI: 1.10, 2.72). A significantly higher RR was noted for the 1° outcome in IFG pts assigned to amlodipine vs. chlorthalidone. Stroke was more common in NG pts assigned to lisinopril vs. chlorthalidone RR: 1.31 (95% CI: 1.10, 1.57). HF was more common in DM and NG pts assigned to amlodipine RR: 1.39 (95% CI: 1.22, 1.59) and 1.30 (95% CI: 1.12, 1.51), respectively or lisinopril: 1.15 (95% CI: 1.00–1.32) and 1.19 (95% CI: 1.02, 1.39), respectively vs. chlorthalidone.	Limitations: Microalbuminuria was not measured. Summary: Our results provide no evidence of superiority for treatment with CCBs or ACEIs compared with a thiazide-type diuretic during first- step antihypertensive therapy in DM, IFG, or NG.

### Data Supplement 47. Nonrandomized Trials, Observational Studies, and/or Registries in DM (Section 9.6)

ADVANCE Hata J, et al., 2013 (248) 23926207	Aim: To assess the effects of visit-to-visit SBP variability and maximum SBP on the risks of macrovascular or microvascular outcomes by using data from the ADVANCE trial. Study type: Observational analysis Size: 8.811 pts	Inclusion criteria: Pts had not experienced major macro- or microvascular events during first 2 y of the ADVANCE trial Exclusion criteria: None	<u>1° endpoint</u> : Composite of CV death, nonfatal MI, nonfatal stroke, new or worsening nephropathy, or retinopathy. <u>Results:</u> Major macro- and micro-vascular events were associated with SBP variability even after adjustment for mean SBP and other confounding factors. For the highest 10% variability, HR: 1.54 (95% CI: 0.99, 2.39) for macrovascular events; for microvascular events, HR: 1.84 (95% CI: 1.19, 2.84).	Summary: Visit-to-visit SBP variability and maximum SBP are independent risk factors for macro- and micro-vascular events.
ADVANCE-ON Zoungas S, et al., 2014 (249) 25234206	Aim: To determine whether the mortality benefit that had been observed among pts originally assigned to BP- lowering therapy were still evident at the end of 6-y follow-up Study type: Observational analysis Size: 8,494 pts	Inclusion criteria: Pts with DM who participated in post- trial follow-up for 6 y Exclusion criteria: See above	<u>1° endpoint</u> : Death from any cause and major macrovascular complications (a composite of nonfatal MI, nonfatal stroke, or death from any CV cause. <u>Results:</u> The reductions in the risk of death from any cause and of death from CV causes that had been observed in the group receiving active BP-lowering treatment during the ADVANCE trial were attenuated but significant at the end of the post-trial follow- up. HRs were 0.95 (95% CI: 0.84–0.99; p=0.03) and 0.88 (95% CI: 0.77–0.99; p=0.04), respectively.	Summary: Benefits were attenuated but still present at the end of 6 y.
ROADMAP Mene J, et al., 2014 (250) 24772521	Aim: To determine whether the ROADMAP olmesartan medoxomil treatment resulted in a potential long-term micro- and macro-vascular benefit. <u>Study type</u> : Observational analysis <u>Size</u> : 1,758 pts; 3.3 y follow- up	Inclusion criteria: See above Exclusion criteria: See above	<u>1° endpoint:</u> See above <u>Results:</u> The original ROADMAP study showed a 23% reduction in microalbuminuria despite good and comparable BP control in both groups. Pts who developed microalbuminuria had a higher incidence of cardio- and cerebrovascular events: OR: 1.77 (95% CI: 1.03–3.03; p=0.039) compared to those in whom this was not the case. DM retinopathy and HF requiring hospitalization also were reduced.	Summary: renal artery stenosis blockade might cause a sustained reduction in micro- and macro-vascular events.
2015 (251)	between BP-lowering	of BP-lowering treatment in	• BP-lowering drug vs. placebo: 26 RCTS	is limited by the scarcity of large trials with

	<u>25668264</u>	treatment and presence of	which entire trial population	<ul> <li>More intensive vs. less intensive BP</li> </ul>	achieved SBP levels in the 120–130 mm Hg
		vascular disease in DM-2	had DM-2 or in which the	lowering: 7 RCTs	range. The relatively short follow-up of
			results of a DM subgroup	• BP-lowering vs. another drug: 17 RCTs	included trails may have prevented
		Study type: Large meta-	were obtained. Studies were	5 5	associations of BP-lowering treatment with
		analysis of	included regardless of the	Results: Baseline BP: A 10-mm Hg SBP	vascular outcomes from being observed,
		40 high quality RCTs (1/1966–	presence or absence of	reduction was associated with a significantly	particularly for outcomes such as HF and
		10/2014) judged low risk of	defined HTN.	lower risk of all-cause mortality RR: 0.87	renal failure, which are often a consequence
		bias		(95% CI: 0.78–0.96), CVD events RR: 0.89	of MI or albuminuria, respectively.
			Exclusion criteria: Trials	(95% CI: 0.80–0.98), and stroke events RR:	
		Size: 100,354 pts with DM; all	conducted predominantly in	0.73 (95% CI: 0.64–0.83). The associations	<u>Summary</u> :
		trials >1,000 pt-y of follow-up	pts with type 1 DM were	for HF and renal failure were not significant.	<ul> <li>This large meta-analysis of 40 RCTs</li> </ul>
		BP-lowering drug vs. placebo:	excluded.	For microvascular events, a 10-mm reduction	provides evidence that BP lowering is
		26 RCTs		in SBP was associated with a lower risk of	associated with lower risks of outcomes in pts
				retinopathy RR: 0.87 (95% CI: 0.76–0.99) and	with initial mean SBP $\geq$ 140 mm Hg compared
		<ul> <li>More intensive vs. less</li> </ul>		albuminuria RR: 0.83 (95% CI: 0.79–0.87).	with those <140 mm Hg with the exception of
		intensive BP lowering: 7 RCTs			stroke, albuminuria and retinopathy. When
		<ul> <li>BP-lowering vs. another</li> </ul>		Stratified by initial SBP:	trials were stratified by achieved SBP
		drug: 17 RCTs		Trials stratified by SBP >140 to <140 mm Hg	treatment was associated with lower risks only
				showed significant interactions for all-cause	in the <130 mm Hg stratum for stroke and
				mortality RR: 0.73 (95% CI: 0.64–0.84) vs.	albuminuria.
				1.07 (95% CI: 0.92–1.26), CVD RR: 0.74	<ul> <li>This meta-analysis shows that although BP</li> </ul>
				(95% CI: 0.65–0.85) vs. RR: 0.96 (95% CI:	lowering was not associated with a lower risk
				0.88–1.05), CHD RR: 0.73 (95% CI: 0.61–	of CVD or CHD events at a baseline SBP
				0.87) vs. RR: 0.97 (95% CI: 0.86–1.10), HF	<140 mm Hg, it does observe lower risks of
				RR: 0.75 (95% CI: 0.59–0.94) vs. RR: 0.97	stroke, retinopathy and progression of
				(95% CI: 0.79–1.19) and albuminuria RR:	albuminuria.
				0.71 (95% CI: 0.63–0.79) vs. RR: 0.86 (95%	<ul> <li>This study provides evidence that for</li> </ul>
				CI: 0.81–0.99).	individuals at high risk for these outcomes
					(history of cerebrovascular disease or mild
ļ				Stratified by achieved SBP:	nonproliferative retinopathy), commencement
				mais stratilied by SBP achieved in the	of therapy below an initial SBP of 140 mm Hg
				treatment group $\geq$ 130 or < 130 mm Hg and	and treatment to SBP <130 may be indicated.
				the associations of a 10-mm Hg SBP	
				reduction compared between the strata	
				snowed significant interactions for all-cause	
				MORTAILTY KK: U. /5 (95% CI: U.65–U.86) VS.	
				RR: 1.06 (95% CI: 0.90–1.265), CVD RR:	
				U. /4 (95% CI: U.64–U.85) VS. RR: U.96 (95%	
				CI: 0.88–1.05), CHD RR: 0.70 (95% CI: 0.58–	
				U.83) VS. KK: U.97 (95% CI: 0.85–1.10), HF	

			RR: 0.75 (95% CI: 0.59–0.95) vs. RR: 1.00 (95% CI: 0.81–1.23) and albuminuria RR: 0.71 (95% CI: 0.64–0.79) vs. RR: 0.86 (95% CI: 0.81–0.90) with higher risk in the ≥130 mm Hg group.	
			Stratified by class of medications: Few differences were observed in the association between BP-lowering treatment and outcomes for regimens based on different classes of medications, except HF, in which diuretics were associated with lower RR: 0.83 (95% CI: 0.72–0.95) than all other classes. This was driven largely by the results of ALLHAT.	
Cheng J, et al., 2014 (252) <u>24687000</u>	Aim: To separately evaluate the effects of ACEIs and ARBs on all-cause mortality, CV deaths, and major CV events in pts with DM Study type: Meta-analysis of 35 high quality RCTs (1966– 2012) Size: 56,444 pts with DM; all trials had follow-up of at least 12 mo	Inclusion criteria: RCTs including post hoc analyses and subgroups for DM with median follow-up of at least 12 mo. Comparisons with placebo, no treatment or other antihypertensive drugs, including ACEIs and ARBs. Exclusion criteria: Cross- over trials	• ACEIs significantly reduced the risk of all- cause mortality by 13% (RR: 0.87; 95% CI: 0.78–0.98), CV deaths by 17% (RR: 0.83; 95% CI: 0.70–0.99), and major CV events by 14% (RR: 0.86; 95% CI: 0.77–0.95), including MI by 21% (RR: 0.79; 95% CI: 0.65–0.95) and HF by 19% (RR: 0.81; 95% CI: 0.71–0.93). Treatment with ARBs did not significantly affect all-cause mortality (RR: 0.94 (95% CI: 0.82–1.08), CV death rate (RR: 1.21 (95% CI: 0.81–1.80) and major CV events (RR: 0.94; 95% CI: 0.85–1.01) with the exception of HF (RR: 0.70; 95% CI: 0.59–0.82).	<ul> <li>Summary:</li> <li>RCTs comparing ACEs vs. active drugs/placebo/no treatment: 26 RCTs (12 active drugs, 11 placebo)</li> <li>RCTs comparing ARBs vs. active drugs/placebo/no treatment: 13 RCTs (3 active drugs, 10 placebo)</li> <li>This meta-analysis provides evidence that ACEIs reduce all-cause mortality, CV mortality, and major CV events in pts with DM, whereas ARBs had no benefits on these outcomes.</li> </ul>
Arguedas JA, et al., 2013 (244) <u>24170669</u>	Aim: To determine if "lower" BP targets (any target <130/85 mm Hg) are associated with reduction in mortality and morbidity compared to "standard" BP targets (<140–160/90–100 mm Hg) in pts with DM. <u>Study type</u> : Meta-analysis of RCTs.	Inclusion criteria: RCTs in which individuals were randomized to a "lower" compared with a "standard" BP target. Exclusion criteria: Studies that did not meet the inclusion criteria. Excluded studies were UKPDS 1998, HTN in Diabetes Study IV	<u>1° outcomes:</u> Total mortality, total serious adverse events, MI, stroke, CHF, and ESRD. <u>Results</u> : Only 1 trial (ACCORD) compared outcomes associated with 'lower' (<120 mm Hg) or 'standard' (<140 mm Hg) SBP targets in 4734 pts. Despite achieving a significantly lower BP (119.3/64.4 mm Hg vs. 133.5/70.5 mm Hg, p<0.0001), and using more antihypertensive medications, the only significant benefit in the group assigned to 'lower' SBP was a reduction in the incidence	Conclusions: Evidence from RCTs does not support BP targets lower than standard targets in pts with HTN and DM.

		Size: 5 RCTs recruiting a total	1996, SANDS 2008, Lewis	of stroke: RR: 0.58 (95% CI: 0.39–0.88;	
		of 7,314 ps.	1999 and the Steno-2 study.	p=0.009), absolute risk reduction 1.1%. The	
		-	_	effect of SBP targets on mortality was	
		<u>Mean follow-up</u> : 4.5 y		compatible with both a reduction and increase	
				in risk: RR: 1.05 (95% CI: 0.84–1.30), low-	
				quality evidence. Trying to achieve the 'lower'	
				SBP target was associated with a significant	
				increase in the number of other serious	
				adverse events: RR: 2.58 (95% CI: 1.70–3.91;	
				p<0.00001), absolute risk increase 2.0%. 4	
				trials (ABCD-H, ABCD-N, ABCD-2V, and a	
				subgroup of HOT) specifically compared	
				clinical outcomes associated with 'lower' vs.	
				'standard' targets for DBP in pts with DM. The	
				total number of pts included in the DBP target	
				analysis was 2580. Pts assigned to 'lower'	
				DBP had a significantly lower achieved BP:	
				128/76 mm Ha vs. 135/83 mm Ha.	
				p < 0.0001. There was a trend towards	
				reduction in total mortality in the group	
				assigned to the 'lower' DBP target' RR: 0.73	
				$(95\% \text{ Cl} \cdot 0.53 - 1.01)$ mainly due to a trend to	
				lower non- CV mortality. There was no	
				difference in stroke: RR: 0.67 (95% CI: 0.42–	
				1.05 in MI: RR: 0.95 (95% CI: 0.64–1.40) or	
				in CHE: RR: 1.06 (95% CI: 0.58–1.92) low	
				quality evidence End-stage renal failure and	
				total serious adverse events were not	
				reported in any of the trials $\Delta$ sensitivity	
				analysis of trials comparing DRP targets <80	
				mm Ha (as suggested in clinical quidelines)	
				vs <00 mm Ha showed similar results. There	
				was a high risk of soloction higs for overy	
				autcome analyzed in favor of the 'lower' target	
				in the trials included for the analysis of DPD	
				taraote	
	Cuchmon MC of	Aim: To accoss whathar	Inclusion critoria: Type 2	I laryers.	Limitations: This trial had an open label
		AIIII. 10 d55855 WITELITEL	DM with Line A1 = > 7 50( > 40	therapy SPD (120 mm Lig or denderd therapy)	<u>Lininations</u> : This that have an open label
	ai., 2010 (234)	(120 mm Ha) reduces major	DIVI WITH HODA IC $\geq 1.5\%$ ; $\geq 40$	SPD 2140 mm Ha	etandard thorapy group was loss than
4	<u>20228401</u>	(< 120 mm Hg) reduces major	y with CVD or $\geq$ 55 y with	SBP<140 (1111) Hy.	stanuaru therapy group was less than
1			anatomical evidence of		

	CV events in type 2 DM at high risk for CV events.	atherosclerosis, albuminuria, LVH, or at least 2 additional risk factors for CVD.	<u>1° outcomes:</u> Nonfatal MI, nonfatal stroke, or CV death.	expected. Pts younger than 40 y or older than 79 y were not included.
	Study type: RCT	Exclusion criteria: BMI ≥45,	Results: Mean SBP in the intensive therapy group was 119.3 mm Hg and in the standard	<b><u>Summary</u></b> : In pts with type 2 DM and high risk for CV events, targeting SBP of <120 as
	<u>Size</u> : 4,733 pts, 4.7 y follow- up	serum creatinine >1.5, and other serious illness.	therapy group was 133.5 mm Hg. The annual 1° outcome 1.87% in the intensive therapy group and 2.09% in the standard therapy group HR: 0.88 (95% CI: 0.073–1.06; p=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the 2 groups, respectively (HR: 0.59; 95% CI: 0.39–0.89; p=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% of the intensive therapy group and 1.3% of the standard therapy group (p<0.001).	compared with <140 mm Hg did not reduce the rate of composite outcome of fatal and nonfatal major CV events and was associated with greater risk for adverse events.
Hartley L, et al.,	Aim: To determine the	Inclusion criteria: ≥3 mo	<u>1° outcomes</u> : Clinical CVD events and major	Limitations: Limited evidence
2014 (253)	effectiveness of	duration, healthy adults or	CVD risk factors	
<u>25436436</u>	transcendental meditation for	adults at high risk of CVD,		Summary: No conclusions as to the
	the 1° prevention of CVD	comparison of no or minimal	<u>Results:</u> No conclusions of the effectiveness	effectiveness of transcendental meditation for
	Chudu tumo, Literatura raviou	intervention.	of transcendental meditation for the 1°	the 1° prevention of CVD. There was
	study type: Literature review	Evolucion critorio: Multi	prevention of CVD	the included studies were small, short term
	UIRCIS	factorial interviews		and at overall serious risk of hiss
	Size: 4 trials with a total of			
	430 pts			
Schmieder RE, et al., 2007 (254)	Study type: Topic review	Inclusion criteria: N/A	<u>1° outcomes</u> : N/A	Limitations: N/A
<u>17416265</u>		Exclusion criteria: N/A	<u>Results:</u> N/A	<u>Summary</u> : N/A
Lv, et al.,	Aim: To assess the renal and	Inclusion criteria:	Results: Compared with standard regimens,	Limitations: All trials used open label, in 2 pts
2013 (127)	Lowering in people with CKD	Kandomized trials of pts     with CKD assigned to	more intensive BP lowering reduced risk of	were blinded, substantial variability in design
23798459	lowening in people with CRD	different target BP that	composite endpoint HR: 0.82 (95% CI: 0.68–	targets by MAP_SRP and DRP or only DRP
	Study type: Systematic	reported kidney failure and	0.98) and ESKD HR: 0.79 (95% CI: 0.67–	Most trials did not include pts with diabetic
	review	CV events.	(n=0.006) and markers of trial quality	kidney disease
	Size: 9 287 nts with CKD and	• IT ITIALS ON 9,287 PTS WITH CKD and 1.267 kidney failure	Intensive BP lowering reduced the risk of	
	1,264 kidney failure events	events (doubling of serum	kidney failure HR: 0.73 (95% CI: 0.62–0.86)	Summary:
	,	creatinine, 50% decline in	but not in pts without proteinuria at baseline	• Renal outcomes: 7 trials (N=5308) recorded
		GFR or ESKD)	HR: 1.12 (95% CI: 0.67–1.87). No clear	a total of 1,264 kidney failure events. A -7.7
		<ul> <li>Included AASK, REIN-2,</li> </ul>	effect on CV events or death.	mm Hg difference in SBP and a -4.9 mm Hg

MDRD, Wuhl (children), Toto,	difference in DBP seen between treatment
Schrier plus 5 trials with CKD	arms. Overall, a more intensive regimen
subgroups, also included the	reduced risk of composite kidney failure
late nonrandomized follow-up	events by 17% (HR: 0.82; 95% CI: 0.68, 0.98),
studies for AASK and MDRD	reduced the risk of ESKD alone by 18%
<ul> <li>BP targets varied</li> </ul>	(pooled HR for composite outcomes: 0.79;
substantially between trials. 2	95% CI: 0.67, 0.93).
trials targeted mean BP <92	<ul> <li>Intensive BP lowering had no effect on</li> </ul>
mm Hg for the intensive	kidney failure in pts who did not have
treatment arm, and 107 mm	proteinuria (3 trials involving 1,218 pts (HR:
Hg in the standard treatment	1.12; 95% CI: 0.67–1.87), but it did reduce the
arm. 1 trial aimed for BP	risk of progressive kidney failure by 27% (5
<130/80 mm Hg vs. a DBP of	trials involving 1,703 pts (HR: 0.73; 95% CI:
90 mm Hg, 1 study targeted	0.62–0.86) in pts who did have proteinuria at
<120/80 mm Hg vs. 135–	baseline.
140/85–90 mm Hg, and 4	• CV outcomes: major CV events reported in
studies had DBP <75-80 mm	5 trials (472 CV events in 5,308 pts with CKD).
Hg vs. from 80–90 mm Hg. A	Intensive BP lowering did not reduce risk of
trial involving pediatric pts	CV events in pts with CKD, but the CIs
targeted a 24-h mean BP	remained wide (RR: 1.09 (95% CI: 0.83)
<the 50th="" percentile,<="" td=""><td>1.42), 6 trials reported stroke outcomes (197</td></the>	1.42), 6 trials reported stroke outcomes (197
compared with the 50th to	events in 5 411 pts) 5 trials reported MI (138
95th percentiles in the control	events in 4 317 nts) and 5 trials reported HF
group. 2 trials had more	(118 events in 5 308 pts). They saw no clear
liberal targets for intensive	effect of intensive treatment on any of these
treatment (<140–150 mm Hg	vascular outcomes
SBP, 85 mm Hg DBP)	<ul> <li>Death: 10 trials involving 6 788 pts reported</li> </ul>
	• Deam. To mais involving 0,700 pis reputed
	intensive PD lowering on risk of all cause
	dooth (DD, 0.04 (05% CI; 0.94, 1.05) or CV
	uediii (KK: 0.94 (93% CI: 0.84, 1.05) 01 CV dooth (DD: 1.20 (05% CI: 0.92, 1.75)
	ueaiii (kk: 1.20 (93% CI: 0.82, 1.75).

# Data Supplement 48. Atrial Fibrillation (Section 9.8)

Study Acronym; Author; Year Published	Aim of Study	Study Type	Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoints	P Value; OR, HR, or RR; & 95% Cl	Study Limitations & Adverse Events
Jibrini, et al., 2008 (255) <u>18223352</u>	Aim: To assess the effectiveness of ACEIs and ARBs in the prevention of AF, and to identify those clinical entities in which RAAS inhibition would most likely benefit the pts.	<u>Study type</u> : Meta-analysis	• 11 published studies; 55, 989 pts (26,973 pts in intervention, 29,016pts in comparator)	Inclusion criteria: Studies of RAAS blockade in CHF, MI, electrical cardioversion, and HTN) with incidence of AF noted during follow-up. Exclusion criteria: Studies without the measurement of AF or use of RAAS blockade.	Intervention: RAAS blockade Intervention: Placebo, amlodipine, BB or thiazide diuretic	<u>1° endpoint</u> (efficacy) and results: AF occurrence or reoccurrence.	Treatment with RAAS blockers reduced RR of AF in pts with HTN by 23% (p<0.001), by 11% in pts after MI (p<0.05), by 51% after electrical cardioversion (p<0.001), by 32% in pts with HF (p<0.001) and by 19% overall (p<0.001).	• Not a comprehensive analysis of all antihypertensive. Adverse events not catalogued in meta-analysis.
Zhao et al., 2015 (256) <u>26668582</u>	Aim: To investigate the effectiveness and safety of ACEIs or angiotensin II receptor blockers (ARBs) on preventing AF in essential hypertensive pts. Study type: Meta-analysis	Intervention: RAAS blockade, n=20,491 <u>Comparator</u> : BB/calcium antagonist, n=22,401	Inclusion criteria: RCTs on the effects of ACEI/ ARBs on essential hypertensive pts. Exclusion criteria: Non- RCTs, subjects who were not treated with ACEI or ARB, and trials not	<u>1° endpoint</u> : AF occurrence or reoccurrence.	• ACEI/ARBs reduced the incidence of AF recurrence compared to calcium antagonists (RR: 0.48; 95% CI: 0.40–0.58; p<0.00001) or b-blockers (RR: 0.39; 95% CI: 0.20– 0.74; p=0.005). ACEI/ARBs may reduce the incidence of AF recurrence and CHF, with fewer serious adverse effects, but did not prevent new onset of AF.	N/A	• Doxazosin was associated with a higher incidence (2%) of AF/AFL prior to having the drug discontinued by the trial. Excluding doxazosin, there was no relationship between treatment drug and AF/AFL incidence.	• 2° analysis of RCT.

<u>Size</u> : 10		mentioning of			
studies,		AF prevention.			
n=42,89	2				

# Data Supplement 49. Valvular Heart Disease (Section 9.9)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Study Intervention (# patients) / Study Comparator (# patients)	Patient Population	Endpoints	P Value; OR, HR, or RR; & 95% Cl	Study Limitations & Adverse Events
Healey et al., 2005 (257) <u>15936615</u>	<u>Aim</u> : Systematic review of all RCT evaluating the benefit of trials of ACEI and ARBs in prevention of AF <u>Study type</u> : Meta- analysis <u>Size</u> : 11 studies included with 56,308 pts	Intervention: n=27,089 RAAS blockade <u>Comparators</u> : n=29,220 placebo or active control antihypertensive	Inclusion criteria: Studies of RAAS blockade in CHF, MI, electrical cardioversion, and HTN) with incidence of AF noted during follow-up Exclusion criteria: Studies without the measurement of AF or use of RAAS blockade.	<u>1° endpoint</u> : AF occurrence or reoccurrence	• ACEIs and ARBs reduced RR of AF by 28% (p=0.0002), greatest in pts with HF [RR reduction: 44%; p=0.007). No significant reduction in AF in pts with HTN (RR reduction: 12%; p=0.4), but 1 trial found a significant 29% reduction in pts with LVH. Following cardioversion there was a large effect (48% RR reduction; 95% CI: 21%– 65%).	• ACEIs and ARBs appear to be effective in prevention of AF probably limited to pts with systolic LV dysfunction or HTN LVH
Jibrini et al., 2008 (255) <u>18223352</u>	Aim: To assess the effectiveness of ACEIs and ARBs in the prevention of AF, and to identify those clinical entities in which RAAS inhibition would most likely benefit the pts. Study type: Meta- analysis	Intervention: n=26,973 RAAS blockade <u>Comparators</u> : n=29,016 placebo, amlodipine, BB or thiazide diuretic	Inclusion criteria: Studies of RAAS blockade in CHF, MI, electrical cardioversion, and HTN) with incidence of AF noted during follow-up Exclusion criteria: Studies without the measurement of AF or use of RAAS blockade.	<u>1° endpoint</u> : AF occurrence or reoccurrence.	• Treatment with RAAS blockers reduced RR of AF in pts with HTN by 23% (p<0.001), by 11% in pts after MI (p<0.05), by 51% after electrical cardioversion (p<0.001), by 32% in pts with HF (p<0.001) and by 19% overall (p<0.001).	N/A

	Size: 11 studies, 55,989 pts					
Zhao et al., 2015 (256) <u>26668582</u>	Aim: To investigate the effectiveness and safety of ACEIs or angiotensin II receptor blockers (ARBs) on preventing AF in essential hypertensive pts. Study type: Meta- analysis Size: 10 studies, n=42,892	Intervention: RAAS blockade, n=20,491 Comparator: BB/calcium antagonist, n=22,401	Inclusion criteria: RCTs on the effects of ACEI/ ARBs on essential hypertensive pts. Exclusion criteria: Non- RCTs, subjects who were not treated with ACEI or ARB, and trials not mentioning of AF prevention.	<u>1° endpoint</u> : AF occurrence or reoccurrence.	• ACEI/ARBs reduced the incidence of AF recurrence compared to calcium antagonists (RR: 0.48; 95% CI: 0.40–0.58; p<0.00001) or b-blockers (RR: 0.39; 95% CI: 0.20–0.74; p=0.005). ACEI/ARBs may reduce the incidence of AF recurrence and CHF, with fewer serious adverse effects, but did not prevent new onset of AF.	N/A
Hansson et al., 1999 (258) <u>10030325</u>	Aim: CAPP Trial was designed to compare the effects of ACE inhibition and conventional therapy on CV morbidity and mortality in pts with HTN. Study type: RCT Size: 10.985	Intervention: Captopril, n=5,592 Comparator: 5,493 pts were allocated to diuretics or BBs	Inclusion criteria: Pts aged 25–66 y with a measured DBP of ≥100 mm Hg on 2 occasions were included. Exclusion criteria: 2° HTN, serum creatinine concentration of more than 150 micromol/L, and disorders that required treatment with BB.	1° endpoint:ratal andnonfatal MI and stroke,and other CV deaths.2° endpoint:New or deterioratedIHD and CHF, AF, DM,TIA s, and death fromall causes.	• Captopril and conventional treatment did not differ in rates of all cardiac events— fatal and nonfatal MI, other CV deaths and sudden deaths, IHD, CHF, or AF (0.94; p=0.30).	N/A
Hansson et al., 1999 (259) <u>10577635</u>	Aim: STOPH-2 aimed to compare the effects of conventional and newer antihypertensive drugs on CV mortality and morbidity in elderly pts.	Intervention: n=2205 pts treated with ACEI Comparator: n=2,213 pts treated with BB or diuretic combination or n=2,196 pts treated with CCB	Inclusion criteria: HTN with BP ≥ 180 mm Hg systolic, aged 70– 84 y Exclusion criteria: Outside of the age range (n=14)	<u>1° endpoint</u> : CV death <u>2° endpoint</u> : CV events, DM and AF	Old and new antihypertensive drugs were similar in prevention of CV mortality or major events. Decrease in BP was of major importance for the prevention of CV events. No difference in AF frequency was found (5.3% with ACEI, 4.1% with CCB and 5.2% with older drugs).	N/A

	Study type: RCT					
	<u></u>					
	Size: 6,614					
Wachtell et al.,	Aim: LIFE trial	Intervention:	Inclusion criteria:	1° endpoint: new	New-onset AF occurred in	N/A
2005 (260)	aimed to determine	n=4,298 treated	Hypertensive pts with LVH	onset of AF	150 pts randomized to	
	whether angiotensin	with losartan	by echo		losartan vs. 221 to atenolol	
15734615	II receptor blockade		5		(6.8 vs.10.1 per 1,000	
	is better than beta-	Comparator:	Exclusion criteria: Prior	2° endpoint: None	person-y; RR: 0.67; 95% CI:	
	blockade in	n=4,182 treated	AF history in 342 pts		0.55–0.83; p<0.001) despite	
	preventing new-	with atenolol			similar BP reduction. Pts	
	onset AF.				receiving losartan tended to	
					stay in sinus rhythm longer	
	Study type: RCT				(p=0.057) than those	
					receiving atenolol.	
	<u>Size</u> : 9,193				Ũ	
Haywood et al.,	Aim: To investigate	Intervention:	Inclusion criteria:	1° endpoint: ECG	AF/AFL occurred in 641	Doxazosin group was
2009 (261)	incidence of	n=42,418 on	Essential HTN with BP	evidence of AF/AFL on	pts on follow-up. Incidence	limited by higher
	development of	diuretics	>140/90 without	follow-up of HTN and	did not differ by class of	cardiac event rates and
19926008	AF/AFL in pts		medications, >180 systolic	dyslipidemia	antihypertensive, other than	early termination of this
	enrolled in this	Comparator:	if on medications		increased frequency in the	portion of the trial.
	comparative trial of	n=39,056			doxazosin group by 33% vs.	
	antihypertensives		Exclusion criteria: Not		chlorthalidone group	
	(ALLHAT).		meeting inclusion criteria		(p=0.05 after risk	
					adjustment).	
	Study type: RCT					
	<u>Size</u> : 81,4/4					
Julius et al.,	Aim: The Valsartan	Intervention:	Inclusion criteria:	1° endpoint: Cardiac	• AF occurred in 2.4% with	N/A
2004 Julius,	Antihypertensive	n=7,649 on	Hypertensive pts, ≥50 y	mortality, morbidity, HF,	valsartan and 2.0% with	
2004 610}	Long-term Use	valsartan	with DM, current	stroke, all-cause death,	amlodipine; p=0.1197.	
	Evaluation (VALUE)		smoking, high total	new onset DM		
<u>15207952</u>	trial: does valsartan	Comparator:	cholesterol, LVH by ECG,			
	reduce cardiac	n=7,596 on	proteinuria on dipstick	Safety endpoint:		
	morbidity and	amiodipine	and CKD (not end-stage)	Hypotension, syncope		
	mortality more than		Fuctorian anitania			
	amoupine for the		EXClusion criteria:	2° endpoint: AF		
	same degree of BP		ESKD, renai artery			
			Stenosis, pregnancy, AMI,			
	high CV rick		PICA OF CABG WITHIN THE			
	nigh CV risk.	1	past 3 mo, clinically			

Study type: RCT	relevant valvular disease, cerebrovascular accident	
<b>Sizo:</b> 15 245	In the past 3 mo, severe	
<u>5120</u> : 15,245	chronic renal failure. CHE	
	requiring ACEI therapy and	
	pts on monotherapy with	
	blockers for both CAD and	
	HTN.	

