

## Supplementary Online Content

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**Supplement.** Supplement to 2014 Evidence-based guideline for the management of high blood pressure in adults: report by the panel appointed to the Eighth Joint National Committee (JNC 8)

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplement to 2014 Evidence-Based  
Guideline for the Management of High  
Blood Pressure in Adults: Report by the  
Panel Appointed to the Eighth Joint  
National Committee (JNC 8)

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## **PANEL MEMBERS**

### **Panel Co-Chairs**

Paul A. James, MD, University of Iowa

Suzanne Oparil, MD, University of Alabama at Birmingham School of Medicine

### **Panel Members**

Barry L. Carter, PharmD, University of Iowa

William C. Cushman, MD, Memphis Veterans Affairs Medical Center and the University of Tennessee

Cheryl Dennison Himmelfarb, RN, ANP, PhD, Johns Hopkins University School of Nursing

Joel Handler, MD, Southern California Kaiser Permanente Medical Group

Daniel T. Lackland, DrPH, Medical University of South Carolina

Michael L. LeFevre, MD, MSPH, University of Missouri

Thomas D. MacKenzie, MD, MSPH, Denver Health and Hospital Authority and the University of Colorado School of Medicine

Olugbenga Ogedegbe, MD, MPH, MS, New York University School of Medicine

Sidney C. Smith, Jr., MD, University of North Carolina at Chapel Hill

Laura P. Svetkey, MD, MHS, Duke University

Sandra J. Taler, MD, Mayo Clinic College of Medicine

Raymond R. Townsend, MD, University of Pennsylvania

Jackson T. Wright, Jr., MD, PhD, Case Western Reserve University

Andrew S. Narva, MD, National Institute of Diabetes and Digestive and Kidney Diseases

Eduardo Ortiz, MD, MPH, At the time of this project, Dr. Ortiz was a Senior Medical Officer with the National Heart, Lung, and Blood Institute. He is currently Director of Clinical Development and Informatics with ProVation Medical, Wolters Kluwer Health.

### **Support Staff**

Cory V. Evans, MPP. At the time of this project, Ms. Evans was a Senior Research Analyst and Contract Lead for JNC 8 with Leidos (formerly, Science Applications International Corporation). She is currently a Research Associate at the Kaiser Permanente Center for Health Research.

Linda J. Lux, MPA, Senior Research Associate at RTI International

## TABLE OF CONTENTS

Executive Summary.....	10
Figure: 2014 Guideline Hypertension Management Algorithm.....	33
Table 1: Comparison of Current Recommendations with JNC 7 Guidelines.....	34
Table 2: Evidence Quality Rating .....	36
Table 3: Strength of Recommendation .....	37
Table 4: Evidence-Based Dosing for Antihypertensive Drugs.....	38
Table 5: Strategies to Dose Antihypertensive Drugs .....	39
Table 6: Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults with Hypertension ....	40
Background .....	45
Panel Members.....	45
Disclosures .....	47
Methods.....	50
How Were the Questions Selected? .....	51
Rationale for the Questions Selected .....	51
Questions .....	51
Inclusion/Exclusion Criteria for the Evidence Review.....	52
Literature Search Yields .....	71
Populations Addressed in this Guideline .....	71
Definition of High Blood Pressure or Hypertension.....	71
Evidence Statements .....	75
Recommendations .....	131
Additional Content.....	138
Measurement and Monitoring of Blood Pressure .....	138
Appropriate Dosing of Antihypertensive Medications .....	139
Research Gaps.....	140
Recommendations from the Lifestyle Working Group.....	141
Lifestyle Workgroup Diet Recommendations.....	141
Lifestyle Physical Activity Recommendation.....	141
Lifestyle for Prevention and Treatment of High Blood Pressure .....	142
History of this Guideline Development Process .....	143
References .....	144

Appendix .....	173
Exhibit A: Evidence from randomized controlled trials on initiating antihypertensive pharmacological therapy at SBP thresholds $\geq$ 160 mmHg .....	173
Exhibit B: Evidence from randomized controlled trials on initiating antihypertensive pharmacological therapy at DBP thresholds $\geq$ 90 mmHg.....	175
Exhibit C: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to specified SBP goals .....	178
Exhibit D: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to specified DBP goals.....	182
Exhibit E: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to mixed SBP and DBP goals .....	187
Exhibit F: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in patients with chronic kidney disease .....	189
Exhibit G: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in patients with chronic kidney disease by baseline proteinuria subgroups.....	191
Exhibit H: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in patients with diabetes.....	194
Exhibit I: Evidence from randomized controlled trials of initial antihypertensive drug therapy with diuretics versus other drugs .....	200
Exhibit J: Evidence from randomized controlled trials of initial antihypertensive drug therapy with beta blockers versus other drugs.....	213
Exhibit K: Evidence from randomized controlled trials of initial antihypertensive drug therapy with calcium channel blockers versus other drugs .....	228
Exhibit L: Evidence from randomized controlled trials of initial antihypertensive drug therapy with ACE inhibitors versus other drugs .....	243
Exhibit M: Evidence from randomized controlled trials of initial antihypertensive drug therapy with ARBs versus other drugs .....	250
Exhibit N: Evidence from randomized controlled trials of antihypertensive drug therapy with combination drugs .....	261
Search Strategy Overview and Syntax of Queries.....	267
Question 1 Search Strategy.....	269
Study Type Query.....	270
Boolean Search .....	270
Boolean Filter .....	272

Question 1 Search Strategy Results and PRISMA Diagram .....	272
Question 2 Search Strategy.....	275
Study Type Query.....	275
Boolean Search .....	275
Boolean Filter .....	277
Question 2 Search Strategy Results and PRISMA Diagram .....	278
Question 3 Search Strategy.....	280
Study Type Query.....	280
Boolean Search .....	280
Boolean Filter .....	282
Question 3 Search Strategy Results and PRISMA Diagram .....	283
Critical Questions identified by the Panel.....	285
Questions 1 through 3 are the questions that form the basis of this report. ....	285
Questions for which search criteria were developed, but a literature search and evidence review were not conducted include Questions 4 and 5:.....	285
Question 4.....	285
Question 4 Inclusion/Exclusion Criteria .....	285
Question 5.....	286
Question 5 Inclusion/Exclusion Criteria .....	287
Questions for which no search criteria was developed: .....	288
Question 6.....	288
Question 7.....	288
Question 8.....	289
Question 9.....	289
Question 10.....	289
Question 11.....	289
Question 12.....	289
Question 13.....	289
Question 14.....	289
Question 15.....	290
Question 16.....	290
Question 17.....	290

Question 18..... 290  
Question 19..... 290  
Question 20..... 290  
Question 21..... 291  
Question 22..... 291  
Question 23..... 291

## Executive Summary

### **Unstructured Abstract:**

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden, while clinicians want guidance on hypertension management using the best scientific evidence. This report takes a rigorous, evidence-based approach to recommend treatment thresholds, goals, and medications in the management of hypertension in adults. Evidence was drawn from randomized controlled trials, which represent the gold standard for determining efficacy and effectiveness. Evidence quality and recommendations were graded based on their effect on important outcomes.

There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy. There is moderate evidence to support initial or add-on antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in persons with CKD to improve kidney outcomes.

Although this guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.

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# Executive Summary

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## **EXECUTIVE SUMMARY**

### **BACKGROUND**

Hypertension remains one of the most important preventable contributors to disease and death. Abundant evidence from randomized controlled trials (RCTs) has shown benefit of antihypertensive drug treatment in reducing important health outcomes in persons with hypertension.<sup>1-3</sup> Clinical guidelines are at the intersection between research evidence and clinical actions that can improve patient outcomes. The Institute of Medicine Report Clinical Practice Guidelines We Can Trust outlined a pathway to guideline development and is the approach that this panel aspired to in the creation of this report.<sup>4</sup>

The panel members appointed to the Eighth Joint National Committee (JNC 8) used rigorous evidence-based methods, developing Evidence Statements and recommendations for blood pressure (BP) treatment based on a systematic review of the literature to meet user needs, especially the needs of the primary care clinician. This report is an executive summary of the evidence and is designed to provide clear recommendations for all clinicians. Major differences from the previous JNC report are summarized in Table 1. The complete evidence summary and detailed description of the evidence review and methods are provided online (see Supplement).

### **THE PROCESS**

The panel members appointed to JNC 8 were selected from more than 400 nominees based on expertise in hypertension (n = 14), primary care (n = 6), including geriatrics (n = 2), cardiology (n = 2), nephrology (n = 3), nursing (n = 1), pharmacology (n = 2), clinical trials (n = 6), evidence-based medicine (n = 3), epidemiology (n = 1), informatics (n = 4), and the development and implementation of clinical guidelines in systems of care (n = 4).

The panel also included a senior scientist from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a senior medical officer from the National Heart, Lung, and Blood Institute (NHLBI), and a senior scientist from NHLBI who withdrew from authorship prior to publication. Two members left the panel early in the process before the evidence review because of new job commitments that prevented them from continuing to serve. Panel members disclosed any potential conflicts of interest including studies evaluated in this report and relationships with industry. Those with conflicts were allowed to participate in discussions as long as they declared their relationships, but they recused themselves from voting on evidence statements and recommendations relevant to their relationships or conflicts. Four panel members (24%) had relationships with industry or potential conflicts to disclose at the outset of the process.

In January 2013, the guideline was submitted for external peer review by NHLBI to 20 reviewers, all of whom had expertise in hypertension, and to 16 federal agencies. Reviewers also had expertise in cardiology,

nephrology, primary care, pharmacology, research (including clinical trials), biostatistics, and other important related fields. Sixteen individual reviewers and 5 federal agencies responded. Reviewers' comments were collected, collated, and anonymized. Comments were reviewed and discussed by the panel from March through June 2013 and incorporated into a revised document. (Reviewers' comments and suggestions, and responses and disposition by the panel are available on request from the authors.)

### **QUESTIONS GUIDING THE EVIDENCE REVIEW**

This evidence-based hypertension guideline focuses on the panel's 3 highest-ranked questions related to high BP management identified through a modified Delphi technique.<sup>5</sup> Nine recommendations are made reflecting these questions. These questions address thresholds and goals for pharmacologic treatment of hypertension and whether particular antihypertensive drugs or drug classes improve important health outcomes compared with other drug classes.

1. In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
2. In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

### **THE EVIDENCE REVIEW**

The evidence review focused on adults aged 18 years or older with hypertension and included studies with the following prespecified subgroups: diabetes, coronary artery disease, peripheral artery disease, heart failure, previous stroke, chronic kidney disease (CKD), proteinuria, older adults, men and women, racial and ethnic groups, and smokers. Studies with sample sizes smaller than 100 were excluded, as were studies with a follow-up period of less than 1 year, because small studies of brief duration are unlikely to yield enough health-related outcome information to permit interpretation of treatment effects. Studies were included in the evidence review only if they reported the effects of the studied interventions on any of these important health outcomes:

- Overall mortality, cardiovascular disease (CVD)–related mortality, CKD-related mortality
- Myocardial infarction, heart failure, hospitalization for heart failure, stroke
- Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), other revascularization (includes carotid, renal, and lower extremity revascularization)
- End-stage renal disease (ESRD) (ie, kidney failure resulting in dialysis or transplantation), doubling of creatinine level, halving of glomerular filtration rate (GFR).

The panel limited its evidence review to RCTs because they are less subject to bias than other study designs and represent the gold standard for determining efficacy and effectiveness.<sup>6</sup> The studies in the evidence review were from original publications of eligible RCTs. These studies were used to create evidence tables and summary tables that were used by the panel for their deliberations (see Supplement). Because the panel conducted its own systematic review using original studies, systematic reviews and meta-analyses of RCTs conducted and published by other groups were not included in the formal evidence review.

Initial search dates for the literature review were January 1, 1966, through December 31, 2009. The search strategy and PRISMA diagram for each question is in the online Supplement. To ensure that no major relevant studies published after December 31, 2009, were excluded from consideration, 2 independent searches of PubMed and CINAHL between December 2009 and August 2013 were conducted with the same MeSH terms as the original search. Three panel members reviewed the results. The panel limited the inclusion criteria of this second search to the following. (1) The study was a major study in hypertension (eg, ACCORD-BP, SPS3; however, SPS3 did not meet strict inclusion criteria because it included nonhypertensive participants. SPS3 would not have changed our conclusions/recommendations because the only significant finding supporting a lower goal for BP occurred in an infrequent secondary outcome).<sup>7,8</sup> (2) The study had at least 2000 participants. (3) The study was multicentered. (4) The study met all the other inclusion/exclusion criteria. The relatively high threshold of 2000 participants was used because of the markedly lower event rates observed in recent RCTs such as ACCORD, suggesting that larger study populations are needed to obtain interpretable results. Additionally, all panel members were asked to identify newly published studies for consideration if they met the above criteria. No additional clinical trials met the previously described inclusion criteria. Studies selected were rated for quality using NHLBI's standardized quality rating tool (see Supplement) and were only included if rated as good or fair.

An external methodology team performed the literature review, summarized data from selected papers into evidence tables, and provided a summary of the evidence. From this evidence review, the panel crafted evidence statements and voted on agreement or disagreement with each statement. For approved evidence statements, the panel then voted on the quality of the evidence (Table 2). Once all evidence statements for each critical question were identified, the panel reviewed the evidence statements to craft the clinical recommendations, voting on each recommendation and on the strength of the recommendation (Table 3). For both evidence statements and recommendations, a record of the vote count (for, against, or recusal) was made without attribution. The panel attempted to achieve 100% consensus whenever possible, but a two-thirds majority was considered acceptable, with the exception of recommendations based on expert opinion, which required a 75% majority agreement to approve.

## **RESULTS (RECOMMENDATIONS)**

The following recommendations are based on the systematic evidence review described above (Box). Recommendations 1 through 5 address questions 1 and 2 concerning thresholds and goals for BP treatment. Recommendations 6, 7, and 8 address question 3 concerning selection of antihypertensive drugs. Recommendation 9 is a summary of strategies based on expert opinion for starting and adding antihypertensive drugs. The evidence statements supporting the recommendations are in the online Supplement.

### **RECOMMENDATION 1**

**In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher and treat to a goal SBP lower than 150 mm Hg and goal DBP lower than 90 mm Hg.**

**Strong Recommendation – Grade A**

### **COROLLARY RECOMMENDATION**

**In the general population aged 60 years or older, if pharmacologic treatment for high BP results in lower achieved SBP (for example, <140 mm Hg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.**

**Expert Opinion – Grade E**

Recommendation 1 is based on evidence statements 1 through 3 from question 2 in which there is moderate- to high-quality evidence from RCTs that in the general population aged 60 years or older, treating high BP to a goal of lower than 150/90 mm Hg reduces stroke, heart failure, and coronary heart disease (CHD). There is also evidence (albeit low quality) from evidence statement 6, question 2 that setting a goal SBP of lower than 140 mm Hg in this age group provides no additional benefit compared with a higher goal SBP of 140 to 160 mm Hg or 140 to 149 mm Hg.<sup>9,10</sup>

To answer question 2 about goal BP, the panel reviewed all RCTs that met the eligibility criteria and that either compared treatment with a particular goal vs no treatment or placebo or compared treatment with one BP goal with treatment to another BP goal. The trials on which these evidence statements and this recommendation are based include HYVET, Syst-Eur, SHEP, JATOS, VALISH, and CARDIO-SIS.<sup>1-3,9-11</sup> Strengths, limitations, and other considerations related to this evidence review are presented in the evidence statement narratives and clearly support the benefit of treating to a BP lower than 150 mm Hg.

The corollary to recommendation 1 reflects that there are many treated hypertensive patients aged 60 years or older in whom SBP is currently lower than 140 mm Hg, based on implementation of previous guideline

recommendations.<sup>12</sup> The panel's opinion is that in these patients, it is not necessary to adjust medication to allow BP to increase. In 2 of the trials that provide evidence supporting an SBP goal lower than 150 mm Hg, the average treated SBP was 143 to 144 mm Hg.<sup>2,3</sup> Many participants in those studies achieved an SBP lower than 140 mm Hg with treatment that was generally well tolerated. Two other trials<sup>9,10</sup> suggest there was no benefit for an SBP goal lower than 140 mm Hg, but the confidence intervals around the effect sizes were wide and did not exclude the possibility of a clinically important benefit. Therefore, the panel included a corollary recommendation based on expert opinion that treatment for hypertension does not need to be adjusted if treatment results in SBP lower than 140 mm Hg and is not associated with adverse effects on health or quality of life.

While all panel members agreed that the evidence supporting recommendation 1 is very strong, the panel was unable to reach unanimity on the recommendation of a goal SBP of lower than 150 mm Hg. Some members recommended continuing the JNC 7 SBP goal of lower than 140 mm Hg for individuals older than 60 years based on expert opinion.<sup>12</sup> These members concluded that the evidence was insufficient to raise the SBP target from lower than 140 to lower than 150 mm Hg in high-risk groups, such as black persons, those with CVD including stroke, and those with multiple risk factors. The panel agreed that more research is needed to identify optimal goals of SBP for patients with high BP.

## **RECOMMENDATION 2**

**In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at DBP of 90 mm Hg or higher and treat to a goal DBP of lower than 90 mm Hg.**

**For ages 30 through 59 years, Strong Recommendation – Grade A**

**For ages 18 through 29 years, Expert Opinion – Grade E**

Recommendation 2 is based on high-quality evidence from 5 DBP trials (HDFP, Hypertension-Stroke Cooperative, MRC, ANBP, and VA Cooperative) that demonstrate improvements in health outcomes among adults aged 30 through 69 years with elevated BP.<sup>13-18</sup> Initiation of antihypertensive treatment at a DBP threshold of 90 mm Hg or higher and treatment to a DBP goal of lower than 90 mm Hg reduces cerebrovascular events, heart failure, and overall mortality (question 1, evidence statements 10, 11, 13; question 2, evidence statement 10). In further support for a DBP goal of lower than 90 mm Hg, the panel found evidence that there is no benefit in treating patients to a goal of either 80 mm Hg or lower or 85 mm Hg or lower compared with 90 mm Hg or lower based on the HOT trial, in which patients were randomized to these 3 goals without statistically significant differences between treatment groups in the primary or secondary outcomes (question 2, evidence statement 14).<sup>19</sup>

In adults younger than 30 years, there are no good- or fair-quality RCTs that assessed the benefits of treating elevated DBP on health outcomes (question 1, evidence statement 14). In the absence of such

evidence, it is the panel's opinion that in adults younger than 30 years, the DBP threshold and goal should be the same as in adults 30 through 59 years of age.

### **RECOMMENDATION 3**

**In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher and treat to a goal SBP of lower than 140 mm Hg.**

#### **Expert Opinion – Grade E**

Recommendation 3 is based on expert opinion. While there is high-quality evidence to support a specific SBP threshold and goal for persons aged 60 years or older (See recommendation 1), the panel found insufficient evidence from good- or fair-quality RCTs to support a specific SBP threshold or goal for persons younger than 60 years. In the absence of such evidence, the panel recommends an SBP treatment threshold of 140 mm Hg or higher and an SBP treatment goal of lower than 140 mm Hg based on several factors.

First, in the absence of any RCTs that compared the current SBP standard of 140 mm Hg with another higher or lower standard in this age group, there was no compelling reason to change current recommendations. Second, in the DBP trials that demonstrated the benefit of treating DBP to lower than 90 mm Hg, many of the study participants who achieved DBP of lower than 90 mm Hg were also likely to have achieved SBPs of lower than 140 mm Hg with treatment. It is not possible to determine whether the outcome benefits in these trials were due to lowering DBP, SBP, or both. Third, given the recommended SBP goal of lower than 140 mm Hg in adults with diabetes or CKD (recommendations 4 and 5), a similar SBP goal for the general population younger than 60 years may facilitate guideline implementation.

### **RECOMMENDATION 4**

**In the population aged 18 years or older with CKD, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher and treat to goal SBP of lower than 140 mm Hg and goal DBP lower than 90 mm Hg.**

#### **Expert Opinion – Grade E**

Based on the inclusion criteria used in the RCTs reviewed by the panel, this recommendation applies to individuals younger than 70 years with an estimated GFR or measured GFR less than 60 mL/min/1.73 m<sup>2</sup> and in people of any age with albuminuria defined as greater than 30 mg of albumin/g of creatinine at any level of GFR.

Recommendation 4 is based on evidence statements 15-17 from question 2. In adults younger than 70 years with CKD, the evidence is insufficient to determine if there is a benefit in mortality, or cardiovascular or cerebrovascular health outcomes with antihypertensive drug therapy to a lower BP goal (for example, <130/80 mm Hg) compared with a goal of lower than 140/90 mm Hg (question 2, evidence statement 15). There is

evidence of moderate quality demonstrating no benefit in slowing the progression of kidney disease from treatment with antihypertensive drug therapy to a lower BP goal (for example, <130/80 mm Hg) compared with a goal of lower than 140/90 mm Hg (question 2, evidence statement 16).

Three trials that met our criteria for review addressed the effect of antihypertensive drug therapy on change in GFR or time to development of ESRD, but only one trial addressed cardiovascular disease end points. Blood pressure goals differed across the trials, with 2 trials (AASK and MDRD) using mean arterial pressure and different targets by age, and 1 trial (REIN-2) using only DBP goals.<sup>20-22</sup> None of the trials showed that treatment to a lower BP goal (for example, <130/80 mm Hg) significantly lowered kidney or cardiovascular disease end points compared with a goal of lower than 140/90 mm Hg.

For patients with proteinuria (>3 g/24 hours), post hoc analysis from only 1 study (MDRD) indicated benefit from treatment to a lower BP goal (<130/80 mm Hg), and this related to kidney outcomes only.<sup>22</sup> Although post hoc observational analyses of data from this trial and others suggested benefit from the lower goal at lower levels of proteinuria, this result was not seen in the primary analyses or in AASK or REIN-2 (question 2, evidence statement 17).<sup>20,21</sup>

Based on available evidence the panel cannot make a recommendation for a BP goal for people aged 70 years or older with GFR less than 60 mL/min/1.73m<sup>2</sup>. The commonly used estimating equations for GFR were not developed in populations with significant numbers of people older than 70 years and have not been validated in older adults. No outcome trials reviewed by the panel included large numbers of adults older than 70 years with CKD. Further, the diagnostic criteria for CKD do not consider age-related decline in kidney function as reflected in estimated GFR. Thus, when weighing the risks and benefits of a lower BP goal for people aged 70 years or older with estimated GFR less than 60 mL/min/1.73m<sup>2</sup>, antihypertensive treatment should be individualized, taking into consideration factors such as frailty, comorbidities, and albuminuria.