# Data Supplement 50. RCTs and Meta-analysis Comparing Valvular Heart Disease (Section 9.9)

Study	Aim of Study;	Study	Patient Population	Endpoints	P Value; OR, HR, or	Study Limitations &
Acronym;	Study Type;	Intervention (#			RR; & 95% CI	Adverse Events
Author;	Study Size (N)	patients)/Study				
Year Published		Comparator (#				
		patients)				
SCOPE-AS	Aim: To determine	Intervention:	Inclusion criteria:	<u>1° endpoint</u> :	<ul> <li>Pts who tolerated</li> </ul>	<ul> <li>Treatment with</li> </ul>
Chockalingam	the clinical tolerance	Enalapril 2.5 mg	Severe aortic stenosis	Improvements in Borg	enalapril (n=34) had	enalapril resulted in
A, et al., 2004	and efficacy of the	BID increasing to	(aortic valve area <0.75	dyspnea index and 6-min	significant improvement	hypotension in 3 of 5
(262)	ACEI enalapril in the	10 mg BID (37	cm <sup>2</sup> , mean aortic gradient	walk distance at 1 mo	in NYHA class, Borg	pts with LV
<u>15077102</u>	setting of symptomatic	pts)	>50 mm Hg, or aortic		index (5.4 ± 1.2 vs. 5.6	dysfunction and
	severe AS.		valve Doppler jet >4.5	Safety endpoint:	± 1.7; p=0.03), and 6-	congestive HF had
		Comparator:	m/s) and symptomatic	Development of	min walk distance (402	hypotension.
	Study type: RCT	Placebo (19 pts)	NYHA class III or IV	hypotension	± 150 vs. 376 ± 174;	5.
			dyspnea or angina		p=0.003) compared with	
	<u>Size</u> : 56 pts			2° endpoint: Minor ACEI	control pts.	
			Exclusion criteria:	intolerance, cough,		
			Persistent hypotension	presyncope, improvement		
			(SBP <90 or mean BP	in NYHA class, and echo		
			<60), severe mitral	parameters		
			stenosis (mitral valve			
			orifice <1.0 cm <sup>2</sup> ), known			
			intolerance for ACEI, and			
			renal dysfunction (serum			
			creatinine >2.5 mg/dL).			

SEAS Rieck ÅE Hypertension, 2012 (263) 22647889	Aim: To determine the impact of HTN on LV structure and outcome during progression of aortic valve stenosis Study type: RCT observational substudy of SEAS trial Size: 1616 pts	Intervention: 1,340 pts with HTN Comparator: 276 pts without HTN	Inclusion criteria: Pts 45- 85 y who had asymptomatic, mild-to- moderate aortic valve stenosis, as assessed on echo, with a peak aortic- jet velocity of 2.5–4 m per second, were eligible for the study.	<u>1° endpoint</u> : Echo LV mass; MACE; mortality	<ul> <li>HTN predicted 51% higher incidence of abnormal LV geometry at final study visit independent of other confounders (p&lt;0.01).</li> <li>HTN was associated with a 56% higher rate of ischemic CV events and a 2-fold increased mortality (both p&lt;0.01).</li> </ul>	No specific randomized intervention for HTN.
Eleid MF, et al., 2013 (264) <u>23956211</u>	Aim: To evaluate the hemodynamic effects of vasodilator therapy in pts with LGSAS <u>Study type</u> : Nitroprusside infusion <u>Size</u> : 24	Intervention: Infusion of IV sodium nitroprusside to reduce BP and arterial afterload (18 pts with hypertensive LGSAS) <u>Comparator</u> : Baseline hemodynamics (6 pts with low EF LGSAS)	Inclusion criteria: Symptomatic pts with HTN (aortic SBP >140 mm Hg) and low-gradient (mean gradient <40 mm Hg) severe aortic stenosis (aortic valve area <1 cm (2)) with preserved EF (EF >50%). Exclusion criteria: Moderate or severe concomitant valvular heart disease (e.g., aortic, mitral or tricuspid regurgitation), reduced left ventricular EF (>50%), age <18 y, and complex CHD.	<b><u>1° endpoint</u>:</b> Nitroprusside reduced mean PA pressure (25±10 mm Hg) and LV end-DBP (11±5 mm Hg; p<0.001 for both compared with baseline). <b><u>2° endpoint</u>:</b> Aortic valve area (0.86±0.11 to 1.02±0.16 cm (2); p=0.001) and mean gradient (27±5 to 29±6 mm Hg; p=0.02) increased with nitroprusside.	• Treatment of HTN with vasodilator therapy results in a lowering of the total LV afterload, with a decrease in LV filling pressures and PA pressures.	No translation to clinical or ambulatory vasodilator use.
RIAS Trial	Aim: To determine if	Intervention: Ramipril ramped	Inclusion criteria: Pts	<u>1° endpoint</u> : Adverse	Reduction in LVM in	A larger clinical
2015 (265)	outcomes in AS.	up from 2.5 to 5 to	severe aortic stenosis	abnormalities; change in	placebo group (mean	confirm these findings
25796267	Study type: RCT	10 mg for 1 y (50 pts)	(valve area <1.5 cm <sup>2</sup> , or peak velocity >3.0 m/s	LVM from baseline to 12 mo measured by CMR.	change -3.9 vs. +4.5 g, respectively; p=0.0057);	and explore their clinical relevance is
	<u>Size</u> : 100	<u>Comparator</u> : Placebo (50 pts)	peak valve gradient >36 mm Hg]), 2 who were asymptomatic as judged by pt-reported symptoms,	2° endpoint: Change in LV EF and function by CMR and echo, change in	preserved tissue Doppler systolic velocity compared with placebo (+0.0 vs0.5 cm/s;	required.

			and who did not have indications for valve replacement surgery. <u>Exclusion criteria</u> : Any other significant (>mild) VHD, excess hypo- or HTN (BP <100/40 or >200/110 mm Hg). Intolerance of ACEIs or ARBs or their prescription over the previous 3 mo	BNP); and change in distance walked on exercise tolerance testing.	p=0.04); trend to less progression of the aortic stenosis (valve area 0.0 cm <sup>2</sup> vs0.2 cm <sup>2</sup> in the placebo arm; p=0.067).	
Scognamiglio R, et al., 1994 (266) <u>8058074</u>	<u>Aim</u> : To assess whether vasodilator therapy reduces or delays the need for valve replacement <u>Study type</u> : RCT <u>Size</u> : 143	Intervention: Nifedipine 20 mg Q12 H (69 pts) Comparator: Digoxin 0.25 mg daily (74 pts)	Inclusion criteria: Asymptomatic pts with isolated, chronic, severe aortic regurgitation and normal LV systolic function Exclusion criteria: Worsening aortic regurgitation within 6 mo, DBP above 90 mm Hg, CAD, aortic valve gradient ≥ 20 mm Hg, other valvular or CHD, poor quality echo or an LV EF <50%.	<u>1° endpoint</u> : Frequency of valve replacement	• At 6 y, a 34% of the digoxin group had undergone valve replacement, but only 15% of the nifedipine group (p<0.001)	• No placebo group, and digoxin is a poor comparator due to toxicity which is now recognized.
Evangelista A, et al., 2005 (267) <u>16192479</u>	Aim: To identify the possible beneficial effects of vasodilator therapy on LV function and the need for aortic-valve replacement. Study type: RCT Size: 95 pts	Intervention: Nifedipine 20 mg Q12 H or enalpril 20 mg daily (32 pts nifedipine, 32 pts enalapril) Comparator: Placebo (31 pts)	Inclusion criteria: Consecutive pts with asymptomatic, chronic, severe aortic regurgitation and normal LV function Exclusion criteria: LVEF <50%, AF, CAD or other nonaortic VHD	1° endpoint: Frequency of valve replacement	• Rate of aortic-valve replacement was similar among the groups: 39% in the control group, 50% in the enalapril group, and 41% in the nifedipine group (p=0.62).	N/A

Scognamiglio R, et al., 1994 (266) <u>8058074</u>	Aim: To assess whether vasodilator therapy delays need for valve replacement in pts with asymptomatic severe AR. Study type: RCT Size: 143 pts	Intervention: 69 pts received nifedipine Comparator: 74 pts received digoxin	Inclusion criteria: Severe aortic regurgitation without symptoms Exclusion criteria: DBP >90, recent worsening of aortic regurgitation, mixed aortic stenosis / aortic regurgitation or any additional valve disease, LVEF <50.	<u>1° endpoint</u> : Worsening symptoms, LVEF decline to <50% or both, requiring valve replacement surgery	• 15% met criteria for valve replacement with nifedipine, but 34% did with digoxin (p<0.001)	No placebo control.
Evangelista A, et al., 2005 (14) <u>16192479</u>	Aim: To assess whether vasodilator therapy delays need for valve replacement in pts with asymptomatic severe AR. Study type: RCT Size: 95 pts	Intervention: 32 pts received enalapril; 32 pts received nifedipine <u>Comparators</u> : 31 pts received placebo	Inclusion criteria: Severe aortic regurgitation without symptoms Exclusion criteria: Not listed.	<u>1° endpoint</u> : Worsening symptoms, LVEF decline to <50% or both, requiring valve replacement surgery	• 41% met criteria for valve replacement with nifedipine, 50% did with enalapril, and 39% in the control group (p=0.62)	• BP of 145/75 average between the 3 groups, indicate lack of severity. Post-Rx BP is not reported.

Data Supplement 51. RCTs Comparing Race/Ethnicity (Section 10.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Leenen F, et al., 2006 (268) <u>16864749</u>	<u>Study type</u> : RCT comparison of an alpha blocker, ACEI, or CCB, each compared to a thiazide-type diuretic. This is post hoc comparison between	<ul> <li>&gt;50 y</li> <li>Lisinopril (n=9,054); Amlodipine (9,048)</li> <li>African American 15,085 (35.5%)</li> <li>White 11,580 (47.0%)</li> </ul>	Amlodipine vs. Lisinopril	<ul> <li>No significant difference in 1° outcome (nonfatal MI and fatal CHD) or other prespecified outcomes:</li> <li>CHD, 1° outcome plus revascularization and hospitalized</li> </ul>	• In African Americans, Lisinopril less effective than amlodipine for BP reduction (mean follow-up BP 2.7/1.6 mm Hg higher with Lisinopril) and in reducing strokes (RR:1.51; 95% CI: 1.22–1.86) and

	CCB vs. ACEI incl in race subgroup.			angina, composite CVD, HF, ESRD, except strokes	combined CVD (RR: 1.13; 95% CI:1.02–1.24; p=0.025)
Wright JT et al. 2008 (269) <u>18227370</u>	Study type: Race subgroup comparison of RCT comparison of an ACEI or CCB compared to a thiazide-type diuretic on nonfatal or fatal CHD in pts with metabolic syndrome	<ul> <li>&gt;50 y</li> <li>African American n=12,818</li> <li>Non-African American n=24,473</li> </ul>	Chlorthalidone vs. Amlodipine, or Lisinopril	<ul> <li>No difference in 1° outcome (nonfatal MI and fatal CHD). Other prespecified outcomes:</li> <li>CHD, 1° outcome plus revascularization and hospitalized angina, composite CVD, stroke, HF, ESRD</li> </ul>	• In African Americans with metabolic/cardiometabolic syndrome: Amlodipine similar for chlorthalidone for all outcomes but inferior for HF (HR: 1.50; 95% CI: 1.18–1.90) and combined CVD (HR: 1.14; 95% CI: 1.00–1.29). Lisinopril less effective for SBP reduction by 4 mm Hg; combined CHD (HR: 1.19 (95% CI: 1.01, 1.40); combined CVD (HR: 1.24; 95% CI: 1.09–1.40); stroke (HR: 1.37; 95% CI: 1.07–1.76); HF (HR: 1.49; 95% CI: 1.17–1.90); and ESRD (HR: 1.70; 95% CI: 1.13–2.55)
Wright JT, et al., 2009 (270) <u>19433694</u>	Study type: Race subgroup comparison of RCT comparison of an alpha blocker vs. a thiazide-type diuretic Size: 9,061	<ul> <li>&gt;50 y</li> <li>(35.5% African American)</li> </ul>	Chlorthalidone vs. Doxazosin	No difference in 1° outcome (nonfatal MI and fatal CHD). Other prespecified outcomes: CHD, 1° outcome plus revascularization and hospitalized angina, composite CVD, stroke, HF, ESRD	• In African Americans: combined CVD (HR: 1.28; 95% CI: 1.16–1.42); HF (HR: 1.84; 95% CI: 1.51–2.24); stroke HR (CI): 1.10–1.73)
SPRINT Wright JT Jr, et al., 2015 (114) 26551272	Aim: To test the effectiveness of a goal SBP<120 mm Hg vs. a goal SBP<140 mm Hg for the prevention of CVD in pts with SBP≥130 mm Hg at baseline. Study type: RCT	Inclusion criteria: SBP≥130 mm Hg, with upper limit varying as number of pre-trial BP- lowering meds increased. age ≥50 y Presence of at least 1 of the following: • Clinical or subclinical CVD • CKD stage 3 or greater • Age≥75 y	Intervention: Intensive BP- lowering treatment to goal SBP<120 mm Hg Comparison: • Standard BP-lowering treatment to goal SBP<140 mm Hg • Net treatment difference ~3 drugs (2.8) on average vs. 2 drugs (1.8) on average	1° endpoint:       CVD (MI, ACS, stroke, HF, CVD death)         HR:       0.75 (0.64–0.89)         Other endpoints:       •         • Total deaths:       0.73 (0.60–0.90)         • 1° or death:       0.78 (0.67–0.90)         • Components of 1° composite mostly consistent in direction other than ACS – no difference.         CKD outcomes:	Summary: • More intensive SBP lowering to a goal of <120 mm Hg with achieved mean of ~121 mm Hg resulted in less CVD and lower total mortality over 3.26 y in comparison with a goal SBP<140 mm Hg and achieved SBP of ~135 mm Hg. • There were small increases in some expected SAEs. Perhaps unexpected, a sizable
	Size: 9361 participants followed median of 3.26 y	Framingham General CVD risk≥15% in 10 y <u>Exclusion criteria:</u> Major ones included DM, history of stroke, ESRD (eGER <20)	• During the trial, mean SBP was 121.5 vs. 134.6.	<ul> <li>1° in CKD pts: reduction in GFR of ≥50% or ESRD 0.89 (0.42–1.87)</li> <li>Incident albuminuria: 0.72 (0.48–1.07)</li> <li>In pts without CKD: reduction in GER ≥30% and to ≤60</li> </ul>	increase in reduced eGFR in the non-CKD group and AKI/ARF overall was observed in the intensive group. While of uncertain etiology and significance, there is speculation this could be an
---	---	---	---	---	---
				<ul> <li>3.49 (2.44–5.10)</li> <li>Incident albuminuria: 0.81 (0.63– 1.04)</li> </ul>	acute hemodynamic effect, especially given the findings regarding albuminuria.
				Adverse events: • SAEs: 1.04; p=0.25 • Significant absolute increases seen in intensive group for hypotension (1%), syncope (0.6%), electrolyte abnormality (0.8%), acute kidney injury/acute renal failure (1.6%) over the study period. • 1.7% fewer pts had orthostatic hypotension in intensive group; p=0.01.	Limitations: Few participants were untreated at baseline ~9%, so SPRINT provides little if any insight at present regarding BP-lowering medication initiation for untreated people with SBP 130–139.
VA Coop 1967 (262) <u>4862069</u>	Study type: RCT to examine effect of treatment of severe HTN Size: 143	<ul> <li>54% African American</li> <li>DBP 115–129 mm Hg</li> </ul>	• HCTZ, Reserpine, Hydralazine vs. placebo	• CVD or stroke events, Grade 3 or 4 retinopathy, doubling of creatinine or BUN. Study terminated early for 27 events vs. 2 events (placebo vs. active)	N/A
VA Coop 1970 (271) <u>4914579</u>	Study type: RCT to examine effect of treatment of mild to moderately severe HTN	<ul> <li>42% African American</li> <li>DBP 90–115 mm Hg</li> </ul>	• HCTZ, Reserpine, Hydralazine vs. placebo	<ul> <li>CVD or stroke events, Grade 3 or 4 retinopathy, doubling of creatinine or BUN</li> </ul>	
	<u>Size</u> : 380				

HTN Detection and Follow-up Program (HDFP) 1979 <u>6480895</u> (272)	Study type: RCT; comparison of stepped care at academic centers vs. usual care provided by community Size: 10,950 pts	<ul> <li>44% African American</li> <li>30–69 y</li> </ul>	Chlorthalidone, Reserpine, Hydralazine, Guanethidine vs. referral to community care	• 23% decrease in mortality in African Americans on Stepped Care	N/A
LIFE Dahlof B, et al. 2002 <u>11937178</u> (14)	Study type: RCT comparison of an ARB compared to a BB on CVD	<ul> <li>55-80 y (mean 66.9 y)</li> <li>African American 533 (6)</li> <li>White 8,503 (92)</li> <li>Asian 43 (0.5)</li> <li>Hispanic 100 (1)</li> <li>Other 14 (0.2)</li> </ul>	Losartan vs. Atenolol	• Interaction of race and treatment on CVD events (p=0.005) CVD increased 55% in African Americans in the Losartan group	N/A
VALUE Julius S, et al. 2006 (265) <u>16864741</u> (273)	Study type: RCT comparison of an ARB vs. a CCB on CVD	<ul> <li>&gt;50 y (mean 67.3 y)</li> <li>African American 658 (4.3)</li> <li>White 13,643 (89.1)</li> <li>Asian 535 (3.5)</li> <li>Other 474 (3.1)</li> </ul>	Valsartan vs. Amlodipine	CVD increased ~20% (NS) in African Americans in Valsartan group	N/A
AASK Norris K, et al. 2006 <u>17059993</u> (174)	Study type: RCT comparison of 2 BP targets and 3 drug regimens on renal outcomes Size: 1,094 pts	<ul> <li>18–70 y; African Americans;</li> <li>eGFR: 25–65 mL/min/1.73 m<sup>2</sup></li> </ul>	• MAP of <92 mm Hg compared to MAP 102–107 mm Hg and an ACEI or CCB each compared to a BB	• No difference between BP targets. ACEI > BB > CCB	N/A
ALLHAT 2002 (274) <u>12479763</u>	Study type: RCT comparison of an alpha blocker, ACEI, or CCB, each compared to a thiazide-type diuretic Size: 42,418	<ul> <li>&gt;50 y</li> <li>African American</li> <li>15,085 (35.5)</li> <li>White 19,977 (47.0)</li> <li>Hispanics 5,299 (12.5)</li> </ul>	Chlorthalidone vs. Doxazosin, Amlodipine, or Lisinopril	No difference in 1° outcome (nonfatal MI and fatal CHD)	• Chlorthalidone (and amlodipine was superior in reducing BP by 4/1 mm Hg and CVD events (stroke and CVD) vs. lisinopril in African Americans
INVEST Pepine CJ, et al., 2003 (275)	Study type: RCT comparison of CCB plus an ACEI	<ul> <li>≥ 50 y with HTN and CHD</li> <li>36% Hispanic</li> </ul>	Verapamil/trandolapril vs. Atenolol/ HCTZ	•No difference in 1° outcome (nonfatal MI, nonfatal stroke, all- cause mortality). Mean SBP	N/A

<u>14657064</u>	compared to a BB plus a thiazide diuretic <u>Size</u> : 22,576	<ul> <li>13% African American</li> <li>49% White</li> </ul>		reduction Hispanics vs. non- Hispanic pts (-21.3 vs17.4 mm Hg; p<0.001)	
Wright JT, et al., 2005 (276) <u>15811979</u>	Study type: Race subgroup comparison of RCT comparison of an alpha blocker, ACEI, or CCB compared to a thiazide-type diuretic	<ul> <li>&gt;50 y</li> <li>African American, n=11,792</li> <li>Non-African American, n=21,565</li> </ul>	Chlorthalidone vs. Amlodipine, or Lisinopril	• No difference in 1° outcome (nonfatal MI and fatal CHD). Other prespecified outcomes: CHD, 1° outcome plus revascularization and hospitalized angina, composite CVD, stroke, HF, ESRD	• In African Americans: Amlodipine similar to chlorthalidone for all outcomes but inferior for HF (HR: 1.37; 95% CI: 1.24–1.51). Lisinopril less effective for SBP reduction by 4 mm Hg, stroke (HR: 1.40; 95% CI: 1.17–1.68), combined CVD (HR: 1.19; 95% CI: 1.09– 1.30), HF (HR: 1.30; 95% CI: 1.10–1.54).

## Data Supplement 52. RCTs Comparing Women With Hypertension (Section 10.2.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Turnbull F, et al., 2008 (277) <u>18852183</u>	Aim: Assess sex differences in response to BP treatment Study type: Meta- analysis of 31 RCTs Size: 103,268 men, 87,349 women	Mean ages: • Women: 63.0 y • Men: 61.7 y	Intervention: N/A Comparator: N/A	<u>1° endpoint</u> : Nonfatal stroke or death from cerebrovascular disease (ICD 430–438); (ii) nonfatal MI or deaths from CHD, excluding SCD (ICD 410–414); (iii) HF causing death or requiring hospitalization (ICD 428); (iv) total major CV events (stroke, CHD events, HF, other CV death); (v) total CV deaths (ICD 396–459); and (vi) total mortality <u>Safety endpoint</u> : N/A	<u>Summary</u> : Achieved BP reductions were comparable for men and women in every comparison made. For the 1° outcome of total major CV events there was no evidence that men and women obtained different levels of protection from BP- lowering or that regimens based on ACEIs, calcium antagonists, ARBs, or diuretics/BBs were more effective in1 sex than the other (all p-homogeneity >0.08).
Wing L, et al., 2003 (278) <u>12584366</u>	Aim: Comparison of ACE vs. Diuretic on incident CVD	Inclusion criteria: Pts 65–84 y	Intervention: ACE Comparator: Diuretic	Endpoint: All CV events or death from any cause Safety endpoint: N/A	<u>Summary</u> : Among male subjects, HR: 0.83 (95% CI: 0.71–0.97; p=0.02); among female subjects, HR: 1.00 (95% CI: 0.83–1.21; p=0.98); the p value for

	Study type: Practice- based RCT open label treatment, blinded event Size: 6,083 pts	Exclusion criteria: Life- threatening illness, contraindication to an ACEI or diuretic, a plasma creatinine concentration of more than 2.5 mg per deciliter (221 micromol per liter), malignant hypertension, or dementia	Note: Clinicians chose which ACE or diuretic		the interaction between sex and treatment-group assignment was 0.15.
Fletcher A, et al., 1988 (279) <u>2907053</u>	Aim: Monitoring event rates in pts assigned to treatment by clinicians <u>Study type:</u> Observational <u>Size:</u> 2,607	Inclusion criteria: Age >18 y Exclusion criteria: N/A	Intervention: N/A	<u>1° endpoint</u> : Total mortality incident "IHD" <u>Safety endpoint</u> : N/A	Summary: BBs reduced mortality in men but not women (p<0.01)
Forette F, et al., 2002 (280) <u>12374512</u>	Aim: Legacy follow-up for dementia prevention Study type: RCT with legacy follow-up Size: 2,902 in the legacy follow-up	Inclusion criteria: Age ≥60 y Exclusion criteria: HTN 2° to a disorder that needed specific medical or surgical treatment; congestive HF; dissecting aortic aneurysm; serum creatinine concentration at presentation of 180 micromol/l or more; stroke or MI in the y before the study; dementia; substance abuse; any disorder prohibiting a sitting or standing position; any severe concomitant or non-CVD	Intervention: Nitrendipine + HCTZ Comparator: Placebo	<u>1° endpoint</u> : Incidence of dementia <u>2° endpoint</u> : Cognitive decline measured by MMSE <u>Safety endpoint</u> : N/A • Cases Active: 21 • Cases Placebo; 43 • Rate 3.3 vs. 7.4 cases/1,000 pt y 0.38 (95% Cl: 0.23–0.64; p<0.001) • MMSE: No impact	<ul> <li>Study discontinued early for CVD benefit so a legacy follow-up with both groups (off protocol) yielded a follow-up of 3.7 y SBP was 149 mm Hg in treatment vs. 156 mm Hg in control arm</li> <li>Summary dementia:</li> <li>Compared with the controls, long-term antihypertensive therapy reduced the risk of dementia by 55%, from 7.4–3.3 cases per 1,000 pt-y (43 vs. 21 cases; p&lt;0.001). After adjustment for sex, age, education, and entry BP, the relative HR associated with the use of nitrendipine was 0.38 (95% CI: 0.23, 0.64), p&lt;0.001.</li> <li>Lack of impact on MMSE not surprising given low sensitivity to change and large sample size</li> </ul>

Study Acronym (if applicable) Author Year	Study Type/Design*; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Pucci M, et al., 2015 (281) <u>25612630</u>	Study type: Review of published reports of fetotoxicity of ACE/ARB antihypertensives in the first trimester of pregnancy. Usually case/control design.	Inclusion criteria: Pregnant women receiving ACE/ARB in the 1 <sup>st</sup> trimester of pregnancy only and comparable controls Exclusion criteria: Use of ACE/ARB later in pregnancy	<u><b>1° endpoint</b></u> : Adverse outcomes of pregnancy <u><b>Results</b></u> : Adverse events are higher in pregnancies of women who receive ACE/ARB in the first trimester of pregnancy but results are not independent of known confounders	<ul> <li>Fetotoxicity in the first trimester of pregnancy cannot be definitely attributed to ACE/ARB treatment; data are inconclusive.</li> <li>Other known causes of fetotoxicity may be responsible for increased risk in the first trimester (HTN, obesity, undiagnosed DM, other anti-hypertensives)</li> </ul>
Moretti ME, et al., 2012 <u>22203847</u> (282)	Study type: Case control comparing pts exposed to ACE/ARB in the first trimester to healthy controls and those on other anti-hypertensives Size: 388 total pts (equally divided)	Inclusion criteria: Mothers calling into the Mother Risk Program re: medication toxicity during pregnancy Exclusion criteria: Non- English speaking	<u>1° endpoint</u> : Malformations and adverse fetal outcomes <u>Results</u> : No difference among groups but study under-powered	Supportive of above review
Ferrer RL, et al., 2000 (283) <u>11094241</u>	Study type: Meta-analysis Size: 46 observational studies and randomized control trials	Inclusion criteria: Pre- specified quality entrance criteria Exclusion criteria: N/A	<ul> <li><u>1° endpoint</u>: Adverse pregnancy outcomes</li> <li><u>Results</u>:</li> <li>Maternal HTN increases risk for 1) perinatal mortality (OR: 3.4:1) and 2) placental abruption (2.1:1)</li> <li>ACEIs are associated with fetopathy (fetal renal failure)</li> </ul>	<ul> <li>HTN by itself is associated with adverse perinatal outcomes</li> <li>ACEIs independently are responsible for some outcomes</li> </ul>