## **RECOMMENDATION 5**

**In the population aged 18 years or older with diabetes, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher and treat to a goal SBP of lower than 140 mm Hg and goal DBP lower than 90 mm Hg.**

### **Expert Opinion – Grade E**

Recommendation 5 is based on evidence statements 18-21 from question 2, which address BP goals in adults with both diabetes and hypertension. There is moderate-quality evidence from 3 trials (SHEP, Syst-Eur, and UKPDS) that treatment to an SBP goal of lower than 150 mm Hg improves cardiovascular and cerebrovascular health outcomes and lowers mortality (see question 2, evidence statement 18) in adults with diabetes and hypertension.<sup>23-25</sup> No RCTs addressed whether treatment to an SBP goal of lower than 140 mm Hg compared with a higher goal (for example, <150 mm Hg) improves health outcomes in adults with diabetes

and hypertension. In the absence of such evidence, the panel recommends an SBP goal of lower than 140 mm Hg and a DBP goal lower than 90 mm Hg in this population based on expert opinion, consistent with the BP goals in recommendation 3 for the general population younger than 60 years with hypertension. Use of a consistent BP goal in the general population younger than 60 years and in adults with diabetes of any age may facilitate guideline implementation. This recommendation for an SBP goal of lower than 140 mm Hg in patients with diabetes is also supported by the ACCORD-BP trial, in which the control group used this goal and had similar outcomes compared with a lower goal.<sup>7</sup>

The panel recognizes that the ADVANCE trial tested the effects of treatment to lower BP on major macrovascular and microvascular events in adults with diabetes who were at increased risk of CVD, but the study did not meet the panel's inclusion criteria because participants were eligible irrespective of baseline BP, and there were no randomized BP treatment thresholds or goals.<sup>26</sup>

The panel also recognizes that an SBP goal of lower than 130 mm Hg is commonly recommended for adults with diabetes and hypertension. However, this lower SBP goal is not supported by any RCT that randomized participants into 2 or more groups in which treatment was initiated at a lower SBP threshold than 140 mm Hg or into treatment groups in which the SBP goal was lower than 140 mm Hg and that assessed the effects of a lower SBP threshold or goal on important health outcomes. The only RCT that compared an SBP treatment goal of lower than 140 mm Hg with a lower SBP goal and assessed the effects on important health outcomes is ACCORD-BP, which compared an SBP treatment goal of lower than 120 mm Hg with a goal lower than 140 mm Hg.<sup>7</sup> There was no difference in the primary outcome, a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. There were also no differences in any of the secondary outcomes except for a reduction in stroke. However, the incidence of stroke in the group treated to lower than 140 mm Hg was much lower than expected, so the absolute difference in fatal and nonfatal stroke between the 2 groups was only 0.21% per year. The panel concluded that the results from ACCORD-BP did not provide sufficient evidence to recommend an SBP goal of lower than 120 mm Hg in adults with diabetes and hypertension.

The panel similarly recommends the same goal DBP in adults with diabetes and hypertension as in the general population (<90 mm Hg). Despite some existing recommendations that adults with diabetes and hypertension should be treated to a DBP goal of lower than 80 mm Hg, the panel did not find sufficient evidence to support such a recommendation. For example, there are no good- or fair-quality RCTs with mortality as a primary or secondary prespecified outcome that compared a DBP goal of lower than 90 mm Hg with a lower goal (evidence statement 21).

In the HOT trial, which is frequently cited to support a lower DBP goal, investigators compared a DBP goal of 90 mm Hg or lower vs a goal of 80 mm Hg or lower.<sup>19</sup> The lower goal was associated with a reduction in a composite CVD outcome (question 2, evidence statement 20), but this was a post hoc analysis of a small

subgroup (8%) of the study population that was not prespecified. As a result, the evidence was graded as low quality.

Another commonly cited study to support a lower DBP goal is UKPDS,<sup>25</sup> which had a BP goal of lower than 150/85 mm Hg in the more-intensively treated group compared with a goal of lower than 180/105 mm Hg in the less-intensively treated group. UKPDS did show that treatment in the lower goal BP group was associated with a significantly lower rate of stroke, heart failure, diabetes-related end points, and deaths related to diabetes. However, the comparison in UKPDS was a DBP goal of lower than 85 mm Hg vs lower than 105 mm Hg; therefore, it is not possible to determine whether treatment to a DBP goal of lower than 85 mm Hg improves outcomes compared with treatment to a DBP goal of lower than 90 mm Hg. In addition, UKPDS was a mixed systolic and diastolic BP goal study (combined SBP and DBP goals), so it cannot be determined if the benefits were due to lowering SBP, DBP, or both.

### **RECOMMENDATION 6**

**In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).**

#### **Moderate Recommendation – Grade B**

For this recommendation, only RCTs that compared one class of antihypertensive medication to another and assessed the effects on health outcomes were reviewed; placebo-controlled RCTs were not included. However, the evidence review was informed by major placebo-controlled hypertension trials, including 3 federally funded trials (VA Cooperative Trial, HDFP, and SHEP), that were pivotal in demonstrating that treatment of hypertension with antihypertensive medications reduces cardiovascular or cerebrovascular events and/or mortality.<sup>3,13,18</sup> These trials all used thiazide-type diuretics compared with placebo or usual care as the basis of therapy. Additional evidence that BP lowering reduces risk comes from trials of  $\beta$ -blocker vs placebo<sup>16,27</sup> and CCB vs placebo.<sup>1</sup>

Each of the 4 drug classes recommended by the panel in recommendation 6 yielded comparable effects on overall mortality and cardiovascular, cerebrovascular, and kidney outcomes, with one exception: heart failure. Initial treatment with a thiazide-type diuretic was more effective than a CCB or ACEI (question 3, evidence statements 14 and 15), and an ACEI was more effective than a CCB (question 3, evidence statement 1) in improving heart failure outcomes. While the panel recognized that improved heart failure outcomes was an important finding that should be considered when selecting a drug for initial therapy for hypertension, the panel did not conclude that it was compelling enough within the context of the overall body of evidence to preclude the use of the other drug classes for initial therapy. The panel also acknowledged that the evidence

supported BP control, rather than a specific agent used to achieve that control, as the most relevant consideration for this recommendation.

The panel did not recommend  $\beta$ -blockers for the initial treatment of hypertension because in one study use of  $\beta$ -blockers resulted in a higher rate of the primary composite outcome of cardiovascular death, myocardial infarction, or stroke compared to use of an ARB, a finding that was driven largely by an increase in stroke (question 3, evidence statement 22).<sup>28</sup> In the other studies that compared a  $\beta$ -blocker to the 4 recommended drug classes, the  $\beta$ -blocker performed similarly to the other drugs (question 3, evidence statement 8) or the evidence was insufficient to make a determination (question 3, evidence statements 7, 12, 21, 23, and 24).

$\alpha$ -Blockers were not recommended as first-line therapy because in one study initial treatment with an  $\alpha$ -blocker resulted in worse cerebrovascular, heart failure, and combined cardiovascular outcomes than initial treatment with a diuretic (question 3, evidence statement 13).<sup>29</sup> There were no RCTs of good or fair quality comparing the following drug classes to the 4 recommended classes: dual  $\alpha_1$ - +  $\beta$ -blocking agents (eg, carvedilol), vasodilating  $\beta$ -blockers (eg, nebivolol), central  $\alpha_2$ -adrenergic agonists (eg, clonidine), direct vasodilators (eg, hydralazine), aldosterone receptor antagonists (eg, spironolactone), adrenergic neuronal depleting agents (reserpine), and loop diuretics (eg, furosemide) (question 3, evidence statement 30). Therefore, these drug classes are not recommended as first-line therapy. In addition, no eligible RCTs were identified that compared a diuretic vs an ARB, or an ACEI vs an ARB. ONTARGET was not eligible because hypertension was not required for inclusion in the study.<sup>30</sup>

Similar to those for the general population, this recommendation applies to those with diabetes because trials including participants with diabetes showed no differences in major cardiovascular or cerebrovascular outcomes from those in the general population (question 3, evidence statements 36-48).

The following important points should be noted. First, many people will require treatment with more than one antihypertensive drug to achieve BP control. While this recommendation applies only to the choice of the initial antihypertensive drug, the panel suggests that any of these 4 classes would be good choices as add-on agents (recommendation 9). Second, this recommendation is specific for thiazide-type diuretics, which include thiazide diuretics, chlorthalidone, and indapamide; it does not include loop or potassium-sparing diuretics. Third, it is important that medications be dosed adequately to achieve results similar to those seen in the RCTs (Table 4). Fourth, RCTs that were limited to specific nonhypertensive populations, such as those with coronary artery disease or heart failure, were not reviewed for this recommendation. Therefore, recommendation 6 should be applied with caution to these populations. Recommendations for those with CKD are addressed in recommendation 8.

## RECOMMENDATION 7

**In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.**

**For general black population: Moderate Recommendation – Grade B**

**For black patients with diabetes: Weak Recommendation – Grade C**

Recommendation 7 is based on evidence statements from question 3. In cases for which evidence for the black population was the same as for the general population, the evidence statements for the general population apply to the black population. However, there are some cases for which the results for black persons were different from the results for the general population (question 3, evidence statements 2, 10, and 17). In those cases, separate evidence statements were developed.

This recommendation stems from a prespecified subgroup analysis of data from a single large trial (ALLHAT) that was rated good.<sup>31</sup> In that study, a thiazide-type diuretic was shown to be more effective in improving cerebrovascular, heart failure, and combined cardiovascular outcomes compared to an ACEI in the black patient subgroup, which included large numbers of diabetic and nondiabetic participants (question 3, evidence statements 10, 15 and 17). Therefore, the recommendation is to choose thiazide-type diuretics over ACEI for black patients. Although a CCB was less effective than a diuretic in preventing heart failure in the black subgroup of this trial (question 3, evidence statement 14), there were no differences in other outcomes (cerebrovascular, CHD, combined cardiovascular, and kidney outcomes, or overall mortality) between a CCB and a diuretic (question 3, evidence statements 6, 8, 11, 18, and 19). Therefore, both thiazide-type diuretics and CCBs are recommended as first-line therapy for hypertension in black patients.

The panel recommended a CCB over an ACEI as first-line therapy in black patients because there was a 51% higher rate (relative risk, 1.51; 95% CI, 1.22-1.86) of stroke in black persons in ALLHAT with the use of an ACEI as initial therapy compared with use of a CCB (question 3, evidence statement 2).<sup>32</sup> The ACEI was also less effective in reducing BP in black individuals compared with the CCB (question 3, evidence statement 2).<sup>32</sup> There were no outcome studies meeting our eligibility criteria that compared diuretics or CCBs vs  $\beta$ -blockers, ARBs, or other renin-angiotensin system inhibitors in black patients.

The recommendation for black patients with diabetes is weaker than the recommendation for the general black population because outcomes for the comparison between initial use of a CCB compared to initial use of an ACEI in black persons with diabetes were not reported in any of the studies eligible for our evidence review. Therefore, this evidence was extrapolated from findings in the black participants in ALLHAT, 46% of whom had diabetes. Additional support comes from a post hoc analysis of black participants in ALLHAT that met the criteria for the metabolic syndrome, 68% of whom had diabetes.<sup>33</sup> However, this study

did not meet the criteria for our review because it was a post hoc analysis. This recommendation also does not address black persons with CKD, who are addressed in recommendation 8.

### **RECOMMENDATION 8**

**In the population aged 18 years or older with CKD and hypertension, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status.**

#### **Moderate Recommendation – Grade B**

The evidence is moderate (question 3, evidence statements 31-32) that treatment with an ACEI or ARB improves kidney outcomes for patients with CKD. This recommendation applies to CKD patients with and without proteinuria, as studies using ACEIs or ARBs showed evidence of improved kidney outcomes in both groups.

This recommendation is based primarily on kidney outcomes because there is less evidence favoring ACEI or ARB for cardiovascular outcomes in patients with CKD. Neither ACEIs nor ARBs improved cardiovascular outcomes for CKD patients compared with a  $\beta$ -blocker or CCB (question 3, evidence statements 33-34). One trial (IDNT) did show improvement in heart failure outcomes with an ARB compared with a CCB, but this trial was restricted to a population with diabetic nephropathy and proteinuria (question 3, evidence statement 5).<sup>34</sup> There are no RCTs in the evidence review that directly compared ACEI to ARB for any cardiovascular outcome. However, both are renin-angiotensin system inhibitors and have been shown to have similar effects on kidney outcomes (question 3, evidence statements 31-32).

Recommendation 8 is specifically directed at those with CKD and hypertension and addresses the potential benefit of specific drugs on kidney outcomes. The AASK study showed the benefit of an ACEI on kidney outcomes in black patients with CKD and provides additional evidence that supports ACEI use in that population.<sup>21</sup> Additional trials that support the benefits of ACEI or ARB therapy did not meet our inclusion criteria because they were not restricted to patients with hypertension.<sup>35,36</sup> Direct renin inhibitors are not included in this recommendation because there were no studies demonstrating their benefits on kidney or cardiovascular outcomes.

The panel noted the potential conflict between this recommendation to use an ACEI or ARB in those with CKD and hypertension and the recommendation to use a diuretic or CCB (recommendation 7) in black persons: what if the person is black and has CKD? To answer this, the panel relied on expert opinion. In black patients with CKD and proteinuria, an ACEI or ARB is recommended as initial therapy because of the higher likelihood of progression to ESRD.<sup>21</sup> In black patients with CKD but without proteinuria, the choice for initial therapy is less clear and includes a thiazide-type diuretic, CCB, ACEI, or ARB. If an ACEI or ARB is not used as the initial drug, then an ACEI or ARB can be added as a second-line drug if necessary to achieve goal BP.

Because the majority of patients with CKD and hypertension will require more than 1 drug to achieve goal BP, it is anticipated that an ACEI or ARB will be used either as initial therapy or as second-line therapy in addition to a diuretic or CCB in black patients with CKD.

Recommendation 8 applies to adults aged 18 years or older with CKD, but there is no evidence to support renin-angiotensin system inhibitor treatment in those older than 75 years. Although treatment with an ACEI or ARB may be beneficial in those older than 75 years, use of a thiazide-type diuretic or CCB is also an option for individuals with CKD in this age group.

Use of an ACEI or an ARB will commonly increase serum creatinine and may produce other metabolic effects such as hyperkalemia, particularly in patients with decreased kidney function. Although an increase in creatinine or potassium level does not always require adjusting medication, use of renin-angiotensin system inhibitors in the CKD population requires monitoring of electrolyte and serum creatinine levels, and in some cases, may require reduction in dose or discontinuation for safety reasons.

### **RECOMMENDATION 9**

**The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed.**

#### **Expert Opinion – Grade E**

Recommendation 9 was developed by the panel in response to a perceived need for further guidance to assist in implementation of recommendations 1 through 8. Recommendation 9 is based on strategies used in RCTs that demonstrated improved patient outcomes and the expertise and clinical experience of panel members. This recommendation differs from the other recommendations because it was not developed in response to the 3 critical questions using a systematic review of the literature. The Figure is an algorithm summarizing the recommendations. However, this algorithm has not been validated with respect to achieving improved patient outcomes.

How should clinicians titrate and combine the drugs recommended in this report? There were no RCTs and thus the panel relied on expert opinion. Three strategies (Table 5) have been used in RCTs of high BP

treatment but were not compared with each other. Based on the evidence reviewed for questions 1 through 3 and on the expert opinion of the panel members, it is not known if one of the strategies results in improved cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality compared with an alternative strategy. There is not likely to be evidence from well-designed RCTs that compare these strategies and assess their effects on important health outcomes. There may be evidence that different strategies result in more rapid attainment of BP goal or in improved adherence, but those are intermediate outcomes that were not included in the evidence review. Therefore, each strategy is an acceptable pharmacologic treatment strategy that can be tailored based on individual circumstances, clinician and patient preferences, and drug tolerability. With each strategy, clinicians should regularly assess BP, encourage evidence-based lifestyle and adherence interventions, and adjust treatment until goal BP is attained and maintained. In most cases, adjusting treatment means intensifying therapy by increasing the drug dose or by adding additional drugs to the regimen. To avoid unnecessary complexity in this report, the hypertension management algorithm (Figure) does not explicitly define all potential drug treatment strategies.

Finally, panel members point out that in specific situations, one antihypertensive drug may be replaced with another if it is perceived not to be effective or if there are adverse effects.

### **LIMITATIONS**

This evidence-based guideline for the management of high BP in adults is not a comprehensive guideline and is limited in scope because of the focused evidence review to address the 3 specific questions (Table 1). Clinicians often provide care for patients with numerous comorbidities or other important issues related to hypertension, but the decision was made to focus on 3 questions considered to be relevant to most physicians and patients. Treatment adherence and medication costs were thought to be beyond the scope of this review, but the panel acknowledges the importance of both issues.

The evidence review did not include observational studies, systematic reviews, or meta-analyses, and the panel did not conduct its own meta-analysis based on prespecified inclusion criteria. Thus, information from these types of studies was not incorporated into the evidence statements or recommendations. Although this may be considered a limitation, the panel decided to focus only on RCTs because they represent the best scientific evidence and because there were a substantial number of studies that included large numbers of patients and met our inclusion criteria. Randomized controlled trials that included participants with normal BP were excluded from our formal analysis. In cases in which high-quality evidence was not available or the evidence was weak or absent, the panel relied on fair-quality evidence, panel members' knowledge of the published literature beyond the RCTs reviewed, and personal experience to make recommendations. The duration of the guideline development process following completion of the systematic search may have caused the panel to miss studies published after our literature review. However, a bridge search was performed

through August 2013, and the panel found no additional studies that would have changed the recommendations.

Many of the reviewed studies were conducted when the overall risk of cardiovascular morbidity and mortality was substantially higher than it is today; therefore, effect sizes may have been overestimated. Further, RCTs that enrolled prehypertensive or nonhypertensive individuals were excluded. Thus, our recommendations do not apply to those without hypertension. In many studies focused on DBP, participants also had elevated SBP so it was not possible to determine whether the benefit observed in those trials arose from lowering DBP, SBP, or both. In addition, the ability to compare studies from different time periods was limited by differences in clinical trial design and analytic techniques.

While physicians use cost, adherence, and often observational data to make treatment decisions, medical interventions should whenever possible be based first and foremost on good science demonstrating benefits to patients. Randomized controlled trials are the gold standard for this assessment and thus were the basis for providing the evidence for our clinical recommendations. Although adverse effects and harms of antihypertensive treatment documented in the RCTs were considered when the panel made its decisions, the review was not designed to determine whether therapy-associated adverse effects and harms resulted in significant changes in important health outcomes. In addition, this guideline was not endorsed by any federal agency or professional society prior to publication and thus is a departure from previous JNC reports. The panel anticipates that an objective assessment of this report following publication will allow open dialogue among endorsing entities and encourage continued attention to rigorous methods in guideline development, thus raising the standard for future guidelines.

## **DISCUSSION**

The recommendations based on RCT evidence in this guideline differ from recommendations in other currently used guidelines supported by expert consensus (Table 6). For example, JNC 7 and other guidelines recommended treatment to lower BP goals in patients with diabetes and CKD based on observational studies.<sup>12</sup> Recently, several guideline documents such as those from the American Diabetes Association have raised the systolic BP goals to values that are similar to those recommended in this evidence-based guideline.<sup>37-42</sup> Other guidelines such as those of the European Society of Hypertension/European Society of Cardiology also recommend a systolic BP goal of lower than 150 mm Hg, but it is not clear at what age cutoff this goal specifically applies.<sup>37</sup> This changing landscape is understandable given the lack of clear RCT evidence in many clinical situations.

## **HISTORY of JNC 8**

The panel was originally constituted as the “Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8).” In March 2008 NHLBI sent letters inviting the co-chairs and committee members to serve on JNC 8. The charge to the committee was as follows:

“The JNC 8 will review and synthesize the latest available scientific evidence, update existing clinical recommendations, and provide guidance to busy primary care clinicians on the best approaches to manage and control hypertension in order to minimize patients’ risk for cardiovascular and other complications.” The committee was also asked to identify and prioritize the most important questions for the evidence review. In June 2013, NHLBI announced its decision to discontinue developing clinical guidelines including those in process, instead partnering with selected organizations that would develop the guidelines.<sup>43,44</sup> Importantly, participation in this process required that these organizations be involved in producing the final content of the report. The panel elected to pursue publication independently to bring the recommendations to the public in a timely manner while maintaining the integrity of the predefined process. This report is therefore not an NHLBI sanctioned report and does not reflect the views of NHLBI.

### **CONCLUSIONS**

It is important to note that this evidence-based guideline has not redefined high BP, and the panel believes that the 140/90 mm Hg definition from JNC 7 remains reasonable. The relationship between naturally occurring BP and risk is linear down to very low BP, but the benefit of treating to these lower levels with antihypertensive drugs is not established. For all persons with hypertension, the potential benefits of a healthy diet, weight control, and regular exercise cannot be overemphasized. These lifestyle treatments have the potential to improve BP control and even reduce medication needs. Although the authors of this hypertension guideline did not conduct an evidence review of lifestyle treatments in patients taking and not taking antihypertensive medication, we support the recommendations of the 2013 Lifestyle Work Group.<sup>45</sup>

The recommendations from this evidence-based guideline from panel members appointed to the Eighth Joint National Committee (JNC 8) offer clinicians an analysis of what is known and not known about BP treatment thresholds, goals, and drug treatment strategies to achieve those goals based on evidence from RCTs. However, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient. We hope that the algorithm will facilitate implementation and be useful to busy clinicians. The strong evidence base of this report should inform quality measures for the treatment of patients with hypertension.

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**Data Access and Responsibility.** Dr. Paul James and Dr. Suzanne Oparil had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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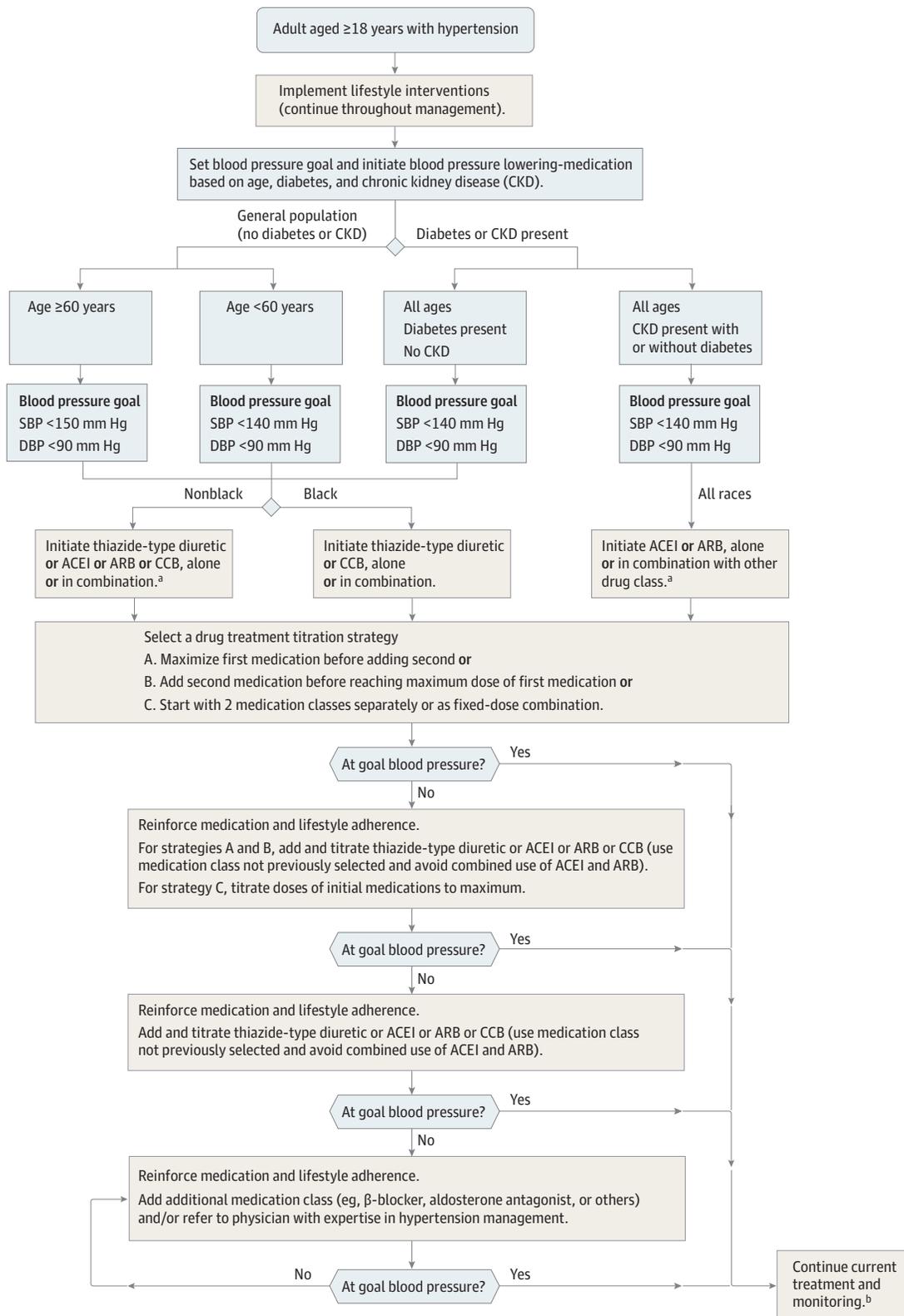
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## Tables and Figures

Figure 1. 2014 Hypertension Guideline Management Algorithm



SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and CCB, calcium channel blocker.

<sup>a</sup>ACEIs and ARBs should not be used in combination.

<sup>b</sup>If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.

**Table 1: Comparison of Current Recommendations with JNC 7 Guidelines**

Topic	JNC 7	2014 Hypertension Guideline
Methodology	<p>Nonsystematic literature review by expert committee including a range of study designs</p> <p>Recommendations based on consensus</p>	<p>Critical questions and review criteria defined by expert panel with input from methodology team</p> <p>Initial systematic review by methodologists restricted to RCT evidence</p> <p>Subsequent review of RCT evidence and recommendations by the panel according to a standardized protocol</p>
Definitions	<p>Defined hypertension and prehypertension</p>	<p>Definitions of hypertension and prehypertension not addressed, but thresholds for pharmacologic treatment were defined</p>
Treatment goals	<p>Separate treatment goals defined for “uncomplicated” hypertension and for subsets with various comorbid conditions (diabetes and CKD)</p>	<p>Similar treatment goals defined for all hypertensive populations except when evidence review supports different goals for a particular subpopulation</p>
Lifestyle recommendations	<p>Recommended lifestyle modifications based on literature review and expert opinion</p>	<p>Lifestyle modifications recommended by endorsing the evidence-based Recommendations of the Lifestyle Work Group</p>
Drug therapy	<p>Recommended 5 classes to be considered as initial therapy but recommended thiazide-type diuretics as initial therapy for most patients without compelling indication for another class</p> <p>Specified particular antihypertensive medication classes for patients with compelling indications, ie, diabetes, CKD, heart failure, myocardial infarction, stroke, and high CVD risk</p> <p>Included a comprehensive table of oral antihypertensive drugs including names and usual dose ranges</p>	<p>Recommended selection among 4 specific medication classes (ACEI or ARB, CCB or diuretics) and doses based on RCT evidence</p> <p>Recommended specific medication classes based on evidence review for racial, CKD, and diabetic subgroups</p> <p>Panel created a table of drugs and doses used in the outcome trials</p>

Scope of topics	Addressed multiple issues (blood pressure measurement methods, patient evaluation components, secondary hypertension, adherence to regimens, resistant hypertension, and hypertension in special populations) based on literature review and expert opinion	Evidence review of RCTs addressed a limited number of questions, those judged by the panel to be of highest priority.
Review process prior to publication	Reviewed by the National High Blood Pressure Education Program Coordinating Committee, a coalition of 39 major professional, public, and voluntary organizations and 7 federal agencies	Reviewed by experts including those affiliated with professional and public organizations and federal agencies; no official sponsorship by any organization should be inferred

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; JNC, Joint National Committee; RCT, randomized controlled trial.

**Table 2: Evidence Quality Rating**

Type of Evidence	Quality Rating <sup>a</sup>
<p>Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes</p> <p>Well-conducted meta-analyses of such studies</p> <p>Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect</p>	High
<p>RCTs with minor limitations affecting confidence in, or applicability of, the results</p> <p>Well-designed, well-executed non-randomized controlled studies and well-designed, well-executed observational studies</p> <p>Well-conducted meta-analyses of such studies</p> <p>Moderately certain about the estimate of effect; further research may have an impact on our confidence in the estimate of effect and may change the estimate</p>	Moderate
<p>RCTs with major limitations</p> <p>Non-randomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results</p> <p>Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports)</p> <p>Physiological studies in humans</p> <p>Meta-analyses of such studies</p> <p>Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.</p>	Low

Abbreviation: RCT, randomized controlled trial.

<sup>a</sup>The evidence quality rating system used in this guideline was developed by the National Heart, Lung, and Blood Institute’s (NHLBI’s) Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI CVD guideline panels and work groups during this project. As a result, it includes the evidence quality rating for many types of studies, including studies that were not used in this guideline. Additional details regarding the evidence quality rating system are available in the online Supplement.

**Table 3: Strength of Recommendation**

Grade	Strength of Recommendation
A	<p>Strong Recommendation</p> <p>There is high certainty based on evidence that the net benefit<sup>a</sup> is substantial.</p>
B	<p>Moderate Recommendation</p> <p>There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.</p>
C	<p>Weak Recommendation</p> <p>There is at least moderate certainty based on evidence that there is a small net benefit.</p>
D	<p>Recommendation against</p> <p>There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.</p>
E	<p>Expert Opinion (“There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.”)</p> <p>Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.</p>
N	<p>No Recommendation for or against (“There is insufficient evidence or evidence is unclear or conflicting.”)</p> <p>Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the committee thought no recommendation should be made. Further research is recommended in this area.</p>

The strength of recommendation grading system used in this guideline was developed by the National Heart, Lung, and Blood Institute’s (NHLBI’s) Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI CVD guideline panels and work groups during this project. Additional details regarding the strength of recommendation grading system are available in the online Supplement.

<sup>a</sup>Net benefit is defined as benefits minus the risks/harms of the service/intervention.

**Table 4: Evidence-Based Dosing for Antihypertensive Drugs**

<b>Antihypertensive Medication</b>	<b>Initial Daily Dose, mg</b>	<b>Target Dose in RCTs Reviewed, mg</b>	<b>No. of Doses per Day</b>
ACE inhibitors			
Captopril	50	150-200	2
Enalapril	5	20	1-2
Lisinopril	10	40	1
Angiotensin receptor blockers			
Eprosartan	400	600-800	1-2
Candesartan	4	12-32	1
Losartan	50	100	1-2
Valsartan	40-80	160-320	1
Irbesartan	75	300	1
β-Blockers			
Atenolol	25-50	100	1
Metoprolol	50	100-200	1-2
Calcium channel blockers			
Amlodipine	2.5	10	1
Diltiazem extended release	120-180	360	1
Nitrendipine	10	20	1-2
Thiazide-type diuretics			
Bendroflumethiazide	5	10	1
Chlorthalidone	12.5	12.5-25	1
Hydrochlorothiazide	12.5-25	25-100 <sup>a</sup>	1-2
Indapamide	1.25	1.25-2.5	1

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.

<sup>a</sup>Current recommended evidence-based dose that balances efficacy and safety is 25-50 mg daily.

**Table 5: Strategies to Dose Antihypertensive Drugs**

Strategy	Description	Details
A	Start one drug, titrate to maximum dose, and then add a second drug	<p>If goal BP is not achieved with the initial drug, titrate the dose of the initial drug up to the maximum recommended dose to achieve goal BP</p> <p>If goal BP is not achieved with the use of one drug despite titration to the maximum recommended dose, add a second drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB) and titrate up to the maximum recommended dose of the second drug to achieve goal BP</p> <p>If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose to achieve goal BP</p>
B	Start one drug and then add a second drug before achieving maximum dose of the initial drug	<p>Start with one drug then add a second drug before achieving the maximum recommended dose of the initial drug, then titrate both drugs up to the maximum recommended doses of both to achieve goal BP</p> <p>If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose to achieve goal BP</p>
C	Begin with 2 drugs at the same time, either as 2 separate pills or as a single pill combination	<p>Initiate therapy with 2 drugs simultaneously, either as 2 separate drugs or as a single pill combination. Some committee members recommend starting therapy with <math>\geq 2</math> drugs when SBP is <math>&gt;160</math> mm Hg and/or DBP is <math>&gt;100</math> mm Hg, or if SBP is <math>&gt;20</math> mm Hg above goal and/or DBP is <math>&gt;10</math> mm Hg above goal. If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB), avoiding the combined use of ACEI and ARB. Titrate the third drug up to the maximum recommended dose.</p>

Abbreviations: ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

<sup>a</sup>This table is not meant to exclude other agents within the classes of antihypertensive medications that have been recommended but reflects those agents and dosing used in randomized controlled trials that demonstrated improved outcomes.

**Table 6: Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults with Hypertension**

<b>Guideline</b>	<b>Population</b>	<b>Goal BP, mm Hg</b>	<b>Initial Drug Treatment Options</b>
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; black: thiazide-type diuretic or CCB
	General <60 y	<140/90	
	Diabetes	<140/90	Thiazide-type diuretic, ACEI, ARB, or CCB
	CKD	<140/90	ACEI or ARB
ESH/ESC 2013 <sup>37</sup>	General nonelderly	<140/90	Diuretic, β-blocker, CCB, ACEI, or ARB
	General elderly <80 y	<150/90	
	General ≥80 y	<150/90	
	Diabetes	<140/85	ACEI or ARB
	CKD no proteinuria	<140/90	ACEI or ARB
	CKD + proteinuria	<130/90	
	CHEP 2013 <sup>38</sup>	General <80 y	<140/90
General ≥80 y		<150/90	
Diabetes		<130/80	ACEI or ARB with additional CVD risk
			ACEI, ARB, thiazide, or DHPCCB without additional CVD risk
CKD		<140/90	ACEI or ARB

<b>Guideline</b>	<b>Population</b>	<b>Goal BP, mm Hg</b>	<b>Initial Drug Treatment Options</b>
ADA 2013 <sup>39</sup>	Diabetes	<140/80	ACEI or ARB
KDIGO 2012 <sup>40</sup>	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	
NICE 2011 <sup>41</sup>	General <80 y	<140/90	<55 y: ACEI or ARB
	General ≥80 y	<150/90	≥55 y or black: CCB
ISHIB 2010 <sup>42</sup>	Black, lower risk	<135/85	Diuretic or CCB
	Target organ damage or CVD risk	<130/80	

Abbreviations: ADA, American Diabetes Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; CKD, chronic kidney disease; CVD, cardiovascular disease; DHPCCB, dihydropyridine calcium channel blocker; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISHIB, International Society for Hypertension in Blacks; JNC, Joint National Committee; KDIGO, Kidney Disease: Improving Global Outcome; NICE, National Institute for Health and Clinical Excellence.

## **Box. Recommendations for Management of Hypertension**

### **Recommendation 1**

In the general population aged  $\geq 60$  years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP)  $\geq 150$  mm Hg or diastolic blood pressure (DBP)  $\geq 90$  mm Hg and treat to a goal SBP  $< 150$  mm Hg and goal DBP  $< 90$  mm Hg. (Strong Recommendation – Grade A)

### *Corollary Recommendation*

In the general population aged  $\geq 60$  years, if pharmacologic treatment for high BP results in lower achieved SBP (eg,  $< 140$  mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)

### **Recommendation 2**

In the general population  $< 60$  years, initiate pharmacologic treatment to lower BP at DBP  $\geq 90$  mm Hg and treat to a goal DBP  $< 90$  mm Hg. (For ages 30-59 years, Strong Recommendation – Grade A; For ages 18-29 years, Expert Opinion – Grade E)

### **Recommendation 3**

In the general population  $< 60$  years, initiate pharmacologic treatment to lower BP at SBP  $\geq 140$  mm Hg and treat to a goal SBP  $< 140$  mm Hg. (Expert Opinion – Grade E)

### **Recommendation 4**

In the population aged  $\geq 18$  years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP  $\geq 140$  mm Hg or DBP  $\geq 90$  mm Hg and treat to goal SBP  $< 140$  mm Hg and goal DBP  $< 90$  mm Hg. (Expert Opinion – Grade E)

### **Recommendation 5**

In the population aged  $\geq 18$  years with diabetes, initiate pharmacologic treatment to lower BP at SBP  $\geq 140$  mm Hg or DBP  $\geq 90$  mm Hg and treat to a goal SBP  $< 140$  mm Hg and goal DBP  $< 90$  mm Hg. (Expert Opinion – Grade E)

### **Recommendation 6**

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)

### **Recommendation 7**

In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general black population: Moderate Recommendation – Grade B; for black patients with diabetes: Weak Recommendation – Grade C)

### **Recommendation 8**

In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation – Grade B)

### **Recommendation 9**

The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed. (Expert Opinion – Grade E)

# Background

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## BACKGROUND

Hypertension remains one of the most important preventable contributors to disease and death. Abundant evidence from randomized controlled trials (RCTs) has shown the benefit of antihypertensive drug treatment in reducing important health outcomes in hypertensive persons. [Staessen, 1997; Beckett, 2008; Shep 1991] Clinical guidelines sit at the intersection between research evidence and clinical actions that can improve patient outcomes. The Institute of Medicine Report “Clinical Practice Guidelines We Can Trust” outlined a pathway to guideline development and is an approach that the JNC 8 Panel aspired to in the creation of this Report. [IOM (Institute of Medicine) 2011]

The Panel used rigorous evidence-based methodology, developing Evidence Statements (ESs) and Recommendations for blood pressure (BP) treatment based on a systematic review of the literature to meet user needs, especially the needs of the primary care clinician. This Report is designed to be user-friendly and to provide clear recommendations for all clinicians. Major differences from the previous JNC Reports are summarized in Table 1.

### Panel Members

Panel members were selected from over 400 nominees. Panel members were selected based on their expertise in hypertension, primary care, cardiology, nephrology, clinical trials, research methodology, evidence-based medicine, epidemiology, guideline development and implementation, nutrition/lifestyle, nursing, pharmacology, systems of care, and informatics. The Panel also included senior scientists from NHLBI and NIDDK with expertise in hypertension, clinical trials, translational research, nephrology, primary care, guideline development, and evidence-based methodology. In assembling the Panel, we sought to achieve a balance of expertise and perspectives. The Panel met for the first time in September 2008.

### Panel Members

#### **Co-Chair: Paul A. James, MD**

Professor and Head, Department of Family Medicine in the Carver College of Medicine, Professor of Occupational and Environmental Health in the College of Public Health, Donald J. and Anna M. Otilie Endowed Chair in Family Medicine  
University of Iowa

#### **Co-Chair: Suzanne Oparil, MD**

Professor of Medicine  
Professor of Cell, Developmental and Integrative Biology  
Director, Vascular Biology and Hypertension Program  
Division of Cardiovascular Disease, Department of Medicine  
University of Alabama at Birmingham School of Medicine

#### **Barry L. Carter, PharmD**

Professor, Department of Pharmacy Practice and Science, College of Pharmacy  
Professor and Associate Head, Research Department of Family Medicine  
University of Iowa

**William C. Cushman, MD, FACP, FAHA, FASH**

Chief, Preventive Medicine, Memphis Veterans Affairs Medical Center  
Lead Consultant in Hypertension to VA Medical Service  
Professor, Preventive Medicine and Medicine  
University of Tennessee

**Cheryl Dennison Himmelfarb, RN, ANP, PhD, FAAN**

Associate Professor  
Department of Health Systems and Outcomes  
Johns Hopkins University School of Nursing  
Division of Health Sciences Informatics  
Johns Hopkins University School of Medicine

**Joel Handler, MD**

Clinical Lead for Hypertension  
Care Management Institute, Kaiser Permanente  
Southern California Permanente Medical Group  
Department of Internal Medicine

**Daniel T. Lackland, DrPH**

Professor, Epidemiology and Medicine  
Department of Neurosciences  
Medical University of South Carolina

**Michael L. LeFevre, MD, MSPH**

Professor, Department of Family and Community Medicine  
University of Missouri

**Thomas D. MacKenzie, MD, MSPH, FACP**

Chief Medical Officer, Denver Health and Hospital Authority  
Associate Professor of Medicine  
University of Colorado School of Medicine

**Olugbenga Ogedegbe, MD, MPH, MS, FAHA**

Professor of Medicine and Population Health  
Division of Health and Behavior  
Department of Population Health  
New York University School of Medicine

**Sidney C. Smith, Jr., MD, FACC, FAHA, FESC**

Director, Center for Cardiovascular Science and Medicine  
Professor of Medicine  
University of North Carolina at Chapel Hill

**Laura P. Svetkey, MD, MHS**

Director, Duke Hypertension Center  
Director of Clinical Research at the Sarah W. Stedman Nutrition and Metabolism Center

Professor of Medicine  
Duke University

**Sandra J. Taler, MD**

Professor of Medicine  
Division of Nephrology and Hypertension  
Mayo Clinic College of Medicine

**Raymond R. Townsend, MD**

Director, Hypertension Section  
Professor of Medicine  
Department of Internal Medicine–Renal  
University of Pennsylvania

**Jackson T. Wright, Jr., MD, PhD**

Director, Clinical Hypertension Program  
Director, William T. Dahms Clinical Research Unit,  
University Hospitals Case Medical Center  
Professor of Medicine  
Case Western Reserve University

**Andrew S. Narva, MD**

Director, National Kidney Disease Education Program  
Division of Kidney, Urologic and Hematologic Diseases  
National Institute of Diabetes and Digestive and Kidney Diseases

**Eduardo Ortiz, MD, MPH (Non-Voting Member)**

At the time of this project, Dr. Ortiz was a Senior Medical Officer with the National Heart, Lung, and Blood Institute (NHLBI). He was also the Program Coordinator for JNC 8 and NHLBI's Evidence-Based Methodology Lead. He is currently Director of Clinical Development and Informatics with ProVation Medical, Wolters Kluwer Health.

**Support Staff**

**Cory V. Evans, MPP**, At the time of this project, Ms. Evans was a Senior Research Analyst and Contract Lead for JNC 8 with Leidos (formerly, Science Applications International Corporation). She is currently a Research Associate with the Kaiser Permanente Center for Health Research.

**Linda J. Lux, MPA**, Senior Research Associate with RTI International

**Note:** The Panel also recognizes the significant contributions of Lawrence J. Fine, MD, DrPH, with the National Heart, Lung, and Blood Institute, for his work with the Panel.

**DISCLOSURES**

Panel members disclosed their relationships with industry and potential conflicts of interest and recused themselves from voting on evidence statements and recommendations relevant to their relationships/potential conflicts. Four Panel members had relationships or potential conflicts to disclose.

For more information, refer to: Guideline Executive Committee Policy on Disclosures:  
[http://www.nhlbi.nih.gov/guidelines/cvd\\_adult/coi-rwi\\_policy.htm](http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm)

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Dr. Cushman reports receipt of institutional grant support from Merck, Lilly and Novartis; and consulting fees from Novartis, Sciele Pharmaceuticals, Takeda, Sanofi-aventis, Gilead, Calpis, Pharmacopeia, Theravance, Daiichi-Sankyo, Noven, Astra Zeneca Spain, Merck, Omron, and Janssen.

Dr. Wright reports receipt of consulting fees from Medtronic, CVRX, Takeda, Daiichi-Sankyo, Novartis and Take Care Health.

Dr. Oparil reports individual and institutional payment related to Board membership for Bayer, Daiichi Sankyo, Novartis, Medtronic and Takeda; and individual consulting fees from Backbeat, Bayer, Boehringer-Ingelheim, Bristol Myers-Squibb, Daiichi Sankyo, Eli Lilly, Medtronic, Merck and Co, Pfizer and Takeda; and receipt of institutional grant funding from AstraZeneca AB, Daiichi Sankyo, Eisai Inc, Gilead, Medtronic Inc., Merck, Novartis, Takeda Global Research and Development Inc.; and individual payment for lectures from Daiichi Sankyo, Merck, Novartis and Pfizer; and individual and institutional payment for development of educational presentations from ASH/ASHR (Daiichi Sankyo, Inc.); and individual and institutional payment from Amarin Pharma Inc., Daiichi Sankyo, Inc., and LipoScience, Inc. for educational grant(s) for the Annual Vascular Biology & Hypertension Symposium; sponsorship.

Dr. Townsend reports Board membership with Medtronic, consultancy for Janssen, GSK and Merck, and educational related payments from Merck, UpToDate, and Medscape. The other authors report no disclosures.

### **Other Acknowledgments**

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# Methods

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## METHODS

### Description of How Panel Members Were Selected

The NHLBI initiated a public call for nominations for panel membership to ensure adequate representation of key specialties and stakeholders and appropriate expertise. A nomination form was posted on the NHLBI website for several weeks and was also distributed to a Guidelines Leadership Group that had given advice to the NHLBI on its guideline efforts. Information from nomination forms, including contact information and areas of clinical and research expertise, was entered into a database.

After the close of the call for nominations, NHLBI staff reviewed the database and selected potential co-chairs. The potential co-chairs provided the NHLBI Conflict of Interest (COI) disclosures and copies of their curriculum vitae. The NHLBI Ethics Office reviewed the COI disclosures of the potential co-chairs. The selected chairs then were formed into a Guidelines Executive Committee, which worked with the NHLBI to select panel members from the list of nominees.

The NHLBI received 440 nominations for panel members. Panel members were selected based on their expertise in hypertension, primary care, cardiology, nephrology, clinical trials, research methodology, evidence-based medicine, epidemiology, guideline development and implementation, nutrition/lifestyle, nursing, pharmacology, systems of care, and informatics. The panel also included senior scientists from NHLBI and NIDDK with expertise in hypertension, clinical trials, translational research, nephrology, primary care, guideline development, and evidence-based methodology.

### Description of How the Panel Developed, Prioritized, and Formatted Questions

The Panel Co-Chairs and NHLBI staff developed an initial set of questions based on their expertise, a brief literature review, and speaking with colleagues to identify topics of the greatest relevance and impact for the target audience of the guideline: primary care providers. These questions were sent to panel members to review and revise, including adding or deleting questions, based on what they thought were the most important clinical questions in hypertension.

This process resulted in 23 questions, which were sent to all panel members. Panel members discussed these questions on multiple conference calls and then independently ranked the top 5 questions felt to be of highest priority. The five highest ranked questions were discussed further and prioritized. This report is focused on the three highest ranked questions.

With support from the methodologist and systematic review team, the highest priority questions were formatted using the PICOTSS framework, and inclusion and exclusion criteria (I/E criteria) were defined. PICOTSS is a standardized framework for a structured research question that is commonly used when conducting evidence-based systematic reviews and includes the following components in the statement of the question or in the question's inclusion and exclusion criteria:

- P** person or population
- I** intervention or exposure
- C** comparator
- O** outcome
- T** timing
- S** setting
- S** study design

Inclusion and exclusion criteria define the parameters for conducting the literature search for a particular question. Inclusion and exclusion criteria were developed with input from the methodologist and systematic review team to ensure that criteria were clear and precise and could be applied consistently across literature identified in the search.

The final questions and criteria were submitted to the literature search team for search strategy development.

### How Were the Questions Selected?

Panel Chairs and NHLBI staff developed an initial set of questions based on their expertise, a brief literature review, and speaking with colleagues. These questions were then sent to Panel members to review and revise, including adding or deleting questions, based on what they thought were the most important clinical questions in hypertension. This process resulted in 23 questions, which were sent to all Panel members. Panel members discussed these questions on multiple conference calls then independently ranked the top 5 questions felt to be of highest priority. The five highest ranked questions were discussed further and prioritized. This report is focused on the three highest ranked questions

### Rationale for the Questions Selected

The rationale for the questions selected by the Panel was based on the following:

- Interest among Panel members regarding the evidence supporting 140/90 mm Hg as a treatment threshold and/or goal for the general population.
- Interest in whether the treatment threshold or goal should be lower than in the general population for those with diabetes, chronic kidney disease, coronary artery disease, stroke, or other co-morbidities or risks, including older adults.
- Concern that having a threshold for initiating treatment that differs from the treatment goal may be confusing to people.
- Interest in the selection of pharmacologic therapy, including whether treatment to lower blood pressure with a particular drug or drug class improves important health outcomes when compared to another drug or drug class.