Data Cumulamant F2	DOTA CAMARA		$(C_{a}, H_{a}, 10, 2, 2)$
Data Nunniement 53	RUISLOMDA	ing Pregnancy	INPETION IN 7 71
Dutu Supprement 55.		ing ricgilaricy	
			```

\*Quality assessment analysis may need to be applied on a case-by-case basis for controversial studies (by ERC chairs).

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator	Endpoint Results (Absolute Event Rates, P value; OR or RR; &	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events;
			(# patients)	95% CI)	Summary
SPRINT Senior	Aim: Intensive SBP goal	Inclusion	Intervention: Medications	<u>1° endpoint</u> : Composite CVD	Limitations: Does not apply to
Williamson JD, et	<120 mm Hg) vs.	criteria: Men and	and dietary advice to	outcome (AMI, non-MI ACS, stroke,	nursing home pts or those with
al., 2016	standard (SBP goal	women age 75+;	achieve SBP of <120 mm	HF, CVD death.	dementia or advance
(190)	<140)	mean age 79.8 y;	Нд		
<u>27195814</u>		38% women;		<u>Results</u> :	Conclusions: Intensive SBP is safe
	Study type: RCT	17% black, 74%	Comparator: Medications	<ul> <li>102 events in the intensive</li> </ul>	and effective for lowering CVD
		Caucasian	and dietary advice to	treatment group vs. 148 events in	events and total mortality in adults
	Size: 2,636; 30% met		achieve SBP of <140 mm	the standard treatment group; HR:	≥75 y
	criteria for being	Exclusion	Нд	0.66; 95% CI: 0.51–0.85 and all-	
	classified as ambulatory	criteria: Nursing		cause mortality (73 deaths vs. 107	
	frail	home residents;	<ul> <li>Achieved SBP:</li> </ul>	deaths, respectively; HR: 0.67; 95%	
		prevalent DM,	Intensive=123.4 mm Hg	CI: 0.49–0.91. No difference in falls.	
	Mean follow-up:3.1 y	stroke, Class	Standard=134.8 mm Hg	orthostatic hypotension, or overall	
		III/IV HF,	5	SAEs.	
		dementia		<ul> <li>NNT for 1° outcome=27 and NNT</li> </ul>	
				for all-cause mortality=41	

Data Supplement 54. RCT for Older Persons (Section 10.3.1)

Data Supplement 55. RCTs Comparing Hypertensive Crises and Emergencies (Section 11.2)

Study	Aim of Study;	Patient Population	Study Intervention	Endpoint Results	Relevant 2° Endpoint (if any);
Acronym;	Study Type;		(# patients) /	(Absolute Event Rates,	Study Limitations;
Author;	Study Size (N)		Study Comparator	P value; OR or RR; & 95%	Adverse Events;
Year Published			(# patients)	CI)	Summary
CLUE	Aim: Compare	Inclusion criteria:	<ul> <li>110 pts randomized to</li> </ul>	Results: Within 39 min,	Limitations: Study unblinded; large number of
Peacock WF, et	safety and efficacy	SBP ≥180 mm Hg on	nicardipine; 116 to	nicardipine pts reached TR	pts without end-organ damage (which usually
al., 2011 (284)	of IV nicardipine vs.	2 consecutive	labetalol. End-organ	than labetalol pts (91.7 vs.	defines a hypertensive emergency); physicians
<u>21707983</u>	labetalol in the	occasions 10 min	damage preceded	82.5%; p=0.039). Of 6 BP	ordered fewer dose titrations of labetalol than
	management of	apart in the ED.	randomization in 63%%	measurements taken 5 min	nicardipine; thus, lack of BP decline might have
	acute HTN.		with no difference	apart, nicardipine pts had a	been due to insufficient dosing by physicians
			between the groups. The	higher rate of 5 and 6 SBP	hesitant to administer successively increasing
	Study type: RCT		target BP range (TR; at	measures in the TR than	doses of labetalol as recommended by the FDA.
			the discretion of the	labetalol pts (47.3 vs. 32.8%;	

	Size: 226 pts		<ul> <li>treating physician) was defined as SBP ± 20 mm Hg.</li> <li>Dosing titrations were those recommended by the FDA.</li> </ul>	p=0.026). Rescue medications did not differ between the nicardipine and labetalol groups. Nicardipine pts were more likely in the TR than labetalol pts (OR: 2.73; 95% CI: 1.1–6.7; p=0.028).	<u>Conclusions</u> : Pts treated with nicardipine are more likely to reach the physician-specified TR than those treated with labetalol. In this study (2014), initial SBP was not a predictor of the ability to achieve the pre-specified TR in 30 min. Subgroup analysis demonstrated the similar results for sub-populations with end-organ damage (n=141) and renal dysfunction (n=104).
Liu-DeRyke X, et al., 2013 (285) <u>23760911</u>	Aim: Compare ability of IV nicardipine and labetalol to lower BP in acute hemorrhagic or ischemic stroke. Study type: RCT (pseudo- randomization) Size: 54 pts	Inclusion criteria: Pts with acute hemorrhagic or ischemic stroke who were at or exceeded AHA guidelines BP recommendations. Exclusion criteria: Traumatic brain injury; intracranial neoplasm, received antihypertensive medication within previous 24 h, brain stem herniation, immediate brain death, acute MI, or bradycardia <50 bpm.	• 28 pts randomized to labetalol and 26 to nicardipine. Goal BP defined using the latest consensus recommendations.	<b><u>Results:</u></b> All pts receiving nicardipine achieved BP goal Compared with 61% in the labetalol group (p<0.001). 89% of the nicardipine group achieved goal within 60 min vs. 25% in the labetalol group (p<0.001). The nicardipine group had better maintenance of BP, greater percent of time spent within goal and less BP variability compared with the labetalol group (p<0.001). Less rescue medication had to be given to the nicardipine than the labetalol group (p<0.001).	Limitations: Very small; pseudo-randomization. Conclusions: In acutely hypertensive stroke pts, a superior BP-lowering response was achieved with nicardipine over labetalol. Despite this, there was no significant difference in clinical outcomes.
CATIS He J, et al., 2014 (202) <u>24240777</u>	Aim: Evaluate whether immediate BP reduction in pts with acute ischemic stroke would reduce death and major disability in 14 d or hospital discharge. Study type: RCT Size: 4.071 pts	Inclusion criteria: Pts had nonthrombolysed ischemic stroke within 48 h of onset and elevated SBP. Baseline SBP was 166.7 mm Hg in the antihypertensive treatment group and 165.6 mm Hg in the control group	• This was a Chinese multicenter, single- blinded, blinded endpoints RCT conducted in 26 hospitals in China. 2,038 pts were randomized to receive antihypertensive treatment and 2,033 were randomized to the control group. The trial was designed to test a BP	Results: In the antihypertensive treatment group, SBP was reduced from 166.7 to 144.7 mm Hg (-12.7%) within 24 h and in the control group from 165.6 to 152.9 mm Hg (-7.2%) (absolute difference -9.1 mm Hg; 95% CI: -10.2– -8.1; p<0.001). Mean SBP was 137.3 mm Hg in the antihypertensive treatment	Limitations: Study excluded pts with BP ≥220/120 mm Hg, so the results do not apply to such pts. Pts treated acutely with thrombolytic therapy were excluded. Trial performed exclusively in Chinese pts. Conclusions: Among pts with acute ischemic stroke, BP reduction with antihypertensive medications, compared to absence of antihypertensive medications, did not reduce the likelihood of death and major disability at 14 d or hospital discharge.

			reduction strategy rather than the efficacy of specific antihypertensive drugs. Pts in the control	group and 146.5 mm Hg in the control group at the 7 <sup>th</sup> d of randomization (absolute difference -9.3 mm Hg; 95%	
			home BP medications.	The 1° outcome did not differ between treatment groups (OR: 1.00; 95% CI:	
			Combination of death and major disability at 14 d or hospital discharge.	0.88–1.14) at 14 d or hospital discharge. The 2° outcome of death and major disability at 3 mo post-	
				treatment follow-up did not differ between the groups.	
INTERAC-2 Anderson CS, et	<u>Study type:</u> RCT	<ul> <li>To compare the management</li> </ul>	<ul> <li>This was an international, multicenter,</li> </ul>	<u>Results:</u> 719 of 1,382 pts receiving intensive treatment	Limitations: No major limitations.
al., 2013 (191) 23713578	<u>Size:</u> 2,839 pts	strategy of targeting SBP<140 mm Hg within 1 h with the current guideline strategy of targeting SBP to <180 mm Hg with the use of agents of the physicians' choosing.	prospective randomized open-treatment, blinded endpoint trial. The pts had onset of spontaneous ICH within 6 h of enrollment. <u>1° outcome</u> : Death or major disability, defined as a score of 3-6 on the modified Rankin scale, at 90 d.	as compared to 785 of 1,412 pts receiving guideline- recommended treatment had a 1° outcome event [OR with intensive treatment: 0.87; 95% CI: 0.75–1.01; p=0.06). Ordinal analysis showed significantly lower modified Rankin scores with intensive treatment (OR for greater disability: 0.87; 95% CI: 0.77–1.00; p=0.04). Mortality was 11.9% in the group receiving intensive treatment and 12.0% in the group receiving guideline- recommended treatment. Nonfatal serious events	<b>Conclusions</b> : In pts with ICH, intensive lowering of BP resulted in a borderline significant reduction in the rate of death or severe disability at 90 d. An ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive lowering of BP. Intensive BP reduction was shown to be safe and to result in significantly better health-related quality of life.
				were not significantly different between the groups.	

PRONTO Peacock WF, et al., 2014 (286) 24655702	<u>Study type:</u> RCT <u>Size:</u> 104 pts	• To determine the efficacy and safety of clevidipine vs. standard-of-care (SOC) iv antihypertensive therapy in hypertensive acute HF.	<ul> <li>This was a randomized, open-label, active control study of clevidipine vs. standard-of-care in ED pts with acute HF with SBP ≥160 mm Hg.</li> <li><u>1° outcome</u>: Co-1° endpoints were median time to and % attaining a SBP within a prespecified TP at 30 min</li> </ul>	<u>Results:</u> More clevidipine pts reached target BP reduction (71%) than did those receiving standard-of- care (37%) and clevidipine was faster to target (p=0.0006). Serious adverse events were similar between clevidipine and standard-of- care.	Limitations: Small study, open-label design. Conclusions: In hypertensive acute HF, clevidipine safely and rapidly reduced BP and improved dyspnea more effectively that standard- of-care.
Farias S, et al., 2014 <u>13849948</u> (287)	<u>Aim</u> : To determine if achievement of target BP is less likely in pts with higher initial BP using a post hoc analysis in a pt subset from CLUE <u>Study type</u> : RCT Post-hoc Analysis <u>Size</u> : 223 pts	Inclusion criteria:SBP $\geq$ 180 mm Hg on2 consecutiveoccasions 10 minapart in the ED.Exclusion criteria:Contraindication togiving either a BB orCCB or clinicalscenarios in which acompelling agentwas indicated.	This was a post hoc analysis of CLUE, an RCT, in which pts were dichotomized using the median presenting SBP as the partition point. Individuals above and below the median were evaluated as to the proportion achieving the 1° outcome. <u>1° outcome</u> : Achievement of target SBP range within 30 min.	<u>Results</u> : Early achievement of target SBP was independent of presenting SBP.	Limitations: 2° analysis of the 1° CLUE study; SBP control only evaluated for the first 30 min posttreatment; no inclusion of critically ill pts; 80% of enrolled subjects were African-American. Conclusions: Presenting SBP does not appear to affect the ultimate ability to reduce BP for pts with marked, acute HTN in the ED when treated with either IV nicardipine or IV labetalol.

# Data Supplement 56. RCTs Assessing Impact of Hypertension Therapy on Dementia Incidence (Section 11.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
SHEP Applegate WB, et al., 1994 (288) 7044825	<u>Aim:</u> Compare loss of instrumental activities of daily	Inclusion criteria: 60–80 y (mean 71.6 y)	Intervention: Chlorthalidone + Atenolol or	<u>1° endpoint</u> : Loss of dementia- related functions (instrumental activities of daily living)	Relevant 2° endpoint: Incidence of surrogate markers for dementia

	treatment vs	Exclusion criteria: History		Cases	Summary: Nonsignificant 16% lower
	nlaceho	and/or signs of major CVDs	Comparator	• Active: 37	incidence of incident instrumental
	placebo	(e.g. previous ML coronary	Placebo	- Active: 57	activity of daily living disability
	Study type: PCT	artery surgery major	T Ideebo		However assignment to the placebo
	Study type. Not	arrbythmias conduction	SBD	• p=0.84 (0.54,1.31)	aroup and the resulting occurrence of
	Sizo, 1 726	defect recent stroke carotid	JDF Treatmont/Diacoba	<ul> <li>No cognitive function instrument</li> </ul>	GV events independently predicted
	<u>SIZE</u> . 4,730	artery disease >2 The and	difference.	included in trial	cv events independently predicted
	Dunation Fu	artery disease, <2 TIAS and	<u>amerence</u> :		missed assessments. However, when
	Duration: 5 y	signs or symptoms in a single	-12 mm Hg		20%–30% and 40%–80% of the
		neurological distribution); other	Achieved mean		subjects who missed the assessment
		major diseases (e.g., cancer,	SPB: 143 mm Hg in		were assumed to be
		alcoholic liver disease,	treatment group vs.		cognitively/functionally impaired,
		established renal dysfunction)	155 mm Hg in		assignment to active treatment reduced
		with competing risk factors for	placebo group		the risk of these outcomes. Thus, in the
		the 1° endpoint; stroke;			SHEP study, the cognitive and
		presence of medical			functional evaluations were biased
		management problems (e.g.,			toward the null effect by differential
		insulin dependent DM, history			dropout. This might have obscured the
		of dementia, evidence of			appraisal of a protective effect of
		alcohol abuse); bradycardia;			treatment on the cognitive and
		people maintained on BBs,			functional decline of older hypertensive
		diuretics, other			adults
		antihypertensive drugs,			
		anticoagulants.			
Syst-Eur	Aim: Incident	Inclusion criteria: ≥60 y	Intervention:	Endpoint: Dementia (defined by	Summary: Trial stopped early for
Forette F, et al.,	dementia		Nitrendipine ±	MMSE)	positive effect on CVD outcomes.
1998 (289)		Exclusion criteria: HTN 2° to	enalapril ± HCTZ		
9802273	Study type: RCT	a disorder that needed specific		Cases:	
		medical or surgical treatment;	Comparator:	Active: 11	
	Size: 2,418 pts	congestive HF; dissecting	Placebo	Placebo: 21	
		aortic aneurysm; serum		• (3.8 vs. 7.7 per 1.000 pt-v)	
	Duration: 2 y	creatinine concentration at	SBP	• n=0.05	
		presentation of 180	treatment/placebo	• p=0.00	
		micromoles/I or more: stroke or	difference:		
		MI in the v before the study:	-8.3 mm Ha		
		dementia: substance abuse:	Achieved SBP in		
		any disorder prohibiting a	152 mm Ha		
		sitting or standing position: any	treatment arm: 160		
		severe concomitant or non-	mm Ha placebo		
		CVD	arm		

Syst-Eur (legacy follow-up) Forette F, et al., 2002 (280) <u>12374512</u>	Aim: Legacy follow- up for dementia prevention Study type: RCT with legacy follow- up Size: 2,902 pts Duration: 3.7 y	Inclusion criteria: ≥60 y Exclusion criteria: HTN 2°ary to a disorder that needed specific medical or surgical treatment; congestive HF; dissecting aortic aneurysm; serum creatinine concentration at presentation of 180 micromoles/I or more; stroke or MI in the y before the study; dementia; substance abuse; any disorder prohibiting a sitting or standing position; any severe concomitant or non- CVD	Intervention: Open label follow-up of Syst-Eur pts originally assigned to Nitrendipine ± enalapril ± HCTZ vs. placebo <u>SBP</u> <u>Treatment/Placebo</u> <u>difference</u> : -7.0 mm Hg Achieved SBP in 149 mm Hg treatment arm 156 mm Hg placebo arm	<ul> <li><u>1° endpoint</u>: Incidence of dementia</li> <li><u>Endpoint 2:</u> Cognitive decline measured by MMSE</li> <li><u>Safety endpoint</u>: N/A</li> <li>Cases active: 21</li> <li>Cases placebo; 43</li> <li>Rate 3.3 vs. 7.4 cases/1,000 pt-y</li> <li>0.38 (95% CI: 0.23–0.64; p&lt;0.001)</li> </ul>	<ul> <li>This legacy follow-up with both groups (off protocol) yielded a follow-up of 3.7 y SBP was 149 mm Hg in treatment vs. 156 mm Hg in control arm</li> <li>Summary dementia: <ul> <li>Compared with the controls, long-term antihypertensive therapy reduced the risk of dementia by 55%, from 7.4–3.3 cases per 1,000 pt-y (43 vs. 21 cases; p&lt;0.001). After adjustment for sex, age, education, and entry BP, the RH rate associated with the use of nitrendipine was 0.38; 95% CI: 0.23–0.64; p&lt;0.001.</li> <li>Lack of impact on MMSE not surprising given low sensitivity to change and large sample size</li> </ul> </li> </ul>
SCOPE Lithell H, et al., 2003 (290) <u>12714861</u>	<u>Aim:</u> Incident dementia (cognitive decline as 2° outcome) <u>Study type:</u> RCT <u>Size:</u> 4,964 <u>Duration:</u> 3.7 y	Inclusion criteria: 70–89 y (mean 76 y) Exclusion criteria: Prevalent dementia; 2º HTN, SBP >180 mm Hg, orthostatic hypotension, need for antihypertensive treatment other than hydrochlorothiazide during run-in; stroke or MI within 6 mo; decompensated HF; serum creatinine>180 micromole/I (men) or>140 micromole/I (women);	Intervention: Candesartan ± HCTZ Comparator: Placebo ± Rx for community based SPB standard SBP Treatment/Placebo difference: -3.2 mm Hg	Endpoint: Incident dementia Also decline in MMSE Dementia Cases: Active: 62 Placebo: 57 p=1.08 (0.75–1.56) Cognitive decline slower in treatment group	<ul> <li>Summary:</li> <li>Mean follow-up 3.7 y. Treatment group SBP=144 mm Hg and placebo 147 mm Hg; thus, relatively minimal differences in achieved SBP between arms</li> <li>There were no significant differences between the treatment groups in either dementia or cognitive decline.</li> </ul>
PROGRESS Tzourio C, et al., 2003 (291) <u>12742805</u>	AIM: Dementia with or without recurrent stroke Study type: RCT Size: 6,105 pts	Inclusion criteria: Prior stroke or TIA, any adult age	Intervention: Perindopril ± indapamide Comparator: Placebo	Endpoint: Dementia alone or with recurrent stroke Dementia cases: Only stroke- related dementia reduction of 34% (95% CI: 3–55), p=0.03.	Summary: Dementia alone was not affected in this trial. Only dementia associated with incident cerebrovascular accident

	<u>Duration:</u> 3.9 y		SBP Treatment/Placebo difference: -9.4 mm Hg • Achieved SBP in 138 mm Hg treatment arm 147 mm Hg placebo arm		
Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-Cog) Peters R, et al., 2008 (292) <u>18614402</u>	<u>Aim</u> : Incident dementia 2º aim <u>Study type</u> : RCT <u>Size</u> : 3,336 <u>Duration:</u> 2.2 y	Inclusion criteria: ≥80 y Exclusion criteria: Prevalent dementia	Intervention: Indapamide ± Perindopril Comparator: Placebo SBP treatment/placebo difference: - 15 mm Hg • Target SBP 150 mm Hg • Achieved SPB in treatment arm=146 mm Hg	<u>1° endpoint</u> : Incident dementia <u>Events:</u> • Treatment=126 • Placebo=137 • 14% reduction not significant HR: 0.86 (95% Cl: 0.67–1.09)	<u>Summary</u> : Stopped early due to benefit in 1° outcome.

Data Supplement 57. RCTs for Patients Undergoing Surgical Procedures (Section 11.5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
POISE Study Group, et al., 2008 (293) <u>16875901</u>	<u>Aim</u> : Definitively establish the effects of BB therapy in pts undergoing noncardiac surgery	Inclusion criteria: Pts undergoing noncardiac surgery with, or at risk for ASVD	Intervention: extended release metoprolol succinate Comparator: Placebo	1° endpoint: Composite of CV death, NF MI, NF cardiac arrest <u>Results</u> : Fewer pts taking metoprolol than placebo reached the 1° endpoint, HR: 0.84; 95% CI 0.70–0.99; p=0.0399.	<u>Limitations</u> : No data for pts <45 y, no data for pts undergoing cardiac surgery <u>Conclusions</u> : This study highlights combined benefits and

Study type: RCT	However more in metoprolol group had	risk of BB regimen in noncardiac
Size: 8.351	death HR: 1.33; 1.03–1.74; p=0.0317 an more had stroke HR: 2.17; 1.26–3.74;	surgery and importance of pt physician discussion in deciding
	p=0.0053.	upon its use.

#### Data Supplement 58. Observational and Nonrandomized Studies for Patients Undergoing Surgical Procedures (Section 11.5)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Howell SJ, et al., 2004 (294) <u>15013960</u>	Study type: A systematic review and meta-analysis Size: 30 observational studies	Inclusion criteria: Available crude OR for association between HTN and periop CV complications along with variance Exclusion criteria: N/A. Studies defining HTN solely on admission BP	<u><b>1° endpoint</b></u> : Periop CV complications <u><b>Results</b></u> : Pts with SBP >180 or DBP >110 mm Hg more prone to periop ischemia, arrhythmias, and CV lability OR: 1.35 (1.17–1.56).	<ul> <li>Pts with SBP &gt;180 or DBP &gt;110 mm Hg more prone to periop ischemia, arrhythmias, and CV lability OR: 1.35 (1.17–1.56). But there was no evidence that deferring surgery in such pts reduces periop risk</li> <li>Conclude that planned surgery should not be deferred on basis of single admission BP. History of target organ damage more important than preop BP in predicting complications</li> </ul>
Hart GR and Anderson RJ, 1981 (295) <u>6114720</u>	<u>Study type</u> : Literature review <u>Size</u> : 72 pts BB s, 148 pts Clonidine	Inclusion criteria: Symptoms on cessation of BBs or clonidine Exclusion criteria: CP Bypass, carotid endarterectomy	<u>1° endpoint</u> : CV symptoms or events after abrupt cessation of BBs or clonidine <u>Results</u> : Symptoms of anxiety, chest pain with tachycardia, HTN, myocardial ischemia; less frequently MI may occur on abrupt withdrawal of BB or Clonidine	• Summary of case reports. CV events such as tachycardia, HTN, angina, myocardial ischemia or infarction can occur after abrupt withdrawal of BB or Clonidine. No information on incidence.
Shammash JB, et al., 2001 (296) <u>11136500</u>	Study type: Prospective observational study Size: 140 pts	Inclusion criteria: Review of 140 pts undergoing vascular surgery at university hospitals Exclusion criteria: N/A	<u>1° endpoint</u> : In-hospital mortality <u>Results</u> : 50% mortality in 8 pts with BB discontinued vs. 1.5% mortality in pts with BB continued. OR: 65.0; p=0.001	• Discontinuing BB immediately after vascular surgery may increase the risk of postoperative CV morbidity and mortality

Lindenauer PK, et al., 2005 (297) <u>16049209</u>	Study type: Retrospective cohort Size: 122,338 pts	Inclusion criteria: Age >18 y, major noncardiac surgery Exclusion criteria: contraindication to BB therapy	<u><b>1° endpoint</b></u> : In-hospital mortality <u><b>Results</b>: On BB therapy, mortality in low risk (RCRI =0) OR: 1.43 (1.29–1.58) to high risk (RCRI) OR 4 or higher OR 0.57 (0.42–0.76)</u>	Periop BB therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk pts undergoing major noncardiac surgery.
Wallace AW, et al., 2010 (298) <u>20864832</u>	Study type: Retrospective study Size: 38,779 operations	Inclusion criteria: All surgical pts at SF VAMC Exclusion criteria: N/A	<u>1° endpoint</u> : 30-d and 1-y mortality <u>Results</u> : Addition of BB therapy associated with reduction in 30-d OR: 0.52 (0.33–83; p=0.006) and 1-y OR: 0.64 (0.51–0.79; p<0.0001) mortality	• Periop BB therapy based upon periop Cardiac Risk Reduction protocol is associated with a reduction in 30-d and 1-y mortality. Periop withdrawal of BB is associated with increased mortality
Andersson C, et al 2014 (299) <u>24247428</u>	<u>Study type</u> : Retrospective cohort study <u>Size</u> : 28,263 pts	Inclusion criteria: Pts with IHD undergoing noncardiac surgery Exclusion criteria: N/A	<u>1° endpoint</u> : 30-d risk of MACE and all- cause mortality <u>Results</u> : Among pts with HF BB Rx HR: 0.78 (0.67–90) for MACE and all-cause mortality 0.80 (0.70-0.92) all-cause mortality; and with recent Hx MI HR: 0.60 (0.42–0.86) MACE, 0.80 (0.53–1.21) all- cause mortality	• Among pts with IHD undergoing noncardiac surgery, use of BB associated with lower risk of 30 d MACE and mortality only among those with HF or recent MI
Hoeks SE, et al., 2007 (300) <u>16935011</u>	Study type: Prospective survey Size: 771 pts	Inclusion criteria: Pts 18 y and older undergoing peripheral vascular surgery <u>Exclusion criteria</u> : N/A	<u><b>1° endpoint</b></u> : 1-y mortality <u><b>Results</b></u> : 1 y BB use had lower mortality c/w non-BB users (HR: 0.4; 95% CI: 0.2– 0.7); BB withdrawal had increased mortality c/w nonusers (HR: 2.7; 95% CI: 1.2–5.9)	Periop BB use was independently associated with lower risk of 1-y mortality while periop withdrawal was associated with higher risk of 1 y mortality
Barrett TW, et al 2007 (301) <u>17702038</u>	Study type: Retrospective cohort study Size: 3,062 pts	Inclusion criteria: Pts undergoing vascular surgery Exclusion criteria: N/A	<u>1° endpoint</u> : Long-term mortality, median follow-up 2.7 y <u>Results</u> : Use of BB over study period c/w no BB reduced mortality (HR: 0.84; 95% CI: 0.73–0.96; p=0.0106)	The use of propensity-adjusted BB c/w use reduced long-term mortality by 16%
London MJ, et al. 2013 (302) <u>23613075</u>	Study type: Retrospective cohort analysis Size: 136,745 pts	Inclusion criteria: Pts undergoing major noncardiac surgery	<u>1° endpoint</u> : All-cause 30-d mortality and cardiac morbidity (cardiac arrest, or non-Q wave MI	● BB therapy was associated with lower rates of 30-d all-cause mortality in pts with ≥2 Revised Cardiac Index Factors

		Exclusion criteria: N/A	<b><u>Results</u></b> : BB exposure lower 30-d mortality in pts with 2 or more RCIF (RR: 0.63; 95%	
			CI: 0.50–0.80; p<.001)	
Turan A, et al.	Study type: Matched	Inclusion criteria:	<u>1° endpoint</u> : Intraoperative and post-	<ul> <li>No association found between use of ACEIs and</li> </ul>
2012 (303)	observational study	Pts with noncardiac	operative upper airway complications, in-	intraoperative or postoperative upper airway
22253266		surgery	hospital complications, and 30-d mortality	complications, in-hospital complications, or 30-d
	<u>Size</u> : 79,228 pts	5 5		mortality
		Exclusion criteria:	Results: ACEI usage was not associated	
		N/A	with either 30-d mortality (OR: 0.93: 95%	
			Cl: 0.73–1.19; p=0.22	
Rosenman DJ, et al	Study type: Review of	Inclusion criteria:	1° endpoint: Hypotension requiring	• Pts receiving immediate preoperative ACEI or
2008 (304)	observational and	Adult pts, most $>18$ y,	vasopressors at or shortly after induction	ARA were more likely to develop hypotension
18698608	randomized studies	nonemergent	of anesthesia	requiring vasopressors at or shortly after induction
<u></u>		surgery using ACEI		of anesthesia. Sufficient data were not present to
	Sizo: 121 pts	or ADA chronically	<b>Deculte:</b> Dts resoluting propherative ACEL	of allestitlesia. Sufficient data were not present to
	<u>312e</u> . 434 pis		<u>Results</u> : Pts receiving preoperative ACEI	assess other outcomes.
		Exclusion criteria:	or ARA more likely to develop hypotension	
		N/A	requiring vasopressors. RR: 1.51; 95% CI:	
			1.14–2.01	
Roshanov P.S., et al.	Study type: International	Inclusion criteria:	1° endpoint: 30-d all-cause death, stroke,	Withholding ACEI/ARB before major noncardiac
2017 (305)	prospective cohort	Pts at least 44 y	or myocardial injury	surgery was associated with a lower risk of death
27775997		undergoing	5 5 5	and postoperative vascular events.
	<u>Size</u> : 14,687 pts	noncardiac surgery	Results: ACEI/ARB users who withheld	
		requiring overnight	ACEI/ARB in the 24 H before surgery were	
		hospital admission	less likely to suffer death. MI or stroke	
		'	0.82; 95% CI: 0.70–0.96; p=0.01	
		Exclusion criteria:		
		N/A		

#### Data Supplement 59. RCTs of Adherence and Compliance with Fixed Dose Combinations Regimens (Section 12.1.1)

Study Acronym;	Aim of Study;	Patient Population	Study Intervention	Endpoint Results	Relevant 2° Endpoint (if any);
Author;	Study Type;		(# patients) /	(Absolute Event Rates,	Study Limitations;
Year Published	Study Size (N)		Study Comparator	P value; OR or RR; & 95%	Adverse Events
			(# patients)	CI)	

COMFORT Matsumura K, et al., 2012 (306) 22447014	Aim: Evaluate whether a combination pill of antihypertensive drugs improves medication adherence in hypertensive pts vs. use of single agents. Study type: Multicenter, open, RCT at 29 sites in Japan. Adherence assessed by pill count. Size: 207 pts	Inclusion criteria: • ≥20 y agent with HTN • Could be treated with an ARB and diuretic Exclusion criteria: • Extremely high BP (≥200 mm Hg SBP or ≥120 mm Hg DBP) • Serious renal or liver dysfunction • Taking >4 tablets, excluding study drugs	Intervention: Combination tablet of (Losartan 50 mg/HCTZ 12.5 mg; n=103) <u>Comparator</u> : ARB and a thiazide diuretic as separate agents (n=104)	<u>1° endpoint</u> : Adherence rates as assessed by pill count 98% in both groups (p=0.89) over entire study period (0–6 mo). <u>Safety endpoint</u> : No differences in serious adverse events (1% vs. 1%; p=0.99) or mild adverse events (6% vs. 10%; p-0.31)	<ul> <li><u>2° endpoint</u>: No significant difference in mean SBP and DBP (0.3 and 0.1 mm Hg respectively; p=0.84/0.96).</li> <li><u>Study limitations</u>:         <ul> <li>Adherence rate very high for both groups and likely does not represent real-world rates.</li> <li>Short duration (6 mo) and thus does not provide much information on medication persistence (continuation of drug therapy long-term)</li> <li>Possible selection bias with 2 run-in phases</li> <li>Different healthcare system (Japan) with medications provided through public medical insurance</li> </ul> </li> </ul>
-----------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Data Supplement 60. Nonrandomized Trials, Observational Studies, and/or Registries of Antihypertensive Medication Adherence Strategies (Section 12.1.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Schroeder K, et al., 2004 (307) <u>15078641</u>	Study type: Systematic review of RCTs. Size: 38 studies testing 58 different interventions containing data on 15,519 pts; 9 studies assessed simplification of dosing regimen	Inclusion criteria: • Database search for all RCTs, all languages, in Cochrane Controlled Trials Register, MEDLINE, EMBASE, and CINAHL (all y through 2002) • Population of interest were pts with essential HTN in primary care, outpatient, or community setting • Interventions aimed to increase adherence to BP-lowering medication • Reported outcome was adherence	<ul> <li><u>1° endpoints</u>: Adherence as assessed by pill counts, self-report, or electronic monitoring system</li> <li><u>Results:</u></li> <li>9 studies assessed simplification of dosing regimen, 7 of which compared adherence associated with frequency of administration (twice daily vs. once daily [n=6] or 3 times daily vs. twice daily [n=1]).</li> <li>All studies examining effect of dosing frequency demonstrated improved adherence (range: 8%, 19.6% improvement; p&lt;0.01 for all).</li> </ul>	• Adherence to antihypertensive medication was significantly improved with once daily vs. multiple daily dosing regimens. Most studies used an electronic monitoring system. Limitations in the systematic review include heterogeneity in pts, interventions, and outcomes, and the majority of studies were of low quality. In addition, different definitions of adherence in the RCTs make it difficult to examine the precise relationship of adherence to BP control.

		• RCT where pt care in intervention group(s) compared to either no intervention or usual care	• Only 1 of the 7 studies demonstrated improved BP control (change in SBP 6 mm Hg; p<0.01). However, different medications used for comparison (once daily amlodipine 5 mg vs. diltiazem SR 60 mg twice daily).	
Iskedjian M, et al., 2002 (308) <u>11911560</u>	Study type: Meta-analysis Size: 8 studies involving a total of 11,485 observations (1,830 for once daily dosing, 4,405 for twice daily dosing, 4,147 for >twice daily dosing, 9,655 for maximum daily dose).	<ul> <li>Inclusion criteria:</li> <li>Database search of MEDLINE, EMBASE, and International Pharmaceutical Abstracts (1980– 1998)</li> <li>1° studies that compared adherence rates between different dosing regimens</li> <li>Prospective trials (e.g., RCTs, cohort studies), retrospective studies, database analyses</li> <li>Any published study using an instrument to measure adherence, but must have used some measurement tool in each comparison group.</li> <li>Adherence rates to solid, oral dosage form for treatment of HTN of at least 10 wk duration</li> </ul>	<ul> <li><u>1° endpoints</u>: Medication adherence rates compared between once daily and maximum daily dose, once daily and twice daily, twice daily and &gt;twice daily</li> <li><u>Results:</u> <ul> <li>Average adherence rates with once daily dosing were greater compared to maximum daily dose regimens (91.4% [SD=2.2%] vs. 83.2% [SD=3.5%]; z=4.46; p&lt;0001.)</li> <li>Average adherence rates with once daily dosing were greater compared to twice daily dosing regimens (92.7% [SD=2.3%] vs. 87.1% [SD=2.9%]; z=2.22; p=0.026.)</li> <li>There was no difference in adherence rates between regimens dosed twice daily or greater than twice daily (90.8% [SD=4.7%] vs. 86.3% [SD=6.7%]; z=1.82; p=0.069).</li> </ul> </li> </ul>	Antihypertensive regimens dosed once daily were associated with significantly improved adherence compared to twice daily or maximum daily dose regimens.
Claxton AJ, et al., 2001 (309) <u>11558866</u>	<u>Study type</u> : Systematic review <u>Size</u> : 76 studies	Inclusion criteria: • Database search of MEDLINE, Psychinfo, HealthStar, Health & Psychological Instruments, and Cochrane library 1986–2000 • Compliance rates assessed using electronic monitoring device • Data pooled to calculate mean compliance with once daily, twice daily, 3 times daily, and 4 times daily dosing regimens	<ul> <li><u>1° endpoints</u>: Mean compliance rates by prescribed dose regimen</li> <li><u>Results:</u></li> <li>26 studies evaluated CVD; 17 HTN only.</li> <li>For all studies, mean dose-taking compliance defined as number of appropriate doses taken during each d was 79% for once daily, 69% for twice daily, 65% for 3 times daily and 51% for 4 times daily dosing (p≤0.001 for once daily, and twice daily vs. 4 times daily; no statistically significant between once daily vs. twice daily or twice daily vs. 3 times daily us. 3 times daily dosing).</li> </ul>	• Medication compliance as measured by electronic monitoring devices were improved with less frequent dosing. Once-daily dosing was associated with the greatest rate of compliance. Limitations of this analysis include heterogeneity of studies and disease states studied.

			• For 14 studies that assessed ability to take doses within prescribed time frame, once daily regimens were associated with better dose-time compliance (74% ± 31%) compared to twice daily (58% ± 23%) or 3 times daily (46% ± 8%); formal statistical analysis not conducted due to too few studies.	
Sherrill B, et al., 2011 (310) <u>22142349</u>	Study type: Meta-analysis to compare health resource use cost, adherence, and persistence between groups of pts taking antihypertensives as SPCs vs. free-equivalent components. Size: 15 retrospective database studies in HTN	<ul> <li>Inclusion criteria:</li> <li>Database search of PubMed, EMBASE, The Cochrane Library, and EconLit (no limit on publication dates)</li> <li>English-language publications</li> <li>Clinical trial or observational study (e.g., database or registry) that compared SPC with free- equivalent components</li> <li>Data on compliance, adherence, persistence, and/or health care costs and/or resource use (unadjusted cost analyses)</li> </ul>	<ul> <li><u>1° endpoints</u>: Health care costs, adherence, persistence</li> <li><u>Results:</u> <ul> <li>All-cause total costs were estimated to be lower with SPC vs. free-equivalent components free-equivalent components by \$2,039 (95% CI: \$1030, \$3047) in 2009 dollars and HTN/CV-related costs were lower by \$709 (95% CI: \$117, \$1,032), 2009 dollars.</li> <li>Adherence as measured by MPR was greater for SPC vs. free-equivalent components (total inverse variance 13.31; 95% CI: 8.26–18.35).</li> <li>Persistence to therapy was greater with SPC than free-equivalent components (risk ratio: 2.13; 95% CI: 1.11–4.09)</li> </ul> </li> </ul>	<ul> <li>Medication adherence and persistence was significantly greater with SPC than free-equivalent components. Costs were also significantly lower with SPC than with free-equivalent components. However, cost data should be interpreted with caution considering unadjusted costs were used in this meta-analysis. In addition, heterogeneity was present in analyses of each outcome. This meta-analysis did not include the observational study by Yang et al. as that study used an adjusted analysis methodology.</li> </ul>
Yang W, et al., 2010 (311) <u>20629600</u>	Study type: Observational analysis using multivariate regression-adjusted analysis to compare compliance/persistence, health care resources, and cost associated with SPC or FC antihypertensives over 6 mo study period both nationally and at the state level. Size: 579,581 pts (382,476 SPC and 197,375 FC) identified in MarketScan Database (2006–2008)	Inclusion criteria: • Pts in MarketScan Database • Diagnosis of HTN based on ICD- 9 codes 401.xx and 405.xx • Pts initiated on any of the following SPC treatments or the same FC: ARB + CCB, ARB + HCTZ, ACEI + HCTZ • For SPC cohort, at least 1 prescription filled in observational window • For FC cohort, pts filled individual components separately within 15 d of each other and with 15 d overlap of supply • ≥18 y	Endpoints: • 1° outcome: Compliance and persistence with the index therapy (SPC or FC) measured by MPR within 6 mo of index date • 2° outcomes: Healthcare resource utilization (number of all-cause hospitalizations, number ER visits, number CV hospitalizations, and CV- related ER visits) and health care costs (all cause medical costs, all-prescription drug costs, CV-related medical service costs, and HTN prescription-related drug costs) Results: • Compliance nationally as assessed by MPR was improved in pts taking SPC vs. FC antihypertensives (difference=11.6%; 95% CI: 11.4%–11.7%).	• This large observational study found that medication compliance/persistence to antihypertensives was improved with SPC compared to FC using an adjusted multivariate regression model. All-cause medical costs were also decreased with the used of SPC antihypertensives, although prescription costs were greater.

		<ul> <li>Continuous eligibility in database for 6 mo after index date</li> <li>Valid 3-digit zip code in database</li> </ul>	<ul> <li>Treatment discontinuation rates were lower with SPC vs. FC antihypertensives (40.7% vs. 59.3%; 95% Cl: 0.46–0.48).</li> <li>There were fewer all-cause hospitalizations and ER visits in SPC vs. FC pts IRR: 0.77 (95% Cl: 0.75–0.79) and IRR: 0.87 (95% Cl: 0.86, 0.89), respectively.</li> <li>All-cause medical costs were reduced with SPC vs. FC (-\$208; 95% Cl: -\$302– -\$114), but antihypertensive prescription costs were greater (\$53; 95% Cl: \$51–\$55).</li> </ul>	
Gupta, et al., 2010 (312) <u>20026768</u>	Study type: Meta-analysis to assess compliance, adherence, persistence, BP control, and safety with FDC antihypertensives compared to their free components Size: 15 studies (n=32,331) with ≥1 evaluated outcome; 3 cohort studies and 2 trials of compliance (n=17,999); 3 cohort studies on persistence (n=12,653); 5 trials of adverse drug effects of FDCs (n=1,775); 9 trials of BP change (n=1,671)	Inclusion criteria: • Database search of PubMed (1966–February 2008), Web of Science (1970 to April 2008), and the Cochrane Controlled Trial (1800–April 2008). • Clinical trials or cohort studies included if published in English and compared an FDC of hypertensive agents with free-drug combination of its components. • Extractable data reported including compliance (or adherence), persistence, BP- lowering effects, adverse effects	<ul> <li><u>1° endpoint:</u></li> <li>Compliance (or adherence) and persistence to therapy</li> <li>BP-lowering efficacy</li> <li>Adverse effects</li> <li><u>Results:</u></li> <li>Use of FDC therapy was associated with a 21% increase in compliance, both in the cohort studies (n=5) and clinical trials (OR: 1.21; 95% CI: 1.00–1.47) and (OR: 1.21; 95% CI: 1.03–1.43). There was a 50% increase in persistence with therapy, but this was not statistically significant (OR: 1.54: 95% CI: 0.95–2.49). Analysis of all 6 retrospective cohort studies indicated that FDC therapy was associated with a 29% increase in compliance and persistence to therapy (OR: 1.29; 95% CI: 1.11–1.50). No sign of heterogeneity of publication bias.</li> <li>FDC therapy was associated with a nonsignificant reduction in SBP (-4.1 mm Hg; 95% CI: -9.8–1.5 mm Hg; p=0.15) and DBP (-3.1 mm Hg; 95% CI: -7.1–0.9 mm Hg; p=0.13) compared to free-drug combinations. Strong evidence of heterogeneity but no evidence of publication bias.</li> <li>FDC therapy was associated with a 20% nonsignificant decrease in adverse effects (OR:</li> </ul>	• Use of FDC therapy is associated with significant improvements in compliance and persistence to antihypertensive therapy and possible improvement in BP control and decreased risk of adverse effects.

			0.80; 95% CI: 0.58, 1.11) compared to free-	
			drug combinations.	
Bangalore S, et al., 2007 (313) <u>17679131</u>	<u>Study type</u> : Meta-analysis to assess if compliance is improved with FDC therapy compared to free-drug regimens in chronic diseases including HTN, HIV, tuberculosis, and DM <u>Size</u> : 9 studies total (n=20,242), 4 of which were in hypertensive populations (n=17,175)	Inclusion criteria: • Database search of MEDLINE (1966–2005) • Studies included if published in English and compared an FDC with free-drug combination of its components and reported medication compliance (adherence) or persistence	<ul> <li><u>1° endpoint</u>: Compliance, considered as either adherence or persistence to medication therapy</li> <li><u>Results:</u></li> <li>Use of FDC therapy was associated with a 26% decreased risk of noncompliance vs. freedrug combinations (pooled RR: 0.74 (95% CI: 0.69, 0.80), p&lt;0.0001) in all diseases states. There was no evidence of heterogeneity.</li> <li>In hypertensive pts, FDC was associated with 24% decreased risk of noncompliance (pooled RR: 0.76 (95% CI: 0.71, 0.81), p&lt;0.0001) compared to free-drug regimen. There was no evidence of publication bias.</li> <li>Marked heterogeneity in how compliance was measured among studies</li> </ul>	• Use of FDC combination therapy in hypertensive pts was associated with a 24% decreased risk of noncompliance compared to use of free-drug regimens.
Kumagai N, et al., 2013 (314) <u>23072348</u>	<u>Study type</u> : Prospective, multicenter, observational study of pts converted from free-drug combinations of an ARB and amlodipine to the same product as a FDC. <u>Size</u> : 196 pts	Inclusion criteria: • Outpatients with essential HTN • Self-measured home BP • Prescribed FDC of an ARB (8 mg candesartan, 80 mg valsartan, or 40 mg telmisartan) and 5 mg) and 5 mg amlodipine • Pts divided into 2 groups: Group 1 received an ARB and amlodipine in the morning as free drug combinations and Group 2 took ARB in the morning and amlodipine in the evening. After 1 mo, both groups converted to once daily FDC product. Exclusion criteria: • Severe renal of liver dysfunction • Severe HF • Prescription of time-specific packs	<ul> <li>Endpoints:</li> <li>Adherence to antihypertensive therapy as measured by self-reporting</li> <li>Self-monitored BP measurements and clinical BP measurements before and after switch to FDC antihypertensive therapy.</li> <li>Drug costs</li> <li>Results:</li> <li>Self-monitoring BP measurements taken during early morning was lower with FDC compared to free-drug combinations (-5 mm Hg SBP, -2 mm Hg DBP; p&lt;0.01 for both)</li> <li>Average clinic BP was lower with FDC compared to free-drug combination (-5 mm Hg SBP, -2 mm Hg SBP; p&lt;-0.01).</li> <li>Self-reported adherence was improved with FDC vs. free-combination agents (~99% vs. 95% p&lt;0.01). SBP was significantly lower in the group with improved adherence (~7.5 mm Hg)</li> </ul>	• Use of FDC with an ARB and amlodipine was associated with improved adherence, lower BP, and decreased health care costs compared to free-drug combination therapy. Limitations to this study include the observational design, low numbers of pts, use of self-reported adherence, short follow-up period, non-U.S. country with a different health care system (Japan), and very high baseline rate of adherence (~95%) as well post-switch to FDC (~99%), which is not what is seen in usual practice.

			<ul> <li>compared to the group without improved drug adherence (~4 mm Hg; p&lt;0.05).</li> <li>Healthcare costs were decreased by 31% per pt from 17,075 yen (\$216.93 USD; Aug. 2012) to 11,815 yen (\$150.10 USD; Aug. 2012) over the 3 mo period.</li> </ul>	
Mazzaglia G, et al., 2009 (315) <u>19805653</u>	Study type: Retrospective cohort Size: 18,046 pts	Inclusion criteria: Newly diagnosed and treated hypertensive pts ≥35 y initially free of CVD identified from Italian general pt registry. Exclusion criteria: CHD, cerebrovascular disorders, congestive HF who had been hospitalized for CABG or coronary angioplasty, those recovered in a cardiology ward before index diagnosis, incident CV event in the 180 d after index diagnosis, pts receiving nitrates	<u>1° endpoint</u> : Describe adherence to antihypertensive therapy and its associate with concurrent drug use, comorbidities, and CV risk factors. Adherence was estimated by calculating the proportion of days which pt had pills available during the follow-up. <u>Results:</u> At baseline (6 mo after index diagnosis), adherence rates were high (≥80% proportion of days covered) in 8.1% of pts, intermediate (40-79% proportion of d covered) in 4.5%, and low (≤40% proportion of d covered) in 51%. Multiple drug treatment (1.62; 95% Cl: 1.43–1.83), dyslipidemia (1.52; 95% Cl: 1.24–1.87), DM (1.40; 95% Cl: 1.15–1.71), obesity (1.50; 95% Cl: 1.26–1.78) and antihypertensive combination therapy (1.29; 95% Cl: 1.15–1.45) were associated with high adherence to treatment (p<0.001).	• High adherence was associated with a 38% decreased risk of CV events compared with low adherence. Combination therapy associated with 29% improved adherence compared to monotherapy.
Jackson KC, et al., 2008 (316) <u>18803997</u>	Study type: Retrospective cohort study Size: 908 pts	Inclusion criteria: • ≥18 y and diagnosis of HTN • Benefit-eligible for pharmacy claims • Antihypertensive naive (no prescription fill for antihypertensive drug ≥110 d prior to index date) • Received 1 of 3 regimens: 1.) 2 pill regimen with valsartan + amlodipine, 2.) 2-pill regimen with valsartan/HCTZ in FDC + amlodipine, 3.) 3-pill regimen with valsartan + HCTZ + amlodipine as free-drug components	<u><b>1° endpoint</b></u> : Adherence as measured by MPR <u><b>Results</b></u> : 224 pts received valsartan + amlodipine, 619 received valsartan/HCTZ + amlodipine, and 65 received valsartan + HCTZ + amlodipine. MPR ratios were 75.4% with valsartan + amlodipine, 73.1% with valsartan/HCTZ + amlodipine, and 60.5% with valsartan + HCTZ + amlodipine (p=0.005). Older age was associated with improved MPR (75.2% for those $\geq$ 64 y. vs. 69.6% for 18 to <36 y; p=0.023).	• An inverse relationship existed between the number of pills and adjusted MPR, with lower adherence noted in 3-pill regimens vs. 2-pill regimens.

		Exclusion criteria: Pts who received <2 prescription fills, did not continuously have prescriptions refilled for each medication, or switched from1 medication to another without a time overlap		
Dickson M, et al., 2008 (317) <u>18303937</u>	<u>Study type</u> : Retrospective cohort study <u>Size</u> : 5,704 pts	Inclusion criteria: • 65–100 y on index date • Received at least 2 prescriptions for study drugs (amlodipine/benazepril FDC n=2336] or DHP-CCB and ACEI as separate agents [n=3368] between 1997–2001 • Continuously eligible for Medicaid for 12 mo following index date Exclusion criteria: • >180 d of hospitalization • <30 d of study drug supply • Any nursing home claims during the12 mo follow-up period	<ul> <li><u>1° endpoint</u>: Determine rates of compliance (MPR) and total costs of care (defined as sum of payments for Medicaid claims for ambulatory care, hospital claims, prescription drug claims, and Medicare ross claims) in pts treated with FDC amlodipine/benazepril vs. a DHP-CCB and ACEI prescribed as free-combination agents.</li> <li><u>Results</u>: MPR was significantly higher for pts receiving FDC compared with free-combination therapy (63.5% vs. 49%; p&lt;0.05). Average total cost of care (2002 value) was \$3,179 with FDC compared to \$5,236 with free-combination agents (p&lt;0.0001). Multivariate regression analysis indicated an increase of 0.5% for each 1-unit increase in MPR, and for each comorbidity there was a 10.4% increase. Total cost of care for FDC group was 12.5% lower than free-combination group (p&lt;0.003)</li> </ul>	• FDC combination therapy with amlodipine/benazepril was associated with better compliance than a DHP-CCB and ACEI as free- combination agents. FDC was also associated with lower total costs of care.

#### Data Supplement 61. RCTs and Meta-analysis on Strategies to Promote Lifestyle Modification (Section 12.1.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% Cl)	Relevant 2° Endpoint; Study Limitations; Adverse Events Summary
Artinian NT, et al., 2010 (318) <u>20625115</u>	<u>Aim</u> : To provide evidence-based recommendations on implementing PA and dietary interventions among adults,	Inclusion criteria: Included studies were limited to adult pts ≥18 y; English language; randomized controlled or quasi-experimental designs	Cognitive-behavioral strategies for promoting behavior change including Goal Setting, Self- Monitoring, Frequent and Prolonged Contact, Feedback and Reinforcement, Self-Efficacy Enhancement, Incentives, Modeling, Problem Solving, Relapse Prevention, Motivational	• Variable, too numerous to summarize here.	• Variable, too numerous to summarize here.

	including adults of racial/ethnic minority and/or socioeconomically disadvantaged populations. <u>Study type:</u> Literature review, evidence synthesis and recommendations using ACC/AHA evidence grading. <u>Size</u> : 70 studies, including 65 RCTs published from 1997–2007.	or meta-analyses; focused on the effects of diet or PA interventions on weight, BP, PA level, aerobic and resistance exercise, fitness, or consumption of calories, fruits, vegetables, fiber, total fat, saturated fat, cholesterol or salt <b>Exclusion criteria</b> : Feeding trials, observational studies of specific nutrients, and observational studies of aerobic capacity were excluded. Given the varying goals and outcomes of the different identified intervention studies, when possible we used a common measure of effect size to quantify and compare the success of each intervention.	Interviewing: also Intervention Processes or Delivery Strategies, including Targeting Single Behaviors Versus Multiple Behaviors, Print- or Media-Only Delivery Strategies, Group, Individual, Technology, and Multicomponent- Based Delivery Strategies, Group-Based Interventions, Individual-Focused Interventions, Computer/Technology-Based Interventions, and Multicomponent Intervention Delivery Strategies; also, Special Considerations for Interventions With Minority and Socioeconomically Disadvantaged Populations, including Setting in Which Healthcare Is Delivered, Peer/Lay Led Versus Professionally Led, Cultural Sensitivity, Literacy Level Sensitivity, Barriers to Behavior Change, and Acculturation. In addition, Fostering Initiation and Maintenance of Behavior Change.		
Eckel RH, et al., 2013 (319) <u>24239922</u>	<u>Document</u> : Guideline	Inclusion criteria: N/A Exclusion criteria: N/A	<u>Comparator</u> : Usual care or other comparison group	N/A	N/A

# Data Supplement 62. RCTs, Meta-analyses, and Systematic Reviews on the Effect of Structured, Team-based Care Interventions for Hypertension Control (Section 12.2)

Study Acronym;	Aim of Study;	Patient Population	Study Intervention (#	Endpoint Results	Relevant 2° Endpoint (if any);
Author;	Study Type;		patients) /	(Absolute Event Rates, P	Study Limitations;
Year Published	Study Size (N)		Study Comparator (#	value; OR or RR; & 95% CI)	Adverse Events
			patients)		Summary

Brownstein JN, et al., 2007 (320) <u>17478270</u>	Aim: Examine the effectiveness of community health workers in supporting the care of pts with HTN <u>Study type</u> : Systematic review <u>Size</u> : 14 studies, including 8 RCTs	Inclusion criteria: Studies examining the effects of an intervention involving community health workers on the care of pts with HTN Exclusion criteria: Studies that focused exclusively on outcomes among community health workers and those involving peers who merely led support groups	Intervention: Community health workers as HTN care team members. Community health workers were broadly defined as health workers who were trained as part of an intervention, had no formal paraprofessional designation, and had relationship with the community being served. The community health workers, predominantly women, were recruited from the community, and resembled the pts in race/ethnicity and socioeconomic background. Roles included: (1) providing health education and information to pts and families; (2) ensuring that pts received services necessary for BP control; (3) providing direct services, including measuring and monitoring BP; (4) providing social support to the pts and their family members; and (5) serving as mediators between pts and the healthcare and social service systems. <u>Comparator</u> : Usual care or	<u>1° endpoint</u> : Differences between groups in BP control groups favored community health worker groups over control and ranged from 4%– 46% over 6–24 mo, across 7 RCTs; though 1 RCT showed no difference between groups. <u>Safety endpoint</u> : N/A	<ul> <li><u>2° endpoints</u>:</li> <li>Appointment keeping: significant improvements ranging from 19%–39% (relative changes) over 12–24 mo in community health worker intervention</li> <li>Adherence to medications: Range of findings included significant improvement in community health worker intervention group compared with control, between-group differences ranged from 8%–14%; 26% greater compliance among pts receiving intense community health worker interventions; and 17% significant improvement in adherence to medication with counseling by community health workers.</li> <li><u>Limitations</u>: High level of heterogeneity of the populations, settings, interventions, and outcomes</li> <li><u>Summary</u>: Including community health workers as part of the HTN care team resulted in significant improvements BP control, appointment keeping, and adherence to antihypertensive medications, primarily among low income, urban African Americans.</li> </ul>
			other comparison group		

Carter BL, et al., 2009 (321) <u>19858431</u>	Aim: Determine potency of interventions for BP involving nurses and pharmacists Study type: Meta- analysis Size: 37 RCTs of team- based HTN care involving nurse or pharmacist intervention	Inclusion criteria: RCT of team-based HTN care involving nurse or pharmacist intervention Exclusion criteria: Absence of above	Intervention: Team-based HTN care involving nurse or pharmacist intervention in nearly all studies involving nurses or pharmacists in clinics, consistent and dedicated case management activities were provided that were distinct from traditional nursing or pharmacist duties. However, pharmacists in community pharmacies usually had to incorporate the intervention with traditional medication dispensing functions. Comparator: Usual care	1° endpoint:OR (95% CI)for controlled BP werenurses:1.69 (1.48, 1.93);pharmacists within primarycare clinics:2.17 (1.75,2.68); and communitypharmacists:2.89 (1.83,4.55).Mean (SD) reductionsin SBP were: nurseintervention,5.84 (8.05) mmHg; pharmacists in clinics,7.76 (7.81) mm Hg; andcommunity pharmacists,9.31 (5.00) mm Hg.There were no significantdifferences between nurseand pharmacist effects(p≥0.19).1° Safety endpoint:N/A	<ul> <li>Stepwise regression was used to compare studies that included a given intervention strategy with studies that did not. Several individual components of the interventions were associated with significant reductions in mean SBP including pharmacist recommended medication to physician (-27.21 mm Hg; p=0.002), counseling about lifestyle modification (-12.63 mm Hg; p=0.03), pharmacist performed the intervention (-11.70 mm Hg; p=0.03), use of a treatment algorithm (-8.46 mm Hg; p&lt;0.001), completion of a drug profile and/or medication history (-8.28 mm Hg; p=0.001), and the overall intervention potency score assigned by the study reviewers (p&lt;0.001). The factors associated with a reduction in DBP were: referral was made to a specialist (-19.61 mm Hg; p=0.04), providing pt education about BP medications (-17.60 mm Hg; p=0.006), pharmacist performed the intervention (-3.94 mm Hg; p=0.04).</li> <li>Summary: Interventions involving pharmacist or pursoe were associated with a provision of a drug profile and here intervention (-3.94 mm Hg; p=0.04).</li> </ul>
					Summary: Interventions involving pharmacists or nurses were associated with significantly improved BP control.
Clark CE, et al., 2010 (322) <u>20732968</u>	<b><u>Aim</u>:</b> Review trials of nurse led interventions for HTN in primary care to clarify the evidence base, establish whether nurse prescribing is an important intervention	Inclusion criteria: RCT of nursing intervention for HTN Exclusion criteria: Absence of above	Intervention: Interventions were categorized as nurse support delivered by either telephone, community monitoring or nurse led clinics. These were held in either primary care or 2° care. 1 study used alternate	<u>1° endpoint:</u> • Compared with usual care, Interventions that included a stepped treatment algorithm showed greater reductions in SBP (weighted MD -8.2 mm Hg (95% CI: -11.5– -4.9);	Summary: Nurse led interventions that included a stepped treatment algorithm or nurse led prescribing showed significantly greater reductions of SBP and DBP than usual care. Telephone monitoring was associated with higher achievement of study targets for BP. Community monitoring showed lower

	Study type: Meta- analysis Size: 32 RCTs of nursing intervention for HTN		sessions with nurses at home and in general practice. 14 studies included a stepped treatment algorithm and 9 included nurse prescribing in the protocol. <u>Comparator</u> : Usual care	<ul> <li>Nurse prescribing showed greater reductions SBP, -8.9 mm Hg, (95% CI: -12.5 5.3), and DBP, -4.0 mm Hg, (95% CI: -5.32.7);</li> <li>Telephone monitoring showed higher achievement of BP targets (RR: 1.24; 95% CI: 1.08–1.43);</li> <li>Community monitoring showed greater reductions in (weighted MD) SBP, -4.8 mm Hg, (95% CI: -7.02.7), and DBP, -3.5 mm Hg, (95% CI: -4.52.5).</li> <li>Safety endpoint: N/A</li> </ul>	outcome SBP, greater reductions in SBP and DBP, and, although pooling of data was not possible, greater achievement of study BP targets.
Proia KK, et al., 2014 (323) 24933494	Aim: Examine current evidence on the effectiveness of team- based care in improving BP outcomes (update of prior systematic review) Study type: Systematic review Size: 52 studies of team-based primary care for pts with 1° HTN	Inclusion criteria: Study of team-based care; conducted in a high-income economy; reported at least 1 BP outcome of interest; included a comparison group or had an interrupted time-series design with at least 2 measurements before and after the intervention; targeted populations with 1° HTN or populations with comorbid conditions such as DM as long as the 1° focus of the intervention was BP control; and did not	Intervention: Team-based care was defined as adding new staff or changing the roles of existing staff to work with a PCP for HTN care. Team members who collaborated with pts and PCPs were predominantly nurses (28 studies); pharmacists (15 studies); both nurses and pharmacists (5 studies); or community health workers, integrated care managers, or behavioral interventionists (4 studies). Key roles included HTN medication management, active pt follow-up, and adherence and self- management support. Interventions were usually	<ul> <li><u>1° endpoint</u>:</li> <li>Proportion with controlled BP: Absolute percentage point (pct pt) change in pts with controlled BP from 33 studies comparing team- based care to usual care: median effect estimate was 12 pct pts (IQI=3.2–20.8 pct pts). Most individual effect estimates in the favorable direction were significant (p&lt;0.05).</li> <li>Reduction in SBP (44 studies): The median reduction in SBP was 5.4 mm Hg (IQI=2.0–7.2 mm Hg). Most individual effect estimates were significant (p&lt;0.05).</li> <li>Reduction in DBP: The overall median reduction in</li> </ul>	<ul> <li><u>2° endpoints</u>: Compared with pts in usual care, the proportion of pts receiving team-based care with "high" medication adherence (defined as taking medications as prescribed &gt;80% of the time) increased by a median of 16.3 pct pts (9 studies).</li> <li><u>Stratified analyses for BP outcomes</u>:</li> <li>Team member role in medication management: Larger improvements in BP outcomes than overall estimates were demonstrated when team members could make changes to medications independent of the PCP or team members could provide medication recommendations and make changes with the PCP's approval as compared to team members providing only adherence support and information on medication and HTN.</li> </ul>

		Exclusion criteria: Inclusion of populations with 2° HTN (e.g., pregnancy) or with a history of CVD (e.g., MI)	implemented across multiple settings in the healthcare system and in the community, where they were implemented in pharmacies and through home outreach visits. <u>Comparator</u> : Usual care	DBP was 1.8 mm Hg (IQI=0.7–3.2 mm Hg) from 38 studies. Safety endpoint: No harm to pts was identified from team- based care interventions in the included studies or the broader literature.	<ul> <li>Number of team members added: Adding ≥2 members demonstrated larger improvements in the proportion of pts with controlled BP and reduction in DBP compared to adding only 1; median reductions in SBP were similar regardless of team size.</li> <li>Improvement in the proportion of pts with controlled BP was similar for studies from both healthcare and community settings.</li> <li>Limitations: Included studies reported significant differences in pt demographics between intervention and comparison groups at baseline, possible contamination within intervention and comparison groups, and issues related to inadequate description of populations and implemented interventions.</li> <li>Summary: There is strong evidence that team- based care is effective in improving BP</li> </ul>
					outcomes, especially when pharmacists
Santschi V, et al.,	Aim: Assess effect of	Inclusion criteria:	Intervention: Pharmacist	1° endpoint: Pharmacist	Summary: Pharmacist interventions,
2014 (324)	pharmacists	RCT of pharmacist	intervention delivered by a	interventions were	alone or in collaboration with other
<u>24721801</u>	interventions on BP and	intervention delivered	pharmacist alone or in	associated with a large	healthcare professionals, improved BP
	determine potential	by a pharmacist alone	collaboration with other	reduction in systolic and DBP	management
			Dharmacist interventions	01 - 7.0 [[[[]] HY (95% CI: -9.0-	
	петегоденену	professionals	mainly included nt	(95% (152.8 mm Ha)	
	Study type: Meta-	Protossionals	education, feedback to	respectively	
	analysis	Exclusion criteria:	physician, and medication		
		Absence of above	management.	Safety endpoint: N/A	
	Size: 39 RCTs were				
	included with 14,224 pts		Comparator: Usual care		

Shaw RJ, et al., 2014 (325) <u>25023250</u>	Aim: Determine whether nurse-managed protocols are effective for outpatient management of pts with DM, HTN, and hyperlipidemia (HTN RCT outcomes only included here) Study type: Meta- analysis Size: 12 RCTs, with 10,362 pts, of nurse- managed protocols for outpatient management of HTN	Inclusion criteria: RCT of nurse- managed protocols for outpatient management of HTN Exclusion criteria: Absence of above	Intervention: Involvement of a registered nurse or a licensed practical nurse functioning beyond the usual scope of practice, such as adjusting medications and conducting interventions based on a written protocol. All studies used a nurse who titrated medications by following a protocol. Comparator: Usual care	<u>1° endpoint:</u> • SBP and DBP decreased by 3.68 mm Hg (95% CI: 1.05–6.31 mm Hg) and 1.56 mm Hg (95% CI: 0.36–2.76 mm Hg), respectively, with high variability (I <sup>2</sup> >70%) • Nurse-managed protocols were more likely to achieve target BP than control protocols (OR: 1.41; 95% CI: 0.98–2.02), though difference was not significant and treatment effects were highly variable (Q 35.20; I <sup>2</sup> =74%). <u>Safety endpoint</u> : N/A	<ul> <li>Included studies of low/good quality as well as moderate/fair, and high quality</li> <li>Descriptions of interventions and protocols were limited</li> <li><u>Summary</u>: Nurse-managed protocols for HTN care were associated with a mean decrease in SBP and DBP but not increase in HTN control.</li> </ul>
Carter BL, et al., 2015 (326) <u>25805647</u>	Aim: Evaluate if a physician/pharmacist collaborative model would be implemented as determined by improved BP control and whether long-term BP control could be sustained Study type: Cluster RCT Size: 32 primary care offices from 15 states enrolled 625 pts with uncontrolled HTN; 54% from racial/ethnic minority groups and 50% with DM or CKD	Inclusion criteria: Offices were required to have an onsite clinical pharmacist must have practiced in the office. Pts were eligible if they were English or Spanish speaking, ≥18 y with uncontrolled BP as measured by the SC on the baseline visit. Exclusion criteria: Absence of above	Intervention: Pharmacist conducted medical record review and a structured interview with the subject, including 1) a medication history; 2) an assessment of knowledge of BP medications, dosages and timing, and potential side effects; and 3) other barriers to BP control (e.g., side effects and nonadherence). The model recommended a telephone call at 2 wk, structured face- to-face visits at baseline, 1, 2, 4, 6, and 8 mo and additional visits if BP remained uncontrolled. The pharmacist created a care plan with recommendations for the physician to adjust	<u>1° endpoint</u> : BP control at 9 mo was 43% in intervention offices compared with 34% in control group (adjusted OR: 1.57 (95% CI: 0.99, 2.50), p=0.059). <u>Safety endpoint</u> : N/A	<ul> <li><u>2° endpoints</u>:</li> <li>The adjusted difference in mean SBP/DBP between the intervention and control groups for all pts at 9 mo was -6.1/-2.9 mm Hg (p=0.002 / p=0.005, respectively), and it was -6.4/-2.9 mm Hg (p=0.009 / p=0.044, respectively) in pts from racial or ethnic minorities.</li> <li>BP control and mean BP were significantly improved in pts from racial minorities in intervention offices at 18 and 24 mo (p=0.048 and p&lt;0.001) compared with the control group.</li> <li><u>Summary</u>: Although the results of the 1° outcome (BP control) were negative, the key 2° endpoint (mean BP) was significantly improved in the intervention group. Thus, the findings for 2° endpoints suggest that team-based care using clinical pharmacists significantly</li> </ul>

	therapy based on the JNC-	reduced BP in subjects from racial
	7, and the BP goals were	minority groups.
	<140/90 mm Hg for	, , , , , , , , , , , , , , , , , , ,
	uncomplicated HTN or	
	<130/80 mm Hg for pts with	
	DM or CKD. The	
	pharmacists did not follow	
	algorithms or protocols other	
	than JNC-7. Physicians	
	were free to accept or to	
	reject any recommendation	
	or to modify the plan.	
	Recommendations	
	to pts focused on	
	medication education,	
	improving adherence, and	
	strategies to implement	
	lifestyle modifications.	
	Comparator: Pharmacists	
	in control offices were	
	instructed to avoid	
	intervention for study pts	
	with HTN, but they could	
	provide usual care curbside	
	consultations if physicians	
	specifically asked questions.	

## Data Supplement 63. Electronic Health Records and Patient Registries (Section 12.3.1)

Study Acronym Author Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Bardach NS, et al., 2013 (327) <u>24026600</u>	<u>Aim:</u> To assess the effect of P4P incentives on quality in EHR-enabled small practices in the	Participating clinics (n=42 for each group) had similar baseline characteristics, with	• A city program provided all participating clinics with the same EHR software with decision support	• Intervention clinics had greater adjusted absolute improvement in rates of appropriate antithrombotic prescription (12.0% vs.	• Although the effect of the intervention was lower than the 10% improvement that we estimated a priori, the absolute risk reduction for BP control among pts with DM was 7.8% (NNT, 13). This