## QUESTIONS

- 1. In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific blood pressure thresholds improve health outcomes?**
- 2. In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?**
- 3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?**

## Inclusion/Exclusion Criteria for the Evidence Review

The Panel decided to limit its evidence review to Randomized Controlled Trials (RCTs) because they are subject to less bias than other types of clinical studies and represent the gold standard for determining efficacy and effectiveness [IOM, 2011]. All of the studies in the evidence review were from original publications of eligible RCTs. These studies were used to create Evidence Tables and Summary Tables that were used by the Panel as the basis for their deliberations. Because the Panel conducted its own systematic review using original studies, systematic reviews and meta-analyses (SR/MA) of RCTs published by other groups were not used in the evidence review (i.e., they were not abstracted and included in the Evidence Tables and Summary Tables). Pilot studies were also excluded. Pilot studies were defined as trials where the specific aims were to conduct a pilot or feasibility study for the purpose of informing a larger clinical trial that occurred later.

The evidence review focused on adults 18 years of age or older with hypertension and included studies with the following prespecified subgroups: diabetes, coronary artery disease, peripheral artery disease, heart failure, previous stroke, chronic kidney disease, proteinuria, older adults, men and women, racial and ethnic groups, and smokers. Studies with sample sizes less than 100 were excluded, as were studies with a follow-up period of less than one year.

Initial search dates for the literature review were January 1, 1966 to December 31, 2009. In order to ensure that no major relevant studies published after December 31, 2009 were excluded from consideration; two independent searches of PubMed and CINAHL between December 2009 and August 2013 were conducted with the same MeSH terms as the original search. Three Panel members reviewed the results. The Panel limited the inclusion criteria of this second search to the following: 1) The study was a major study in the field (e.g., ACCORD-BP, SPS3\*) {{728 ACCORD Study Group 2010; 729 SPS3 Study Group 2013}} 2) It had at least 2,000 participants; 3) It was multi-centered; and 4) It met all the other inclusion/exclusion criteria. Additionally, all Panel members were asked to identify newly published studies for consideration if they met the above criteria. There were no additional clinical trials that fit the previously described inclusion criteria. Studies selected were rated for quality using NHLBI's standardized quality rating tool and were only included if rated as Good or Fair.

Studies selected in this manner were also rated for quality using NHLBI's standardized quality rating tool and were only included if rated as Good or Fair. Although the Panel understands that this approach may result in selection bias for studies identified after December 31, 2009, the Panel thought that it was important to identify and include seminal studies like ACCORD that were published after the end of the literature search. Although it would have been ideal to continually update the literature search until publication of this report, such an approach was not feasible.

The Panel only included studies that measured the effects of the studied interventions on the following important health outcomes:

Overall mortality, mortality related to CVD, mortality related to chronic kidney disease (CKD)  
Myocardial infarction, heart failure, hospitalization for heart failure, stroke

\* SPS3 did not meet strict inclusion criteria because it included non-hypertensive participants. It would not have changed our conclusions/recommendations since the only significant finding supporting a lower goal occurred in an infrequent secondary outcome.

Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), peripheral revascularization (includes carotid, renal, and lower extremity revascularization)

End stage renal disease (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of estimated glomerular filtration rate (eGFR)

For Question 1, we originally looked for studies that randomized participants into groups where pharmacologic therapy to lower blood pressure was initiated at different blood pressure thresholds. For example, we looked for studies where treatment was initiated at a systolic blood pressure of 160 mm Hg in one group and compared to treatment initiated at a systolic BP of 140 mm Hg in another group. We found that no RCTs had been conducted that compared two or more different treatment thresholds. Therefore, we had to broaden the inclusion criteria to include RCTs that had a specific criterion for initiating treatment in one group (e.g., initiating treatment if systolic blood pressure was  $\geq 160$  mm Hg) and compared it to a group that received placebo, usual care, or no treatment.

Evidence statements were graded for quality as high, moderate, or low using a grading system developed by NHLBI's Evidence-Based Methodology Lead with input from NHLBI staff, the external methodology team and the Guideline Panels and Work Groups. This grading system was adapted (with modifications) from the approach used by the United States Preventive Services Task Force. Recommendations were graded as Strong Recommendation (Grade A), Moderate Recommendation (Grade B), Weak Recommendation (Grade C), Recommendation Against (Grade D), Expert Opinion (Grade E), or No Recommendation for or Against (Grade N), which also was adapted (with modifications) from the United States Preventive Services Task Force.

### **Literature Search Infrastructure, Search Strategy Development and Validation**

The literature search was performed using an integrated suite of search engines that explored a central repository of citations and full-text journal articles. The central repository, search engines, search results, and web-based modules for literature screening and data abstraction were integrated within a technology platform called the Virtual Collaborative Workspace (VCW). The VCW was custom-developed for the NHLBI guidelines initiative.

The central repository consisted of 1.9 million citations and 71,000 full text articles related to cardiovascular disease risk reduction. Citations were acquired from: PubMed, Embase, Cinahl, Cochrane, PsycInfo, Wilson Science, and Biological Abstracts databases. Literature searches were conducted using a collection of search engines including: TeraText, Content Analyst, Collexis, and Lucene. These engines were used for executing search strategies, and Lucene was used in correlating the search with screening results.

For every question, literature search and screening were conducted according to the understanding of the question and the inclusion/exclusion criteria that provided specific characteristics of studies relevant to the question. Criteria were framed in the PICOTSS format specifying Population, Intervention,

Comparator, Outcomes, Timing, Settings, and Study Design. The question and PICOTSS components were translated into a search strategy involving Boolean and conceptual queries.

A Boolean query encodes both inclusion and exclusion rules. It grants access to the maximum quantity of citations, which are then analyzed by text analytics tools and ranked to produce a selection for literature screening that was conducted by two independent reviewers in the VCW's web-based module. Boolean queries select citations by matching words in titles and abstracts, as well as Medical Subject Headings (MeSH) and subheadings. The number of citations resulting from Boolean queries ranged from a few hundred to several thousand depending on the question. The text analytics tools suite included:

- A natural language processing module for automated extraction of data elements in support of application of inclusion/exclusion criteria. Frequently extracted and utilized data elements were study size and intervention follow-up period.
- Content Analyst for automatically expanding vocabulary of queries, conceptual retrieval, and conceptual clustering. The conceptual query engine employed in Content Analyst leverages word frequency features and co-occurrence in similar contexts to index, select and rank results. The indexing utilizes the Singular Value Decomposition (SVD) algebraic method.
- TeraText for ranking search results and a variety of fast operations on the inverted index.

Search strategy development was intertwined with the results of literature screening, which provided feedback on search quality and context. Screened literature was categorized into two subsets: relevant or not relevant to the question. Next, results were analyzed to determine the characteristics of relevant versus not relevant citations. Additional keywords and MeSH terms were used to expand or contract the scope of the query as driven by characteristics of relevant citations. If a revised search strategy produced more citations than the original strategy, the new citations resulting from the larger result set were added for literature review. The search strategy refinement/literature review cycle was repeated until all citations covered by the most recent Boolean query were screened.

Each search strategy was developed and implemented in the VCW. The search strategy was reviewed by the methodologist and panel members, and was available for viewing and printing at any time by panel members and staff collaborating on the systematic review. It was available for execution and supplying literature updates until the literature search and screening cut-off date.

Search strategies for a sample of questions were validated by an independent methodology team. This validation process involved the methodology team developing and executing a separate search strategy and screening a random sample of citations against I/E criteria. These results were compared to the search and screening results developed by the systematic review team. Based on the validation process, the searches were considered appropriate. As an additional validation method, studies identified in systematic reviews and meta-analyses were cross-checked against a question's include list to ensure completeness of the search strategy.

### **Literature Review Process**

Using results of the search strategy, criteria were applied to screen the literature for inclusion or exclusion in the evidence base for the question. The I/E criteria addressed the parameters in the PICOTSS framework and determined the types of studies that were eligible and appropriate to answer the question. Additional criteria such as sample size restrictions were included by the panel to fit the context of the question.

### **Pilot Literature Screening**

During Pilot Literature Screening, two reviewers independently screened the first 50 titles/abstracts in the search strategy results by applying I/E criteria. Reviewers voted to include or exclude the publication for full text review. Reviewers compared their results to ensure that I/E criteria were applied consistently. Discrepancies in votes were discussed and clarification on criteria was sought from the panel where appropriate. For example, if criteria were not specific enough to be clearly applied to include or exclude a citation, guidance was sought to define the criteria more explicitly.

During this phase, reviewers provided feedback to the literature search team about the relevance of search strategy results; this feedback was used to further refine and optimize the search.

### **Phase 1: Title and Abstract Screening Phase**

After completion of the Pilot Mode, two reviewers independently screened the search results at the title and abstract level by applying the I/E criteria. Reviewers voted to include or exclude the publication for full text review.

Titles and abstracts that one or both reviewers voted to include advanced to Phase 2: Full Text Screening. Titles and abstracts that both reviewers voted to exclude were not reviewed further. These citations were maintained in the VCW and marked as “excluded at the title/abstract phase.”

### **Phase 2: Full Text Screening Phase**

Titles and abstracts that at least one reviewer voted to include were reviewed at the full text level in Phase 2. In this Phase, two reviewers independently applied the I/E criteria to the full text article and voted as follows: include, exclude, or undecided. The reviewer had to specify the rationale for exclusion in this phase.

Articles that both reviewers voted to include were moved to the Include List. Articles that both reviewers voted to exclude were moved to the Exclude List. These citations were maintained in the VCW and identified as “excluded at the full article phase”. The rationale for exclusion was noted. Any article with discrepant votes (i.e., one include and one undecided, one include and one exclude, etc.) advanced to Phase 3.

### **Phase 3: Resolution and Consultation Phase**

In this phase, reviewers discussed their vote (include, exclude, or undecided) and cited the relevant criteria for their decision. The two reviewers attempted to achieve consensus through collaborative discussion. If consensus was not reached by the two reviewers, input was sought from the methodologist. If a decision was not reached after consultation with the methodologist, input was sought from the panel. However the methodologist had the final decision. The final disposition of the article (include or exclude) was recorded in the VCW along with comments from the adjudication process.

All the citations that were screened for each question were maintained in the VCW, along with the votes and comments of each reviewer.

### **Description of Methods for Assessing the Quality of Individual Studies**

Articles meeting the criteria after the three phase literature review process were then quality rated independently by two trained raters. Studies rated Good or Fair were included in the evidence review.

### Design of the Quality Assessment Tools

Appraisal of individual study quality was based on six quality assessment tools developed jointly by NHLBI and the methodology team. The development of these tools was guided by an initial review of methods and tools that have been used by others working in the field of systematic reviews and evidence-based medicine, including AHRQ's Evidence-Based Practice Centers, United States Preventive Services Task Force, The Cochrane Collaborative, and the National Health Service Centre for Reviews and Dissemination, adapted to meet the needs of this project. These quality assessment tools were used in the evidence reviews for the High Blood Pressure, High Blood Cholesterol, and Overweight/Obesity Panels and the Lifestyle and Risk Assessment Work Groups.

These tools were designed to assist reviewers in focusing on key concepts for critical appraisal of the internal validity of a study but were not designed to generate a numeric score. The tools were specific to individual types of included study designs. Because the Panel limited its evidence review to RCTs, only the quality assessment tool for controlled intervention studies was used for the questions addressed by the Panel. This quality assessment tool is provided in Exhibit 1.

The tools include items for evaluation of potential flaws in study methods or implementation, such as sources of bias (e.g., selection, performance, attrition, or detection bias), confounding, study power, and strength of causality in the association between interventions and outcomes. Quality reviewers could select "yes," "no," or "cannot determine (CD)/not reported (NR)/not applicable (NA)" in response to each item in the tool. For each item where "no" was checked, reviewers were instructed to consider the potential risk of bias that could be introduced by that flaw in study design or implementation. CD and NR were also noted as representing potential flaws.

A detailed guidance document accompanied each of the six quality assessment tools. The guidance documents were specific to each tool and provided more detailed descriptions and examples of application of the items for evaluation of potential flaws in study methods or implementation, as well as justifications for item inclusion. For some items, examples were provided to clarify the intent of the question and the appropriate rater response.

### Significance of the Quality Ratings of Good, Fair, or Poor

Reviewers used the study ratings on the range of items included in each tool to judge each study to be of "good," "fair," or "poor" quality. The ratings on the different items were used by the reviewers to assess the risk of bias in the study due to flaws in study design or implementation.

In general terms, a good study has the least risk of bias, and results are considered to be valid. A fair study is susceptible to some bias that may be of concern, but the risk of bias is not deemed sufficient to invalidate its results. The fair quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses.

A poor rating indicates that there is a significant risk of bias. Studies rated poor were excluded from the body of evidence used by the panel to deliberate, draw conclusions, and make recommendations. The only exception allowed for this general policy of excluding poor studies was if there was no other evidence available; in such cases, poor quality studies could be considered. However, this exception did not apply to the questions addressed by the Panel because there were good and/or fair quality studies that met the I/E criteria for each question.

### Training on the Use of the Quality Assessment Tools

The methodology team conducted a series of training sessions on the use of the quality assessment tools. Initial training consisted of two two-day, in-person training sessions. Individuals trained in quality rating were Masters or PhD level staff with backgrounds in public health or the health sciences. Training sessions provided instruction on identifying correct study designs, the theory behind evidence-based research and quality assessment, explanations and rationales for the items in each tool, and methods for achieving overall judgments regarding quality ratings of good, fair, or poor. Participants engaged in interactive training exercises where they evaluated multiple articles, first with the instructors and then working together in groups. Reviewers were also instructed to refer to related articles on study methods if such papers were cited in the articles being rated.

Following the in-person training sessions, the methodology team assigned several articles with pertinent study designs to test the abilities of each reviewer. The reviewers were asked to individually identify the correct study design, complete the appropriate quality assessment tool, and submit it to the methodology team for grading against a methodologist-developed key. A second round of training sessions was then conducted via conference calls to review the results and resolve any remaining issues.

### Quality Assessment Process

Each article that met the inclusion criteria for a question was rated for quality by two independent reviewers using the appropriate tool for the assigned article. If the ratings differed, the reviewers discussed the article in an effort to reach consensus. If consensus was not achieved, the article was forwarded to a methodologist for quality adjudication.

Panel members could appeal the quality rating of a particular study or publication and make their case for why they disagreed with the initial quality rating. Any issues of concern would then be discussed on a panel call, and if other panel members agreed that the quality rating should be re-assessed, the reviewers would conduct another assessment of the study or publication with input from the lead methodologist. However, all final decisions on quality ratings were made by the methodology team, not by panel members, to ensure the objectivity of the quality rating process.

### Quality Assessment Tool for Controlled Intervention Studies

The quality assessment tool for controlled intervention studies is included below in Exhibit 1. The guidance document for the tool is also included in Exhibit 1. Because the Panel decided to limit its evidence review to RCTs, only the quality assessment tool for controlled intervention studies was used for the questions addressed by the Panel.

This tool addresses 14 elements of quality assessment. They include randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat (ITT) analysis, adequacy of blinding, the overall percentage of study participants lost to follow-up, the differential rates of loss to follow-up between the intervention and control groups, and other factors.

## EXHIBIT 1

### Quality Assessment of Controlled Intervention Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?			
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?			
3. Was the treatment allocation concealed (so that assignments could not be predicted)?			
4. Were study participants and providers blinded to treatment group assignment?			
5. Were the people assessing the outcomes blinded to the participants' group assignments?			
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?			
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?			
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?			
9. Was there high adherence to the intervention protocols for each treatment group?			
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?			
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?			
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?			
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?			
<b>Quality Rating (Good, Fair, Poor) (see guidance)</b>			
<b>Rater #1 initials:</b>		<b>Rater #2 initials:</b>	
<b>Additional Comments (If POOR, please state why):</b>			

\*CD: cannot determine; NA: not applicable; NR: not reported

### **Guidance for Assessing the Quality of Controlled Intervention Studies**

## Descriptions by question # in the controlled intervention study tool:

### **1. Described as randomized**

Literally, was the study described as randomized? A study does not satisfy quality criteria as randomized simply because the authors call it *randomized*. But as a first step, did the authors of the study say it was randomized?

### **2 – 3. Treatment Allocation—two interrelated pieces**

- Adequate randomization: the randomization is adequate if it occurred according to the play of chance (e.g., computer generated sequence in more recent studies, or random number table in older studies).

Inadequate randomization: “randomization” is inadequate if there is a pre-set plan (e.g., alternation where every other subject is assigned to treatment arm or another method of allocation is used such as time or day of hospital admission or clinic visit, zip code, phone number, etc.). In fact, this is not randomization at all – it is another method of assignment to groups. If assignment is not by the play of chance then the answer is NO.

There may be some tricky scenarios that will require careful reading and consideration for the role of chance in assignment. For example, sites are randomized to receive treatment or not so all individuals at the site are thereby assigned to a treatment group. This scenario used for group-randomized trials GRTs, which can be truly randomized, but often are “quasi-experimental” studies with comparison groups rather than true control groups. (We anticipate few if any GRTs in this evidence review.)

- Allocation concealment

This means that one does not know in advance, or cannot guess accurately, to what group the next person eligible for randomization will be assigned. Methods include sequentially numbered opaque sealed envelopes, numbered or coded containers, central randomization by a coordinating center, and computer generated randomization that is not revealed ahead of time.

### **4 – 5. Blinding**

Blinding means that one does not know to which group – intervention or control – the participant is assigned. It is also sometimes called “masking.” You are looking to see if each of the following is blinded to knowledge of treatment assignment: the person assessing the primary outcome(s) for the study (e.g., taking the measurements, examining medical records to determine type of event as in an adjudication committee); the person receiving the intervention (e.g., patient or study participant); and the person providing the intervention (e.g., physician, nurse, pharmacist, or behavioral interventionist).

Generally placebo-controlled medication studies are blinded to patient, provider, and outcome assessors; behavioral or lifestyle studies may often be blinded only to the outcome assessors. Sometimes the person providing the intervention is the same person doing the outcome assessment. If so, make note of it in your comments section.

### **6. Similarity of groups at baseline**

This question relates to whether the intervention and control groups have similar characteristics on average. The whole point of doing a randomized trial is to create similar groups to enable valid comparisons of intervention effects between groups. If there is a significant difference, you should see it

when you abstract baseline characteristics. Baseline characteristics for intervention groups are usually presented in a table in the article (often Table 1).

Groups can differ at baseline without raising red flags if: (1) the differences would not be expected to have any bearing on the interventions and outcomes; or (2) the differences are not statistically significant. If you have any concerns about baseline difference in the groups, write them down in the comments section and consider them in your overall determination of the study quality.

## **7 – 8. Drop-out**

By “drop-out” we mean participants for whom there are no endpoint measurements – the most common reason being that they dropped out of the study (for whatever reason) and were lost to follow-up.

Generally, an acceptable overall dropout rate is considered 20% or less of participants who were randomized/allocated into each group, and an acceptable differential drop-out is considered an absolute difference between groups of 15 percentage points at most (calculated by subtracting the drop-out rate of one group minus the drop-out rate of the other group). However, these are general rates, and higher overall drop-out rates may be acceptable under certain circumstances. If you are conducting a systematic review on the comparative efficacy of antidepressants, then setting the cap at 20% for an overall drop-out is appropriate. On the other hand, if you are looking at joint space narrowing for targeted immune modulators (TIMs), where studies comparing TIMs for this outcome are generally of longer duration and drop-outs are more likely, it may be reasonable to raise the cap for defining an acceptable overall drop-out rate. This type of decision should be made with input from the content experts and decided before conducting your systematic review.

The same flexibility does not apply to the differential drop-out rate, which should be capped at 15%. If you have a differential drop-out rate of 15% or higher between study arms, there is a high risk of bias, which constitutes a fatal flaw resulting in a Poor quality rating for the study.

## **9. Adherence**

Did participants in each treatment group adhere to the protocols for assigned interventions? For example, if Group 1 was assigned to 10 mg/day of Drug A, did most of them take 10 mg/day of drug A? Another example is a study evaluating the difference between a 30-lb weight loss and a 10-lb weight loss on specific clinical outcomes (for example, heart attacks), but the 30-lb weight loss group did not achieve its intended weight loss target. A third example is whether a large percentage of participants assigned to one group “crossed over” and received the intervention provided to the other group. A final example is when one group that was assigned to receive a particular drug at a particular dose had a large percentage of participants who didn’t end up taking the drug or the dose as designed in the protocol.

## **10. Avoid other interventions**

Changes that occur in the study outcomes being assessed should be attributable to the interventions being compared in the study. If participants in any of the groups receive other interventions that are not part of the study protocol and that could affect the outcomes being assessed, and they receive these interventions differentially, there is cause for concern, as it could bias the results. For example, if you had a study comparing two different dietary interventions on serum cholesterol, but one of the groups had a significantly higher percentage of participants taking statin drugs, it could unduly influence the results of the study because you wouldn’t know whether the difference in outcome was due to the dietary intervention or the drugs.

### **11. Outcome measures assessment**

What tools or methods were used to measure outcomes in the study? Were the tools/methods accurate and reliable – for example, have they been validated, or are they objective? This is important as it indicates the confidence you can have in the reported outcomes. Perhaps even more important is whether the outcomes were assessed in the same manner within groups and between groups. One example is that a self-report of dietary salt intake is not as valid and reliable as testing urine for sodium content. Another example is measurement of blood pressure that just uses clinicians' usual measurement approaches rather than measurers being trained on a standard approach using the same instrument and taking BP multiple times. In each of these cases, the question would get a "NO" for the former and a "YES" for the latter scenario. Another example of a "NO" is when an intervention group is seen much more often, enabling more opportunities to report clinical events, than the control group.

### **12. Power calculation**

Generally, a paragraph in the methods section of the study will explain sample size needed to detect differences in primary outcomes. The current standard is at least 80% power to detect a clinically-relevant difference in an outcome using a two-sided alpha of 0.05. Often, however, older studies will not report anything about power.

### **13. Prespecified outcomes**

Outcomes reported in the study must have been prespecified in order to be hypothesis testing – which is the whole purpose of doing a RCT. If they are not prespecified, then the study may be reporting ad hoc analyses, simply looking for differences that support the findings they wanted. In addition to outcomes, the subgroups being examined should be prespecified in order to be considered hypothesis testing. Most RCTs conduct numerous post hoc analyses as a way of exploring findings and generating additional hypotheses. The intent of this question is to give more weight to reports that are not simply exploratory in nature.

### **14. Intention-to-treat (ITT) analysis**

Intention-to-treat means everybody who was randomized is analyzed according to the original group to which they are assigned. This is an extremely important concept, because doing an ITT analysis preserves the whole reason for doing a randomized trial—that is to compare groups that differ only in the intervention being tested. Once the ITT philosophy is not followed, you are not really sure that the main reason for doing an RCT is upheld as the groups being compared may no longer be the same. If a study does not use an ITT analysis, it should probably be rated as poor. However, if some other analysis is used and you think it is valid, explain in the "other" box of the quality review form. Some studies will use a *completers analysis* (analyzes only the participants that completed the intervention and the study), which introduces significant potential for bias. Characteristics of participants who do not complete the study are unlikely to be the same as those who do. The likely impact of participants who withdraw from the study treatment must be considered carefully. ITT analysis provides a more conservative (potentially less biased) estimate of effectiveness.

### **Some general guidance for determining the overall quality rating**

The questions on the form are designed to help you to focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity is the extent to which the results (effects) reported in a study can truly be attributed to the intervention being evaluated and not to flaws in the design or conduct of the study – in other words the ability for the study to draw causal conclusions about the effects of the intervention being tested. Any such flaws can increase the risk of bias. Critical appraisal involves considering the risk of potential for allocation bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other – examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above). High potential for risk of bias translates to a rating of poor quality. Low potential for risk of bias translates to a rating of good quality. (Again, the greater the risk of bias, the lower the quality rating of the study.)

Fatal flaws: if a study has a “fatal flaw” then risk of bias is significant and the study is of poor quality. Examples of fatal flaws in RCTs include high drop-out, high differential drop-out, no ITT analysis or/unsuitable statistical analysis (e.g., completers-only analysis).

Generally, when you evaluate a study you will not see a “fatal flaw,” but you will find some risk of bias. By focusing on the concepts underlying the questions in the tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check “no” you should ask what the potential for bias is as a result. That is, does this factor cause you to doubt the results that are reported in the study?

We can provide some background reading for you on critical appraisal. But the best approach is for you to think about the questions in the tool and how each tells you something about the potential for bias for any study. We are reluctant to give you general rules as each study has nuances that are a little bit different. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal.

We will provide you some examples of studies that fall into each of the categories: good/fair/poor. But again, these will be examples. Each study must be assessed on its own given the details that are reported.

### **Data Abstraction and Review Process**

Articles rated good or fair during the quality rating process were abstracted into the VCW using a web-based data entry form. Requirements for abstraction were specified in an Evidence Table template that was developed by the methodologist for each question. The Evidence Table template included data elements relevant to the question such as study characteristics, interventions, population demographics, and outcomes.

The abstractor carefully read the article and entered the required information into the web-based tool. Once abstraction was complete, an independent quality control review was conducted. During this review, data were checked for accuracy, completeness, and the use of standard formatting.

### **Development of Evidence Tables, Summary Tables, and Exhibits**

#### **Evidence Tables**

For each question, methodologists worked with the Panel to identify the key data elements needed to answer the question. Using the PICOTSS criteria as the foundation, Panel members determined what information was needed from each study to be able to understand the design, sample and baseline characteristics in order to interpret the outcomes of interest. A template for a standard evidence table was created and then populated with data from several example studies for review by the Panel to ensure

that all of the appropriate study characteristics were being considered. Once a final template was agreed upon, evidence tables were generated by pulling the appropriate data elements from the master abstraction database for those studies that met the inclusion criteria for the question. Only studies rated Good and Fair were included in the Evidence Tables.

The templates for the Panel's questions included the following data elements:

- Study Characteristics: author, year, study name, country and setting, funding, study design, research objective, year study began, overall study N, quality rating
- Criteria for Study Inclusion/Exclusion and Endpoints: inclusion/exclusion criteria for the study, primary outcome, secondary outcome, composite outcome definitions
- Study Design Details: treatment groups, description of interventions, duration of treatment, duration of follow-up, run-in, wash-out, sample size
- Baseline Population Characteristics: age, sex, race/ethnicity, mean blood pressure, coronary heart disease, cerebrovascular disease, heart failure, diabetes, chronic kidney disease, peripheral artery disease, smoking status, previous antihypertensive therapy, history of MI, history of stroke, mean heart rate, mean GFR, mean serum creatinine, mean creatinine clearance
- Results: outcomes of interest as prespecified in the criteria for the question, adverse events, attrition, adherence

Studies were listed in alphabetical order by study name (if none, the first author's last name). For secondary articles related to a primary article for a study (i.e., a prespecified subgroup analysis published in a separate paper), entries were made in chronological order after the primary article.

### Summary Tables

To enable a more targeted focus on the specific aspects of a question, methodologists developed summary tables, or abbreviated evidence tables, in concert with the Panel. A summary table presents a smaller set of data elements than the Evidence Tables and might be designed to address the general population or a specific subpopulation, such as patients with diabetes. Templates generally provided the following information:

- Study Characteristics: study name, author/year, design, overall study numbers, quality rating
- Sample Characteristics: relevant inclusion criteria
- Study Design Details: intervention doses and duration
- Results: outcomes, attrition, adherence

The ordering of studies in the Summary Tables was determined by the question addressed by the Table. For Question 1, studies were listed by ascending blood pressure treatment initiation threshold; separate Summary Tables were created for systolic, diastolic, and mixed systolic/diastolic treatment initiation thresholds. For Question 2, studies were listed by ascending blood pressure treatment goal; separate Summary Tables were created for systolic, diastolic, and mixed systolic/diastolic treatment goals. For Question 3, studies were listed in alphabetical order of the intervention drug, and by ascending dose order within drugs; separate Summary Tables were created for each drug class.

### Exhibits

The Panel used an even more concise view of the eligible evidence to summarize evidence and develop evidence statements. These materials were called exhibits. In exhibits, each outcome was given a color

coded symbol that was designed to enable panel members to quickly compare and summarize outcomes across trials in a one-to-two page view. A sample exhibit used for Question 1 is provided in Exhibit 2 below.

An outcome was given a circle symbol if it was the primary outcome of the study; a triangle was used if the outcome was secondary or not specified. The symbol was green if the p value between the intervention and comparison group was  $<0.05$ ; yellow if the p value was  $p \geq 0.05$  and  $\leq 0.10$ ; clear if the p value was  $>0.10$ ; and blue if the p value was not reported.

## EXHIBIT 2: SAMPLE OF EVIDENCE EXHIBIT

<b>Legend</b> Shapes: Circle = Primary outcome; Triangle = Secondary outcome or not specified Colors: Green = Statistically significant where the treated group did better ( $p < 0.05$ ); Yellow = $p \geq 0.05$ and $\leq 0.10$ ; Clear = $p > 0.10$				
Trial, year Population Sample size Trial duration Quality Rating	Overall Mortality	Coronary Heart Disease (includes non-fatal MI, fatal MI, sudden death or combination)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal or combination)	Heart Failure (includes fatal, non-fatal, or combination)
<b>EWPHE, 1985</b>  Adults, ages $\geq 60$ years, SBP 160-239 and DBP 90-119 mmHg  N = 840  Mean 4.6 yrs  Fair	 All cause mortality: 9% decrease in bt CI (-28, 15) p = 0.41	 Cardiac mortality: 38% reduction in bt group per 1000 py, $p = 0.036$ Fatal cardiac events: at 1 year 11% reduction in bt per 1000 py $p < 0.05$	 Non-fatal cerebrovascular events, at 1 year: 11% decrease in bt per 1000 py, $p < 0.05$   Cerebrovascular deaths: 32% decrease in bt CI (-61, 19) $p = 0.16$	 Severe CHF: at 1 year: 8% decrease in bt per 1000 py $p < 0.05$
<b>HYVET, 2008</b>  Adults, ages $\geq 80$ years, SBP $\geq 160$ and DBP 90-109 at start of trial but relaxed later to $< 110$ mmHg  N = 3,845  Mean 2.1 years  Good	 Death from any cause: Unadj HR: 0.79 CI (0.65, 0.95) $p = 0.02$ *study stopped early due to mortality reduction	 Death from cardiac cause: Unadj HR: 0.71 CI (0.42, 1.19) $p = 0.19$ Fatal and non-fatal MI: Unadj HR: 0.72 CI (0.30, 1.70) $p = 0.45$	 Death from stroke: Unadj HR: 0.61 CI (0.38, 0.99) $p = 0.046$   Fatal or non-fatal stroke: Unadj HR: 0.70 CI (0.49, 1.01) $p = 0.06$	 Death from HF: unadj HR: 0.48 CI (0.18, 1.28) $p = 0.14$   Fatal or non-fatal HF: Unadj HR: 0.36 CI (0.22, 0.58) $p < 0.001$
<b>SHEP, 1991</b>  Adults, ages $\geq 60$ years, SBP 160-219 and DBP $< 90$ mmHg  N = 4,736  Mean 4.5 years  Good	 Total deaths: RR: 0.87 CI (0.73, 1.05) $p = \text{NR}$	 Non-fatal MI: RR: 0.67 CI (0.47, 0.96) $p = \text{NR}$ Symptomatic MI events: 63 vs 98 (bt vs control) $p = 0.005$ CHD RR: 0.75 CI (0.60, 0.94) $p = \text{NR}$ Non-fatal MI or CHD deaths RR: 0.73 CI (0.57, 0.94) $p = \text{NR}$   MI deaths: RR: 0.57 CI (0.30-1.08) $p = \text{NR}$ Total CHD deaths: RR: 0.80 CI (0.57, 1.13) $p = \text{NR}$ Sudden death ( $< 1$ hour): RR: 1.00 CI (0.56, 1.78) $p = \text{NR}$ Rapid deaths (1-24 hours): RR: 0.87 CI (0.48, 1.56) $p = \text{NR}$	 Non-fatal plus fatal stroke: RR: 0.64 (0.50, 0.82) $p = 0.0003$	 Fatal and non-fatal HF: RR: 0.51 (0.37, 0.71) $p < 0.001$
<b>Syst-Eur, 1997</b>  Adults, ages $\geq 60$ years, SBP 160-219 and DBP $< 95$ mmHg  N = 4,695  Median 24 months  Good	 Total mortality: Adj HR: 0.86 CI (0.67, 1.10) $p = \text{NR}$	 Fatal and non-fatal cardiac endpoints: Adj HR: 0.71 CI (0.54, 0.94) $p < 0.05$   Fatal MI: 56% decrease in bt group per 1000 py, CI (-82, 9) $p = 0.08$   Non-fatal MI: 20% decrease in bt group per 1000 py, CI (-53, 34) $p = 0.40$ Coronary mortality: 27% decrease in bt group per 1000 py, CI (-54, 15) $p = 0.17$ Sudden death: 12% decrease in bt group per 1000 py, CI (-49, 52) $p = 0.65$ Fatal and non-fatal MI: 30% decrease in bt group per 1000 py, CI (-56, 9) $p = 0.12$	 Non-fatal stroke: 44% decrease in active (rate/1000 py) CI (-63, -14), $p = 0.007$   Death due to Stroke: 27% decrease in bt group per 1000 py CI (-62, 39), $p = 0.33$   Fatal and non-fatal stroke combined: Adj HR: 0.59 (0.38, 0.79) $p < 0.01$	 Non-fatal HF: 36% decrease in bt group per 1000 py CI (-60, 2) $p = 0.06$   Fatal HF: 24% decrease in active (rate/1000 py) CI (-70, 93) $p = 0.57$ Fatal & non-fatal HF: 29% decrease in bt group per 1000 py CI (-53, 10) $p = 0.12$

## **Process for the Development of Evidence Statements, Recommendations, and Panel Voting**

Using the Exhibits (and Summary and Evidence Tables as needed), Evidence Statements were written by Panel members with input from the methodology team and oversight by the NHLBI Lead. In cases where the evidence was too limited or inconclusive, no evidence statement was developed, or a statement of insufficient evidence was made.

The methodology team provided the Panel with overarching guidance on how to grade the overall level of evidence (high, moderate, or low), and the Panel used this guidance to grade each Evidence Statement. This guidance is documented in the following section.

Panel members that had relationships with industry (RWI) or other possible conflicts of interest (COI) were allowed to participate in discussions leading up to voting as long as they declared their relationships, but they had to recuse themselves from voting on any issue relating to their RWI or COI. Voting was conducted by a Panel Chair asking each member to signify his or her vote. NHLBI program staff and contractors did not vote.

Once Evidence Statements were finalized, attention turned to developing Recommendations. Recommendations were developed using a similar process to Evidence Statements. For approval of a recommendation rated E (Expert Opinion) at least 75% of the panel members had to support it.

For both Evidence Statements and Recommendations, the Panel took a verbal 'straw poll' and a final electronic vote. Nonbinding 'straw polls' were taken to ensure that there was general acceptance among the panel for the Evidence Statement or Recommendation before moving to the next one and because 100% participation from all panel members was not possible on every call when voting took place. 'Straw polls' were open so that differing viewpoints could be offered and to facilitate further discussion and revisions as needed to address areas of disagreement. Final votes were collected by email ballot and were confidential.

For both Evidence Statements and Recommendations, a record of the vote count (for, against, or recusal) was made without attribution. The panel strove for 100% consensus whenever possible, but a majority was considered acceptable, with the exception of Recommendations based on Expert Opinion, which required a 75% majority to pass.

### **Grading the Body of Evidence: Description of Methods for**

The NHLBI Adult Cardiovascular Disease Guidelines Project applied related but distinct processes for grading the bodies of evidence for questions, for different outcomes included within questions, and for recommendations developed from those bodies of evidence. Each of these processes is described in turn below.

#### **Grading the Body of Evidence**

In developing the system for grading the body of evidence, NHLBI's Evidence-Based Methodology Lead reviewed a number of systems, including GRADE, United States Preventive Services Task Force (USPSTF), ACC/AHA, American Academy of Pediatrics, Strength of Recommendation Taxonomy, Canadian Task Force on Preventive Health Care, Scottish Intercollegiate Guidelines Network, and Center for Evidence Based Medicine in Oxford. In particular, GRADE, USPSTF, and ACC/AHA were considered at length. However, none of those systems fully met the needs of the project. Therefore, NHLBI's Evidence-Based Methodology Lead, with input from NHLBI staff, the external methodology team, and the Guideline Panels

and Work Groups, developed a hybrid version that incorporated features of those systems. This system was used by all Panels and Work Groups in the Adult Cardiovascular Disease Guidelines Project and was strongly supported by the Expert Panels and Work Groups. In using the system, decisions about evidence grading were made by the Panels and Work Groups and methodology team working collaboratively to apply the system and guidance in a thoughtful manner.

Once the Panel reached consensus on the wording of an evidence statement, the next step was to grade the strength of the body of supporting evidence. The strength of the body of evidence represents the degree of certainty, based on the overall body of evidence, that an effect or association is correct. The strength of evidence was graded as High, Moderate, or Low. The following table illustrates various types of evidence and the strength of evidence they represent.

<b>Type of Evidence</b>	<b>Strength of Evidence Grade</b>
<ul style="list-style-type: none"> <li>• Well-designed, well-executed randomized controlled trials (RCTs) that adequately represent populations to which the results are applied and directly assess effects on health outcomes;</li> <li>• Meta-analyses of such studies.</li> <li>• <i>There is high confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of effect.</i></li> </ul>	<b>High</b>
<ul style="list-style-type: none"> <li>• RCTs with minor limitations affecting confidence in, or applicability of, the results, including minor flaws in design or execution;</li> <li>• Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies;</li> <li>• Meta-analyses of such studies;</li> <li>• <i>There is moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.</i></li> </ul>	<b>Moderate</b>
<ul style="list-style-type: none"> <li>• RCTs with major limitations;</li> <li>• Nonrandomized intervention studies and observational studies with major limitations affecting confidence in, or applicability of, the results;</li> <li>• Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports)</li> <li>• Physiological studies in humans.</li> </ul>	<b>Low</b>

Type of Evidence	Strength of Evidence Grade
<ul style="list-style-type: none"> <li>• Meta-analyses of such studies;</li> <li>• <i>There is low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.</i></li> </ul>	

Guidance was provided by methodologists for assessing the strength of the body of evidence supporting each evidence statement or recommendation using four domains: 1) risk of bias; 2) consistency; 3) directness; and 4) precision. Each domain was assessed and discussed, and the aggregate assessment was used to increase or decrease the strength of the evidence, as determined by the Evidence Grading System shown above. The four domains are explained in more detail below:

### **Risk of bias**

Risk of bias refers to the likelihood that the body of included studies for a given question or outcome is biased due to flaws in the design or conduct of the studies. Risk of bias and internal validity are similar concepts that are inversely correlated. A study with a low risk of bias has high internal validity and is more likely to provide correct results than one with high risk of bias and low internal validity. At the individual study level, risk of bias is determined by rating the quality of each individual study using standard rating instruments, such as the study quality rating tools presented and discussed in the previous section of this report. Overall risk of bias for the body of evidence regarding a particular question, summary table, or outcome is then assessed by the aggregate quality of studies available for that particular question or outcome. Panel members reviewed the individual study quality ratings with methodologists to determine the aggregate quality of the studies available for a particular question, summary table, or outcome. If the risk of bias is low, it increases the strength of evidence rating for the strength of the overall body of evidence; if the risk of bias is high, it decreases the strength of evidence rating.

### **Consistency**

Consistency is the degree to which reported effect sizes are similar across the included studies for a particular question or outcome. Consistency enhances the overall strength of evidence and is assessed through effect sizes being in the same direction (e.g., multiple studies demonstrate an improvement in a particular outcome), and the range of effect sizes across studies being narrow. Inconsistent evidence is reflected in effect sizes that are in different directions, a broad range of effect sizes, non-overlapping confidence intervals, or unexplained clinical or statistical heterogeneity. Studies included for a particular question or outcome can have effect sizes that are consistent, inconsistent, or unknown (or not applicable). The latter occurs in situations where there is only a single study. For this project, consistent with the EPC approach, evidence from a single study generally was considered insufficient for a high strength of evidence rating because a single trial, no matter how large or well designed, may not provide definitive evidence of a particular effect until confirmed by another trial. However, a very large, multi-centered, well-designed, well-executed RCT that performs well in the other domains could in some circumstances be considered high-quality evidence after thoughtful consideration.

## **Directness**

Directness has two aspects: the direct line of causality and the degree to which findings from a specific population can be applied to a broader population. The first defines directness as whether the evidence being assessed reflects a single direct link between the intervention (or service, approach, exposure, etc.) of interest and the ultimate health outcome under consideration. Indirect evidence relies on intermediate or surrogate outcomes that serve as links along a causal pathway. Evidence that an intervention results in changes in important health outcomes (e.g., mortality, morbidity) increases the strength of the evidence. Evidence that an intervention results in changes limited to intermediate or surrogate outcomes (e.g., a blood measurement) decreases the strength of the evidence. However, the importance of each link in the chain should be considered, including existing evidence that a change in an intermediate outcome affects important health outcomes.

The Panel focused its review on studies that assessed the effects on important health outcomes, which were predefined by the inclusion/exclusion criteria for each question. Intermediate outcomes or surrogate measures were not considered.

Another example of directness involves whether the bodies of evidence used to compare interventions are the same. For example, if Drug A is compared to placebo in one study and Drug B is compared to placebo in another study, using those two studies to compare Drug A versus Drug B yields indirect evidence and provides a lower strength of the evidence than direct head-to-head comparison studies of Drug A versus Drug B. This type of indirect evidence was not used by the Panel. For example, Question 3, which focused on comparative benefits and harms of various antihypertensive drugs and drug classes, included only head-to-head drug trials.

The second aspect of directness refers to the degree to which participants or interventions in the study are different from those to whom the study results are being applied. This concept is referred to as applicability. If the population or interventions are similar, the evidence is direct and strengthened. If they are different, the evidence is indirect and weakened.

## **Precision**

Precision is the degree of certainty about an estimate of effect for a specific outcome of interest. Indicators of precision are statistical significance and confidence intervals. Precise estimates enable firm conclusions to be drawn about an intervention's effect relative to another intervention or control. An imprecise estimate is where the confidence interval is so wide that the superiority or inferiority of an intervention cannot be determined. Precision is related to the statistical power of the study. An outcome that was not the primary outcome or not prespecified will generally be less precise than the primary outcome of a study. In a meta-analysis, precision is reflected by the confidence interval around the summary effect size. For systematic reviews, where there are multiple studies, but no quantitative summary estimate, the quantitative information from each study should be considered in determining the overall precision of the body of included studies, since some studies may be more precise than others. Determining precision across many studies without conducting a formal meta-analysis is challenging and requires judgment. A more precise body of evidence increases the strength of evidence and less precision reduces the strength of a body of evidence.

Following discussion of the four criteria for the strength of evidence grading options, other issues were also considered in some cases. For example, the objectivity and validity of an outcome measure is an

important issue that needs to be considered. Total mortality is an objective measure that is usually recorded accurately. On the other hand, revascularization had less emphasis placed on it by the Panel compared to the other clinical endpoints because it is a softer endpoint with wide practice variation that is often performed without appropriate indications.

After detailed discussions by the Panel regarding all of the evidence grading criteria, a vote was taken to grade the strength of evidence for each evidence statement and recommendation. The methodologists provided input and made recommendations on grading the strength of the evidence, but they did not participate in the voting process. The final evidence grading decision was determined by a majority vote. If there were dissenting opinions, the Panel tried to achieve consensus by further discussion and modification in an effort to achieve unanimity whenever possible.

## LITERATURE SEARCH YIELDS

For Question 1, 1498 articles were screened. Of these, 1457 articles were excluded because they did not meet the prespecified inclusion criteria. Of the 41 included articles, 7 were rated as good, 18 rated as fair, and 16 rated as poor, thus resulting in 25 articles abstracted.

For Question 2, 1980 articles were screened. Of these, 1915 articles were excluded because they did not meet the prespecified inclusion criteria. Of the 65 included articles, 14 were rated as good, 23 rated as fair, and 28 rated as poor, thus resulting in 37 articles abstracted.

For Question 3, 2668 articles were screened. Of these, 2570 articles were excluded because they did not meet the prespecified inclusion criteria. Of the 98 included articles, 17 were rated as good, 47 rated as fair, and 34 rated as poor, thus resulting in 64 articles abstracted.

Detailed search strategy for each question is provided in the appendix.

## POPULATIONS ADDRESSED IN THIS GUIDELINE

The Recommendations and Evidence Statements in this guideline are based on the results of RCTs that were eligible for the evidence review based on prespecified inclusion and exclusion criteria. The prespecified criteria required only that study participants were adults 18 years of age or older and that they had hypertension as defined by the study. Participants with specific co-morbidities were not excluded from the evidence review. In fact, many of the hypertension treatment trials required participants to have at least one additional cardiovascular risk factor or co-morbidity, such as diabetes, previous myocardial infarction or stroke, left ventricular hypertrophy, or dyslipidemia [Jamerson, 2008; ALLHAT, 2002; Brown, 2000; Dahlöf, 2005; Dahlöf, 2002]. Therefore, for the purposes of this guideline, the term '*general population*' does not specifically exclude people with these conditions. It does, however, exclude people who were ineligible for these studies, such as those with acute illnesses, hospitalized patients, and emergency department patients.

In addition to trials in the general adult population, the Panel also examined trials that were restricted to participants with hypertension and diabetes [UKPDS, 1998; ACCORD, 2010; Estacio, 2000] or hypertension and chronic kidney disease [Wright, 2002; Ruggenenti, 2005; Khlar, 1994; Esnault, 2008; Marin, 2001; Lewis, 2001]. The Panel also reviewed evidence from trials looking at prespecified subgroups with hypertension and diabetes or hypertension and chronic kidney disease that were part of a larger trial; however, a subgroup analysis of a trial was only included if the diabetes or chronic kidney disease subgroup analysis was prespecified. The evidence from these trials and analyses formed the basis for Recommendations (4, 5, 6b, 7b, and 8) and the Evidence Statements specific to these populations.

## DEFINITION OF HIGH BLOOD PRESSURE OR HYPERTENSION

For the purposes of this report, the definition for high blood pressure or hypertension was derived from the studies that were included in our evidence review, which usually defined high blood pressure or hypertension as a systolic blood pressure greater than or equal to 140 mm Hg, a diastolic blood pressure greater than or equal to 90 mm Hg, or both. The Panel did not set out to define high blood pressure or hypertension; its task was to take an evidence-based approach to answer the three questions discussed in the previous sections and to make evidence-based recommendations regarding blood pressure treatment thresholds and goals based on data from RCTs that demonstrate benefits on important health outcomes. In the absence of further evidence to make a change to the previously established definition of high blood pressure or hypertension, the Panel supports maintaining the current definition of a systolic

blood pressure greater than or equal to 140 mm Hg, a diastolic blood pressure greater than or equal to 90 mm Hg, or both in the setting of properly taken office measurements.