Ĩ		context of an established QI initiative. Study type and size: A cluster-randomized trial of small (<10 clinicians) primary care clinics in New York City from April 2009 through March 2010.	a mean of 4,592 (median, 2,500) pts at the intervention group clinics and 3,042 (median, 2,000) at the control group clinics.	and pt registry functionalities and QI specialists offering technical assistance. • Incentivized clinics were paid for each pt whose care met the performance criteria, but they received higher payments for pts with comorbidities, who had Medicaid insurance, or who were uninsured (maximum payments \$ 200/nt;	6.1%, difference: 6.0% (95% CI: 2.2%, 9.7%), p=0.001 for interaction term), BP control (no comorbidities: 9.7% vs. 4.3%, difference: 5.5% (95% CI: 1.6%, 9.3%), p=0.01 for interaction term; with DM: 9.0% vs. 1.2%, difference: 7.8% (95% CI: 3.2%, 12.4%), p=0.007 for interaction term; with DM or ischemic vascular disease: 9.5% vs. 1.7%, difference: 7.8% (95% CI: 3.0%	suggests that, for every 13 pts seeing incentivized clinicians, 1 more pt would achieve BP control. The 7.8% absolute change in BP control for pts with DM represents a 46% relative increase in BP control among intervention pts compared with the baseline of 16.8%. Further research is needed to determine whether this effect of the P4P intervention on BP control increases or decreases over time. However, this NNT to achieve BP control through incentives, taken together with the large relative increase in percentage of nts with BP control
				\$100,000/clinic). Quality reports were given quarterly to both the intervention and control groups.	12.6%), p=0.01 for interaction term), and in smoking cessation interventions (12.4% vs. 7.7%, difference: 4.7% (95% CI: -0.3%, 9.6%), p=0.02 for interaction term). Intervention clinics performed better on all measures for Medicaid and uninsured pts except	and the potential effect of BP control on risk of ischemic vascular events, suggests a reasonable opportunity to reduce morbidity and mortality through P4P as structured in this study. <u>Limitations:</u> Some clinics exited the program after randomization, with more control clinics leaving than intervention clinics. Additionally, this intervention occurred in the setting of a voluntary QI
					cholesterol control, but no differences were statistically significant.	program. This may reflect a high level of intrinsic motivation to improve among practices in the study, as demonstrated by engagement with the QI specialists
	Banerjee D, et al., 2012 (328) <u>22031453</u>	Study type: 3-y, cross-sectional sample using pt EHRs.	<ul> <li>• 251,590 pts ≥18 y. Underlying HTN was defined as 2 or more abnormal BP readings</li> <li>≥140/90 mm Hg and/or pharmaceutical treatment. Appropriate HTN diagnosis was defined by the reporting of ICD-9 codes (401.0–</li> </ul>	• To identify prevalent and incident HTN cases in a large outpatient healthcare system, examine the diagnosis rates of prevalent and incident HTN, and identify clinical and demographic factors	• The prevalence of HTN was 28.7%, and the diagnosis rate was 62.9%. The incidence of HTN was 13.3%, with a diagnosis rate of 19.9%. Predictors of diagnosis for prevalent HTN included older age, Asian, African American, higher BMI, and increased number	Outpatient EHR diagnosis rates are suboptimal, yet EHR diagnosis of HTN is strongly associated with treatment. Targeted efforts to improve diagnosis should be a priority.

		401.9). Factors associated with HTN diagnosis were assessed through multivariate analyses of pt clinical and demographic characteristics.	associated with appropriate HTN diagnosis.	of ABP readings. Predictors for incident HTN diagnosis were similar. In pts with 2 or more abnormal BP readings, HTN diagnosis was associated with significantly higher medication treatment rates (92.6% vs. 15.8%; p<0.0001).	
Jaffe MG, et al., 2013 (329) <u>23989679</u>	Aim: Study the effect of a multipronged, system-based, Ol approach on HTN control. Study type: Observational Size: All pts with HTN in the KPNC system were included	Inclusion criteria: 350,000 pts in the KPNC system with HTN in 2001, increasing to 650,000 in 2009 Eligibility: • ≥2 HTN diagnoses coded in primary care visits in the prior 2 y • ≥1 primary care HTN diagnoses and 1 or more hospitalizations with a 1° or 2° HTN diagnosis in the prior 2 y • ≥1 primary care HTN diagnoses and 1 or more filled prescriptions for HTN medication within the prior 6 mo, or • ≥1 primary care HTN diagnoses and 1 or more stroke-related hospitalizations or a history of coronary disease, HF, or DM	Intervention: KPNC HTN Program includes: HTN registry, HTN control monitoring and feedback system, evidence-based practice guidelines, medical assistant BP recheck program, and promotion of single polypill formulation (lisinopril- hydrochlorothiazide) <u>Comparator</u> : Insured pts in California from 2006–2009 who were included in the HEDIS commercial measurement by California health insurance plans participating in the NCQA quality measure reporting process. A 2° comparison group was included to obtain the reported national mean NCQA HEDIS commercial rates of	<ul> <li><u>1° endpoint</u>:</li> <li>HTN control rates in KPNC pts with HTN improved from 43.6% (95% CI: 39.4%, 48.6%) in 2001 to 80.4% (95% CI: 75.6%, 84.4%) by the end of the study period (p&lt;0.001 for trend).</li> <li>By comparison, national mean NCQA HEDIS commercial measurement HTN control increased from 55.4%–64.1%.</li> <li>California mean NCQA HEDIS commercial rates of HTN control were similar to those reported nationally from 2006–2009 (63.4%– 69.4%).</li> <li><u>1° Safety endpoint</u>: N/A</li> </ul>	• A system-based approach to HTN control that includes performance measurement and QI strategies led to a significant improvement in HTN control (80%, compared to 44% baseline control) in a large population of pts in a managed care health plan.

			HTN control from 2001–2009 from health plans that participated in the NCQA HEDIS quality measure reporting process.		
Rakotz MK, et al., 2014 (330) 25024244	<u>Aim</u> : The goal of this study was to develop a technology-based strategy to identify pts with undiagnosed HTN in 23 primary care practices and integrate this innovation into a continuous QI initiative in a large, integrated health system.	• Of the 139,666 active adult primary care pts in these 23 practices, 47,822 already had a diagnosis of HTN, white- coat HTN, pre-HTN, or elevated BP. The 3 screening algorithms for undiagnosed HTN were applied to the remaining pts' EHRs. There were 1,586 pts who met the criteria of 1 or more of the algorithms and were therefore considered at risk for undiagnosed HTN.	<ul> <li>In phase 1, we reviewed EHRs using algorithms designed to identify pts at risk for undiagnosed HTN. We then invited each at-risk pt to complete an automated office BP protocol. In phase 2, we instituted a QI process that included regular physician feedback and office- based computer alerts to evaluate at-risk pts not screened in phase 1. Study pts were observed for 24 additional mo to determine rates of diagnostic resolution. After phase 1, we established a continuous QI initiative to further evaluate pts who remained at risk for undiagnosed HTN. In this 24-mo follow-up phase (phase 2), all primary care physicians received monthly lists of their pts who continued to be at risk for undiagnosed HTN.</li> </ul>	• Of the 1,033 at-risk pts who remained active during phase 2, 740 (72%) were classified by the end of the follow-up period: 361 had HTN diagnosed, 290 had either white coat HTN, pre- HTN, or elevated BP diagnosed, and 89 had normal BP. By the end of the follow-up period, 293 pts (28%) had not been classified and remained at risk for undiagnosed HTN.	• Although we used multiple algorithms to identify pts with elevated BP readings, it is unlikely that we identified all pts with undiagnosed HTN.

			These nts were		
			contacted by staff via		
			telenhone or letter to		
			arrange a follow-up		
			annointmont Those nts		
			romained on the		
			nbysicians' lists until an		
			privationalis lists unui an		
			evaluation was		
			diagnesis was entered		
			diagnosis was entered		
			into the chart that		
			indicated the pris at-risk		
			status nad been		
			resolved. In addition,		
			when an at-risk pt		
			arrived for an office visit		
			for any reason, a best		
			practice advisory was		
			prominently displayed		
			on that pt's EHR screen		
			to notify the medical		
			assistant and physician		
			that an automated		
			office BP measurement		
			was needed.		
Borden WB, et al.,	Aim: The purpose of	<ul> <li>Using the National CV</li> </ul>	N/A	<ul> <li>Of 1,185,253 pts in the</li> </ul>	<ul> <li>Among U.S. ambulatory cardiology</li> </ul>
2014 (331)	this study was to	Data Registry PINNACLE		study cohort, 706,859	pts with HTN, nearly 1 in 7 who did not
<u>25447261</u>	examine the effect of	Registry, we assessed		(59.6%) achieved the 2003	meet JNC-7 recommendations would
	the 2014 expert panel	the proportion of		JNC-7 goals. Using the	now meet the 2014 treatment goals.
	BP management	1,185,253 pts who met		2014 recommendations,	
	recommendations on	the 2003 and 2014 panel		880,378 (74.3%) pts were at	
	pts managed in U.S.	recommendations,		goal. Among the 173,519	
	ambulatory CV	highlighting the		(14.6%) for whom goal	
	practices.	populations of pts for		achievement changed,	
		whom the BP goals		40,323 (23.2%) had a prior	
		changed.		stroke or TIA, and 112,174	
				(64.6%) had CAD. In	
				addition, the average	
				Framingham risk score in	

	this group was $8.5 \pm 3.2\%$ ,	
	and the 10-y atherosclerotic	
	CVD risk score was 28.0 ±	
	19.5%.	

Data Supplement 64. RCTs, Meta-analyses, and Systematic Reviews on the Effect of Telehealth Interventions to Improve Hypertension Control (Section 12.3.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Burke LE, et al., 2015 (332) <u>26271892</u>	Aim: Review of the Scientific Literature on mHealth Tools Related to CVD Prevention Study type: Systematic review Size: 69 studies of the use of mobile technologies to reduce CVD risk behaviors	Inclusion criteria Studies of electronic and mobile technology tools in CV prevention; published from 2004–2014 in English language; enrolling adults except for smoking cessation, for which adolescents were also included; conducted in the U.S. and in developed countries. Exclusion criteria: Absence of above.	Intervention: Mobile technologies to reduce CVD risk behaviors- varied across studies <u>Comparator</u> : Varied across studies.	<u>1º endpoint</u> : Varied across studies. <u>1º Safety endpoint</u> : N/A	<u>Summary</u> : mHealth or mobile technologies have the potential to transform the delivery of health- related messages and ongoing interventions targeting behavior change. Moreover, the use of monitoring devices (e.g., Bluetooth- enabled BP monitors and blood glucose monitors) permits the sharing of important pt self-management parameters with healthcare providers in real time and the delivery of feedback and guidance to pts when they need it. Furthermore, using mHealth tools for monitoring provides the clinician data that far exceed what can be measured in the brief clinical encounter and reflect the status of physiological or behavioral measures in the person's natural setting.
Liu S, et al., 2013 (333) <u>23618507</u>	<u>Aim</u> : Assess the efficacy of e- counselling in reducing BP	Inclusion criteria: 1) Trials that investigated the effect of Internet-based lifestyle interventions on SBP and DBP, 2) trials that included	Intervention: Internet- based intervention as preventive e-counselling or advice using Web sites or e-mails to modify exercise or diet as a	<u>1° endpoint</u> : MD in BP reduction (Internet- based – usual care): SBP: -3.8 mm Hg (95% CI: - 5.63– -2.06), I <sup>2</sup> =61	Behavior change techniques that were used in more than 50% of the successful internet-based interventions included the following: providing information on consequences of behavior in general

	Study type:	supplemental compensate	means of improving DD	DDD: $2.1 \text{ mm} \text{ Llg} (0E0/ CL)$	(04.0/) incorporating foodbook on
	<u>Study type</u> :	supplemental components	means of improving BP	DBP: -2.1 mm Hg (95% CI: -	(86%), incorporating reedback on
	Systematic review,	such as mobile lext	control. These Internet-	3.510.65), 12=57	performance (86%), prompting sell-
	meta-analysis	messages, telephone, or	based interventions were		monitoring of benaviors (71%), and
		in-person support, 3)	primarily self-guided,	Influence of intervention	giving instructions on how to perform
	Size: 13 RCTs or case-	intervention duration of at	and access was gained	attributes:	the targeted behavior change (71%).
	control studies	least 8 wk, and 4) SBP	via desktop computer,	Intervention duration:	
		and DBP reported as 1° or	laptop, tablet, or smart	Long-term ( <u>≥</u> 6 mo)	Summary: Internet-based
		2° outcome, measured at	phone. The duration of	intervention: SBP -5.8 mm Hg	interventions reduced SBP and DBP
		a clinic or office.	each intervention had to	(95% CI: -4.3– -4.1)	significantly compared to usual care.
			be at least 8 wk in order	Short-term (<6 mo)	Internet-based interventions had
		Exclusion criteria:	to achieve clinically	intervention: SBP -3.47 mm	greater effect on BP lowering if they
		Absence of above.	meaningful outcomes.	Ha (95% CI: -5.21.7)	were 1) long-term ( $\geq 6$ mo) in
			including the pt's ability	DBP mean reduction: results	duration and 2) used $>5$ behavior
			to learn and adhere to	not reported not statistically	change techniques
			complex new behaviors	significant	change teerniques.
			and to allow for sufficient	# of behavior change	
			time to domonstrate a	tochniquos:	
			stable reduction in PD	<u>SE bobavior chango</u>	
			Stable reduction in DF. The majority $(0/12)$ of	≥5 bellavior change	
			The majority (9/13) of		
			Interventions had	Hg (95% CI: -7.43– -4.42) /	
			supplemental	DBP -2.45 mm Hg (95% CI: -	
			components that were	3.50– -1.41)	
			not internet-based, such	<5 behavior change	
			as text messages, in-	techniques: SBP -2.69 mm	
			person visits, and live	Hg (95% CI: -4.61– -0.78) /	
			support and 10/13	DBP -0.02 mm Hg (95% CI: -	
			targeted both exercise	1.20–1.17)	
			and diet behaviors.		
				1° Safety endpoint: N/A	
			Comparator: Usual care		
			with no internet-based		
			strategy.		
Omboni S, et al.,	Aim: Review data from	Inclusion criteria:	Intervention: HBPT had	1° endpoint: Compared to	Limitations:
2013 (334)	RCTs on the	English language	to be based on the use	usual care, HBPT improved:	HBPT intervention features
23299557	effectiveness of HBPT	Published up to Feb	of an electronic	• Office SBP by 4.71 mm Ha	(telemonitoring systems and self-
	vs. usual care with	2012	automated BP monitor	(95% CI: 6.18–3.24 <sup>.</sup>	monitoring programs) as well as
	respect to improvement	RCT testing HBPT vs	storing values obtained	$p < 0.001$ · $l^2 = 52.2\%$ · $p = 0.003$	inclusion criteria and demographic
	of BP control.	usual care	at the pt's home and	• Office DBP by 2.45 mm Hg	and clinical characteristics of the
	healthcare resources		transferring them to a	(05% CI+ 2 22_1 57)	comparative groups varied across
	utilization and costs		remote computer	(75.70  Cl.  5.55 - 1.57)	somparative groups varied deross
1			remote computer	μ<0.001); I <sup>2</sup> =40.4%; μ=0.048	

pt's quality of life and	Exclusion criteria:	through a telephone line	Office BP Control (<140/90	studies and contributed to the high	
adverse events.	Absence of above	(wired or wireless), a	mm Hg nondiabetic pts and	heterogeneity of the studies	
		modem or an Internet	<130/80 mm Hg diabetic pts):	<ul> <li>Most studies were powered to test</li> </ul>	
Study type: Meta-		connection. At least 1	RR: 1.16 (95% CI: 1.04–1.29;	differences in BP lowering, not 2°	
analysis		self BP measurement	p<0.001); I <sup>2</sup> =69%; p<0.001	outcomes	
		had to be available for			
Size: 23 unique RCTs		each pt in the	2° endpoint: Compared to	Summary: HBPT yielded greater SBP	
with 7037 pts (though		intervention group.	usual care, HBPT improved:	and DBP reductions and a larger	
not all studies reported			<ul> <li>Greater prescription of</li> </ul>	proportion of pts achieving BP control	
on all outcomes of		Comparator: Usual care	antihypertensive medications:	than usual care. HBPT vs. usual care	
interest)			weighted MD 0.40 (95% CI:	resulted in greater prescription of	
			0.17–0.62; p<0.001);	antihypertensive medications and	
			I <sup>2</sup> =84.2%; p<0.001	rewer office visits but no difference in	
			Lower number of office	inerapeulic agnerence. Healincare	
			visits: weighted MD -0.18	LUSIS WERE HIGHER WITH HEPT I INAN	
			(95% CI: -0.37–0.00);	costs wore evoluted modical costs	
			I <sup>2</sup> =32.7%; p=0.146	wore similar between groups. Use of	
			Quality of life physical	HBPT vs. usual care improved quality	
			component of SF-12 or SF-36	of life physical component but not	
			questionnaire: weighted MD	mental Authors note that the amount	
			2.78 (95%  CI:  1.15-4.41);	of office BP reduction attributable to	
			1 <sup>2</sup> =0.0%; μ=0.853	HBPT was in line with that observed in	
			Inere was no dilierence     between LIPDT and yourd	RCTs of antihypertensive drugs	
				compared with placebo. The estimate	
			- Thoronoutin adherence	was also larger than that usually	
				related to HBP self-monitoring, which	
			[92% IDPT VS. 90% USUAI	speaks in favor of a possible added	
			difference 1 20% (05% Cl	value of the teletransmission	
			$2 31_4 00 \cdot n_0 491$	approach.	
			12-0.00% n=0.888		
			Ouality of life mental		
			$\sim$ component of SE-12 or SE-26		
			questionnaire: weighted MD		
			0 11 (95% Cl <sup>·</sup> -1 65–1 43)		
			$l^2=0.0\%$ p=0.984		
			Cost:		
			Healthcare costs were		
			significantly higher in the		
				HBPT group vs. usual care: weighted MD 662.92 (95% CI: 540.81–785.04) euros per pt; l <sup>2</sup> =99.6%; p<0.001, but costs were similar when only medical costs (excluding HBPT-related costs) were considered (-12.4; 95% CI: - 930.52–906.23) euros; p=0.767. <u>Safety endpoint</u> : No difference was observed in the risk of adverse events (RR: 1.22; 95% CI: 0.86– 1.71; p=0.111)	
----------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
Verberk W, et al., 2011 (335) 21527847	<u>Aim</u> : Examine the usefulness of telecare for HTN management <u>Study type</u> : Meta- analysis <u>Size</u> : 9 RCTs with 2,501 pts	Inclusion criteria: 1) Published in the English language, 2) pts were diagnosed as hypertensive and performed BP self- measurement at home, 3) RCTs that compared telecare of BP with usual care, 4) data were transmitted to healthcare providers by telephone, modem, Internet, or mail, and 5) either change in BP or the number of pts that reached their target BP was an outcome and was provided in the study. Date restrictions not reported. Exclusion criteria:	Intervention: Telecare for HTN management (treatment and/or coaching). Telecare involved a data transmission process to collect data on a pt's health status to allow remote HTN management. Procedures varied in length and frequency of contact and method of delivery (i.e., often telephone or cell phone with or without internet/computer; with or without behavioral counseling by nurse or pharmacist), often as an adjunct to "usual care" clinical visits.	<u>1° endpoint</u> : Difference in BP Reduction (Telecare-Usual care): <ul> <li>SBP 5.2 ± 1.5 mm Hg (95% CI: 2.31–8.07)</li> <li>DBP 2.1 ± 0.8 mm Hg (95% CI: 0.52–3.69)</li> </ul> <u>Safety endpoint</u> : N/A	Limitations: Telecare intervention methods varied greatly across studies Summary: Telecare led to a greater decrease in SBP and DBP compared with usual care. Telecare seems a valuable tool to support HTN management.

Agarwal R. et al.,	Aim: Ouantify both the	Inclusion criteria:	Intervention: Home BP	1° endpoint: Compared with	2º endpoints:
2011 (27)	magnitude and	Studies that randomized	monitoring as an adjunct	usual care alone, home-	More frequent reductions in
21115879	mechanisms of benefit	pts to control or home BP	to usual care for HTN	based BP monitoring	antibypertensive medication
	(including effect on	monitoring group		•Reduced SBP: -2.63 mm Hg	(presumably due to identification of
	therapeutic inertia) of	5554	Comparator: Usual care	$(95\% \text{ Cl} \cdot 4.24 - 1.02)$ and	white coat HTNI): RR: 2.02 (95% CI:
	home BP monitoring on	Exclusion criteria:	with BP monitoring in	<ul> <li>Poducod DRD: 1.68 mm</li> </ul>	1 32_3 11)
	BP reduction.	Absence of above	clinic	$H_{\alpha}$ (05% CI: 2.58 0.70)	• Lowered therapoutic inertia (i.e.
	Therapeutic inertia was			• Creater reduction in SPD by	• Lowered inerapedite inertia (i.e.,
	defined as no change			Greater reduction in SDP by	olovated RD: DD for unchanged
	in medications			MDPNI III.el verilions was seen	modication 0.82 (05% CI: 0.68, 0.00)
	combined with			(offect cize, 2,20, 05% Ch	medication 0.82 (95 % Ci. 0.06–0.99)
	uncontrolled BP.			(effect Size - 5.20, 95% CL -	Limitations: Different inclusion and
				4.001.73) VS. HUITE DF	ovelusion critoria, different RD
	Study type:				moasuromont tochniquos, drug
	Systematic review and			9370 CI2.200.31,	titration protocols of populations and
	meta-analysis			p=0.029). This infulling is	duration of follow up across studios
				relevant to telemonitoring	likely introduced significant
	Size: 37 RCTs with				hotorogonoity in offect size
	9 446 pts. Trial settings				neterogeneity in enect size.
	included community				Summary: Home PD monitoring loads
	(n=5) dialysis unit				<u>Summary</u> . Home be momenting leads
	(n=2) general				to a sinal but significant reduction in
	(n=2), general practices (n=18)				SBP and DBP. Greater reduction in
	hospitals and general				SBP IS Seen when HBPM IS
	nospitals and general nractice (n-1) and				accompanied by specific programs to
	hospital-based				titrate antinypertensive drugs. I such
	outnationt units (n=11)				strategy is telemonitoring, in which BP
	outpatient units (n= n).				readings obtained at nome are
					relayed to the provider who can then
					take appropriate action, thus reducing
					therapeutic inertia.

Data Supplement 65. RCTs and Observational Studies that Report on the Effect of Performance Measures and on Hypertension Control (Section 12.4.1)

Study Acronym;	Aim of Study;	Patient Population	Study Intervention (# patients)	Endpoint Results	Relevant 2° Endpoint (if any);
Author;	Study Type;		1	(Absolute Event Rates, P	Study Limitations;
Year Published	Study Size (N)		Study Comparator (# patients)	value; OR or RR; & 95%	Adverse Events
				CI)	

© 2017 American College of Cardiology Foundation and American Heart Association, Inc.

Svetkey LP, et al., 2009 (336) <u>19920081</u>	Aim: Study the effect of physician intervention and/or pt intervention vs. usual care, to assess the impact of education, monitoring, and feedback protocol to help improve HTN control Study type: Nested 2×2 RCT Size: 8 primary care practices, 32 physicians, 574 pts	Inclusion criteria: Practices: matched pairs (intervention vs. usual care) by specialty (internal medicine vs. family physician) and by pt socioeconomic mix. All physicians were invited to participate. <u>Pt eligibility:</u> ≥25 y, hypertensive by billing code. <u>Pt exclusion:</u> Self- reported CKD, CVD event within past 6 mo, pregnant, breastfeeding, or planning a pregnancy.	<ul> <li><u>Physician Intervention</u>: 18 mo of online training, self-monitoring, quarterly feedback reports.</li> <li><u>Pt Intervention</u>: 20 weekly group sessions for 6 mo, followed by 12 monthly telephone counseling contacts, focused on weight loss, DASH dietary patter, exercise, and reduce sodium intake.</li> <li><u>Comparator</u>: Usual care</li> </ul>	<u>1° endpoint</u> : Pt intervention + physician intervention group had greatest BP lowering at 6 mo (-9.7 mm Hg ± 12.7), but at 18 mo there was no significant difference between groups. <u>1° Safety endpoint</u> : N/A	• This trial suggests that pt level monitoring and feedback, in combination with physician level monitoring and feedback, provides additional 6 mo BP control above and beyond usual care. The impact of the intervention diminished after the weekly pt group sessions ended and monthly telephone calls began instead.
Jaffe MG, et al., 2013 (329) <u>23989679</u>	Aim: Study the effect of a multipronged, system- based, QI approach on HTN control. Study type: Observational Size: All pts with HTN in the KPNC system were included	Inclusion criteria: 350,000 pts in the KPNC system with HTN in 2001, increasing to 650,000 in 2009 Eligibility: • ≥2 HTN diagnoses coded in primary care visits in the prior 2 y • ≥1 primary care HTN diagnoses and 1 or more hospitalizations with a 1° or 2° HTN diagnosis in the prior 2 y • ≥1 primary care HTN diagnoses and 1 or more filled prescriptions for HTN medication within the prior 6 mo, or	Intervention: KPNC HTN Program includes: HTN registry, HTN control monitoring and feedback system, evidence- based practice guidelines, medical assistant BP recheck program, and promotion of single polypill formulation (lisinopril-hydrochlorothiazide) Comparator: Insured pts in California from 2006–2009 who were included in the HEDIS commercial measurement by California health insurance plans participating in the NCQA quality measure reporting process. A 2° comparison group was included to obtain the reported national mean NCQA HEDIS commercial rates of HTN control from 2001–	<ul> <li><u>1° endpoint</u>:</li> <li>HTN control rates in KPNC pts with HTN improved from 43.6% (95% CI: 39.4%–48.6%) in 2001 to 80.4% (95% CI: 75.6%–84.4%) by the end of the study period (p&lt;0.001 for trend).</li> <li>By comparison, national mean NCQA HEDIS commercial measurement HTN control increased from 55.4%–64.1%.</li> <li>California mean NCQA HEDIS commercial rates of HTN control were similar to those reported nationally from 2006–2009 (63.4%–69.4%).</li> </ul>	• A system-based approach to HTN control that includes performance measurement and QI strategies led to a significant improvement in HTN control (80%, compared to 44% baseline control) in a large population of pts in a managed care health plan.

		• ≥1 primary care HTN diagnoses and 1 or more stroke-related hospitalizations or a history of coronary disease, HF, or DM	2009 from health plans that participated in the NCQA HEDIS quality measure reporting process.	<u>1° Safety endpoint</u> : N/A	
Lusignan Sd, et <u>4</u> al., 2013 (337) <u>23536132</u> ii U U U U U U U U U U U U U U U U U U	<u>Aim</u> : Study the effect of an audit-based education intervention to guidelines/prompts, vs. usual care, to help improve BP control in pts with CKD <u>Study type</u> : Cluster RCT <u>Size</u> : 93 general practices (30 audit-based education intervention, 32 Guidelines/prompts, and 31 usual care)	Inclusion criteria: All pts with CKD in the participating practices	Intervention: Audit-based education vs. guidelines/prompts Comparator: Usual care	<u>1° endpoint</u> : SBP was significantly lower in the audit-based education group (-2.41 mm Hg; 95% CI: 0.59–4.29). There was no significant change in BP in the other 2 groups. <u>1° Safety endpoint</u> : No reports of harm.	• This trial suggests that an intervention that includes specific performance and feedback reports improves BP control in pts with CKD, compared to usual care. To the contrary, the use of practice guidelines and prompts did not improve BP control compared to usual care.

Data Supplement 66. RCTs, Meta-analyses, and Systematic Reviews on Quality Improvement Strategies on Hypertension Treatment Outcomes (Section 12.4.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events Summary
Walsh JM, et al., 2006 (338) <u>16799359</u>	<u>Aim</u> : Assess the effectiveness of QI strategies in lowering BP <u>Study type</u> : Systematic review	Inclusion criteria: Trials, controlled before–after studies, and interrupted time series evaluating QI interventions targeting HTN control and reporting BP outcomes.	Intervention: QI interventions targeting some component of provider behavior or organizational change to improve HTN control <u>Comparator</u> : Contemporaneous	<ul> <li>The majority of articles described interventions consisting of more than 1 strategy with the median number of QI strategies per comparison =3. Results are organized below by type of QI strategy.</li> <li>Variety of strategies used</li> </ul>	Limitations: Studies varied by design, population, sample size, setting, and methodological quality. Definition of each QI strategy varied across studies. Few studies assessed a single QI strategy; because most studies included more than 1 QI strategy, it could not be discerned which individual QI strategies had the

Size: 44 articles	Exclusion criteria:	observation of cohorts	SBP/DBP, median reduction:	greatest effects or whether certain
reporting 57	Articles focusing only on	differing primarily with	4.5 mm Hg (IQR: 1.5–11.0)/	combinations of individual QI
comparisons	2° HTN or specialized	respect to exposure to	2.1 mm Hg (IQR: -0.2–5.0)	strategies were more "potent" than
	subpopulations (e.g., HTN	the QI intervention	SBP/DBP control: 16% (IQR:	others.
	in pts with alcoholism)		10.3–32.2)/ 6% (IQR: 1.5–	
			17.5)	Summary: QI strategies are
			Provider reminders	associated with improved HTN
			SBP/DBP, median reduction:	control. QI strategies improved SBP
			1.2 mm Hg (IQR: 1.0–1.9)/ 0.3	and the proportion of pts achieving
			mm Hg (IQR: -0.2–1.7)	SBP control and had a more modest
			DBP control: 5% (IQR: 2.0-	effect on DBP and the proportion of
			7.0)	pts achieving DBP control. Team
			<ul> <li>Facilitated relay of clinical</li> </ul>	change (i.e., a focus on HTN by
			<u>data</u>	someone in addition to the pt's
			SBP/DBP, median reduction:	physician) had the largest effect on
			8.0 mm Hg (IQR: 2.5–12.3)/	both SBP and DBP. All of the
			1.8 mm Hg (IQR: -0.1–4.5)	strategies assessed may be beneficial
			SBP/DBP control: 25% (IQR:	in terms of clinically meaningful
			17.0–34.2)/ 2% (IQR: 1.6–5.0)	reductions in BP under some
			<ul> <li>Audit and feedback</li> </ul>	circumstances and in varying
			SBP/DBP, median reduction:	complinations.
			1.5 mm Hg (IQR: 1.2–1.7)/ 0.6	
			mm Hg (IQR: 0.4–1.0)	
			SBP/DBP control: -3.5% (IQR:	
			-5./-1.4)/ 2.0% (IQR: 1./-4.3)	
			Provider education	
			SBP/DBP, median reduction:	
			3.3 mm Hg (IQR: 1.2–5.4)/ 0.6	
			mm Hg (IQR: -0.7V3.4)	
			SBP/DBP control: 11% (IQR:	
			1.4–13.1)/ 4% (IQR: 1./–11.3)	
			• <u>Pleducation</u>	
			SBP/DBP, median reduction:	
			8.1 mm Hg (IQR: $3.3-11.8$ )/	
			SPD/DPD control 10% (IOD)	
			11 / 22 2)/ 17% (IOD: 11 /	
			24 5)	
			Promotion of solf	
			• <u>Fromotion of Sell-</u>	
			Inanayement	

				SBP/DBP, median reduction:	
				3.3 mm Hg (IQR: 2.6–10.1)/	
				2.8 mm Hg (IQR: 0.4–6.7)	
				SBP/DBP control: 13%/ 9%	
				(IQR: 5.3–11.4)	
				• Pt reminders	
				SBP/DBP median reduction	
				$3.3 \text{ mm Hg} (IOR \cdot 2.3 - 4.5)/0.4$	
				mm Hg (IOR: $-2.4-5.0$ )	
				DBP control: 2% (IOR: 1.1–	
				9.4)	
				• Team change	
				SBP/DBP, median reduction:	
				9.7 mm Hg (IQR: 4.2–14.0)	
				(p<0.05)/ 4.2 mm Hg (IQR:	
				0.2–6.8) (p<0.05)	
				SBP/DBP control: 22% (IQR:	
				9.0–33.8)/ 17% (IQR: 5.7–	
				24.5)	
				<ul> <li>Financial incentives</li> </ul>	
				SBP/DBP, median reduction: -	
				13.3 mm Hg/ 0.0 mm Hg (IQR:	
				-2.0–2.5)	
				DBP control: 4% (IQR: -1.1-	
				9.4)	
				Safety endpoint: N/A	
Carter BL, et al.,	Aim: Determine	Inclusion criteria: RCT of	Intervention: Team-	<u>1° endpoint:</u>	<ul> <li>Stepwise regression was used to</li> </ul>
2009 (321)	potency of	team-based HTN care	based HTN care	OR (95% CI) for controlled	compare studies that included a given
<u>19858431</u>	interventions for BP	involving nurse or	involving nurse or	BP were: nurses: 1.69 (1.48,	intervention strategy with studies that
	involving nurses and	pharmacist intervention	pharmacist intervention	1.93); pharmacists within	did not. Several individual
	pharmacists		In nearly all studies	primary care clinics: 2.17	components of the interventions were
		Exclusion criteria:	involving nurses or	(1.75, 2.68); and community	associated with significant reductions
	Study type: Meta-	Absence of above	pharmacists in clinics,	pharmacists: 2.89 (1.83, 4.55).	in mean SBP including pharmacist
	analysis		consistent and dedicated	<ul> <li>Mean (SD) reductions in</li> </ul>	recommended medication to physician
			case management	SBP were: nurse intervention:	(-27.21 mm Hg; p=0.002), counseling
	Size: 3/ RC1s of		activities were provided	5.84 (8.05) mm Hg;	about lifestyle modification (-12.63
	team-based HIN care		that were distinct from	pharmacists in clinics:	mm Hg; p=0.03), pharmacist
	involving nurse or		traditional nursing or	7.76(7.81) mm Hg; and	performed the intervention (-11.70 mm
					Hg; p=0.03), use of a treatment

<u>г</u> т					
	intervention		However, pharmacists in community pharmacies usually had to incorporate the intervention with traditional medication dispensing functions. <u>Comparator</u> : Usual care	<ul> <li>(5.00) mm Hg.</li> <li>There were no significant differences between nurse and pharmacist effects (p≥0.19).</li> <li>Safety endpoint: N/A</li> </ul>	algorithm (-0.40 mini rig, p<0.001), completion of a drug profile and/or medication history (-8.28 mm Hg; p=0.001), and the overall intervention potency score assigned by the study reviewers (p<0.001). The factors associated with a reduction in DBP were: referral was made to a specialist (-19.61 mm Hg; p=0.04), providing pt education about BP medications (- 17.60 mm Hg; p=0.003), completion of a drug profile and/or medication history (-7.27 mm Hg; p=0.006), pharmacist performed the intervention (-4.03 mm Hg; p=0.04), or nurse performed the intervention (-3.94 mm Hg; p=0.04). <u>Summary</u> : Interventions involving pharmacists or nurses were associated with significantly improved BP control
Agarwal R, et al., 2011 (27) <u>21115879</u>	<u>Aim</u> : Quantify both the magnitude and mechanisms of benefit (including effect on therapeutic inertia) of home BP monitoring on BP reduction. Therapeutic inertia was defined as no change in medications combined with uncontrolled BP. <u>Study type</u> : Systematic Review and Meta-analysis	Inclusion criteria:         Studies that randomized         pts to control or home BP         monitoring group         Exclusion criteria:         Absence of above	Intervention: Home BP monitoring as an adjunct to usual care for HTN Comparator: Usual care with BP monitoring in clinic	<ul> <li><u>1° endpoint</u>: Compared with usual care alone, home-based BP monitoring:</li> <li>Reduced SBP: -2.63 mm Hg (95% CI: -4.241.02) and</li> <li>Reduced DBP: -1.68 mm Hg (95% CI: -2.580.79)</li> <li>Greater reduction in SBP by home BP monitoring interventions was seen with added telemonitoring effect size: -3.20 (95% CI: -4.661.73) vs. home BP monitoring effect size: -1.26; 95% CI: -2.200.31; p=0.029.</li> <li>Safety endpoint: N/A</li> </ul>	<ul> <li><u>2° endpoints</u>:</li> <li>More frequent reductions in antihypertensive medication (presumably due to identification of white coat HTN): RR: 2.02; 95% CI: 1.32–3.11</li> <li>Lowered therapeutic inertia (i.e., unchanged medication despite elevated BP: RR for unchanged medication 0.82 (95% CI: 0.68–0.99)</li> <li><u>Limitations</u>: Different inclusion and exclusion criteria, different BP measurement techniques, drug titration protocols, pt populations, and duration of follow-up across studies likely introduced significant heterogeneity in effect size.</li> </ul>

	Size: 37 RCTs with 9446 pts. Trial settings included community (n=5), dialysis unit (n=2), general practices (n=18), hospitals and general practice (n=1), and hospital-based outpatient units (n=11).				Summary: • Home BP monitoring leads to small but significant reduction in SBP and DBP. Greater reduction in SBP is seen accompanied by specific programs to titrate antihypertensive drugs. One such strategy is telemonitoring, in which BP readings obtained at home are relayed to the provider who can then take appropriate action.
Anchala R, et al., 2012 (339) 23071713	Aim: Evaluate the role of decision support systems in prevention of CVD among pts Systematic review and meta-analysis Size: 10 studies with 5 studies reporting effect on BP (BP results only reported here)	Inclusion criteria: 1) Cross-sectional, case control, cohort, and RCTs, 2) Studies conducted among adult pts ≥18, 3) studies on prevention of CV disorders (MI, stroke, CHD, peripheral vascular disorders and HF) and management of HTN, 4) studies on interventions including: decision support systems, clinical decision supports systems, computerized decision support systems, clinical decision making tools and medical decision making Exclusion criteria: Absence of above	Intervention: Decision support systems, clinical decision supports systems, computerized decision support systems, clinical decision making tools and medical decision making in the management of HTN <u>Comparator</u> : Usual care	<u>1° endpoint</u> : • Reduction in SBP (5 studies): 2.32 mm Hg (95% CI: -3.96– -0.69) • Reduction in DBP (2 studies): 0.42 mm Hg (95% CI: -2.30–1.47) <u>Safety endpoint</u> : N/A	<ul> <li><u>Limitations</u>:</li> <li>Small number of studies of varied quality.</li> <li>Interventions varied across studies.</li> <li><u>Summary</u>: Clinical decision support resulted in modest reduction of SBP and no significant reduction of DBP.</li> </ul>
Proia KK, et al., 2014 (323) <u>24933494</u>	<u>Aim</u> : Examine current evidence on the effectiveness of team- based care in improving BP outcomes (update of	Inclusion criteria: Study of team-based care; conducted in a high- income economy; reported at least 1 BP outcome of interest; included a comparison group or had	Intervention: Team- based care was defined as adding new staff or changing the roles of existing staff to work with a PCP for HTN care. Team members who	<ul> <li><u>1° endpoint</u>:</li> <li>Proportion with controlled BP: Absolute percentage point (pct pt) change in pts with controlled BP from 33 studies comparing team-based care to usual care: median effect</li> </ul>	<u>2° endpoints</u> : Compared with pts in usual care, the proportion of pts receiving team-based care with "high" medication adherence (defined as taking medications as prescribed >80% of the time) increased by a median of 16.3 pct pts (9 studies).

prior systematic	an interrunted time-series	collaborated with pts and	estimate was 12 nct nts	
review)	design with at least 2	PCPs were	$( \Omega  = 3.2 = 20.8 \text{ nct nts})$ Most	Stratified analyses for BP
Totiony	measurements before and	predominantly nurses	individual effect estimates in	outcomes.
Study type:	after the intervention.	(28 studies):	the favorable direction were	• Team member role in medication
Systematic review	targeted populations with	nharmacists (15	significant ( $n < 0.05$ )	management: Larger improvements in
Systematic review	1° HTN or populations	studies), both nurses	Reduction in SBP (11	BP outcomes than overall estimates
Size: 52 studies of	with comorbid conditions	and pharmacists (5	studios): The modian	wore domonstrated when team
team-based primary	such as DM as long as the	studies): or community	roduction in SPD was 5.4 mm	members could make changes to
care for nts with 1°	nrimary focus of the	health workers	Ha $( \Omega  = 2.0, 7.2 \text{ mm Ha})$	modications independent of the DCD
HTN	intervention was BP	integrated care	Most individual offoct	or toam mombors could provide
	control: and did not	managers or behavioral	estimates were significant	medication recommendations and
	control, and did not	interventionists (4	(n < 0.05)	make changes with the DCP's
	Exclusion criteria:	studies) Key roles	Poduction in DPD: The	approval as compared to team
	Inclusion of populations	included HTN	• Reduction in DDF. The	members providing only adherence
	with 2° HTN (e.g.,	medication	DRP was 1.8 mm Hg	support and information on medication
	pregnancy) or with a	management, active pt	(101-0.7-3.2  mm Ha) from 38	and HTN
	history of CVD (e.g., MI)	follow-up, and	studies	Number of team members added:
	(	adherence and self-	Studies.	Adding >2 members demonstrated
		management support.	Safety endpoint: No harm to	larger improvements in the proportion
		Interventions were	nts was identified from team-	of pts with controlled BP and reduction
		usually implemented	based care interventions in the	in DBP compared to adding only 1:
		across multiple settings	included studies or the	median reductions in SBP were
		in the healthcare system	broader literature.	similar regardless of team size.
		and in the community,		Improvement in the proportion of pts
		where they were		with controlled BP was similar for
		implemented in		studies from both healthcare and
		pharmacies and through		community settings.
		home outreach visits.		l source and source an
				Limitations: Included studies
		Comparator: Usual care		reported significant differences in pt
				demographics between intervention
				and comparison groups at baseline.
				possible contamination within
				intervention and comparison groups,
				and issues related to inadequate
				description of populations and
				implemented interventions.
				Summary: There is strong evidence
				that team-based care is effective in

				improving BP outcomes, especially when pharmacists and nurses are part of the team.
--	--	--	--	-------------------------------------------------------------------------------------------

Data Supplement 67. Nonrandomized Trials, Observational Studies, and/or Registries of Effect of Quality Improvement Strategies on Hypertension Treatment Outcomes (Section 12.4.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Thomas KL, et al., 2014 (340) <u>25351480</u>	Study type: Community- based HTN QI program [multifaceted BP control program using a web-based health portal (Heart360), community health coaches, and PA guidance] to improve HTN control in a diverse community setting Design: Pre-post study without a concurrent control Size: 1756 pts with HTN from 8 clinics: • Median age, 60 y • Female, 65.6% • African American, 76.1%	Inclusion criteria: Individuals from pt sites >18 y with a previous billing diagnosis of HTN (ICD-9 code 401.X) or a previous clinical diagnosis of HTN in the medical record. Exclusion criteria: Did not reside in Durham County or had a neurocognitive disorder that prevented enrollment	<u>1° endpoint</u> : 1) Difference in SBP and DBP from enrollment (BP obtained in the clinic at enrollment) to the last BP as measured in clinic within 6 mo after enrollment, 2) proportion of pts that achieved BP <140/90 mm Hg by last clinic visit within 6 mo, and 3) proportion of pts with BP <140/90 mm Hg or drop in SBP ≥10 mm Hg by last visit relative to their enrollment BP. <u>Results:</u> • Mean change in BP: -4.7 mm Hg (SD ± 21.4) / -2.8 mm Hg (SD ± 11.8) after 6 mo • BP control (<140/90 mm Hg) rate: Increased from 51% at baseline to 63% at 6 mo • Proportion with BP<140/90 or ≥10 mm Hg decrease in SBP at 6 mo was 69% • Among those who were in tiers 1 (BP=140/90– 159/99 mm Hg) and 2 (BP≥159/99 mm Hg) at enrollment (n=889), BP change was -8.8 mm Hg (SD ± 15.8) / -5.0 mm Hg (SD ± 10.0) and -23.7 mm Hg (SD ± 26.5) / -10.1 mm Hg (SD ± 14.1), respectively.	Summary: A multicomponent- tiered HTN program that included team-based care with PAs and community health coaches was associated with improved BP control in a diverse community- based population. Though the web-based approach presented technical challenges for some pts, there was a direct association between higher use of Heart360 and larger recorded BP declines as entered into Heart360. This provides some indirect evidence that those pts who were more engaged with their BP self-monitoring achieved better BP control.
Jaffe MG, et al., 2013 (329) <u>23989679</u>	Study type: Quasi- experimental evaluation of multi-faceted QI program that included 1) Health system- wide HTN registry, 2) HTN control rates (with provider audit and feedback), 3)	Inclusion criteria: Pts identified with HTN within an integrated health care delivery system (KPNC) from 2001–2009	<u>1° endpoint</u> : BP control using NCQA HEDIS measures <u>Results:</u> BP control increased from 44%–80% from 2001–2009 with the KPNC QI program compared to 55.4% to 64.1% for the national mean and 63.4% to	Summary: Implementation of a large-scale HTN program was associated with a significant increase in HTN control compared with state and national control rates.

evidence-based practice HTN guideline, 4) medical assistant visits for follow-up measurements with no pt copayment for these follow-up visits, and 5) promotion of single-pill combination therapy.	Exclusion criteria: None stated	69.4% for the Ca mean from 2006 to 2009 NCQA HEDIS commercial measurement comparison groups.	
Design: Contemporaneous control group external to healthcare system			
Size: Kaiser HTN registry increased from 349,937 pts in 2001 to 652,763 in 2009.			

## Data Supplement 68. RCTs Comparing Financial Incentives (Section 12.5)

Study Acronym; Author;	Aim of Study; Study Type;	Patient Population	Study Intervention (# patients) /	Endpoint Results (Absolute Event Rates, P value; OR or	Relevant 2° Endpoint (if any); Study Limitations; Adverse
Year Published	Study Size (N)		Study Comparator (# patients)	RR; & 95% CI)	Events Summary
Peterson LA, et al., 2013 (341) <u>24026599</u> Hysong, SJ, et al., 2012 (342) <u>23145846</u>	Aim: To test the effect of explicit financial incentives to reward guideline recommended HTN care. Study type: Cluster randomized trial of 12 VA Outpatient clinics with 5 performance	• Study population was providers, not pts: a minimum of 5 fulltime PCPs from 12 hospital- based primary care clinics in 5 A Networks. Then, the clinics were randomized to 1 of 4 study groups, 1) physician level (individual) incentives, 2) practice-	Interventions: Education, Financial Incentives, Audit and Feedback; Intervention group pts received up to 5 incentive payments in their paychecks ~every 4 mo and were notified each time a payment was posted.	<u>1° endpoint</u> : In unadjusted analyses, the percentage of pts either with controlled HTN or receiving an appropriate response increased for each incentive group between baseline and final performance period, 75% to 84% in the individual group, 80% to 85% in the practice group, and 79% to88% in the combined group.	Summary: • Mean (SD) total payments over the study were \$4,270 (\$459), \$2672 (\$153), and \$1,648 (\$248) for the combined, individual, and practice- level interventions, respectively. Change in BP control or appropriate response to uncontrolled BP compared with the control group was significantly greater only in the individual incentives group. Change
	washout	physician-level plus	groups,1 paid incentives	control group, 86%. The	in guideline-recommended medication use was not significant
	Size: 83 PCPs and 42 nonphysician	practice-level (combined) incentives, and 4) no incentives (control).	at the practice level,1 paid incentives at the physician level, 1 paid	adjusted estimated ab-solute change over the study of the pts meeting the combined BP or	compared with the control group. The effect of the incentive was not sustained after a washout.

 $^{\odot}$  2017 American College of Cardiology Foundation and American Heart Association, Inc.

	personnel (e.g., nurses, pharmacists). <u>Main Outcomes and</u> <u>Measures:</u> Among a random sample, number of pts achieving guideline- recommended BP thresholds or receiving an appropriate response to uncontrolled BP, number of pts prescribed guideline- recommended medications, and number who developed hypotension.		for both levels and the 4 <sup>th</sup> paid no incentives. (19–20 physicians in each group)	appropriate response measure was 8.84% (95% CI: 4.20%– 11.80%) for the individual group, 3.70% (95% CI: 0.24%, 7.68%) for the practice group, 5.54% (95% CI: 1.92%–9.52%) for the combined group, and 0.47% (95% CI: -3.12%–4.04%) for the control group. The adjusted estimated absolute difference over the study in the change between the proportion of the physician's pts achieving BP control or receiving an appropriate response for the individual incentive group and the controls was 8.36% (95% CI: 2.40%–13.00%; p=0.005).	• Financial incentives may constitute an insufficiently strong intervention to influence goal commitment when providers attribute performance to external forces beyond their control.
Karunaratne K, et al., 2013 (343) <u>23658247</u>	Aim: The aim of this study was to evaluate the effectiveness of renal indicators outlined in P4P on the management of HTN in primary care. To estimate the cost implications of the resulting changes in prescribing patterns of antihypertensive medication following introduction of such indicators. Study type: Prospective cohort study using a large primary care database.	Inclusion criteria: A total of 10,040 pts had confirmed stage 3–5 CKD in the 2 y pre-QOF and formed the study cohort. Exclusion criteria: None	Intervention: The implementation of national estimated GFR reporting and the inclusion of renal- specific indicators in a primary care P4P system since April 2006 has promoted identification and better management of risk factors related to CKD. In the UK, the P4P framework is known as the QOF. <u>Comparator</u> : N/A	• Mean age of the cohort at the start of the study period was 64.8 y, 55% were female. In those pts with stage 3–5 CKD 83.9% were hypertensive, defined by a pre-P4P BP of >140/85 or currently taking antihypertensive medication. The proportion of pts with CKD 3–5 attaining the BP target of 145/80 increased from 41.5% in the pre-QOF period to 50.0% in the post-QOF period. This increase was even more marked for those with HTN in the pre-QOF period (28.8%–45.1%). In the hypertensive pts, mean BP fell from 146/79 mm Hg to 140/76 in the first 2 y post-P4P [p<0.01, analysis of variance].	Summary: Population BP control has improved since the introduction of P4P renal indicators, and this improvement has been sustained. This was associated with a significant increase in the use of antihypertensive medication, resulting in increased prescription cost. Longer-term follow-up will establish whether or not this translates to improved outcomes in terms of progression of CKD, CVD and pt mortality.

 $^{\odot}$  2017 American College of Cardiology Foundation and American Heart Association, Inc.

	This cohort was taken from a database collated as part of a clinical decision support system used to assist the management of CKD in primary care. <u>Size</u> : 90,250 pts on general practitioner registers with a valid serum creatinine estimation in the 6-y study period. A total of 10 040 pts had confirmed stage 3–5 CKD in the 2 y pre- QOF and formed the study cohort.			BP reduction was sustained in the last 2 y of the study, 139/75 (p<0.01, analysis of variance). The proportion of hypertensive pts taking ACEIs or angiotensin blockers increased, this was also sustained in the third time period. An increase in the prescribing of diuretics, CCBs and BBs was also observed. The additional cost of increased prescribing was calculated to be euro 25.00 per hypertensive pt based on GP prescription data.	
Serumaga B, et al., 2011 (344) <u>21266440</u>	Aim: The aim of this study was to evaluate the effectiveness of renal indicators outlined in P4P on the management of HTN in primary care. To estimate the cost implications of the resulting changes in prescribing patterns of	Inclusion criteria: Pts with HTN diagnosed between Jan. 2000–Aug. 2007. Exclusion criteria: None	Intervention: The UK P4P incentive (the Quality and Outcomes Framework), which was implemented in April 2004 and included specific targets for general practitioners to show high quality care for pts with HTN (and other diseases)	• After accounting for secular trends, no changes in BP monitoring: level change: 0.85 (95% Cl: -3.04-4.74), p=0.669 and trend change: -0.01, (95% Cl: -0.24-0.21), p=0.615, control: -1.19 (95% Cl: -2.06- 1.09), p=0.109 and -0.01 (95% Cl: -0.06-0.03), p=0.569, or treatment intensity; 0.67: (95% Cl: -1.27, 2.81), p=0.412 and	Summary: Good quality of care for HTN was stable or improving before P4P was introduced. P4P had no discernible effects on processes of care or on HTN related clinical outcomes. Generous financial incentives, as designed in the UK P4P policy, may not be sufficient to improve quality of care and outcomes for HTN and other common chronic conditions
	rescribing patterns of antihypertensive medication following introduction of such indicators. <u>Study type:</u> Interrupted time series study		Comparator: None	CI: -1.27-2.81), p=0.412 and 0.02 (95% CI: -0.23-0.19, p=0.706 were attributable to P4P. P4P had no effect on the cumulative incidence of stroke, MI, renal failure, HF, or all- cause mortality in both treatments experienced and newly treated subgroups.	

Bardach NS, et al., 2013 (327) 24026600	Size: 470,725 pts with HTN diagnosed between Jan 2000– Aug 2007. Aim: To assess the effect of P4P incentives on quality in EHR-enabled small practices in the context of an established QI initiative.	• Participating clinics (n=42 for each group) had similar baseline characteristics, with a mean of 4,592 (median, 2,500) pts at the intervention group clinics	• A city program provided all participating clinics with the same EHR software with decision support and pt registry functionalities and QI specialists	<ul> <li>Intervention clinics had greater adjusted absolute improvement in rates of appropriate antithrombotic prescription 12.0% vs. 6.1%, difference: 6.0% (95% CI: 2.2%–9.7%; p=0.001 for interaction term), BP</li> </ul>	<u>Summary</u> : In our study, although the effect of the intervention was lower than the 10% improvement that we estimated a priori, the absolute risk reduction for BP control among pts with DM was 7.8% (NNT, 13). This suggests that, for every 13 pts
	Study Type & Size: A cluster-randomized trial of small (<10 clinicians) primary care clinics in New York City from April 2009–March 2010.	2,000) at the control group clinics.	assistance. • Incentivized clinics were paid for each pt whose care met the performance criteria, but they received higher payments for pts with comorbidities, who had Medicaid insurance, or who were uninsured (maximum payments: \$200/pt; 100,000/clinic). Quality reports were given quarterly to both the intervention and control groups.	vs. 4.3%, difference: 5.5% (95% Cl: 1.6%–9.3%; p=0.01 for interaction term); with DM: 9.0% vs. 1.2%, difference: 7.8% (95% Cl: 3.2%–12.4%; p=0.007 for interaction term); with DM or ischemic vascular disease: 9.5% vs. 1.7%, difference: 7.8% (95% Cl: 3.0%–2.6%; p=0.01 for interaction term), and in smoking cessation interventions (12.4% vs. 7.7%), difference: 4.7% (95% Cl: -0.3%–9.6%; p=0.02 for interaction term). Intervention clinics performed better on all measures for Medicaid and uninsured pts except cholesterol control, but no differences were statistically significant.	pt would achieve BP control. The 7.8% absolute change in BP control for pts with DM represents a 46% relative increase in BP control among intervention pts compared with the baseline of 16.8%. Further research is needed to determine whether this effect of the P4P intervention on BP control increases or decreases over time. However, this NNT to achieve BP control through incentives, taken together with the large relative increase in percentage of pts with BP control and the potential effect of BP control on risk of ischemic vascular events, suggests a reasonable opportunity to reduce morbidity and mortality through P4P as structured in this study.
					program after randomization, with more control clinics leaving than intervention clinics. Additionally, this intervention occurred in the setting of a voluntary QI program. This may reflect a high level of intrinsic

					motivation to improve among practices in the study, as demonstrated by engagement with the QI specialists
Maimaris W, et al., 2013 (345) <u>23935461</u>	Aim: To assess strategies for influencing HTN care including procurement of essential medications, the existence of simple national guidelines for HTN management, introduction of financial incentives for health care practitioners to diagnose or treat HTN, and enhanced health insurance coverage. Study type: Systematic review examining the effect of national or regional health system arrangements on HTN care and control	Study selection criteria based on: 1) HTN awareness. Defined as pts with clinically measured hypertensives who have been diagnosed by a health care professional as hypertensive. 2) HTN treatment. Defined as the use of at least 1 antihypertensive medication in a pt with known HTN. 3) Antihypertensive medication adherence. Defined as consistently taking the antihypertensive medication regimen as prescribed by the health care provider. 4) HTN control: defined as the achievement of BP<140/90 mm Hg (or other explicitly defined threshold) in individuals being treated for HTN, or, alternatively, measured by the mean BP amongst individuals with HTN.	• The screening process is described using an adapted PRISMA flowchart. 5,514 articles were screened by title and abstract for inclusion. The full text of 122 of the 5,514 articles was obtained and assessed for eligibility. 53 studies met eligibility criteria for this review. 51 of the included studies were quantitative. Of the 51 quantitative. Of the 51 quantitative studies, 1 was an RCT; 12 were cohort studies, 2 of which were retrospective; 3 were case-control studies; 32 were cross-sectional studies; and 3 were ecological studies. 42 of the 53 studies (79%) were carried out in countries classified by the World Bank as high- income countries, 36 of which were in the U.S. 6 studies were carried out in upper middle-income countries, 3 in lower middle-income	<ul> <li>Health insurance status: 15 cross-sectional studies reported comparisons of HTN outcomes in insured and uninsured pts. 8 of these 15 studies reported that insurance was associated with improved HTN treatment, control or medication adherence. The 7 other cross- sectional studies that compared HTN outcomes in insured pts and uninsured pts, reported no significant negative or positive associations between insurance status and HTN outcome.</li> <li>Medication costs or medication co-payments: All 6 of these studies reported significant associations between reduced co-payments or costs and improved HTN control or medication adherence.</li> <li>Co-payments for medical care: 14 quantitative studies measured the association of medication co-payments or costs with HTN control or treatment adherence, 9 of which were set in the U.S., and 1 in each of Cameroon, China, Finland, Israel, and Brazil. 2 of the 14 studies had a low risk of bias. 7 of the 14 studies were cohort study, and 6 were cross- sectional studies. All 7 cohort</li> </ul>	• Although lacking longitudinal studies, we found a large positive association between having a routine physician or place of care for HTN management and treatment, awareness, control, and adherence to antihypertensive treatment, again in the U.S. publication and reporting bias noted by authors.

	countries, and 1 in a	studies reported associations	
	low-income country.	between increased medication	
	5	costs or co-payments and	
		reductions in HTN control or	
		reduced adherence to	
		antihypertensive medication.	
		although for 1 of these 7 cohort	
		studies the association between	
		increased consyments and	
		reduced medication adherence	
		was only found for low	
		modication co paymonts and at	
		high co payment lovels	
		modication adherence was	
		actually found to increase (OD	
		for modioation adherence up	
		tor medication adherence vs.	
		baseline of 1 for \$0 co-	
		payments was 0.72 for \$1-\$9	
		co-payments ( $p=0.05$ ), 1.02 for	
		\$10-\$29 co-payments (p=0.05),	
		and 1.32 for co-payments . \$30	
		(p=0.05)	
		<ul> <li>Physician remuneration</li> </ul>	
		models: 2 studies evaluated the	
		association of physician	
		remuneration models with HTN	
		control or treatment adherence,	
		1 an ecological study set in	
		Canada, and 1 a U.S. cross-	
		sectional study. Neither study	
		had a low risk of bias. The U.S.	
		study reported improved rates of	
		HTN control amongst pts treated	
		under a capitation model	
		compared to fee-for service pts	
		(adjusted OR for HTN control:	
		1.82 (95% CI: 1.02–3.27) for	
		capitation vs. fee-for-service	
		pts). The Canadian study	
		reported highest rates of HTN	

		treatment and control among	
		model compared to fee for	
		niouei, compared to ree-tor-	
		service and salary model. HTN	
		awareness levels were nignest	
		in practices with a fixed salary	
		remuneration model.	

## Additional Data Supplement Tables and Figures



### Data Supplement A. Treatment of HFrEF Stages C and D

Colors correspond to COR in Table 1. For all medical therapies dosing should be optimized and serial assessment exercised.

\*See text for important treatment directions.

<sup>†</sup>Hydral-Nitrates Green Box- The combination of ISDN/HYD with ARNI has not been robustly tested. BP response should be carefully followed.

### ‡See 2013 HF guideline.

§Participation in investigational studies is also appropriate for stage C, NYHA class II and III HF.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; CRT-D, cardiac resynchronization therapy-device; COR, class of recommendation; Dx, diagnosis; GDMT, guideline-directed management and therapy; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ISDN/HYD, isosorbide dinitrate hydral-nitrates; LBBB, left bundle-branch block; LVEF, left ventricular

ejection fraction; LVAD, left ventricular assist device; NSR, normal sinus rhythm; and NYHA, New York Heart Association.

Hill-Bon	e Compliance Scale (346)	
How o	often do you:	Response:
1. 2. 3. 4.	Forget to take your high BP medicine? Decide NOT to take your high BP medicine? Eat salty foods Shake salt on your food before you eat it?	<ol> <li>All of the Time</li> <li>Most of the Time</li> <li>Some of the Time</li> <li>None of the Time</li> </ol>
5. 6.	Eat fast food? Make the next appointment before you leave the doctor's office?	Medication taking subscale: Items 1,2, 8.9.10.11.12.13.14.
7. 8. 9.	Miss scheduled appointments? Forget to get prescriptions filled? Run out of high BP pills?	Reducing sodium intake subscale: Items 3,4,5.
10. 11. 12. 13.	Skip your high BP medicine before you go to the doctor? Miss taking your high BP pills when you feel better? Miss taking your high BP pills when you feel sick? Take someone else's high BP pills?	6,7.
14.	Miss taking your high BP pills when you are careless?	

### Data Supplement B. Medication Adherence Assessment Scales

BP indicates blood pressure.

## Data Supplement C. Categories Defining Normal BP, Elevated BP, and Stages 1, 2, and 3 Hypertension

		SBP (mm Hg) →					
		<120	120–129	130–139	140–159	160+	
DBP (mm Hg)	<80	Normal	Elevated	Stage 1	Stage 2	Stage 2	
	80–89	Stage 1	Stage 1	Stage 1	Stage 2	Stage 2	
$\downarrow$	90–99	Stage 2	Stage 2	Stage 2	Stage 2	Stage 2	
	100+	Stage 2	Stage 2	Stage 2	Stage 2	Stage 2	

© 2017 American College of Cardiology Foundation and American Heart Association, Inc.

#### 2017 Hypertension Guideline Data Supplements

Stages 1, 2, and 3 refer to the stage of hypertension.

BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Class	Drug	Dosage Strengths (mg/mg)	Daily Frequency*
2-drug combinations			-
ACE Inhibitors + Thiazide	Benazepril/Hydrochlorothiazide	10/12.5, 20/12.5, 20/25	1
	Captopril/Hydrochlorothiazide	25/15, 50/15, 25/25, 50/25	2
	Enalapril/Hydrochlorothiazide	5/12.5, 10/25	1 or 2
	Fosinopril/Hydrochlorothiazide	10/12.5, 20/12.5	1
	Lisinopril/Hydrochlorothiazide	10/12.5, 20/12.5, 20/25	1
	Moexipril/Hydrochlorothiazide	7.5/12.5, 15/12.5, 15/25	1 or 2
	Quinapril/Hydrochlorothiazide	10/12.5, 20/12.5, 20/25	1 or 2
ARBs + Thiazide	Azilsartan/Chlorthalidone	40/12.5, 40/25	1
	Candesartan/Hydrochlorothiazide	16/12.5, 32/12.5, 32/25	1
	Eprosartan/Hydrochlorothiazide	600/12.5, 600/25	1
	Irbesartan/Hydrochlorothiazide	150/12.5, 300/12.5, 300/25	1
	Losartan/Hydrochlorothiazide	50/12.5, 100/12.5, 100/25	1 or 2
	Olmesartan/Hydrochlorothiazide	20/12.5, 40/12.5, 40/25	1
	Telmisartan/Hydrochlorothiazide	40/12.5, 80/12.5, 80/25	1
	Valsartan/Hydrochlorothiazide	80/12.5, 160/12.5, 320/12.5,	1
		160/25, 320/25	
CCB – dihydropyridine + ACEIs	Amlodipine/Benazepril	2.5/10, 5/10, 5/20, 10/20, 5/40,	1
, .,		10/40	
	Enalapril/Felodipine	5/5	1
	Perindopril/Amlodipine	3.5/2.5, 7/5, 14/10	1
CCB – dihydropyridine + ARB	Amlodipine/Olmesartan	5/20, 10/20, 4/40	1
, , ,	Amlodipine/Valsartan	5/160. 10/160. 5/320. 10/320	1
	Telmisartan/Amlodipine	40/5, 80/5, 40/10, 80/10	1
CCB – nondihydropyridine + ACEIs	Trandolapril/Verapamil	2/180, 1/250, 2/240, 4/240	1
Beta blocker + Thiazide	Atenolol/Chlorthalidone	50/25. 100/25	1
	Bisoprolol/Hydrochlorothiazide	2.5/6.25. 5/6.25. 10/6.25	1
	Metoprolol succinate/Hydrochlorothiazide	25/12.5. 50/12.5. 100/12.5	1
	Metoprolol tartrate/ Hydrochlorothiazide	50/25, 100/25, 100/50	1 or 2
	Nadolol/Bendroflumethiazide	40/5.80/5	1
	Propranolol/Hydrochlorothiazide	40/25, 80/25	1 or 2
Direct renin inhibitor + CCB –	Aliskiren/amlodipine	150/5, 150/10, 300/5, 300/10	1
ainyaropyriaine	Alializan (II) dae akleyethieride		4
Direct renin inhibitor + Inlazide	Aliskiren/ Hydrochlorothlazide	150/12.5, 150/25, 300/12.5, 300/25	1
dihydropyridine	Aliskiren/Amiodipine	150/5, 150/10, 300/5, 300/10	1
Direct renin inhibitor + Thiazide	Aliskiren/Hydrochlorothiazide	150/12 5 150/25 300/12 5 300/25	1
Central acting agent + Thiazide	Clonidine/Chlorthalidone	0 1/15 0 2/15 0 3/15	1 or 2
	Methyldona/Hydrochlorothiazide	250/15 250/25	2
Diuretic- potassium sparing +	Amiloride/Hydrochlorothiazide	5/50	1
Thiazide	Triamterene/Hydrochlorothiazide	27 5/25 75/50	1
Diurotic aldostorono antagonist +	Spiropolactopo/Hydrochlorothiazide	25/25	1 or 2
	spironolacione/ rivurocinorotinazide	23/23	1012
3-drug combinations			I
ARB + CCB - dibydropyriding +	Amlodinine/Valsartan/Hydrochlorothiazido	5/160/12 5 10/160/12 5 5/160/25	1
Thiazide		10/160/25, 10/320/25	1
	Olmesartan/Amlodipine/	20/5/12.5, 40/5/12.5, 40/5/25,	1
	Hydrochlorothiazide	40/10/12.5, 40/10/25	
Direct renin inhibitor + CCB –	Aliskiren/Amlodipine/Hydrochlorothiazide	150/5/12.5, 300/5/12.5, 300/5/25,	1
dihydropyridine + Thiazide		300/10/12.5, 300/10/25	

## Data Supplement D. Fixed-Dose Combination Antihypertensive Drugs

\*Dosages may vary from those listed in the FDA approved labeling <a href="http://dailymed.nlm.nih.gov/dailymed/index.cfm">http://dailymed.nlm.nih.gov/dailymed/index.cfm</a>).

© 2017 American College of Cardiology Foundation and American Heart Association, Inc.

#### 2017 Hypertension Guideline Data Supplements

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and CCB, calcium channel blocker.

From Chobanian et al. JNC 7. (347)

## Data Supplement E. Examples of Hypertension Quality Improvement Strategies

Quality Improvement Strategy	Examples	
	Feedback of performance to individual providers	
	Benchmarking – provision of outcomes data from top performers for	
Audit and feedback on performance	comparison with provider's own data	
Addit and reedback on performance	<ul> <li>Performance measures, quality indicators and reports</li> </ul>	
	<ul> <li>Use of registries to track BP control status at system and provider levels</li> </ul>	
Provider education	<ul> <li>In person, online, or other education to improve BP measurement and management skills</li> </ul>	
	<ul> <li>Training to improve communication, cultural competency, and ability to inspire and support lifestyle modification</li> </ul>	
	Intensive education strategies promoting hypertension self-	
Patient education	management	
	Cultural and linguistic tailoring of materials to increase acceptability	
Promotion of colf management	Reduce barriers for patients to receive and adhere to medications and	
	to implement lifestyle modification	
Patient reminder systems	<ul> <li>Postcards, calls, texts, or emails to patients</li> </ul>	
(for follow-up appointments, BP checks, and self-management)	Telehealth-delivered reminders	
	<ul> <li>Standardization of BP measurement using an automated device and standardized protocol</li> </ul>	
	Screening to identify all patients eligible for hypertension management	
	<ul> <li>Systematic follow-up of patients for the initiation and intensification of antihypertensive therapy</li> </ul>	
System change	<ul> <li>Decision support to providers to guide protocol-based treatment decisions</li> </ul>	
	Physician or other clinical champion designated to lead hypertension	
	care improvement initiatives	
	Hypertension specialist available for consult	
	Partner with community resources to support BP management	

BP indicates blood pressure.

Adapted with permission from Walsh et al. (348).

# Data Supplement F. Barriers and Improvement Strategies in Antihypertensive Medication Adherence (349-353)

Barriers	Improvement Strategies
Patient Level	
<ul> <li>Multiple comorbid conditions requiring complex medication regimens</li> <li>Convenience factors (e.g., dosing frequency)</li> <li>Health beliefs</li> <li>Behavioral factors</li> <li>Lack of involvement in the treatment decision-making process</li> <li>Issues with treatment of asymptomatic diseases (e.g., treatment side effects)</li> <li>Resource constraints</li> <li>Suboptimal health literacy</li> </ul>	<ul> <li>Educate patients about hypertension, consequences of hypertension, and possible adverse effects of medications</li> <li>Collaborate with patient to establish goals of therapy and plan of care</li> <li>Maintain contact with patients; consider telehealth approaches (Section 12.3.2).</li> <li>Integrate pill-taking into daily routine activities of daily living with adherence support tools such as reminders, pillboxes, packaging, or other aids</li> <li>Use motivation interventions to support medication adherence and lifestyle modification efforts</li> <li>Use medication adherence scales to facilitate identification of barriers and facilitators to and behaviors associated with adequate adherence</li> <li>Address health literacy         <ul> <li>Teach-back method</li> <li>Empower patients to ask questions</li> <li>Use visual, interactive education</li> <li>Health literacy universal precautions tool kit</li> <li>Provide medication lite/pictorial medication schedule</li> </ul> </li> </ul>