# Evidence Statements

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## EVIDENCE STATEMENTS

The language within the Evidence Statements is specific and a note of clarification is in order. Where there is evidence, the language is easily interpreted. “Evidence is insufficient” means that evidence was found within the studies examined, but it was not of sufficient quality to make a recommendation. “No RCTs of good or fair quality” means that no study was found with sufficient quality on which to base a recommendation but that evidence was found within the literature search criteria among poorer quality studies. “No RCTs of any quality” means that no studies were found within the entire literature search including poor quality studies.

### EVIDENCE STATEMENTS FOR QUESTION 1

**Question 1: In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?**

Exhibits for Question 1 Evidence Statements are provided in the Appendix.

- [Exhibit A: Evidence from randomized controlled trials on initiating antihypertensive pharmacologic therapy at SBP Thresholds  \$\geq\$  160 mmHg](#)
- [Exhibit B: Evidence from randomized controlled trials on initiating antihypertensive pharmacologic therapy at DBP Thresholds  \$\geq\$  90 mmHg](#)

**Question 1, Evidence Statement 1:** Initiating treatment with antihypertensive medication to lower BP in adults 60 years of age or older with systolic BP  $\geq$ 160 mm Hg reduces cerebrovascular morbidity and mortality (includes fatal stroke, nonfatal stroke or a combination of fatal and nonfatal stroke).

Evidence Quality: High

**Rationale/Comments:** Four studies contributed to this evidence statement (EWPHE, HYVET, SHEP, and Syst-Eur) [Amery, 1985; Fletcher, 1991; Beckett, 2008; SHEP, 1991; Staessen, 1997]. Three studies were rated as Good with study populations ranging in size from 3,845 to 4,736 (HYVET, SHEP, and Syst-Eur), while one study was rated as Fair and had 840 participants (EWPHE). Cerebrovascular morbidity and/or mortality were the primary outcomes in each of these four trials. In each trial, initiation of antihypertensive medication at a systolic blood pressure of 160 mm Hg or greater decreased cerebrovascular morbidity or mortality. In SHEP and Syst-Eur, combined fatal and non-fatal stroke was reduced by 36% ( $p=0.0003$ ) and 42% ( $p=0.003$ ), respectively. In HYVET, there was a 30% reduction in fatal or non-fatal stroke, but the  $p$ -value was 0.06. However, HYVET was stopped early because of a 21% reduction in mortality in the active treatment group. If the study had not been stopped early, the reduction in fatal or non-fatal stroke may have been significant by the end of the trial. In EWPHE, a much smaller trial with 840 participants that was rated as Fair, there was an 11% reduction in non-fatal cerebrovascular events at one year ( $p < 0.05$ ) and a 32% non-significant decrease ( $p = 0.16$ ) in cerebrovascular mortality at the end of the trial, which had a mean follow-up of 4.6 years.

**Question 1, Evidence Statement 2:** Initiating treatment with antihypertensive medication to lower BP in adults 60 years of age or older with systolic BP  $\geq$ 160 mm Hg reduces fatal and non-fatal heart failure.

Evidence Quality: High

**Rationale/Comments:** The same four studies used for Evidence Statement 1 on cerebrovascular events contributed to this statement (EWPHE, HYVET, SHEP, and Syst-Eur) [Fletcher, 1991; Beckett, 2008; Kostis, 1997; Staessen, 1997]. Heart failure was a secondary outcome in these four trials. In three of the trials (EWPHE, HYVET, and SHEP), initiation of antihypertensive medication at a systolic blood pressure of 160 mm Hg or greater significantly reduced heart failure events. In HYVET and SHEP, fatal and non-fatal heart failure were reduced by 64% ( $p < 0.001$ ) and 49% ( $p < 0.001$ ), respectively. EWPHE, a much smaller study, had an 8% reduction in HF at 1 year ( $p < 0.05$ ); however heart failure events at the end of the trial, which had a mean follow-up of 4.6 years, were not reported for the intent-to-treat analysis [Fletcher, 1991; Amery, 1985]. For our evidence review, only intent-to-treat analyses were considered. Syst-Eur had a 29% reduction in fatal and non-fatal heart failure ( $p = 0.12$ ) and a 36% reduction in non-fatal heart failure ( $p = 0.06$ ), but they were not statistically significant.

**Question 1, Evidence Statement 3:** Initiating treatment with antihypertensive medication to lower BP in adults 60 years of age or older with systolic BP  $\geq 160$  mm Hg reduces coronary heart disease (includes: CHD mortality, fatal MI, non-fatal MI).  
Evidence Quality: Moderate

**Rationale/Comments:** The same four studies used for Evidence Statements 1 and 2 on cerebrovascular events and heart failure contributed to this statement (EWPHE, HYVET, SHEP, and Syst-Eur) [Amery, 1985; Fletcher, 1991; Beckett, 2008; SHEP, 1991; Perry, 2000; Staessen, 1997; Staessen, 1998]. Because the studies did not all use the same coronary heart disease (CHD) outcomes, the Panel considered CHD to include fatal MI, non-fatal MI, or CHD mortality. Coronary heart disease was a secondary outcome in all four trials. In three of the trials (EWPHE, SHEP, and Syst-Eur), initiation of antihypertensive medication at a systolic blood pressure of 160 mm Hg or greater significantly reduced at least one CHD outcome (fatal MI, non-fatal MI, or CHD mortality). In some trials, the difference in fatal events was significant, whereas in others the difference in non-fatal events and the combination of fatal and nonfatal events was significant. In all of these trials, the direction and magnitude of the CHD results were similar.

In SHEP, non-fatal MI was lowered by 33% (95% CI, 0.47, 0.96), and non-fatal MI or CHD deaths were lowered by 27% (95% CI, 0.57, 0.94). In EWPHE cardiac mortality was lowered by 38% ( $p = 0.036$ ). In Syst-Eur there was a 30% reduction in fatal and non-fatal MI, but the  $p$  value was 0.12 (95% CI, -56%, 9%); there was also a 56% reduction in fatal MI, but the  $p$  value was 0.08 (95% CI, -82%, 9%). Syst-Eur also reported a 29% reduction in fatal and non-fatal cardiac endpoints ( $p < 0.05$ ); however, this composite outcome included heart failure (which was addressed in Evidence Statement 2), MI and sudden death. Reductions in CHD outcomes in HYVET were not statistically significant.

The quality of evidence was considered moderate because CHD was a secondary outcome in all four studies. In addition, despite the fact that all the CHD outcomes were in the same direction (showing benefit), in two of the studies (SHEP and Syst-Eur), there was a mix of significant and non-significant CHD results, and in one study (HYVET), none of the CHD results was significant.

**Question 1, Evidence Statement 4:** Initiating treatment with antihypertensive medication to lower BP in adults 80 years of age or older with systolic BP  $\geq 160$  mm Hg reduces overall mortality.  
Evidence Quality: Moderate

**Rationale/Comments:** One study (HYVET) contributed to this Evidence Statement [Beckett, 2008]. HYVET was the only RCT conducted exclusively in adults 80 years of age or older where antihypertensive

medication was initiated at a systolic blood pressure of 160 mm Hg or greater. HYVET had 3,845 participants and was rated a Good study. It showed a significant 21% reduction in overall mortality in the treated group ( $p = 0.02$ ; 95% CI, 0.65-0.95), resulting in the study being stopped early because of this benefit. Even though HYVET was rated a Good study, the overall evidence supporting this statement was graded as moderate because the evidence comes from only one study, and overall mortality was a secondary outcome. EWPHE, SHEP, and Syst-Eur also showed reductions in overall mortality ranging from 9% to 14%, but their findings were not significant, and most of their study participants were younger than 80 years of age [Amery, 1985; SHEP, 1991; Staessen, 1997].

**Question 1, Evidence Statement 5:** The evidence is insufficient to determine whether there is a reduction in all-cause mortality with initiation of antihypertensive medication to lower BP in adults 60 to 79 years of age with systolic BP  $\geq 160$  mm Hg.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** There were three trials that contributed to this Evidence Statement (EWPHE, SHEP, and Syst-Eur) [Amery, 1985; SHEP, 1991; Staessen, 1997]. Two of these trials (SHEP; 4,736 participants and Syst-Eur; 4,695 participants) were rated as Good, and one trial (EWPHE; 840 participants) was rated as Fair. None of these trials showed a statistically significant reduction in overall mortality.

The Panel graded the evidence as insufficient because overall mortality was a secondary outcome in all three trials – i.e., none of the studies was designed to detect a difference in overall mortality. Therefore, there was uncertainty as to whether the results were non-significant because there was truly no difference in overall mortality between the treatment and comparison groups, or because the studies were not adequately powered to detect a difference.

A fourth study (Syst-China) [Liu, 1998] met our initial screening eligibility criteria but was subsequently excluded based on its Poor quality rating. It was rated as Poor because the randomization technique and allocation concealment were not adequate, participants were not similar at baseline, and the study eligibility criteria were not met in 19.3% of participants. Syst-China did show a significant 39% decrease in all-cause mortality ( $p=0.003$ ), but it was a secondary outcome.

**Question 1, Evidence Statement 6:** In adults less than 60 years of age with hypertension, there are no RCTs of good or fair quality to determine whether initiating treatment with antihypertensive medication to lower BP at any systolic BP threshold improves cardiovascular outcomes, cerebrovascular outcomes, or mortality.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** The Panel found one study (The Oslo Study) meeting the inclusion criteria where antihypertensive medication was initiated at a specific systolic blood pressure threshold in adults less than 60 years of age [Helgeland, 1980]. However, it was subsequently excluded because of a Poor quality rating.

The Oslo Study included 785 men 40 to 49 years of age, and treatment was initiated at a systolic blood pressure threshold of 150 mm Hg. This study was rated Poor because it was not blinded: there was a 17% crossover rate from the control group to the active treatment group, and it was likely underpowered to detect significant differences in these outcomes because it only had 785 participants and 59 total

cardiovascular events (25 in the treatment group versus 34 in the control;  $p > 0.10$ ). They did detect a significant decrease in cerebrovascular events in the treated group ( $p < 0.02$ ), but there were only 7 events. There was no benefit in terms of total cardiovascular events, coronary events, or total mortality.

The Panel found one other study [Carter, 1970] where antihypertensive medication was initiated at a specific systolic blood pressure threshold, but it did not meet the inclusion criteria because it had less than 100 participants ( $n = 97$ ), and only 28 of them were less than 60 years of age. In addition, the study was not blinded, randomization and allocation concealment techniques were not clear, and it was likely underpowered to detect significant differences in these outcomes.

**Question 1, Evidence Statement 7:** The evidence is insufficient to determine whether initiating treatment with antihypertensive medication at a SBP threshold of 140 mm Hg improves cardiovascular outcomes, cerebrovascular outcomes, or mortality.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** There is only one placebo or usual care RCT (Hypertension-Stroke Cooperative Study) that assessed whether initiating treatment with antihypertensive medication at a systolic blood pressure threshold of 140 mm Hg improves cardiovascular outcomes, cerebrovascular outcomes, or mortality [HSCoop, 1974]. It was rated as Fair. The study included 452 participants, all of whom had a stroke or TIA in the previous year, and the primary outcome was recurrent stroke. Of the 16 study endpoints that met the question's prespecified criteria, the only benefit was a reduction in non-fatal heart failure, which was a secondary outcome with few events (0 events in the treatment group versus 6 events in the placebo group;  $p = 0.012$ ). The Panel graded the evidence as insufficient because it consisted of only one small study in a secondary prevention population.

**Question 1, Evidence Statement 8:** The evidence is insufficient to determine whether initiating treatment with antihypertensive medication to lower blood pressure in pre-hypertensive patients (SBP 120-139 mm Hg, DBP 80-89 mm Hg) improves cardiovascular outcomes, cerebrovascular outcomes, or mortality.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** There is only one placebo or usual care RCT that assessed whether initiating treatment with antihypertensive medication in people with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg improves cardiovascular outcomes, cerebrovascular outcomes, or mortality. The PHARAO trial, which was rated as Fair, initiated treatment with antihypertensive medication in participants with systolic blood pressure 130-139 mm Hg and/or diastolic blood pressure 85-89 mm Hg [Lüders, 2008]. It included 1,008 participants, and the primary outcome was the development of office hypertension (defined as either office-based systolic blood pressure or diastolic blood pressure or both greater than 140/90 mm Hg) or the intake of any antihypertensive drug other than the study drug. Cerebrovascular and cardiovascular events and death were secondary outcomes. There were no significant differences between the treatment group and control group in any cerebrovascular outcomes, cardiovascular outcomes, or mortality.

Similar to PHARAO, the TROPHY study also investigated whether pharmacologic treatment of a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg prevents or postpones the development of hypertension [Julius, 2006]. TROPHY was conducted in participants with a systolic blood pressure of 130 to 139 mm Hg and diastolic blood pressure of 89 mm Hg or lower, or systolic blood

pressure of 139 mm Hg or lower and diastolic blood pressure of 85 to 89 mm Hg. This trial did not meet the inclusion criteria for this question because it did not report cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality, though the power was low in both studies.

The Panel graded the evidence as insufficient because there was only one study (PHARAO) which was rated as Fair. In addition, cardiovascular outcomes, cerebrovascular outcomes, and mortality were all secondary endpoints, so it is unclear whether the lack of treatment benefit is real or because the study was not powered to detect a significant difference in these outcomes. As a result, there is insufficient evidence to draw conclusions about whether treatment of individuals with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg improves important health outcomes.

**Question 1, Evidence Statement 9:** There are no RCTs of any quality that assessed whether initiating treatment with antihypertensive medication to lower BP at one threshold improved cardiovascular outcomes, cerebrovascular outcomes, or mortality when compared to initiating treatment at another threshold.

Evidence Quality: Unable to determine because there is no evidence

**Rationale/Comments:** There were no studies that randomized a group of patients to start treatment at one blood pressure threshold (for example, SBP 140 mm Hg) and compared them to another group of patients starting treatment at a different blood pressure threshold (for example, SBP 160 mm Hg) and measured the effects of initiating treatment at different blood pressure thresholds on cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

**Question 1, Evidence Statement 10:** Initiating treatment with antihypertensive medication to lower BP in adults 30 years of age or older with diastolic BP  $\geq 90$  mm Hg reduces cerebrovascular morbidity and mortality (includes fatal stroke, nonfatal stroke or a combination of fatal and nonfatal stroke).

Evidence Quality: High

**Rationale/Comments:** Six studies contributed to this evidence statement (EWPHE, HDFP, Hypertension-Stroke Cooperative, HYVET, MRC and VA Cooperative) [Amery, 1985; Fletcher, 1991; HDFP, 1979; HDFP, 1982b; HSCoop 1974; Beckett, 2008; MRC, 1985; VACoop, 1970]. Two studies were rated as Good with study populations of 380 and 3,845 (VA Cooperative and HYVET), while four studies were rated as Fair and ranged in size from 840 to 17,454 (EWPHE, HDFP, Hypertension-Stroke Cooperative, and MRC). Cerebrovascular morbidity and/or mortality were the primary outcomes in four of the six contributing trials (EWPHE, Hypertension-Stroke Cooperative, HYVET, and MRC).

In each trial, initiation of antihypertensive medication at a diastolic blood pressure threshold of 90 mm Hg or greater decreased cerebrovascular morbidity or mortality. Findings were consistent in direction and magnitude across trials. For fatal and non-fatal stroke, HDFP showed a 35% reduction ( $p < 0.01$ ) and MRC showed a 45% reduction ( $p = 0.006$ , once-off testing). In HYVET, there was a 30% reduction in fatal or non-fatal stroke, but the p-value was 0.06. However, HYVET was stopped early because of a 21% reduction in mortality in the active treatment group. If the study had not been stopped early, the reduction in fatal or non-fatal stroke would likely have been significant by the end of the trial.

For fatal stroke, HYVET showed a 39% reduction in the active treatment group ( $p = 0.046$ ) and EWPHE showed a 32% reduction, but it was not significant ( $p = 0.16$ ). In MRC, active treatment reduced fatal stroke by 34% (18 fatal strokes in the active treatment group versus 27 in the placebo group), but the p-

value was not reported. Similarly, there were fewer fatal strokes in HDFP in the stepped care group as compared to the usual care group, but the p-value was not reported (29 fatal strokes in the stepped care group versus 52 in the usual care group). Active treatment reduced non-fatal stroke in EWPHE by 11% at one year ( $p < 0.05$ ). MRC showed a 49% decrease in non-fatal stroke (42 non-fatal strokes in the active treatment group versus 82 in the placebo group); however, the p-value was not reported.

In the diastolic blood pressure studies, many of the participants also had elevated systolic blood pressures, which makes it difficult, if not impossible, to determine if the benefit was due to lowering the diastolic blood pressure versus lowering the systolic blood pressure versus lowering both. Nonetheless, when DBP was targeted, the evidence indicates that cerebrovascular outcomes improved.

**Question 1, Evidence Statement 11:** Initiating treatment with antihypertensive medication to lower blood pressure in adults 30 years of age or older with diastolic blood pressure  $\geq 90$  mmHg reduces heart failure.

Evidence Quality: Moderate

**Rationale/Comments:** Four RCTs contributed to this evidence statement (EWPHE, Hypertension-Stroke Cooperative, HYVET, and VA Cooperative) [Fletcher, 1991; HS Coop, 1974; Beckett, 2008; VA Coop, 1970]. Heart failure was a secondary outcome in all four trials. There were two additional trials (HDFP and MRC) in which antihypertensive medication was initiated at a diastolic blood pressure threshold of 90 mm Hg or greater, but they did not report on heart failure outcomes [HDFP, 1979; HDFP, 1982b; MRC 1985].

In three of the trials (EWPHE, Hypertension-Stroke Cooperative, and HYVET), initiation of antihypertensive medication at a diastolic blood pressure of 90 mm Hg or greater significantly reduced heart failure events. In HYVET, fatal or non-fatal heart failure was lowered by 64% ( $p < 0.001$ ). EWPHE, a much smaller study, had an 8% ARR in HF at 1 year ( $p < 0.05$ ). However, heart failure events at the end of the trial, which had a mean follow-up of 4.6 years, were not reported for the intent-to-treat analysis [Fletcher, 1991; Amery, 1985]. For our evidence review, only intent-to-treat analyses were considered. Hypertension-Stroke Cooperative found a significant reduction in HF ( $p = 0.012$ ); however there were very few events (0 events in the active treatment group and 6 in the placebo group). Similarly, in the VA Cooperative trial there were fewer events in the active treatment group as compared to the placebo group (0 vs 11), but the p-value was not reported.

Even though there were four contributing trials showing consistent results, the Panel graded the evidence as Moderate because heart failure was a secondary outcome in each trial. In addition, there were few heart failure events in three of the four studies, and heart failure was not assessed in a standard systematic way in the older hypertension trials.

**Question 1, Evidence Statement 12:** The evidence is insufficient to determine whether initiating treatment with antihypertensive medication to lower BP in adults 30 years of age or older with diastolic BP  $\geq 90$  mm Hg reduces coronary heart disease events (includes CHD mortality, fatal MI, non-fatal MI).  
Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Six studies were relevant to this evidence statement (EWPHE, HDFP, Hypertension-Stroke Cooperative, HYVET, MRC and VA Cooperative) [Amery, 1985; Fletcher, 1991; HDFP, 1979; HS Coop 1974; Beckett, 2008; MRC, 1985; VA Coop, 1970]. Two studies were rated as Good

with study populations of 380 and 3,845 (VA Cooperative and HYVET), while four studies were rated as Fair and ranged in size from 840 to 17,454 (EWPHE, HDFP, Hypertension-Stroke Cooperative, and MRC).

Coronary heart disease events were the primary outcome in only one trial (MRC). In MRC, coronary events were lowered by 6% in the active treatment group, but the finding was not significant (the p-value was not reported, but the 95% confidence interval was -31% to 21%). Only one trial (EWPHE) showed a significant decrease in coronary heart disease events (38% decrease in cardiac mortality at 4.6 years,  $p=0.036$ ) when treatment was initiated at a diastolic blood pressure threshold of 90 mm Hg or greater.

The Panel graded the evidence as insufficient because coronary heart disease events were the primary outcome in only one (MRC) of the six contributing trials. In the one trial (EWPHE) that they found a significant difference, coronary heart disease events were a secondary outcome. Therefore, it was unclear whether the results were mostly non-significant because there were no differences in coronary heart disease events between the treatment and comparison groups, or because the trials were not powered to detect differences in these outcomes.

**Question 1, Evidence Statement 13:** Initiating treatment with antihypertensive medication to lower BP in adults 30 years of age or older with diastolic BP  $\geq 90$  mm Hg reduces overall mortality.

Evidence Quality: Low

**Rationale/Comments:** Six studies contributed to this evidence statement (EWPHE, HDFP, Hypertension-Stroke Cooperative, HYVET, MRC and VA Cooperative) [Amery, 1985; HDFP, 1979; HS Coop 1974; Beckett, 2008; MRC, 1985; VA Coop, 1970]. Two studies were rated as Good with study populations of 380 and 3,845 (VA Cooperative and HYVET), while four studies were rated as Fair and ranged in size from 840 to 17,454 (EWPHE, HDFP, Hypertension-Stroke Cooperative, and MRC). Overall mortality was the primary outcome in only one of the six relevant trials (HDFP).

Two studies, HDFP and HYVET, showed a significant mortality benefit when antihypertensive treatment was initiated at a diastolic blood pressure threshold of 90 mm Hg or greater. In HDFP, which included participants 30 to 69 years of age, the stepped-care group experienced a 1.3% absolute decrease in mortality at 5 years compared to the usual care group (6.4% in stepped care compared to 7.7% in usual care,  $p<0.01$ ). HYVET, which was conducted in participants 80 years of age or older, showed a significant 21% decrease in mortality in the treatment group and was stopped early due to this benefit. In two (EWPHE, MRC) of the other four trials, there was no significant difference in mortality. In the other two trials (Hypertension-Stroke Cooperative, VA Cooperative), p-values were not reported. In one of those trials (Hypertension-Stroke Cooperative), there was an increase in mortality (20 deaths in the treatment group, 14 deaths in the placebo group), while in the other trial (VA Cooperative), there was a decrease in mortality (8 deaths in the treatment group, 19 deaths in the placebo group).

The Panel graded the evidence as Low because out of the six contributing trials, only one (HDFP) assessed overall mortality as the primary outcome, and it showed only a 1.3% absolute benefit. HYVET also showed a benefit, but the study population was 80 years of age or older.

**Question 1, Evidence Statement 14:** There are no RCTs of good or fair quality that assessed whether initiating treatment with antihypertensive medication to lower BP at any diastolic BP threshold improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality in adults less than 30 years of age.

Vote: Agree with the statement (17/17); Evidence Quality: Unable to determine because there is no evidence

**Rationale/Comments:** There were three trials (Hypertension-Stroke Cooperative, Sprackling, and USPHS) with entry eligibility criteria that allowed for participants less than 30 years of age [HS Coop 1974; Sprackling, 1981; Smith, 1977]; however, it was unclear whether any of the participants in those trials were actually less than 30 years of age. Sprackling (mean age was 81 years, and only 4 participants were less than 65 years of age) and USPHS (age range 21-55 years, with a mean entry age of 44 years) were subsequently excluded because they were rated as Poor. Hypertension-Stroke Cooperative, rated as Fair, was conducted in participants less than 75 years of age who had a stroke or TIA in the previous year. It had 452 participants, and 74 of them were less than 50 years of age. However, it is not reported whether any of the participants were less than 30 years of age. Given that it was a secondary prevention trial in persons with a stroke or TIA, and the mean age of participants entering the trial was 59, the Panel thought that there probably were very few, if any, participants less than 30 years of age in the study.

There were no RCTs of any quality (good, fair, or poor) that assessed whether initiating antihypertensive treatment at any diastolic blood pressure threshold improved cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality in adults *exclusively* less than 30 years of age.