Provider and Health System Levels	o Provide medication isty pictorial medication schedule
<ul> <li>Prescription of complex drug regimens</li> <li>Inadequate communication with patient about regimen, adverse effects, treatment goals</li> <li>Inadequate communication among multiple providers</li> <li>Office visit time limitations</li> <li>Limited access to care, pharmacies, prescription refills</li> </ul>	<ul> <li>Assess for nonadherence and explore barriers to medication adherence</li> <li>Use a multifactorial approach to optimize adherence</li> <li>Participate in training to enhance communication skills and increase cultural competence</li> <li>Use a multifactorial approach to optimize adherence</li> <li>Reduce complexity of medication regimen</li> <li>Utilize agents that are dosed once daily over those which require multiple daily doses</li> <li>Utilize fixed-dose combination agents when available and simplify drug regimens</li> <li>Consider overall side effect profile and preferentially use agents that are well tolerated</li> <li>Use low-cost and generic antihypertensives from drug classes where RCTs have demonstrated a reduction in cardiovascular events when appropriate (354)</li> <li>Use team-based care approaches (Section 12.2)</li> <li>Use health information technology-based approaches (Section 12.3)</li> </ul>

RCTs indicate randomized controlled trials.

## Data Supplement G. Examples of Strategies to Promote Lifestyle Modification Interventions in Patients With Hypertension (318, 319, 355-361)

	Lifestyle Modification Intervention	References
Tobacco Cessation	Ask all adults about tobacco use	(361, 362)
	<ul> <li>Advise them to stop using tobacco</li> </ul>	
	Provide behavioral interventions	
	Consider pharmacotherapy for tobacco cessation	
Weight Loss	Offer or refer obese adults to intensive cognitive and behavioral	(355, 356)
	interventions aimed at to improve weight status and other risk factors	
	for important health outcomes.	
Sodium Reduction	Offer or refer to behavioral counselling aimed at reduced intake of	
	dietary sodium	
	<ul> <li>Encourage use of food labels to choose lower sodium products</li> </ul>	
Alcohol	<ul> <li>Screen adults ≥18 y of age for alcohol misuse and provide persons</li> </ul>	(357, 358)
	engaged in risky or hazardous drinking with behavioral counseling	
	interventions to reduce alcohol misuse.	
Physical Activity	Use medium- to high-intensity behavioral counseling interventions to	(359, 360)
and Diet	improve intermediate health outcomes; addressing barriers, such as	
	lack of access to affordable healthier foods, transportation barriers	
	and poor local safety.	

### Data Supplement H. Responsibilities and Roles of the Hypertension Team

#### **Hypertension Team Responsibilities**

E a lla sur a la alta alta

- Communication and care coordination among various team members, the patient and family members or • other support persons.
- Effective use of evidence-based diagnosis and management guidelines •
- Regular, structured follow-up mechanisms and reminder systems to monitor patient progress .
- Engage patients in their care by shared decision making

- Medication adherence support and appropriate education about hypertension medication
- Medication addition and titration using evidence-based treatment algorithms
- Use of evidence-based tools and resources designed to maximize self-management (including health • behavior change, lifestyle modification, etc.) non nations characteristics and needs

<ul> <li>Follow a single, personalized plan of</li> </ul>	r care based upon patient characteristics and needs
Individual Hypertension Team Members	Roles (examples)
Primary Care Physician, Physician	Routine and complex hypertension care, managing primary care
Assistant, Advanced Practice Nurse	issues.
Cardiologist	Routine and complex hypertension care, especially for patient with
	cardiac disease or high risk for major cardiovascular events.
Nephrologist, Endocrinologist,	Management of complex hypertension care, especially due to
Hypertension Specialist	secondary causes, and/or resistant hypertension.
Nurse (including in-office, home care,	Accurate assessment of BP, medication reconciliation, patient
internal and external population health	education, self-management, lifestyle modification and adherence.
personnel)	
Clinical Pharmacist	Comprehensive medication management, which involves identification
	and documentation of medication-related problems, initiating,
	modifying, and discontinuing medication to address identified
	problems, and educating patients on their medication regimen.
Dietician	Ongoing patient-centered counseling to assess dietary habits and
	preferences, set and monitor goals for healthy lifestyle
Social Worker	Assess for psychosocial, cultural and financial barriers, find solutions
	to overcome these barriers.
Community Health Providers	Assess for psychosocial, cultural and financial barriers, identify and
	promote acceptable community-based resources to overcome these
	barriers.

BP indicates blood pressure.

## Data Supplement I. Examples of Telehealth Strategies and Technologies to Promote Effective Hypertension Management

Telehealth strategies
Automated BP data capture and transmission of the patient's self-measured BP
• Self-management support including education, reminders, and feedback that is automated or delivered by a
healthcare professional
Medication titration and follow-up monitoring protocols/algorithm
Prescription refill reminders
Medication adherence assessments
Self-monitoring of lifestyle behaviors
Integration of behavior change techniques, including in person or e-counseling
Case/care/population health management
Commonly used telehealth technologies
Wired "land line" telephone
Wireless smart phone applications
Internet-based website via computers and handheld devices
Text messaging
E-mail messaging
Social networking and social media websites/applications
Wireless BP measurement devices
Electronic pill dispensers/counters

BP indicates blood pressure.

## Data Supplement J. Publicly Available Performance Measures Used to Assess Hypertension Care Quality Services (363-367)

Quality Measure	Source	Description	Additional information
Controlling High BP PQRS Measure #236; NQF #0018	NCQA	Percentage of patients 18–85 y of age who had a diagnosis of hypertension and whose BP was adequately controlled (<140/90 mm Hg during the measurement period)	Used in the CMS, PQRS, MSSP, Medicare Advantage "Stars" ratings; component of Commercial Health Plan HEDIS quality measure set
Comprehensive Diabetes Care: BP Control (<140/90 mm Hg) NQF #0061	NCQA	The percentage of patients 18–75 y of age with DM (type 1 and type 2) whose most recent BP level taken during the measurement y is <140/90 mm Hg	<ul> <li>Used for:</li> <li>Accreditation</li> <li>Decision-making by businesses about health plan purchasing</li> <li>Decision-making by consumers about health plan/provider choice</li> <li>External oversight/Medicaid</li> <li>External oversight/Medicare</li> <li>External oversight/State government program</li> <li>Internal quality improvement</li> <li>Public reporting</li> </ul>
Adult Kidney Disease: BP Management PQRS #122	PCPI, RPA	Percentage of patient visits for those patients ≥18 y of age with a diagnosis of CKD (stage 3, 4, or 5, not receiving renal replacement therapy) with a BP<140/90 mm Hg OR ≥140/90 mm Hg with a documented plan of care	Used in PQRS
Percentage of patients ≥18 y of age with BP documented in the medical record (every 2 y if <120/80 mm Hg, every y if 120–139/80–89 mm Hg)	ICSI	This measure is used to assess the percentage of patients age 18 y of age and older with BP documented in the medical record (every 2 y if <120/80 mm Hg, every y if 120– 139/80–89 mm Hg)	Used for internal quality improvement
Controlling High BP for People with Serious Mental Illness NQF #2602	NCQA	The percentage of patients 18–85 y of age with serious mental illness who had a diagnosis of hypertension and whose BP was adequately controlled during the measurement	<ul> <li>Current Use:</li> <li>Accreditation</li> <li>Decision-making by businesses about health plan purchasing</li> <li>Decision-making by consumers about health plan/provider choice</li> <li>External oversight/Medicaid</li> <li>External oversight/state government program \internal quality improvement</li> </ul>
Diabetes Care for People with Serious Mental Illness: BP Control (<140/90 mm Hg) NQF #2606	NCQA	The percentage of patients 18–75 y of age with a serious mental illness and DM (type 1 and type 2) whose most recent BP reading during the measurement year is <140/90 mm Hg	<ul> <li>Current Use:</li> <li>Accreditation</li> <li>Decision-making by businesses about health plan purchasing</li> <li>Decision-making by consumers about health plan/provider choice</li> <li>External oversight/Medicaid</li> </ul>

Quality Measure	Source	Description	Additional information
			<ul> <li>External oversight/state government program</li> <li>Internal quality improvement</li> </ul>
Hypertension diagnosis and treatment: percentage of adult patients ≥18 y of age diagnosed with hypertension who are not at goal for hypertension and have received counseling on diet and physical activity in the past 12 mo	ICSI	Used to assess the percentage adult patients ≥ 18 y of age diagnosed with hypertension who are not at goal for hypertension and have received counseling on diet and physical activity in the past 12 mo	Used for Internal Quality Improvement
Ambulatory care sensitive conditions: age-standardized acute care hospitalization rate for conditions where appropriate ambulatory care prevents or reduces the need for admission to the hospital per 100,000 population <75 y of age	СІНІ	Used to assess the age-standardized acute care hospitalization rate for conditions where appropriate ambulatory care prevents or reduces the need for admission to the hospital per 100,000 population <75 y of age	<ul> <li>Used for:</li> <li>Monitoring health state(s)</li> <li>National health policymaking</li> <li>National reporting</li> <li>State/Provincial health policymaking</li> </ul>
Hypertension: the relative resource use by members with hypertension during the measurement y	NCQA	Used to assess the relative resource use by members with hypertension by reporting total standard cost and service frequency for all services for which the organization has paid or expects to pay during the measurement y	<ul> <li>Used for:</li> <li>Accreditation</li> <li>External oversight/Medicaid</li> <li>External oversight/Medicare</li> <li>External oversight/State government program</li> <li>Monitoring and planning</li> <li>Public reporting</li> </ul>

BP indicates blood pressure; CIHI, Canadian Institute for Health Information; CKD, chronic kidney disease; CMS, Centers for Medicare and Medicaid Services; DM, diabetes mellitus; HEDIS, healthcare Effectiveness Data and Information Set; ICSI, Institute for Clinical Systems Improvement; MSSP, Medicare Shared Savings Program; NCQA, National Committee for Quality Assurance; NQF, National Quality Forum; OR, odds ratio; PCPI, Physician Consortium for Performance Improvement; and PQRS, Physician Quality Reporting System; and RPA, Renal Physicians Association.

## Data Supplement K. Online Quality Improvement Resources for Treatment and Control of Hypertension

<u>American College of Cardiology/American Heart Association/Centers for Disease Control</u> Science Advisory for the Effective Approach to High Blood Pressure Control<sup>i</sup>

http://content.onlinejacc.org/article.aspx?articleid=1778408

<u>American Medical Association</u> Measure, Act and Partner (M.A.P.) to help patients control blood pressure and ultimately prevent heart disease

http://www.ama-assn.org/ama/pub/about-ama/strategic-focus/improving-health-outcomes/improving-blood-pressure-control.page

<u>United States Health and Human Services (HHS)/Centers for Disease Control (CDC)</u> Million Hearts Campaign Evidence-based Treatment Protocols for Improving Blood Pressure Control

http://millionhearts.hhs.gov/resources/protocols.html

**Department of Defense/Veterans' Affairs** 

http://www.healthquality.va.gov/guidelines/CD/htn/

Kaiser Permanente Hypertension Management programs to improve blood pressure control

http://kpcmi.org/how-we-work/hypertension-control/

Institute for Clinical Systems Improvement (ICSI) Hypertension Diagnosis and Treatment Guidelines

https://www.icsi.org/guidelines more/catalog guidelines and more/catalog guidelines/catalog cardiovascular g uidelines/hypertension/

New York Health and Hospitals Corporation (HHC) Hypertension Collaborative Care Pathway

http://millionhearts.hhs.gov/Docs/NYC HHC Hypertension Protocol.pdf

### References

- 1. Wilson PW, Kannel WB, Silbershatz H, et al. Clustering of metabolic factors and coronary heart disease. Arch. Intern. Med. 1999; 159:1104-9.
- 2. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. The New England journal of medicine. 2012; 366:321-9.
- 3. Franklin SS, Thijs L, Hansen TW, et al. Significance of white-coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes population. Hypertension. 2012; 59:564-71.
- 4. Guo X, Zhang X, Guo L, et al. Association between pre-hypertension and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Curr. Hypertens. Rep. 2013; 15:703-16.
- 5. Huang Y, Wang S, Cai X, et al. Prehypertension and incidence of cardiovascular disease: a meta-analysis. BMC Med. 2013; 11:177.
- 6. Huang Y, Cai X, Zhang J, et al. Prehypertension and Incidence of ESRD: a systematic review and meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014; 63:76-83.
- Huang Y, Cai X, Li Y, et al. Prehypertension and the risk of stroke: a meta-analysis. Neurology. 2014; 82:1153-61.
- 8. Huang Y, Su L, Cai X, et al. Association of all-cause and cardiovascular mortality with prehypertension: a metaanalysis. Am. Heart J. 2014; 167:160-8.
- 9. Huang Y, Cai X, Liu C, et al. Prehypertension and the risk of coronary heart disease in Asian and Western populations: a meta-analysis. Journal of the American Heart Association. 2015; 4.
- 10. Lee M, Saver JL, Chang B, et al. Presence of baseline prehypertension and risk of incident stroke: a metaanalysis. Neurology. 2011; 77:1330-7.
- 11. Shen L, Ma H, Xiang MX, et al. Meta-analysis of cohort studies of baseline prehypertension and risk of coronary heart disease. The American journal of cardiology. 2013; 112:266-71.
- Wang S, Wu H, Zhang Q, et al. Impact of baseline prehypertension on cardiovascular events and all-cause mortality in the general population: a meta-analysis of prospective cohort studies. Int. J. Cardiol. 2013; 168:4857-60.
- Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT).
   J. Clin. Hypertens. (Greenwich). 2002; 4:393-404.
- 14. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002; 359:995-1003.
- 15. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: metaanalysis on 11,000 participants from 42 trials. The American journal of medicine. 2009; 122:290-300.
- 16. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360:1903-13.
- 17. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016; 387:957-67.
- Law MR, Morris JK and Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ (Clinical research ed.). 2009; 338:b1665.

- 19. Sundstrom J, Arima H, Jackson R, et al. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. Ann. Intern. Med. 2015; 162:184-91.
- 20. Thomopoulos C, Parati G and Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels--overview and meta-analyses of randomized trials. J. Hypertens. 2014; 32:2296-304.
- 21. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2015.
- 22. Pickering TG, James GD, Boddie C, et al. How common is white coat hypertension? JAMA. 1988; 259:225-8.
- 23. Uhlig K, Balk EM, Patel K, et al. Self-measured blood pressure monitoring: comparative effectiveness. Comparative Effectiveness Review No. 45. Rockville, MD: Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, 2012.
- 24. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. JAMA. 2014; 312:799-808.
- 25. Margolis KL, Asche SE, Bergdall AR, et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial. JAMA. 2013; 310:46-56.
- 26. Yi SS, Tabaei BP, Angell SY, et al. Self-blood pressure monitoring in an urban, ethnically diverse population: a randomized clinical trial utilizing the electronic health record. Circulation.Cardiovascular quality and outcomes. 2015; 8:138-45.
- 27. Agarwal R, Bills JE, Hecht TJ, et al. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. Hypertension. 2011; 57:29-38.
- 28. Fagard RH and Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. J. Hypertens. 2007; 25:2193-8.
- 29. Viera AJ, Hinderliter AL, Kshirsagar AV, et al. Reproducibility of masked hypertension in adults with untreated borderline office blood pressure: comparison of ambulatory and home monitoring. Am. J. Hypertens. 2010; 23:1190-7.
- 30. Viera AJ, Lin FC, Tuttle LA, et al. Reproducibility of masked hypertension among adults 30 years or older. Blood Press. Monit. 2014; 19:208-15.
- 31. Bayo J, Cos FX, Roca C, et al. Home blood pressure self-monitoring: diagnostic performance in white-coat hypertension. Blood Press. Monit. 2006; 11:47-52.
- 32. Asayama K, Thijs L, Li Y, et al. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. Hypertension 2014; 64:935-42.
- 33. Conen D, Aeschbacher S, Thijs L, et al. Age-specific differences between conventional and ambulatory daytime blood pressure values. Hypertension. 2014; 64:1073-9.
- 34. Nasothimiou EG, Tzamouranis D, Rarra V, et al. Diagnostic accuracy of home vs. ambulatory blood pressure monitoring in untreated and treated hypertension. Hypertension research : official journal of the Japanese Society of Hypertension. 2012; 35:750-5.
- 35. Coll de TG, Llibre JB, Poncelas AR, et al. Isolated clinical hypertension diagnosis: self-home BP, ambulatory BP monitoring, or both simultaneously? Blood Press. Monit. 2011; 16:11-5.
- 36. Stergiou GS, Salgami EV, Tzamouranis DG, et al. Masked hypertension assessed by ambulatory blood pressure versus home blood pressure monitoring: is it the same phenomenon? Am. J. Hypertens. 2005; 18:772-8.
- 37. Sega R, Trocino G, Lanzarotti A, et al. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: Data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). Circulation. 2001; 104:1385-92.

- 38. Vinyoles E, Felip A, Pujol E, et al. Clinical characteristics of isolated clinic hypertension. J. Hypertens. 2008; 26:438-45.
- 39. Piper MA, Evans CV, Burda BU, et al. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. Ann. Intern. Med. 2015; 162:192-204.
- 40. Alwan H, Pruijm M, Ponte B, et al. Epidemiology of masked and white-coat hypertension: the family-based SKIPOGH study. PLoS One. 2014; 9:e92522.
- 41. Stergiou GS, Asayama K, Thijs L, et al. Prognosis of white-coat and masked hypertension: International Database of HOme blood pressure in relation to Cardiovascular Outcome. Hypertension. 2014; 63:675-82.
- 42. Pierdomenico SD and Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. Am. J. Hypertens. 2011; 24:52-8.
- 43. Hansen TW, Kikuya M, Thijs L, et al. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. J. Hypertens. 2007; 25:1554-64.
- 44. National Instutite for Health and Clinical Excellence. Hypertension: the clinical management of primary hypertnesion in adults: clincial guidelines: methods, evidence and recommendations. 2011.
- 45. Verdecchia P, Reboldi GP, Angeli F, et al. Short- and long-term incidence of stroke in white-coat hypertension. Hypertension. 2005; 45:203-8.
- 46. Mancia G, Bombelli M, Brambilla G, et al. Long-term prognostic value of white coat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. Hypertension. 2013; 62:168-74.
- 47. Tomiyama M, Horio T, Yoshii M, et al. Masked hypertension and target organ damage in treated hypertensive patients. Am. J. Hypertens. 2006; 19:880-6.
- 48. Ohkubo T, Kikuya M, Metoki H, et al. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. J. Am. Coll. Cardiol. 2005; 46:508-15.
- 49. Tientcheu D, Ayers C, Das SR, et al. Target Organ Complications and Cardiovascular Events Associated With Masked Hypertension and White-Coat Hypertension: Analysis From the Dallas Heart Study. J. Am. Coll. Cardiol. 2015; 66:2159-69.
- 50. Lawes CM, Rodgers A, Bennett DA, et al. Blood pressure and cardiovascular disease in the Asia Pacific region. J. Hypertens. 2003; 21:707-16.
- 51. Riaz IB, Husnain M, Riaz H, et al. Meta-analysis of revascularization versus medical therapy for atherosclerotic renal artery stenosis. The American journal of cardiology. 2014; 114:1116-23.
- 52. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. The New England journal of medicine. 2014; 370:13-22.
- 53. Brunstr"m M and Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ (Clinical research ed.). 2016; 352:i717.
- 54. Thomopoulos C, Parati G and Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels updated overview and meta-analyses of randomized trials. J. Hypertens. 2016; 34:613-22.
- 55. Julius S, Nesbitt SD, Egan BM, et al. Feasibility of treating prehypertension with an angiotensin-receptor blocker. The New England journal of medicine. 2006; 354:1685-97.
- 56. Ference BA, Julius S, Mahajan N, et al. Clinical effect of naturally random allocation to lower systolic blood pressure beginning before the development of hypertension. Hypertension. 2014; 63:1182-8.

- 57. Barbe F, Duran-Cantolla J, Capote F, et al. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. Am. J. Respir. Crit. Care Med. 2010; 181:718-26.
- 58. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA. 2013; 310:2407-15.
- 59. Lozano L, Tovar JL, Sampol G, et al. Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial. J. Hypertens. 2010; 28:2161-8.
- 60. Muxfeldt ES, Margallo V, Costa LM, et al. Effects of continuous positive airway pressure treatment on clinic and ambulatory blood pressures in patients with obstructive sleep apnea and resistant hypertension: a randomized controlled trial. Hypertension. 2015; 65:736-42.
- 61. Pedrosa RP, Drager LF, de Paula LK, et al. Effects of OSA treatment on BP in patients with resistant hypertension: a randomized trial. Chest. 2013; 144:1487-94.
- 62. Whelton SP, Hyre AD, Pedersen B, et al. Effect of dietary fiber intake on blood pressure: a meta-analysis of randomized, controlled clinical trials. J. Hypertens. 2005; 23:475-81.
- 63. Streppel MT, Arends LR, van tV, et al. Dietary fiber and blood pressure: a meta-analysis of randomized placebo-controlled trials. Arch. Intern. Med. 2005; 165:150-6.
- 64. Evans CE, Greenwood DC, Threapleton DE, et al. Effects of dietary fibre type on blood pressure: a systematic review and meta-analysis of randomized controlled trials of healthy individuals. J. Hypertens. 2015; 33:897-911.
- 65. Campbell F, Dickinson HO, Critchley JA, et al. A systematic review of fish-oil supplements for the prevention and treatment of hypertension. European journal of preventive cardiology. 2013; 20:107-20.
- 66. Rodriguez-Leyva D, Weighell W, Edel AL, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. Hypertension. 2013; 62:1081-9.
- 67. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA. 1997; 277:1624-32.
- 68. Aburto NJ, Hanson S, Gutierrez H, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ (Clinical research ed.). 2013; 346:f1378.
- 69. Geleijnse JM, Kok FJ and Grobbee DE. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. J. Hum. Hypertens. 2003; 17:471-80.
- 70. Rebholz CM, Friedman EE, Powers LJ, et al. Dietary protein intake and blood pressure: a meta-analysis of randomized controlled trials. Am. J. Epidemiol. 2012; 176 Suppl 7:S27-S43.
- 71. Tielemans SM, Altorf-van der Kuil W, Engberink MF, et al. Intake of total protein, plant protein and animal protein in relation to blood pressure: a meta-analysis of observational and intervention studies. J. Hum. Hypertens. 2013; 27:564-71.
- 72. Dong JY, Zhang ZL, Wang PY, et al. Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in type 2 diabetes: meta-analysis of randomised controlled trials. The British journal of nutrition. 2013; 110:781-9.
- 73. Dong JY, Szeto IM, Makinen K, et al. Effect of probiotic fermented milk on blood pressure: a meta-analysis of randomised controlled trials. Br. J. Nutr. 2013; 110:1188-94.
- 74. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. The New England journal of medicine. 2014; 371:624-34.
- 75. He FJ, Fan S, MacGregor GA, et al. Plasma sodium and blood pressure in individuals on haemodialysis. J. Hum. Hypertens. 2013; 27:85-9.

- 76. Graudal NA, Hubeck-Graudal T and Jurgens G. Effects of low-sodium diet vs. high-sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride (Cochrane Review). Am. J. Hypertens. 2012; 25:1-15.
- 77. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. The New England journal of medicine. 2001; 344:3-10.
- 78. Kumanyika SK, Cook NR, Cutler JA, et al. Sodium reduction for hypertension prevention in overweight adults: further results from the Trials of Hypertension Prevention Phase II. J. Hum. Hypertens. 2005; 19:33-45.
- 79. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA. 1992; 267:1213-20.
- 80. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). BMJ (Clinical research ed.). 2007; 334:885-8.
- 81. Canter PH and Ernst E. Insufficient evidence to conclude whether or not Transcendental Meditation decreases blood pressure: results of a systematic review of randomized clinical trials. J. Hypertens. 2004; 22:2049-54.
- 82. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. The New England journal of medicine. 1997; 336:1117-24.
- 83. Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. JAMA. 2003; 289:2083-93.
- 84. Appel LJ, Sacks FM, Carey VJ, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA. 2005; 294:2455-64.
- 85. Bazzano LA, Hu T, Reynolds K, et al. Effects of low-carbohydrate and low-fat diets: a randomized trial. Ann. Intern. Med. 2014; 161:309-18.
- Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch. Intern. Med. 2006; 166:285-93.
- 87. Nordmann AJ, Suter-Zimmermann K, Bucher HC, et al. Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. The American journal of medicine. 2011; 124:841-51.
- 88. Yokoyama Y, Nishimura K, Barnard ND, et al. Vegetarian diets and blood pressure: a meta-analysis. JAMA internal medicine. 2014; 174:577-87.
- 89. Toledo E, Hu FB, Estruch R, et al. Effect of the Mediterranean diet on blood pressure in the PREDIMED trial: results from a randomized controlled trial. BMC Med. 2013; 11:207.
- 90. Xin X, He J, Frontini MG, et al. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2001; 38:1112-7.
- 91. Stewart SH, Latham PK, Miller PM, et al. Blood pressure reduction during treatment for alcohol dependence: results from the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study. Addiction. 2008; 103:1622-8.
- 92. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J. Hypertens. 2006; 24:215-33.
- 93. Wallace P, Cutler S and Haines A. Randomised controlled trial of general practitioner intervention in patients with excessive alcohol consumption. BMJ. 1988; 297:663-8.
- 94. Lang T, Nicaud V, Darne B, et al. Improving hypertension control among excessive alcohol drinkers: a randomised controlled trial in France. The WALPA Group. J. Epidemiol. Community Health. 1995; 49:610-6.
- 95. van Mierlo LA, Arends LR, Streppel MT, et al. Blood pressure response to calcium supplementation: a metaanalysis of randomized controlled trials. J. Hum. Hypertens. 2006; 20:571-80.

- 96. Whelton SP, Chin A, Xin X, et al. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann. Intern. Med. 2002; 136:493-503.
- 97. Cornelissen VA and Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. Journal of the American Heart Association. 2013; 2:e004473.
- 98. Rossi AM, Moullec G, Lavoie KL, et al. The evolution of a Canadian Hypertension Education Program recommendation: the impact of resistance training on resting blood pressure in adults as an example. The Canadian journal of cardiology. 2013; 29:622-7.
- 99. Garcia-Hermoso A, Saavedra JM and Escalante Y. Effects of exercise on resting blood pressure in obese children: a meta-analysis of randomized controlled trials. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2013; 14:919-28.
- 100. Carlson DJ, Dieberg G, Hess NC, et al. Isometric exercise training for blood pressure management: a systematic review and meta-analysis. Mayo Clin. Proc. 2014; 89:327-34.
- 101. Cornelissen VA, Fagard RH, Coeckelberghs E, et al. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. Hypertension. 2011; 58:950-8.
- 102. Kass L, Weekes J and Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. Eur. J. Clin. Nutr. 2012; 66:411-8.
- 103. Neter JE, Stam BE, Kok FJ, et al. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2003; 42:878-84.
- 104. Ho M, Garnett SP, Baur L, et al. Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. Pediatrics. 2012; 130:e1647-e71.
- 105. Cai L, Wu Y, Wilson RF, et al. Effect of childhood obesity prevention programs on blood pressure: a systematic review and meta-analysis. Circulation. 2014; 129:1832-9.
- 106. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. Arch. Intern. Med. 1997; 157:657-67.
- 107. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA. 1998; 279:839-46.
- 108. Devereux RB, Wachtell K, Gerdts E, et al. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA. 2004; 292:2350-6.
- 109. Armstrong AC, Jacobs DR, Jr., Gidding SS, et al. Framingham score and LV mass predict events in young adults: CARDIA study. Int. J. Cardiol. 2014; 172:350-5.
- 110. Okwuosa TM, Soliman EZ, Lopez F, et al. Left ventricular hypertrophy and cardiovascular disease risk prediction and reclassification in blacks and whites: the Atherosclerosis Risk in Communities Study. Am. Heart J. 2015; 169:155-61.
- 111. Zalawadiya SK, Gunasekaran PC, Bavishi CP, et al. Left ventricular hypertrophy and risk reclassification for coronary events in multi-ethnic adults. European journal of preventive cardiology. 2015; 22:673-9.
- 112. Sundstrom J, Arima H, Woodward M, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014; 384:591-8.
- Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA. 2011; 305:913-22.
- 114. Wright JT, Jr., Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. The New England journal of medicine. 2015; 373:2103-16.

- 115. Lawes CM, Bennett DA, Lewington S, et al. Blood pressure and coronary heart disease: a review of the evidence. Semin. Vasc. Med. 2002; 2:355-68.
- 116. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. The New England journal of medicine. 2016.
- 117. Neaton JD, Grimm RH, Jr., Prineas RJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA. 1993; 270:713-24.
- 118. van DS, Kengne AP, Chalmers J, et al. Effects of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes. Diabetes Res. Clin. Pract. 2012; 98:83-90.
- 119. Montgomery AA, Fahey T, Ben-Shlomo Y, et al. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: a Markov decision analysis. J. Hypertens. 2003; 21:1753-9.
- 120. Kassai B, Boissel JP, Cucherat M, et al. Treatment of high blood pressure and gain in event-free life expectancy. Vascular health and risk management. 2005; 1:163-9.
- 121. Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: metaanalysis of randomized trials. J. Hypertens. 2011; 29:4-16.
- 122. Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin. Trials. 2014; 11:532-46.
- 123. Cushman WC, Grimm RH, Jr., Cutler JA, et al. Rationale and design for the blood pressure intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. The American journal of cardiology. 2007; 99:44i-55i.
- 124. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. The New England journal of medicine. 2013; 369:1892-903.
- 125. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. The New England journal of medicine. 2012; 367:2204-13.
- 126. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. The New England journal of medicine. 2008; 358:1547-59.
- 127. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013; 185:949-57.
- 128. Xu W, Goldberg SI, Shubina M, et al. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study. BMJ (Clinical research ed.). 2015; 350:h158.
- 129. Birtwhistle RV, Godwin MS, Delva MD, et al. Randomised equivalence trial comparing three month and six month follow up of patients with hypertension by family practitioners. BMJ (Clinical research ed.). 2004; 328:204.
- 130. Brennan T, Spettell C, Villagra V, et al. Disease management to promote blood pressure control among African Americans. Population health management. 2010; 13:65-72.
- 131. Bosworth HB, Olsen MK, Grubber JM, et al. Two self-management interventions to improve hypertension control: a randomized trial. Ann. Intern. Med. 2009; 151:687-95.
- 132. Bosworth HB, Powers BJ, Olsen MK, et al. Home blood pressure management and improved blood pressure control: results from a randomized controlled trial. Arch. Intern. Med. 2011; 171:1173-80.
- 133. Green BB, Cook AJ, Ralston JD, et al. Effectiveness of home blood pressure monitoring, Web communication, and pharmacist care on hypertension control: a randomized controlled trial. JAMA. 2008; 299:2857-67.
- 134. Heisler M, Hofer TP, Schmittdiel JA, et al. Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems: the adherence and intensification of medications cluster randomized, controlled pragmatic trial. Circulation. 2012; 125:2863-72.
- 135. Bangalore S, Gong Y, Cooper-DeHoff RM, et al. 2014 Eighth Joint National Committee panel recommendation for blood pressure targets revisited: results from the INVEST study. J. Am. Coll. Cardiol. 2014; 64:784-93.
- 136. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. The New England journal of medicine. 2000; 342:145-53.
- 137. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. The New England journal of medicine. 1992; 327:669-77.
- 138. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003; 362:782-8.
- 139. Goldstein S and Hjalmarson A. The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF Trial. Clin. Cardiol. 1999; 22 Suppl 5:V30-V5.
- 140. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. The New England journal of medicine. 2001; 344:1651-8.
- 141. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001; 357:1385-90.