## EVIDENCE STATEMENTS FOR QUESTION 2

**Question 2: In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?**

### Statements for the General Population

Exhibits for Question 2 Evidence Statements for the general adult population are provided in the Appendix.

- [Exhibit C: Evidence from randomized controlled trials on treatment with antihypertensive pharmacologic therapy to specified SBP goals](#)
- [Exhibit D: Evidence from randomized controlled trials on treatment with antihypertensive pharmacologic therapy to specified DBP goals](#)
- [Exhibit E: Evidence from randomized controlled trials on treatment with antihypertensive pharmacologic therapy to mixed SBP and DBP goals](#)

**Question 2, Evidence Statement 1:** Treatment with antihypertensive medication to lower SBP in adults 60 years of age or older to a systolic BP goal <150 mm Hg reduces cerebrovascular morbidity and mortality (includes fatal stroke, nonfatal stroke or a combination of fatal and nonfatal stroke).  
Evidence Quality: High

**Rationale/Comments:** Three studies contributed to this evidence statement (HYVET, Syst-Eur, and SHEP) [Beckett, 2008; Staessen, 1997; SHEP, 1991]. All three studies were rated as Good with study populations ranging in size from 3,845 to 4,736. Syst-Eur and SHEP included adults age 60 or older and HYVET included adults age 80 or older. Cerebrovascular morbidity and/or mortality were the primary outcomes in each of these trials.

HYVET and Syst-Eur had systolic blood pressure goals of less than 150 mm Hg. The systolic blood pressure goal in SHEP was based on baseline blood pressure; the goal for individuals with a systolic blood pressure of greater than 180 mm Hg at baseline was less than 160 mm Hg, and the goal for those

with systolic blood pressures between 160 and 179 mm Hg at baseline was a decrease of at least 20 mmHg. Thus, systolic blood pressure goals in SHEP ranged from 140 mm Hg to 159 mm Hg, unlike the other two studies, which used a fixed goal of <150 mm Hg.

In all three trials, cerebrovascular morbidity or mortality was significantly reduced when participants were treated with antihypertensive medications to a systolic blood pressure goal of less than 150 mm Hg. In SHEP and Syst-Eur, combined fatal and non-fatal stroke were reduced by 36% (p=0.0003) and 42% (p=0.003), respectively. In HYVET, there was a 30% reduction in fatal or non-fatal stroke, but the p-value was 0.06. However, HYVET was stopped early because of a 21% reduction in mortality in the treatment group.

**Question 2, Evidence Statement 2:** Treatment with antihypertensive medication to lower SBP in adults 60 years of age or older to a systolic BP goal <150 mm Hg reduces fatal and nonfatal heart failure.  
Evidence Quality: Moderate

**Rationale/Comments:** The same three studies used for Evidence Statement 1 on cerebrovascular events contributed to this statement (HYVET, Syst-Eur, and SHEP) [Beckett, 2008; Staessen, 1997; Kostis 1997]. All three studies were rated as Good, and heart failure was a secondary outcome in each trial. In HYVET, fatal and non-fatal heart failure were lowered by 64% (p<0.001) even though the study was stopped early because of a 21% reduction in mortality in the treatment group. In SHEP, fatal and non-fatal heart failure were lowered by 49% (p<0.001). Syst-Eur showed a 29% reduction in fatal and non-fatal heart failure (p=0.12) and a 36% reduction in non-fatal heart failure (p=0.06), but they were not statistically significant.

The Panel rated the evidence quality moderate because heart failure was a secondary outcome in all three studies. In addition, the decrease in heart failure was not significant in Syst-Eur but the findings were in the same direction as the other trials.

**Question 2, Evidence Statement 3:** Treatment with antihypertensive medication to lower SBP in adults 60 years of age or older to a systolic BP goal <150 mm Hg reduces coronary heart disease (includes non-fatal MI, fatal MI, CHD death, or sudden death).  
Evidence Quality: Moderate

**Rationale/Comments:** The same three studies used for Evidence Statements 1 and 2 on cerebrovascular events and heart failure contributed to this statement (HYVET, Syst-Eur, and SHEP) [Beckett, 2008; Staessen, 1997; Staessen, 1998; SHEP 1991; SHEP 1993; Perry 2000]. Because the studies did not all use the same CHD outcomes, the Panel considered CHD to include non-fatal MI, fatal MI, CHD death, or sudden death. Coronary heart disease was a secondary outcome in all three trials.

In SHEP, treatment with antihypertensive medication reduced CHD events by 25% (95% CI: 0.60, 0.94), non-fatal MI by 33% (95% CI: 0.47, 0.96), and non-fatal MI or CHD deaths by 27% (95% CI: 0.57, 0.94). In Syst-Eur, treatment reduced fatal and non-fatal cardiac endpoints by 29% (95% CI: 0.54, 0.94). However, these cardiac endpoints consisted of heart failure, myocardial infarction, and sudden death. Reductions in the individual CHD component outcomes were not significant. In HYVET, none of the CHD outcomes was significantly reduced, but the study was stopped early because of a 21% reduction in mortality in the treatment group.

Determining the overall quality of evidence was challenging for several reasons. In all three studies, CHD was a secondary outcome. In two of the studies (SHEP and Syst-Eur), there were significant reductions in CHD outcomes, but Syst-Eur used a composite outcome that included heart failure. In HYVET, there were no significant reductions in CHD outcomes, but the trial was stopped early because of the mortality benefit. After factoring in all these issues, the Panel graded the overall quality as Moderate.

**Question 2, Evidence Statement 4:** Treatment with antihypertensive medication to lower SBP in adults 80 years of age or older to a systolic BP goal <150 mm Hg reduces overall mortality.

Evidence Quality: Moderate

**Rationale/Comments:** One study (HYVET) contributed to this Evidence Statement [Beckett, 2008]. HYVET was the only RCT conducted exclusively in adults 80 years of age or older where participants were treated to a systolic blood pressure goal of less than 150 mm Hg. HYVET had 3,845 participants and was rated a Good study. It showed a significant 21% reduction in overall mortality in the treated group ( $p = 0.02$ ; 95% CI, 0.65-0.95), resulting in the study being stopped early because of this benefit. Even though HYVET was rated a Good study, the overall evidence supporting this statement was graded as moderate because the evidence comes from only one study, and overall mortality was a secondary outcome in that study. Syst-Eur and SHEP also showed reductions in overall mortality of 14% and 13%, respectively, but their findings were not significant, and most of their study participants were younger than 80 years of age [Staessen, 1997; SHEP, 1991]. In Syst-Eur, 9.3% of participants were 80 years of age or older at baseline; in SHEP, the proportion was 13.7%. Thus, the small percentages of participants in Syst-Eur and SHEP who were 80 years of age or older provided limited data for this evidence statement, further supporting a moderate quality of evidence.

**Question 2, Evidence Statement 5:** In the general population less than 80 years of age, the evidence is insufficient to determine whether treatment with antihypertensive medication to lower SBP to a goal <150 mm Hg reduces overall mortality.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Two studies, Syst-Eur and SHEP, contributed to this evidence statement [Staessen, 1997; SHEP, 1991]. Both were large studies rated as Good, and overall mortality was a secondary outcome in each trial. Syst-Eur and SHEP showed non-significant reductions in overall mortality of 14% (95% CI: 0.67, 1.09) and 13% (95% CI: 0.73, 1.05), respectively.

The Panel graded the evidence as insufficient because overall mortality was a secondary outcome in both trials. Therefore, it was uncertain whether the non-significant results were because there was truly no difference in overall mortality between the treatment and comparison groups or because the studies were not adequately powered to detect a difference.

**Question 2, Evidence Statement 6:** In the general population  $\geq 65$  years of age with hypertension, there is evidence that treatment with antihypertensive medication to a systolic blood pressure goal <140 mm Hg compared to a higher goal does not improve cardiovascular outcomes, cerebrovascular outcomes, or mortality.

Evidence Quality: Low

**Rationale/Comments:** Two studies (JATOS and VALISH) contributed to this evidence statement [JATOS, 2008; Ogiyama, 2010]. Both studies were rated as Good with study populations of 3,260 and 4,418,

respectively. JATOS compared a systolic blood pressure goal of less than 140 mm Hg to a goal of 140-160 mm Hg in adults 65 to 85 years of age. VALISH compared a systolic blood pressure goal of less than 140 mm Hg to a goal of 140-149 mm Hg in adults 70-85 years of age. Both studies were conducted in Japan and used composite measures as their primary outcomes. The primary composite outcome in JATOS included: cerebrovascular disease, cardiac and vascular disease, and renal failure. The primary composite outcome in VALISH included: sudden death, fatal or nonfatal stroke, fatal or nonfatal MI, heart failure death, other cardiovascular death, unplanned hospitalization for cardiovascular disease, and renal dysfunction (defined as a doubling of serum creatinine or dialysis).

None of the primary or individual secondary outcomes in JATOS or VALISH was significant but it is likely that power was low. For some outcomes, there were more events in the groups treated to a lower goal; for other outcomes, there were more events in the groups treated to a higher goal. For example, in JATOS there were 52 cerebrovascular events in the lower goal group compared to 49 events in the higher goal group, whereas in VALISH, there were 16 cerebrovascular events in the lower goal group compared to 23 events in the higher goal group.

The majority of Panel members thought these studies represented evidence of no benefit rather than insufficient evidence because the outcomes of interest were primary outcomes in both studies. However, the Panel considered the overall evidence quality to be Low because of concerns by some Panel members that the duration of follow-up (2 years in JATOS and a mean of 2.85 years in VALISH) may not have been long enough to detect significant changes in these outcomes. In addition, the studies were conducted in Japan, so there were concerns about the applicability of the results to broader populations.

There were a few Panel members who did not agree with the statement because they thought there was insufficient evidence to support it. After a lengthy discussion by the Panel and a re-vote, the majority of Panel members supported the statement but thought that it represented low quality evidence.

**Question 2, Evidence Statement 7:** In the general population <65 years of age with hypertension, there are no RCTs that tested whether treatment with antihypertensive drug therapy to a systolic blood pressure goal <140 mm Hg compared to a higher goal (for example, <150 mm Hg) improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.  
Evidence Quality: Unable to determine because there is no evidence

**Rationale/Comments:** No additional comments.

**Question 2, Evidence Statement 8:** In the general population with hypertension, the evidence is insufficient to determine if there is a benefit in cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality of treatment with antihypertensive drug therapy to a systolic blood pressure goal <140 mm Hg compared to a lower goal (for example, <130 mm Hg).  
Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** One study contributed to this evidence statement (Cardio-Sis) [Verdecchia et al, 2009]. Cardio-Sis compared a systolic blood pressure goal of less than 130 mm Hg to a goal of less than 140 mm Hg in adults 55 years of age or older. Cardio-Sis had a sample size of 1,111 and was rated as a Good study. However, the primary outcome was prevalence of left ventricular hypertrophy (LVH) by electrocardiogram (ECG) at the final 2-year visit. Although the study showed a decrease in LVH by ECG

with the lower blood pressure goal, LVH is an intermediate measure, not a health outcome as required by the inclusion/exclusion criteria for all the questions.

Overall mortality, MI, cerebrovascular events and heart failure were all secondary outcomes in Cardio-Sis. None of the differences in these outcomes was statistically significant, and they had wide confidence intervals. Cardio-Sis did show a significant 67% reduction in coronary revascularization ( $p = 0.032$ ), which was an outcome of interest. However, the Panel placed less emphasis on this outcome compared to the other clinical endpoints because it is a softer endpoint with wide practice variation that is frequently performed without appropriate indications. There was also a significant 50% reduction in a secondary composite outcome of death from any cause, MI, stroke, TIA, atrial fibrillation, admission for heart failure, angina, or coronary revascularization ( $p = 0.003$ ). The Panel also placed less emphasis on this endpoint because it was a composite made up of so many components, including many softer endpoints like angina, revascularization, admission for heart failure, and atrial fibrillation.

The Panel graded the evidence as insufficient as opposed to low quality evidence of no benefit because there was only one contributing trial, and the relevant outcomes were all secondary. Moreover, there was an achieved systolic blood pressure difference of only 3.8 mm Hg between groups, whereas the intended systolic blood pressure difference between groups was 10 mm Hg. Some Panel members also believed that a sample size of 1,111 with median follow-up of 2 years was not adequate to assess meaningful differences in cardiovascular or cerebrovascular health outcomes or mortality.

**Question 2, Evidence Statement 9:** In the general population <55 years of age with hypertension, there are no RCTs that tested whether treatment with antihypertensive medication to any systolic blood pressure goal improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

Evidence Quality: Unable to determine because there is no evidence

**Rationale/Comments:** There are no RCTs of any quality (good, fair, or poor) in the general population less than 55 years of age that assessed whether treatment to any systolic blood pressure goal improved cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality. There are, however, studies in special populations (for example, diabetes or CKD) that included participants less than 55 years of age. This evidence is addressed in subsequent Evidence Statements specific to these subgroups.

**Question 2, Evidence Statement 10:** In the general population with hypertension, treatment with antihypertensive medication to a DBP goal <90 mm Hg reduces cerebrovascular morbidity and mortality (includes fatal stroke, nonfatal stroke or a combination of fatal and nonfatal stroke).

Evidence Quality: High

**Rationale/Comments:** Four studies contributed to this evidence statement (MRC, VA Cooperative, ANBP, and HDFP) [MRC, 1985; VA, 1970; ANBP, 1980; HDFP, 1979b; HDFP, 1982b]. One study was rated as Good (VA Cooperative), and three studies were rated as Fair (MRC, ANBP, and HDFP). Cerebrovascular morbidity and/or mortality was a primary outcome in one of the four contributing trials (MRC).

MRC showed a 45% five-year reduction in fatal and non-fatal stroke ( $p=0.006$  once off testing;  $p < 0.01$  sequential analysis), while HDFP showed a 34.5% five-year reduction in fatal and non-fatal stroke ( $p < 0.01$ ). MRC had a diastolic blood pressure goal of less than 90 mm Hg. HDFP had a DBP goal of 90 mm

Hg for those entering the trial with a DBP of 100 mm Hg or greater, or if they were already receiving antihypertensive medication; it had a goal of a 10 mm Hg decrease in DBP for those entering the study with a DBP between 90 and 99 mm Hg.

P values and confidence intervals were not reported for cerebrovascular outcomes in the VA Cooperative or ANBP studies; however, there were fewer events in the treated group compared to the placebo group for every type of cerebrovascular event reported. In the VA Cooperative study, there were 5 total cerebrovascular events in the treated group compared to 20 in the placebo group. In the ANBP study, there were 17 total cerebrovascular events in the treated group compared to 31 in the placebo group.

**Question 2, Evidence Statement 11:** In the general population with hypertension, the evidence is insufficient to determine if treatment with antihypertensive medication to a diastolic blood pressure goal <90 mm Hg reduces heart failure.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Although four trials [MRC, 1985; VA Coop, 1970; ANBP, 1980; HDFP, 1979b] treated patients to a goal diastolic blood pressure of less than 90 mm Hg, only two of these trials (VA Cooperative and ANBP) reported heart failure outcomes. VA Cooperative was rated as Good and ANBP was rated as Fair. Heart failure was a secondary outcome in these trials.

In VA Cooperative, there was a suggestion of benefit (0 events in the treated group and 11 events in the placebo group), but no p value was reported. In ANBP, there were 3 events each in the treated and placebo groups, and no p value was reported.

The Panel graded the evidence as insufficient because heart failure outcomes were reported in only two trials, they were secondary outcomes in both trials, and there were too few heart failure events to draw meaningful conclusions.

**Question 2, Evidence Statement 12:** In the general population with hypertension, the evidence is insufficient to determine whether treatment with antihypertensive medication to a diastolic blood pressure goal <90 mm Hg reduces coronary heart disease events (includes CHD mortality, non-fatal MI, and fatal MI).

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Four studies (MRC, VA Cooperative, ANBP, and HDFP) contributed to this evidence statement [MRC, 1985; VA Coop, 1970; ANBP, 1980; HDFP, 1979b]. One study was rated as Good (VA Cooperative), and three studies were rated as Fair (MRC, ANBP, and HDFP). Coronary events were a primary outcome in one of the four contributing trials (MRC).

Only 1 trial (MRC) reported confidence intervals or p-values for coronary heart disease outcomes. MRC showed a non-significant 6% reduction in total coronary events in the treated group, which had a goal diastolic blood pressure of less than 90 mm Hg (the p-value was not reported, but the 95% confidence interval was -31% to 21%).

The other three trials showed inconsistent results for coronary heart disease outcomes. For example, in VA Cooperative and ANBP, there were more non-fatal MIs in the treated group (5 versus 2 in VA Cooperative and 28 versus 22 in ANBP). However, in both trials, there were fewer total coronary heart

disease events in the treated group (11 versus 13 in VA Cooperative and 98 versus 109 in ANBP). In HDFP, there appeared to be a benefit in the stepped care group compared to the usual care group in terms of deaths from MI (51 versus 69 events). However, P-values and confidence intervals were not reported in these three trials; therefore, it is not clear whether these differences were statistically significant.

The Panel graded the evidence as insufficient because coronary heart disease events were the primary outcome in only one of four contributing trials (MRC). In that trial, the 6% reduction in coronary events was not significant. In the other three trials, confidence intervals or p-values for coronary heart disease outcomes were not reported. Therefore, it is not clear whether the differences in outcomes were significant. The lack of information about statistical significance in three of the trials, in addition to inconsistent results in VA Cooperative and ANBP between non-fatal and total coronary heart disease events, led the Panel to conclude that there was insufficient evidence to conclude whether treating patients to a diastolic blood pressure goal of less than 90 mm Hg reduces coronary heart disease events.

**Question 2, Evidence Statement 13:** In the general population 30 years of age or older with hypertension, the evidence is insufficient to determine whether there is a benefit in overall mortality of treatment with antihypertensive drug therapy to a diastolic blood pressure goal <90 mm Hg.  
Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Four studies (MRC, VA Cooperative, ANBP, and HDFP) contributed to this evidence statement [MRC, 1985; VA Coop, 1970; ANBP, 1980; HDFP, 1979b]. One study was rated as Good (VA Cooperative), and three studies were rated as Fair (MRC, ANBP, and HDFP). Overall mortality was a primary outcome in one of the four contributing trials (HDFP).

HDFP, which had 10,940 study participants 30-69 years of age, was the only study that assessed overall mortality as a primary outcome and showed a significant mortality benefit, with the stepped care group experiencing a 1.3% absolute decrease in mortality at 5 years compared to the usual care group (6.4% in stepped care versus 7.7% in usual care,  $p < 0.01$ ). In the other three trials, overall mortality was either not significant or significance was not reported. MRC, a larger study with 17,354 study participants 35-64 years of age, showed a non-significant 2% reduction in overall mortality (p-value was not reported, but the 95% confidence interval was -16% to 18%). In the other two studies (VA Cooperative and ANBP), there were few events, and significance was not reported. There was a trend towards possible benefit in the treated groups in VA Cooperative (0 versus 4 deaths) and ANBP (25 versus 35 deaths); however, there were few events, and significance was not reported. Therefore, although HDFP did show a small benefit, the majority of the Panel thought that the overall evidence was insufficient to draw a meaningful conclusion.

**Question 2, Evidence Statement 14:** In the general population with hypertension, there is evidence of no benefit in cardiovascular outcomes, cerebrovascular outcomes, or mortality of treatment with antihypertensive drug therapy to a diastolic blood pressure goal of either  $\leq 80$  mm Hg or  $\leq 85$  mm Hg compared to a goal  $\leq 90$  mm Hg.  
Evidence Quality: Low

**Rationale/Comments:** One trial, HOT, contributes to this Evidence Statement [Hansson, 1998]. HOT was rated as Fair and included 18,790 participants. HOT compared three goal diastolic pressures:  $\leq 80$  mm Hg,

≤85 mm Hg, and ≤90 mm Hg. The primary outcome was a composite of major cardiovascular events, which included fatal and nonfatal MI, fatal and nonfatal stroke, and all other cardiovascular deaths.

Neither the primary outcome nor any of the secondary outcomes in H0T reached statistical significance. The relative risk for the primary outcome was close to 1 for each diastolic blood pressure goal comparison, and the confidence intervals crossed 1: 0.99 (95% CI, 0.83, 1.19) for the ≤90 versus ≤85 comparison; 1.08 (95% CI, 0.89, 1.29) for the ≤85 versus ≤80 comparison; and 1.07 (95% CI, 0.89, 1.28) for the ≤90 versus ≤80 comparison. There was a 37% increase in MI (a component of the primary composite outcome) that almost reached statistical significance for the ≤90 mm Hg group compared to the ≤80 mm Hg group, but the confidence interval crossed 1 (95% CI, 0.99, 1.91). There were more deaths in the ≤80 mm Hg group (207 deaths) compared to the ≤85 group (194 deaths) and the ≤90 group (188 deaths); however, none of these differences was statistically significant.

The Panel graded the Evidence Statement as evidence of no benefit, Low Quality, as opposed to Insufficient Evidence, because H0T was a large trial with a primary outcome that was directly related to the question. During deliberations, the Panel noted that the groups assigned to different diastolic blood pressure goals achieved smaller differences in blood pressure than were anticipated based on the study design; for example, the mean achieved diastolic blood pressure difference between the ≤90 mm Hg group and the ≤80 group was only 4.0 mm Hg. The failure to achieve the stated blood pressure goal differences in each group, together with the fact that it was only one study that was rated Fair, resulted in the Low Quality grading.

### Statements for the Population with Chronic Kidney Disease

Exhibits F and G for the Question 2 Evidence Statements for the population with chronic kidney disease are provided in the Appendix.

- [Exhibit F: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in participants with chronic kidney disease](#)
- [Exhibit G: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in participants with chronic kidney disease by baseline proteinuria subgroups](#)

**Question 2, Evidence Statement 15:** [CKD Subpopulation] In the population less than 70 years of age with chronic kidney disease (without diabetes), the evidence is insufficient to determine if there is a benefit in cardiovascular outcomes, cerebrovascular outcomes, or mortality of treatment with antihypertensive drug therapy to a lower blood pressure goal (for example, <130/80 mm Hg) compared to a goal of <140/90 mm Hg.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Three trials (AASK, MDRD, REIN-2) contributed to this evidence statement [Wright, 2002; Contreras, 2005; Norris, 2006; Khlar, 1994; Ruggenenti, 2005]. One trial was rated as Good (AASK) with a study population of 1,094 and two trials were rated as Fair (REIN-2, MDRD) with study populations of 335 and 840, respectively. All three trials included participants between the ages of 18 and 70. The primary outcome in AASK and MDRD was change in glomerular filtration rate (GFR), and the primary outcome in REIN-2 was time to end stage renal disease (ESRD). All study participants in AASK were black with hypertension, while MDRD included white and black, hypertensive and normotensive participants. Racial demographics were not reported for REIN-2 though it was conducted in Italy.

There were differences in the study entry criteria for kidney function across all three trials. In AASK, all participants had hypertensive renal disease with a GFR of 20-65 mL/min per 1.73 m<sup>2</sup>. MDRD consisted of 2 studies. Study 1 included subjects with a GFR of 25-55 ml/min/1.73 m<sup>2</sup> who were randomized to usual or low BP goal; Study 2 consisted of participants with a GFR of 13-25 ml/min/1.73 m<sup>2</sup> who were randomized to a usual or low BP goal. In REIN-2, participants had non-diabetic nephropathy and persistent proteinuria, defined as urinary protein excretion greater than 1 gram per 24 hours for at least 3 months.