- 142. Herlitz J, Wikstrand J, Denny M, et al. Effects of metoprolol CR/XL on mortality and hospitalizations in patients with heart failure and history of hypertension. J. Card. Fail. 2002; 8:8-14.
- 143. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999; 353:9-13.
- 144. Elkayam U, Amin J, Mehra A, et al. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation. 1990; 82:1954-61.
- 145. The Multicenter Diltiazem Postinfarction Trial Research G. The effect of diltiazem on mortality and reinfarction after myocardial infarction. The New England journal of medicine. 1988; 319:385-92.
- 146. Goldstein RE, Boccuzzi SJ, Cruess D, et al. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. Circulation. 1991; 83:52-60.
- 147. Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ (Clinical research ed.). 1999; 318:1730-7.
- 148. de Peuter OR, Lussana F, Peters RJ, et al. A systematic review of selective and non-selective beta blockers for prevention of vascular events in patients with acute coronary syndrome or heart failure. The Netherlands journal of medicine. 2009; 67:284-94.
- 149. Leon MB, Rosing DR, Bonow RO, et al. Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. The American journal of cardiology. 1981; 48:131-9.
- 150. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997; 350:757-64.
- 151. Bangalore S, Qin J, Sloan S, et al. What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation. 2010; 122:2142-51.

- 152. Cohn JN and Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. The New England journal of medicine. 2001; 345:1667-75.
- 153. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. The New England journal of medicine. 1991; 325:293-302.
- 154. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993; 342:821-8.
- 155. Garg R and Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA. 1995; 273:1450-6.
- 156. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. The New England journal of medicine. 2003; 349:1893-906.
- 157. Maggioni AP, Anand I, Gottlieb SO, et al. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. J. Am. Coll. Cardiol. 2002; 40:1414-21.
- 158. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003; 362:772-6.
- 159. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. The New England journal of medicine. 2003; 348:1309-21.
- 160. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. The New England journal of medicine. 2004; 351:2049-57.
- Pfeffer MA, Claggett B, Assmann SF, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation. 2015; 131:34-42.
- 162. Aronow WS, Ahn C and Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. The American journal of cardiology. 1997; 80:207-9.
- 163. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. JAMA. 1997; 278:212-6.
- 164. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. The New England journal of medicine. 2008; 358:1887-98.
- 165. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J. Am. Coll. Cardiol. 2009; 53:2150-8.
- 166. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003; 362:777-81.
- 167. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. The New England journal of medicine. 2008; 359:2456-67.
- 168. Piller LB, Baraniuk S, Simpson LM, et al. Long-term follow-up of participants with heart failure in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). Circulation. 2011; 124:1811-8.

- 169. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. The New England journal of medicine. 1994; 330:877-84.
- 170. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann. Intern. Med. 1995; 123:754-62.
- 171. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet. 2005; 365:939-46.
- 172. Wright JT, Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002; 288:2421-31.
- 173. Contreras G, Greene T, Agodoa LY, et al. Blood pressure control, drug therapy, and kidney disease. Hypertension. 2005; 46:44-50.
- 174. Norris K, Bourgoigne J, Gassman J, et al. Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2006; 48:739-51.
- 175. Esnault VL, Brown EA, Apetrei E, et al. The effects of amlodipine and enalapril on renal function in adults with hypertension and nondiabetic nephropathies: a 3-year, randomized, multicenter, double-blind, placebo-controlled study. Clin. Ther. 2008; 30:482-98.
- 176. Marin R, Ruilope LM, Aljama P, et al. A random comparison of fosinopril and nifedipine GITS in patients with primary renal disease. J. Hypertens. 2001; 19:1871-6.
- 177. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. Lancet. 2010; 375:1173-81.
- 178. Parving HH, Persson F, Lewis JB, et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy. The New England journal of medicine. 2008; 358:2433-46.
- 179. Upadhyay A, Earley A, Haynes SM, et al. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann. Intern. Med. 2011; 154:541-8.
- Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann. Intern. Med. 2003; 139:244-52.
- 181. Giatras I, Lau J and Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. Ann. Intern. Med. 1997; 127:337-45.
- 182. White HD, Aylward PE, Huang Z, et al. Mortality and morbidity remain high despite captopril and/or Valsartan therapy in elderly patients with left ventricular systolic dysfunction, heart failure, or both after acute myocardial infarction: results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). Circulation. 2005; 112:3391-9.
- Midtvedt K, Ihlen H, Hartmann A, et al. Reduction of left ventricular mass by lisinopril and nifedipine in hypertensive renal transplant recipients: a prospective randomized double-blind study. Transplantation. 2001; 72:107-11.
- 184. Midtvedt K, Hartmann A, Foss A, et al. Sustained improvement of renal graft function for two years in hypertensive renal transplant recipients treated with nifedipine as compared to lisinopril. Transplantation. 2001; 72:1787-92.
- 185. Suwelack B, Gerhardt U, Hausberg M, et al. Comparison of quinapril versus atenolol: effects on blood pressure and cardiac mass after renal transplantation. The American journal of cardiology. 2000; 86:583-5, A10.

- 186. Paoletti E, Cassottana P, Amidone M, et al. ACE inhibitors and persistent left ventricular hypertrophy after renal transplantation: a randomized clinical trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2007; 50:133-42.
- 187. Cross NB, Webster AC, Masson P, et al. Antihypertensive treatment for kidney transplant recipients. The Cochrane database of systematic reviews. 2009:CD003598.
- 188. Jennings DL and Taber DJ. Use of renin-angiotensin-aldosterone system inhibitors within the first eight to twelve weeks after renal transplantation. The Annals of pharmacotherapy. 2008; 42:116-20.
- 189. Ninomiya T, Perkovic V, Turnbull F, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. BMJ (Clinical research ed.). 2013; 347:f5680.
- 190. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. JAMA. 2016; 315:2673-82.
- 191. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. The New England journal of medicine. 2013; 368:2355-65.
- 192. Antihypertensive treatment of acute cerebral hemorrhage. Crit. Care Med. 2010; 38:637-48.
- 193. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. The Lancet.Neurology. 2008; 7:391-9.
- 194. Tsivgoulis G, Katsanos AH, Butcher KS, et al. Intensive blood pressure reduction in acute intracerebral hemorrhage: a meta-analysis. Neurology. 2014; 83:1523-9.
- 195. Wang H, Tang Y, Rong X, et al. Effects of early blood pressure lowering on early and long-term outcomes after acute stroke: an updated meta-analysis. PLoS One. 2014; 9:e97917.
- 196. Zhao R, Liu FD, Wang S, et al. Blood Pressure Reduction in the Acute Phase of an Ischemic Stroke Does Not Improve Short- or Long-Term Dependency or Mortality: A Meta-Analysis of Current Literature. Medicine. 2015; 94:e896.
- 197. Ahmed N, Nasman P and Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. Stroke; a journal of cerebral circulation. 2000; 31:1250-5.
- 198. Bath PM and Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. The Cochrane database of systematic reviews. 2014; 10:CD000039.
- 199. Ahmed N, Wahlgren N, Brainin M, et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). Stroke; a journal of cerebral circulation. 2009; 40:2442-9.
- 200. Schrader J, Luders S, Kulschewski A, et al. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke; a journal of cerebral circulation. 2003; 34:1699-703.
- 201. Sandset EC, Bath PM, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet. 2011; 377:741-50.
- 202. He J, Zhang Y, Xu T, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA. 2014; 311:479-89.
- 203. Robinson TG, Potter JF, Ford GA, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. The Lancet.Neurology. 2010; 9:767-75.
- 204. Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. The Lancet.Neurology. 2009; 8:48-56.

- 205. Bath PM, Woodhouse L, Scutt P, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. Lancet. 2015; 385:617-28.
- 206. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. The New England journal of medicine. 2008; 359:1317-29.
- 207. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. The New England journal of medicine. 1995; 333:1581-7.
- 208. Post-stroke antihypertensive treatment study. A preliminary result. Chin. Med. J. 1995; 108:710-7.
- 209. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001; 358:1033-41.
- 210. Schrader J, Luders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke; a journal of cerebral circulation. 2005; 36:1218-26.
- 211. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. The New England journal of medicine. 2008; 359:1225-37.
- 212. Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet. 2013; 382:507-15.
- 213. Rashid P, Leonardi-Bee J and Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. Stroke; a journal of cerebral circulation. 2003; 34:2741-8.
- 214. Lakhan SE and Sapko MT. Blood pressure lowering treatment for preventing stroke recurrence: a systematic review and meta-analysis. Int. Arch. Med. 2009; 2:30.
- 215. Liu L, Wang Z, Gong L, et al. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. Hypertension research : official journal of the Japanese Society of Hypertension. 2009; 32:1032-40.
- 216. Lee M, Saver JL, Hong KS, et al. Does achieving an intensive versus usual blood pressure level prevent stroke? Ann. Neurol. 2012; 71:133-40.
- 217. Lee M, Saver JL, Hong KS, et al. Renin-Angiotensin system modulators modestly reduce vascular risk in persons with prior stroke. Stroke; a journal of cerebral circulation. 2012; 43:113-9.
- 218. Arima H, Chalmers J, Woodward M, et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. J. Hypertens. 2006; 24:1201-8.
- White CL, Szychowski JM, Pergola PE, et al. Can blood pressure be lowered safely in older adults with lacunar stroke? The Secondary Prevention of Small Subcortical Strokes study experience. J. Am. Geriatr. Soc. 2015; 63:722-9.
- 220. Ovbiagele B, Diener HC, Yusuf S, et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. JAMA. 2011; 306:2137-44.
- 221. Ovbiagele B. Low-normal systolic blood pressure and secondary stroke risk. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2013; 22:633-8.
- 222. Lin MP, Ovbiagele B, Markovic D, et al. Systolic blood pressure and mortality after stroke: too low, no go? Stroke; a journal of cerebral circulation. 2015; 46:1307-13.
- 223. Kim J, Gall SL, Nelson MR, et al. Lower systolic blood pressure is associated with poorer survival in long-term survivors of stroke. J. Hypertens. 2014; 32:904-11.
- 224. Wang WT, You LK, Chiang CE, et al. Comparative Effectiveness of Blood Pressure-lowering Drugs in Patients who have Already Suffered From Stroke: Traditional and Bayesian Network Meta-analysis of Randomized Trials. Medicine (Baltimore). 2016; 95:e3302.

- 225. Katsanos AH, Filippatou A, Manios E, et al. Blood Pressure Reduction and Secondary Stroke Prevention: A Systematic Review and Metaregression Analysis of Randomized Clinical Trials. Hypertension. 2017; 69:171-9.
- 226. Ostergren J, Sleight P, Dagenais G, et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. Eur. Heart J. 2004; 25:17-24.
- 227. Overlack A, Adamczak M, Bachmann W, et al. ACE-inhibition with perindopril in essential hypertensive patients with concomitant diseases. The Perindopril Therapeutic Safety Collaborative Research Group. The American journal of medicine. 1994; 97:126-34.
- 228. Schweizer J, Kirch W, Koch R, et al. Effect of high dose verapamil on restenosis after peripheral angioplasty. J. Am. Coll. Cardiol. 1998; 31:1299-305.
- Espinola-Klein C, Weisser G, Jagodzinski A, et al. beta-Blockers in patients with intermittent claudication and arterial hypertension: results from the nebivolol or metoprolol in arterial occlusive disease trial. Hypertension. 2011; 58:148-54.
- 230. Bavry AA, Anderson RD, Gong Y, et al. Outcomes Among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. Hypertension 2010; 55:48-53.
- Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. J. Hypertens. 2006; 24:2163-8.
- 232. Piller LB, Simpson LM, Baraniuk S, et al. Characteristics and long-term follow-up of participants with peripheral arterial disease during ALLHAT. J. Gen. Intern. Med. 2014; 29:1475-83.
- 233. Kaplan NM. Vascular outcome in type 2 diabetes: an ADVANCE? Lancet. 2007; 370:804-5.
- 234. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. The New England journal of medicine. 2010; 362:1575-85.
- 235. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care. 2014; 37:1721-8.
- 236. Soliman EZ, Byington RP, Bigger JT, et al. Effect of Intensive Blood Pressure Lowering on Left Ventricular Hypertrophy in Patients With Diabetes Mellitus: Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial. Hypertension. 2015; 66:1123-9.
- 237. Weber MA, Bakris GL, Jamerson K, et al. Cardiovascular events during differing hypertension therapies in patients with diabetes. J. Am. Coll. Cardiol. 2010; 56:77-85.
- 238. Ostergren J, Poulter NR, Sever PS, et al. The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressurelowering limb: effects in patients with type II diabetes. J. Hypertens. 2008; 26:2103-11.
- Kostis JB, Wilson AC, Freudenberger RS, et al. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. The American journal of cardiology. 2005; 95:29-35.
- 240. Menne J, Izzo JL, Jr., Ito S, et al. Prevention of microalbuminuria in patients with type 2 diabetes and hypertension. J. Hypertens. 2012; 30:811-8.
- 241. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. The New England journal of medicine. 1998; 338:645-52.
- 242. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998; 351:1755-62.
- 243. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ (Clinical research ed.). 1998; 317:703-13.

- 244. Arguedas JA, Leiva V and Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. The Cochrane database of systematic reviews. 2013; 10:CD008277.
- 245. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet. 2015; 385:2047-56.
- 246. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch. Intern. Med. 2005; 165:1410-9.
- 247. Whelton PK, Barzilay J, Cushman WC, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch.Intern.Med. 2005; 165:1401-9.
- 248. Hata J, Arima H, Rothwell PM, et al. Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: the ADVANCE trial. Circulation. 2013; 128:1325-34.
- 249. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. The New England journal of medicine. 2014; 371:1392-406.
- 250. Menne J, Ritz E, Ruilope LM, et al. The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) observational follow-up study: benefits of RAS blockade with olmesartan treatment are sustained after study discontinuation. Journal of the American Heart Association. 2014; 3:e000810.
- 251. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and metaanalysis. JAMA. 2015; 313:603-15.
- 252. Cheng J, Zhang W, Zhang X, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. JAMA internal medicine. 2014; 174:773-85.
- 253. Hartley L, Mavrodaris A, Flowers N, et al. Transcendental meditation for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews. 2014; 12:CD010359.
- 254. Schmieder RE, Hilgers KF, Schlaich MP, et al. Renin-angiotensin system and cardiovascular risk. Lancet. 2007; 369:1208-19.
- 255. Jibrini MB, Molnar J and Arora RR. Prevention of atrial fibrillation by way of abrogation of the reninangiotensin system: a systematic review and meta-analysis. Am. J. Ther. 2008; 15:36-43.
- 256. Zhao D, Wang ZM and Wang LS. Prevention of atrial fibrillation with renin-angiotensin system inhibitors on essential hypertensive patients: a meta-analysis of randomized controlled trials. Journal of biomedical research. 2015; 29:475-85.
- 257. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J. Am. Coll. Cardiol. 2005; 45:1832-9.
- 258. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet. 1999; 353:611-6.
- 259. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet. 1999; 354:1751-6.
- 260. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J. Am. Coll. Cardiol. 2005; 45:712-9.

- 261. Haywood LJ, Ford CE, Crow RS, et al. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). J. Am. Coll. Cardiol. 2009; 54:2023-31.
- 262. Chockalingam A, Venkatesan S, Subramaniam T, et al. Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS). Am. Heart J. 2004; 147:E19.
- 263. Rieck E, Cramariuc D, Boman K, et al. Hypertension in aortic stenosis: implications for left ventricular structure and cardiovascular events. Hypertension. 2012; 60:90-7.
- 264. Eleid MF, Nishimura RA, Sorajja P, et al. Systemic hypertension in low-gradient severe aortic stenosis with preserved ejection fraction. Circulation. 2013; 128:1349-53.
- Bull S, Loudon M, Francis JM, et al. A prospective, double-blind, randomized controlled trial of the angiotensinconverting enzyme inhibitor Ramipril In Aortic Stenosis (RIAS trial). Eur. Heart J. Cardiovasc. Imaging. 2015; 16:834-41.
- 266. Scognamiglio R, Rahimtoola SH, Fasoli G, et al. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. The New England journal of medicine. 1994; 331:689-94.
- 267. Evangelista A, Tornos P, Sambola A, et al. Long-term vasodilator therapy in patients with severe aortic regurgitation. The New England journal of medicine. 2005; 353:1342-9.
- 268. Leenen FH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertension 2006; 48:374-84.
- 269. Wright JT, Jr., Harris-Haywood S, Pressel S, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch.Intern.Med. 2008; 168:207-17.
- 270. Wright JT, Jr., Probstfield JL, Cushman WC, et al. ALLHAT findings revisited in the context of subsequent analyses, other trials, and meta-analyses. Arch.Intern.Med. 2009; 169:832-42.
- 271. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA. 1970; 213:1143-52.
- 272. Five-year findings of the Hypertension Detection and Follow-up Program: mortality by race-sex and blood pressure level. A further analysis. Hypertension Detection and Follow-up Program Cooperative Group. J. Community Health. 1984; 9:314-27.
- 273. Julius S, Weber MA, Kjeldsen SE, et al. The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial: outcomes in patients receiving monotherapy. Hypertension. 2006; 48:385-91.
- 274. The AO and Coordinators for the ACG. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288:2981-97.
- 275. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003; 290:2805-16.
- 276. Wright JT, Jr., Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. JAMA. 2005; 293:1595-608.
- 277. Turnbull F, Woodward M, Neal B, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. Eur. Heart J. 2008; 29:2669-80.
- 278. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. The New England journal of medicine. 2003; 348:583-92.

- 279. Fletcher A, Beevers DG, Bulpitt C, et al. Beta adrenoceptor blockade is associated with increased survival in male but not female hypertensive patients: a report from the DHSS Hypertension Care Computing Project (DHCCP). J. Hum. Hypertens. 1988; 2:219-27.
- 280. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch. Intern. Med. 2002; 162:2046-52.
- 281. Pucci M, Sarween N, Knox E, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in women of childbearing age: risks versus benefits. Expert Rev. Clin. Pharmacol. 2015; 8:221-31.
- 282. Moretti ME, Caprara D, Drehuta I, et al. The Fetal Safety of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers. Obstet. Gynecol. Int. 2012; 2012:658310.
- 283. Ferrer RL, Sibai BM, Mulrow CD, et al. Management of mild chronic hypertension during pregnancy: a review. Obstet. Gynecol. 2000; 96:849-60.
- 284. Peacock WF, Varon J, Baumann BM, et al. CLUE: a randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the emergency department. Crit. Care. 2011; 15:R157.
- 285. Liu-DeRyke X, Levy PD, Parker D, Jr., et al. A prospective evaluation of labetalol versus nicardipine for blood pressure management in patients with acute stroke. Neurocrit. Care. 2013; 19:41-7.
- 286. Peacock WF, Chandra A, Char D, et al. Clevidipine in acute heart failure: Results of the A Study of Blood Pressure Control in Acute Heart Failure-A Pilot Study (PRONTO). Am. Heart J. 2014; 167:529-36.
- 287. Farias S, Peacock WF, Gonzalez M, et al. Impact of initial blood pressure on antihypertensive response in patients with acute hypertension. The American journal of emergency medicine. 2014; 32:833-6.
- 288. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch. Intern. Med. 1994; 154:2154-60.
- 289. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998; 352:1347-51.
- 290. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J. Hypertens. 2003; 21:875-86.
- 291. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch. Intern. Med. 2003; 163:1069-75.
- 292. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. The Lancet.Neurology. 2008; 7:683-9.
- 293. Devereaux PJ, Yang H, Guyatt GH, et al. Rationale, design, and organization of the PeriOperative ISchemic Evaluation (POISE) trial: a randomised controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery. Am. Heart J. 2006; 152:223-30.
- 294. Howell SJ, Sear JW and Foex P. Hypertension, hypertensive heart disease and perioperative cardiac risk. Br. J. Anaesth. 2004; 92:570-83.
- 295. Hart GR and Anderson RJ. Withdrawal syndromes and the cessation of antihypertensive therapy. Arch. Intern. Med. 1981; 141:1125-7.
- 296. Shammash JB, Trost JC, Gold JM, et al. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. Am. Heart J. 2001; 141:148-53.
- 297. Lindenauer PK, Pekow P, Wang K, et al. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. The New England journal of medicine. 2005; 353:349-61.
- 298. Wallace AW, Au S and Cason BA. Association of the pattern of use of perioperative beta-blockade and postoperative mortality. Anesthesiology. 2010; 113:794-805.

- 299. Andersson C, M, rie C, Jorgensen M, et al. Association of f-blocker therapy with risks of adverse cardiovascular events and deaths in patients with ischemic heart disease undergoing noncardiac surgery: a Danish nationwide cohort study. JAMA internal medicine. 2014; 174:336-44.
- 300. Hoeks SE, Scholte Op Reimer WJM, van UH, et al. Increase of 1-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2007; 33:13-9.
- 301. Barrett TW, Mori M and De Boer D. Association of ambulatory use of statins and beta-blockers with long-term mortality after vascular surgery. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2007; 2:241-52.
- 302. London MJ, Hur K, Schwartz GG, et al. Association of perioperative f-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. JAMA. 2013; 309:1704-13.
- 303. Turan A, You J, Shiba A, et al. Angiotensin converting enzyme inhibitors are not associated with respiratory complications or mortality after noncardiac surgery. Anesth. Analg. 2012; 114:552-60.
- 304. Rosenman DJ, McDonald FS, Ebbert JO, et al. Clinical consequences of withholding versus administering reninangiotensin-aldosterone system antagonists in the preoperative period. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2008; 3:319-25.
- 305. Roshanov PS, Rochwerg B, Patel A, et al. Withholding versus Continuing Angiotensin-converting Enzyme Inhibitors or Angiotensin II Receptor Blockers before Noncardiac Surgery: An Analysis of the Vascular events In noncardiac Surgery patlents cOhort evaluation Prospective Cohort. Anesthesiology. 2016.
- 306. Matsumura K, Arima H, Tominaga M, et al. Does a combination pill of antihypertensive drugs improve medication adherence in Japanese? A randomized controlled trial. Circulation journal : official journal of the Japanese Circulation Society. 2012; 76:1415-22.
- 307. Schroeder K, Fahey T and Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? Systematic review of randomized controlled trials. Arch. Intern. Med. 2004; 164:722-32.
- 308. Iskedjian M, Einarson TR, MacKeigan LD, et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin. Ther. 2002; 24:302-16.
- 309. Claxton AJ, Cramer J and Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin. Ther. 2001; 23:1296-310.
- 310. Sherrill B, Halpern M, Khan S, et al. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. J. Clin. Hypertens. (Greenwich). 2011; 13:898-909.
- 311. Yang W, Chang J, Kahler KH, et al. Evaluation of compliance and health care utilization in patients treated with single pill vs. free combination antihypertensives. Curr. Med. Res. Opin. 2010; 26:2065-76.
- 312. Gupta AK, Arshad S and Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010; 55:399-407.
- 313. Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. The American journal of medicine. 2007; 120:713-9.
- 314. Kumagai N, Onishi K, Hoshino K, et al. Improving drug adherence using fixed combinations caused beneficial treatment outcomes and decreased health-care costs in patients with hypertension. Clinical and experimental hypertension (New York, N.Y.: 1993). 2013; 35:355-60.
- 315. Mazzaglia G, Ambrosioni E, Alacqua M, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. Circulation. 2009; 120:1598-605.
- 316. Jackson KC, Sheng X, Nelson RE, et al. Adherence with multiple-combination antihypertensive pharmacotherapies in a US managed care database. Clin. Ther. 2008; 30:1558-63.

- 317. Dickson M and Plauschinat CA. Compliance with antihypertensive therapy in the elderly: a comparison of fixed-dose combination amlodipine/benazepril versus component-based free-combination therapy. American journal of cardiovascular drugs : drugs, devices, and other interventions. 2008; 8:45-50.
- 318. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. Circulation. 2010; 122:406-41.
- Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J. Am. Coll. Cardiol. 2013; published online before print November 7, 2013. doi:10.1016/j.jacc.2013.11.003.
- 320. Brownstein JN, Chowdhury FM, Norris SL, et al. Effectiveness of community health workers in the care of people with hypertension. Am. J. Prev. Med. 2007; 32:435-47.
- 321. Carter BL, Rogers M, Daly J, et al. The potency of team-based care interventions for hypertension: a metaanalysis. Arch. Intern. Med. 2009; 169:1748-55.
- 322. Clark CE, Smith LF, Taylor RS, et al. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. BMJ (Clinical research ed.). 2010; 341:c3995.
- 323. Proia KK, Thota AB, Njie GJ, et al. Team-based care and improved blood pressure control: a community guide systematic review. Am. J. Prev. Med. 2014; 47:86-99.
- 324. Santschi V, Chiolero A, Colosimo AL, et al. Improving blood pressure control through pharmacist interventions: a meta-analysis of randomized controlled trials. Journal of the American Heart Association. 2014; 3:e000718.
- 325. Shaw RJ, McDuffie JR, Hendrix CC, et al. Effects of nurse-managed protocols in the outpatient management of adults with chronic conditions: a systematic review and meta-analysis. Ann. Intern. Med. 2014; 161:113-21.
- 326. Carter BL, Coffey CS, Ardery G, et al. Cluster-randomized trial of a physician/pharmacist collaborative model to improve blood pressure control. Circulation.Cardiovascular quality and outcomes. 2015; 8:235-43.
- 327. Bardach NS, Wang JJ, De Leon SF, et al. Effect of pay-for-performance incentives on quality of care in small practices with electronic health records: a randomized trial. JAMA. 2013; 310:1051-9.
- 328. Banerjee D, Chung S, Wong EC, et al. Underdiagnosis of hypertension using electronic health records. Am. J. Hypertens. 2012; 25:97-102.
- 329. Jaffe MG, Lee GA, Young JD, et al. Improved blood pressure control associated with a large-scale hypertension program. JAMA. 2013; 310:699-705.
- 330. Rakotz MK, Ewigman BG, Sarav M, et al. A technology-based quality innovation to identify undiagnosed hypertension among active primary care patients. Ann. Fam. Med. 2014; 12:352-8.
- Borden WB, Maddox TM, Tang F, et al. Impact of the 2014 expert panel recommendations for management of high blood pressure on contemporary cardiovascular practice: insights from the NCDR PINNACLE registry. J. Am. Coll. Cardiol. 2014; 64:2196-203.
- 332. Burke LE, Ma J, Azar KM, et al. Current Science on Consumer Use of Mobile Health for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association. Circulation. 2015; 132:1157-213.
- 333. Liu S, Dunford SD, Leung YW, et al. Reducing blood pressure with Internet-based interventions: a metaanalysis. The Canadian journal of cardiology. 2013; 29:613-21.
- 334. Omboni S, Gazzola T, Carabelli G, et al. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. J. Hypertens. 2013; 31:455-67.
- 335. Verberk WJ, Kessels AG and Thien T. Telecare is a valuable tool for hypertension management, a systematic review and meta-analysis. Blood Press. Monit. 2011; 16:149-55.

- 336. Svetkey LP, Pollak KI, Yancy WS, Jr., et al. Hypertension improvement project: randomized trial of quality improvement for physicians and lifestyle modification for patients. Hypertension. 2009; 54:1226-33.
- 337. Lusignan S, Gallagher H, Jones S, et al. Audit-based education lowers systolic blood pressure in chronic kidney disease: the Quality Improvement in CKD (QICKD) trial results. Kidney Int. 2013; 84:609-20.
- 338. Walsh JM, McDonald KM, Shojania KG, et al. Quality improvement strategies for hypertension management: a systematic review. Med. Care. 2006; 44:646-57.
- 339. Anchala R, Pinto MP, Shroufi A, et al. The role of Decision Support System (DSS) in prevention of cardiovascular disease: a systematic review and meta-analysis. PLoS One. 2012; 7:e47064.
- 340. Thomas KL, Shah BR, Elliot-Bynum S, et al. Check it, change it: a community-based, multifaceted intervention to improve blood pressure control. Circulation.Cardiovascular quality and outcomes. 2014; 7:828-34.
- 341. Petersen LA, Simpson K, Pietz K, et al. Effects of individual physician-level and practice-level financial incentives on hypertension care: a randomized trial. JAMA. 2013; 310:1042-50.
- 342. Hysong SJ, Simpson K, Pietz K, et al. Financial incentives and physician commitment to guidelinerecommended hypertension management. The American journal of managed care. 2012; 18:e378-e91.
- 343. Karunaratne K, Stevens P, Irving J, et al. The impact of pay for performance on the control of blood pressure in people with chronic kidney disease stage 3-5. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association European Renal Association. 2013; 28:2107-16.
- Serumaga B, Ross-Degnan D, Avery AJ, et al. Effect of pay for performance on the management and outcomes of hypertension in the United Kingdom: interrupted time series study. BMJ (Clinical research ed.). 2011; 342:d108.
- 345. Maimaris W, Paty J, Perel P, et al. The influence of health systems on hypertension awareness, treatment, and control: a systematic literature review. PLoS Med. 2013; 10:e1001490.
- 346. Kim MT, Hill MN, Bone LR, et al. Development and testing of the Hill-Bone Compliance to High Blood Pressure Therapy Scale. Prog. Cardiovasc. Nurs. 2000; 15:90-6.
- 347. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42:1206-52.
- 348. Walsh J, McDonald KM, Shojania KG, et al. Closing the quality gap: a critical analysis of quality improvement strategies. Technical Review 9. ed. Rockville, MD: 2005.
- 349. Gwadry-Sridhar FH, Manias E, Lal L, et al. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: a systematic review by the ISPOR medication adherence and persistence special interest group. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013; 16:863-71.
- 350. Brown MT and Bussell JK. Medication adherence: WHO cares? Mayo Clin. Proc. 2011; 86:304-14.
- 351. Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. The Cochrane database of systematic reviews. 2014; 11:CD000011.
- 352. Viswanathan M, olin CE, ones CD, et al. Medication adherence interventions: comparative effectiveness. Closing the quality gap: revisiting the state of the science. Evidence Report No.208. Rockville, MD: Agency for Healthcare Research and Quality, 2012.
- 353. Krousel-Wood MA, Muntner P, Islam T, et al. Barriers to and determinants of medication adherence in hypertension management: perspective of the cohort study of medication adherence among older adults. The Medical clinics of North America. 2009; 93:753-69.
- 354. Choudhry NK, Denberg TD and Qaseem A. Improving Adherence to Therapy and Clinical Outcomes While Containing Costs: Opportunities From the Greater Use of Generic Medications: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Ann. Intern. Med. 2016; 164:41-9.

- 355. Leblanc ES, O'Connor E, Whitlock EP, et al. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann. Intern. Med. 2011; 155:434-47.
- 356. Final recommendation statement obesity in adults: screening and management. 2012.
- 357. Jonas DE, Garbutt JC, Amick HR, et al. Behavioral counseling after screening for alcohol misuse in primary care: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann. Intern. Med. 2012; 157:645-54.
- 358. Alcohol misuse: screening and behavioral counseling interventions in primary care. 2013.
- 359. Lin JS, O'Connor E, Whitlock EP, et al. Behavioral counseling to promote physical activity and a healthful diet to prevent cardiovascular disease in adults: a systematic review for the U.S. Preventive Services Task Force. Ann. Intern. Med. 2010; 153:736-50.
- 360. Healthful diet and physical activity for cardiovascular disease prevention in adults: behavioral counseling. 2012.
- 361. Tobacco smoking cessation in adults, including pregnant women: behavioral and pharmacotherapy interventions. 2015.
- Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann. Intern. Med. 2009; 150:551-5.
- 363. Centers for Medicare and Medicaid Services. 2016.
- 364. American Medical Association, Physician Consortium for Performance Improvement. 2016.
- 365. National committee for Quality Assurance. 2016.
- 366. National Quality Forum. 2016.
- 367. Agency for Healthcare Research and Quality Natioanl Quality Measures Clearinghouse. 2016.