Direct comparison of blood pressure goals across trials was not possible because the goals in each trial were different. AASK compared a mean arterial pressure (MAP) goal of ≤92 mm Hg to a MAP goal of 102-107 mm Hg (as an example, a BP of 140/90 equals a MAP of 107, and a BP of 125/85 equals a MAP of 92). In MDRD, blood pressure goals were based on age. In the lower goal group, the MAP goal was ≤92 mm Hg for those 18-60 years of age and ≤98 for those ≥61 years of age; in the usual goal group, the MAP goal was ≤107 mm Hg for those 18-60 and ≤113 for those ≥61 years of age. In REIN-2, a blood pressure goal of <130/80 mm Hg was compared to a diastolic goal of <90 mm Hg, irrespective of systolic blood pressure.

AASK found no significant differences in major CHD events, stroke, heart failure, death, or a composite of cardiovascular outcomes, but these outcomes were secondary. AASK was the only one of the three relevant trials in this population to report cardiovascular or cerebrovascular outcomes.

After the AASK trial phase was completed, participants in whom ESRD had not been diagnosed were invited to enroll in the cohort phase in which the blood pressure target was 130/80 mm Hg; total follow-up time including the cohort phase ranged from 8.8 to 12.2 years [Appel, 2010]. As in the trial phase, there were no significant differences in the doubling of serum creatinine, ESRD, or death during the extended follow-up period. Because participants were no longer randomized in the cohort phase, this analysis did not meet the study design criterion for the question; thus, it was not included in the evidence review. However, during deliberations, the Panel discussed the findings of the cohort phase and felt they were noteworthy because of the consistency with the RCT evidence.

The Panel graded the evidence as insufficient because of the lack of trials assessing cardiovascular outcomes, cerebrovascular outcomes, or mortality as primary outcomes. Only AASK reported cardiovascular outcomes, cerebrovascular outcomes, and mortality, but they were secondary outcomes. AASK found no differences in these outcomes; therefore it is unclear whether the lack of benefit from the lower goal is real or because the study was not powered to detect a significant difference in these outcomes.

**Question 2, Evidence Statement 16:** [CKD Subpopulation] In the population less than 70 years of age with hypertension and chronic kidney disease (without diabetes), there is evidence of no benefit of treatment with antihypertensive drug therapy to a lower blood pressure goal (for example, <130/80 mm Hg) compared to a goal of <140/90 mm Hg on the progression of kidney disease.

Evidence Quality: Moderate

**Rationale/Comments:** Three trials contributed to this evidence statement (AASK, MDRD, REIN-2) [Wright, 2002; Khlar, 1994; Ruggenti, 2005]. One trial was rated as Good (AASK) with a study population of 1,094, and two trials were rated as Fair (REIN-2, MDRD) with study populations of 335 and

840, respectively. All three trials included participants between the ages of 18 and 70. The primary outcome in AASK and MDRD was change in GFR and the primary outcome in REIN-2 was time to ESRD. For this evidence statement, a change in GFR represented progression of kidney disease; however, this was not one of the health outcomes prespecified by the Panel for any of its questions.

As described in Evidence Statement 15, direct comparison of blood pressure goals across trials was not possible because the goals in each trial were different. AASK compared a mean arterial pressure (MAP) goal of  $\leq 92$  mm Hg to a MAP goal of 102-107 mm Hg. In MDRD, blood pressure goals were based on age. In the lower goal group, the MAP goal was  $\leq 92$  mm Hg for those 18-60 years of age and  $\leq 98$  for those  $\geq 61$  years of age; in the usual goal group, the MAP goal was  $\leq 107$  mm Hg for those 18-60 and  $\leq 113$  for those  $\geq 61$  years of age. In REIN-2, a blood pressure goal of  $< 130/80$  mm Hg was compared to a diastolic goal of  $< 90$  mm Hg, irrespective of systolic blood pressure.

None of the three trials showed that treatment to the lower blood pressure goal (e.g., 130/80 mm Hg) compared to a blood pressure goal of  $< 140/90$  mm Hg significantly reduced the incidence of ESRD, GFR by 50% or by 25 mL/min/1.73 meters<sup>2</sup> from baseline, cardiovascular outcomes, cerebrovascular outcomes, or mortality. In AASK, treatment to the lower blood pressure goal showed no additional benefit in slowing the progression of kidney disease as measured by the slope of the loss of GFR. However this was not an outcome prespecified by the Panel for consideration. The secondary clinical composite outcome in AASK (which included ESRD, reduction in GFR by 50% or by 25 mL/min/1.73 meters<sup>2</sup> from baseline, or death) showed a non-significant 2% reduction in the lower goal group ( $p=0.85$ ). In REIN-2, where time to ESRD was the primary outcome, there were more ESRD events in the group treated to the lower goal (38 versus 34 events), but the hazard ratio was 1.00 (95% CI, 0.61, 1.64). Similarly, the median rate of GFR decline in REIN-2 was not significantly different between the group treated to the lower blood pressure goal of  $< 130/80$  mmHg and the group treated to the higher diastolic blood pressure goal of  $< 90$  mmHg.

MDRD consisted of two studies. Study 1 randomized participants to a low or usual blood pressure goal (described above). Study 2 randomized participants to the same low or usual blood pressure goal. Study 1 included participants with a GFR of 25-55 ml/min 1.73 m<sup>2</sup> and Study 2 included subjects with a GFR of 13-24 ml/min 1.73 m<sup>2</sup>. In Study 1, the rate of decline in GFR measured from 4 months to the end of the study (mean study duration was 2.2 years) was significantly lower in the low goal group than the usual goal group (2.8 compared to 3.9 ml/min,  $p=0.006$ ). However, when calculated from baseline to 3 years, the difference was not significant (10.7 compared to 12.3 ml/min/3 years,  $p=0.18$ ). In Study 2, the difference in the rate of decline in GFR between groups was not significant (3.7 compared to 4.2 ml/min,  $p=0.28$ ). MDRD also found a non-significant 15% reduction in ESRD or death in the lower goal group (95% CI, 0.60, 1.22).

The Panel graded the evidence as Moderate because all three trials had consistent findings that showed no benefit of treatment to a lower blood pressure goal compared to a goal of  $< 140/90$  mm Hg. Additionally, change in GFR was the primary outcome in two of the trials, one of which was rated as Good (AASK).

**Question 2, Evidence Statement 17:** [Proteinuria Subgroups] In the population with hypertension and proteinuria (without diabetes), there is insufficient evidence to determine whether there is a benefit of treatment with antihypertensive drug therapy to a lower blood pressure goal (for example,  $< 130/80$  mm

Hg) compared to a goal of <140/90 mm Hg on cardiovascular outcomes, cerebrovascular outcomes, or mortality.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Three trials contributed to this evidence statement (AASK, MDRD, REIN-2) [Wright, 2002; Contreras, 2005; Khlar, 1994; Ruggenenti, 2005]. One trial was rated as Good (AASK) with a study population of 1,094, and two trials were rated as Fair (REIN-2, MDRD) with study populations of 335 and 840. The primary outcome in AASK and MDRD was change in GFR and the primary outcome in REIN-2 was time to ESRD. Analyses by baseline proteinuria were performed in each trial. In AASK and REIN-2, the analyses were prespecified; in MDRD the analysis was post hoc.

Only one of the three trials (AASK) reported on cardiovascular outcomes, cerebrovascular outcomes, or mortality, but not by the level of baseline proteinuria. The Panel graded the evidence as insufficient because of the lack of evidence for these specific outcomes.

Although it was not part of this evidence statement, these trials do report kidney outcomes by baseline proteinuria subgroups. From these three trials, the Panel concluded that there may be a trend towards a benefit in treating to lower blood pressure goals (for example, 130/80 mm Hg) compared to a goal <140/90 in those with more severe proteinuria. When analyzed by baseline proteinuria strata, there were no significant differences between the low or usual goal groups in the rate of change in GFR in AASK; however, the p-value for the interaction of proteinuria and blood pressure goal was 0.004 for the total GFR slope for a proteinuria level above and below ~300 mg/day. This interaction suggests a benefit for the lower goal over the usual goal in those with higher baseline proteinuria. MDRD showed a significant benefit in GFR decline in 54 subjects with urinary protein excretion greater than 3 grams per day at baseline (the p-value and confidence intervals were not reported, but the confidence intervals did not overlap in the published figure); the p-values were significant for the interaction.

There were non-significant differences in the clinical composite outcome in AASK, which included a reduction in GFR by 50% or by 25 ml/min/m<sup>2</sup>, ESRD, and death; however, the p-value for the interaction based on proteinuria was 0.007. REIN-2 found no significant differences in ESRD between the lower goal (130/80 mm Hg) and conventional goal (<90 mm Hg diastolic) for subgroups of patients analyzed by baseline proteinuria strata of 1-3 grams per 24 hours and greater than 3 grams per 24 hours.

Thus, despite evidence that suggests patients with proteinuria (particularly >3gm/day) may benefit from a lower BP goal compared to a goal <140/90 mm Hg, there is insufficient evidence to draw a firm conclusion and make such a recommendation.

### Statements for the Population with Diabetes

Exhibits for Question 2 Evidence Statements for the population with diabetes are provided in the Appendix.

- [Exhibit H: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in participants with diabetes](#)

**Question 2, Evidence Statement 18:** [Diabetes Subpopulation] In the population with diabetes and hypertension, treatment to a systolic blood pressure goal of <150 mm Hg improves cardiovascular outcomes, cerebrovascular outcomes, or mortality.

Evidence Quality: Moderate

**Rationale/Comments:** Three trials (SHEP, Syst-Eur, and UKPDS) contributed to this evidence statement [Curb, 1996; Tuomilehto, 1999; UKPDS, 1998]. UKPDS had a study population of 1,148 and all participants had diabetes at baseline. SHEP and Syst-Eur included participants with and without diabetes; approximately 10% of the population in each trial had diabetes at baseline (583 in SHEP and 492 in Syst-Eur). UKPDS was rated as Fair, as were the diabetes subgroup analyses for SHEP and Syst-Eur. The primary outcome in both SHEP and Syst-Eur was fatal and non-fatal stroke. UKPDS specified three primary endpoints: first clinical endpoint related to diabetes, death related to diabetes, and death from all causes.

Syst-Eur and UKPDS had systolic blood pressure goals of less than 150 mm Hg. The systolic blood pressure goal in SHEP was based on baseline blood pressure; the goal for individuals with a systolic blood pressure greater than 180 mm Hg at baseline was less than 160 mm Hg, and the goal for those with systolic blood pressures between 160 and 179 mm Hg at baseline was a decrease of at least 20 mmHg. Thus, systolic blood pressure goals in SHEP ranged from 140 mm Hg to 159 mm Hg, unlike the other two studies, which used a fixed goal of <150 mm Hg.

SHEP showed a significant 54% reduction in nonfatal MI and fatal CHD in participants with diabetes (95% CI, 0.24, 0.88). SHEP also showed a 56% reduction in major CHD events (95% CI, 0.25, 0.77) and a 34% reduction in CVD events (95% CI, 0.46, 0.94). Syst-Eur showed a 57% reduction in fatal and nonfatal cardiac events in this population, but the p-value was 0.06 (95% CI, -6, 82). In UKPDS, participants treated to the lower goal of <150/85 mm Hg had a non-significant 21% reduction in MI (p=0.13) (95% CI, 0.59, 1.07), but there were more sudden deaths (1.8 versus 1.3 per 1000 patient years) than in those treated to the higher goal of <180/105 mm Hg; however, these were secondary outcomes and not significant.

Two of the three trials showed a benefit in cerebrovascular outcomes of treatment to a systolic blood pressure goal of <150 mm Hg. Syst-Eur showed a significant 69% reduction in fatal and nonfatal stroke (p=0.02) (95% CI, 14, 89) and UKPDS showed a significant 44% reduction in stroke (p=0.013) (95% CI, 0.35, 0.89). In SHEP, however, the incidence of fatal and non-fatal stroke in participants with diabetes was 22% lower, but it was not significant (95% CI, 0.45, 1.34)). In Syst-Eur and SHEP, fatal and nonfatal stroke was the primary outcome, while in UKPDS, stroke was a secondary outcome.

Overall mortality was not significantly different in the three trials. In SHEP, there was a non-significant 26% reduction (95% CI, 0.46, 1.18); in Syst-Eur, there was a non-significant 49% reduction ((p=0.09) (95% CI, -9, 69); in UKPDS there was a non-significant 18% reduction (p=0.17) (95% CI, 0.62, 1.08). In UKPDS, overall mortality was one of three prespecified primary outcomes. The other two primary endpoints in UKPDS were any diabetes-related endpoint and deaths related to diabetes. Both were significantly lower in the tight control group treated to a goal blood pressure of <150/85 mm Hg; there was a 24% reduction in clinical endpoints related to diabetes (p=0.0046) (95% CI, 0.62, 0.92) and a 32% reduction in deaths related to diabetes (p=0.019) (95% CI, 0.49, 0.94). The definition of diabetes-related endpoints and deaths related to diabetes in UKPDS can be found in the summary table.

The Panel graded the evidence as Moderate. Although there are three trials and each showed a significant benefit for at least one outcome listed in the evidence statement, all three trials were rated as Fair, and the number of participants with diabetes in SHEP and Syst-Eur was small. The diabetes subgroup analyses in SHEP and Syst-Eur were also post-hoc analyses, which diminished the quality of the evidence.

**Question 2, Evidence Statement 19:** [Diabetes Subpopulation] In the population with diabetes and pre-hypertension or hypertension, treatment to a systolic blood pressure goal <120 mm Hg compared to <140 mm Hg reduces cerebrovascular events, but there is no evidence of benefit on overall mortality, coronary heart disease events, heart failure, or a composite cardiovascular outcome.  
Evidence Quality: Moderate

**Rationale/Comments:** One study (ACCORD) contributed to this evidence statement [ACCORD Study Group, 2010]. ACCORD was rated as Good and included 4,733 participants with diabetes. ACCORD compared a systolic blood pressure goal of <120 mm Hg to a systolic blood pressure goal of <140 mm Hg in participants with type 2 diabetes, glycosylated hemoglobin  $\geq 7.5\%$ , and SBP between 130-180 mm Hg. The primary outcome was the first occurrence of a major cardiovascular event, which was defined as a composite of nonfatal MI, nonfatal stroke, or cardiovascular death.

The only significant differences in outcomes between the lower (<120 mm Hg) and higher (<140 mm Hg) systolic blood pressure arms of the study were in total strokes and nonfatal strokes, which were prespecified secondary outcomes. In the group treated to the lower goal of <120 mm Hg, total strokes were 41% ( $p=0.01$ ) lower and nonfatal strokes were 36% ( $p=0.03$ ) lower. There was no difference between groups for the primary composite outcome of major cardiovascular events (HR 0.88; 95% CI 0.73, 1.06) ( $p=0.20$ ) or any of the other secondary outcomes: overall mortality (HR 1.07; 95% CI 0.85, 1.35) ( $p=0.55$ ), major coronary disease events (HR 0.94; 95% CI 0.79, 1.12) ( $p=0.50$ ), or heart failure (HR 0.94; 95% CI 0.70, 1.26) ( $p=0.67$ ).

The Panel graded the evidence as Moderate. Although ACCORD was rated as Good, it was only one trial, and the Panel noted that the event rate was 50% less than expected, thereby reducing its power.

**Question 2, Evidence Statement 20:** [Diabetes Subpopulation] In the population 50 years of age or older with diabetes and a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg or hypertension, treatment with antihypertensive medication to a diastolic goal blood pressure  $\leq 80$  mm Hg compared to  $\leq 90$  mm Hg reduces a composite of fatal and nonfatal MI, fatal and nonfatal stroke, all other CV deaths.  
Evidence Quality: Low

**Rationale/Comments:** One trial (HOT) contributed to this evidence statement [Hansson, 1998]. Eight percent ( $n=1,501$ ) of the total HOT population ( $n=18,790$ ) had diabetes at baseline. HOT was rated Fair and followed participants for a mean of 3.8 years. HOT compared three diastolic blood pressure goals:  $\leq 80$  mm Hg,  $\leq 85$  mm Hg, and  $\leq 90$  mm Hg. The primary outcome was a composite of major cardiovascular events which included fatal and nonfatal MI, fatal and nonfatal stroke, and all other cardiovascular death. Results of the diabetes subgroup analysis were reported in the primary paper; however, the authors did not state that diabetes was a prespecified subgroup.

Major cardiovascular events were significantly higher by 106% in the  $\leq 90$  mm Hg goal group compared to the  $\leq 80$  mm Hg group (45 versus 22 events; HR 2.06; 95% CI 1.24, 3.44). The difference was not significant in the  $\leq 90$  mm Hg group compared to the  $\leq 85$  mm Hg group (45 versus 34 events; HR 1.32; 95% CI 0.84, 2.06) or the  $\leq 85$  mm Hg group compared to the  $\leq 80$  mm Hg group (34 versus 22 events; HR 1.56; 95% CI 0.91, 2.67).

UKPDS, a study in 1,148 participants with diabetes that was rated Fair, found that treatment to a goal BP of <150/85 mm Hg compared to a goal BP of <180/105 mm Hg significantly lowered stroke, heart failure, diabetes-related endpoints, and deaths related to diabetes. However, UKPDS did not contribute to this evidence statement and could not be compared directly to HOT because UKPDS used different diastolic BP comparisons than HOT, and UKPDS also included systolic blood pressure goals. In addition, UKPDS was conducted in a younger population (ages 25 to 65) compared to participants in HOT (ages 50 to 80).

The Panel graded the quality of evidence as Low because it was based on one study, only 8% of the HOT study population had diabetes, and the Panel could not confirm whether the diabetes subgroup analysis was prespecified. While UKPDS appears to support the evidence statement, interpreting the results of UKPDS in light of this evidence statement is difficult because of its use of mixed systolic and diastolic blood pressure goals.

**Question 2, Evidence Statement 21:** [Diabetes Subpopulation] In the population with diabetes and a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg or hypertension, there is insufficient evidence to determine whether treatment with antihypertensive medication to a lower diastolic goal (for example,  $\leq 80$  mm Hg) compared to a blood pressure goal  $\leq 90$  mm Hg reduces overall mortality.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Three trials contributed to this evidence statement (ABCD Hypertensive Cohort, HOT, and UKPDS) [Estacio, 2000; Hansson, 1998; UKPDS, 1998]. All three trials were rated as Fair. ABCD and UKPDS included 470 and 1,148 participants, respectively, and all participants had diabetes at baseline. HOT included participants with and without diabetes; 8% (n=1,501) of the total HOT population (n=18,790) had diabetes at baseline. The authors did not report that diabetes was a prespecified subgroup in HOT. Overall mortality was one of three specified primary outcomes in UKPDS. Overall mortality was not explicitly identified as a primary or secondary outcome in HOT or ABCD.

Although all three trials compared a lower diastolic blood pressure goal to a higher goal, direct comparisons across the three trials were not possible because different blood pressure goals were tested in each study and UKPDS included a systolic blood pressure goal. The ABCD Hypertensive Cohort compared a diastolic blood pressure goal of 75 mm Hg to a goal of 80-89 mm Hg. HOT compared three diastolic blood pressure goals:  $\leq 80$  mm Hg,  $\leq 85$  mm Hg, and  $\leq 90$  mm Hg. UKPDS compared a blood pressure goal of <150/85 mm Hg to a goal of <180/105.

ABCD showed a significant reduction in overall mortality in the group treated to a diastolic blood pressure goal of 75 mm Hg compared to the group treated to 80-89 mm Hg (5.5% versus 10.7%,  $p=0.037$ ). In the HOT diabetes subgroup, there was a non-significant 56% reduction in overall mortality in the group treated to a diastolic blood pressure goal of  $\leq 80$  mm Hg compared to the group treated to a goal of  $\leq 90$  mm Hg (HR 0.56; 95% CI 0.31, 1.02). In UKPDS, there was a non-significant 18% reduction in overall mortality in the group treated to <150/85 mm Hg compared to the group treated to <180/105 (RR 0.82; 95% CI 0.62, 1.08) ( $p=0.17$ ).

The Panel graded the evidence as insufficient. Although there were three relevant trials, overall mortality was a primary outcome in only one trial (UKPDS). Furthermore, ABCD, which showed a significant benefit for overall mortality in the lower goal group, was a small trial with only 470 participants. The diabetes subgroup in HOT represented only 8% of the total study population and was not prespecified.

## EVIDENCE STATEMENTS FOR QUESTION 3

**Question 3: In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?**

### Statements for the General Population

#### Summary of Evidence Statements for the General Population

The tables below summarize the evidence for the drug comparisons in Question 3. Evidence Statements and the rationale/comments for these Statements are provided in the following section. Unless otherwise stated, the comparisons below refer to the general population as defined in the report.

#### ACEI versus CCBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Moderate	ACEI ES1
Cardiovascular	Similar	Moderate	ACEI ES1
Cerebrovascular	Similar in overall population CCB better in blacks	Moderate Moderate	ACEI ES1 ACEI ES2
Heart failure	ACEI better	Moderate	ACEI ES1
Kidney	Similar	Moderate	ACEI ES1

**Summary:** ACEI are better than CCBs for heart failure outcomes. In blacks, ACEI are better than CCBs for heart failure outcomes but CCBs are better than ACEIs for cerebrovascular outcomes. In both blacks and non-blacks, ACEI and CCBs are similar with respect to overall mortality, cardiovascular outcomes, and kidney outcomes.

#### ACEI versus ARBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	No trials	N/A	ARB ES4
Cardiovascular	No trials	N/A	ARB ES4
Cerebrovascular	No trials	N/A	ARB ES4
Kidney	No trials	N/A	ARB ES4

**Summary:** No eligible trials compared ACEI with ARBs with respect to overall mortality, cardiovascular outcomes, cerebrovascular outcomes, or kidney outcomes.

#### Beta Blockers versus ACE Inhibitors

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Kidney	Insufficient evidence	Insufficient	BB ES23

**Summary:** There is insufficient evidence for beta blockers compared to ACE inhibitors with respect to kidney outcomes. There are no trials comparing beta blockers to ACE inhibitors for any other outcomes.

#### Beta Blockers versus CCBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Insufficient evidence	Insufficient	BB ES21

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Cardiovascular	Insufficient evidence	Insufficient	BB ES21
Cerebrovascular	Insufficient evidence	Insufficient	BB ES21
Kidney	Insufficient evidence	Insufficient	BB ES21 BB ES23

**Summary:** *There is insufficient evidence for beta blockers compared to calcium channel blockers with respect to overall mortality, cardiovascular outcomes, cerebrovascular outcomes, and kidney outcomes.*

#### Beta Blockers versus ARBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Low	BB ES22
Cerebrovascular	ARB better	Low	BB ES22
CHD	Similar	Low	BB ES22
Heart failure	Similar	Low	BB ES22
Kidney	Insufficient evidence	Insufficient	BB ES23
Composite	ARB better	Low	BB ES22

**Summary:** *ARBs are better than beta blockers for cerebrovascular outcomes and composite outcomes but are similar for overall mortality, CHD outcomes, and heart failure outcomes; there is insufficient evidence with respect to kidney outcomes.*

#### CCBs versus ARBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	High/moderate	CCB ES26
Cerebrovascular	Insufficient	Insufficient	CCB ES27
CHD	Insufficient	Insufficient	CCB ES27
Heart failure	Insufficient	Insufficient	CCB ES27
Kidney	Insufficient	Insufficient	CCB ES27
Composite	Similar	Low	CCB ES28

**Summary:** *CCBs and ARBs are similar with respect to overall mortality and composite outcomes. There is insufficient evidence for CCBs compared to ARBs for cerebrovascular outcomes, CHD outcomes, heart failure outcomes, and kidney outcomes.*

#### Thiazide and Thiazide-type Diuretics versus Beta Blockers

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Insufficient evidence	Insufficient	Diuretic ES7
Cerebrovascular	Insufficient evidence	Insufficient	Diuretic ES12
CHD	Similar	Moderate	Diuretic ES8
Kidney	Insufficient evidence	Insufficient	BB ES23

**Summary:** *All reference to diuretics in these tables refers to thiazide and thiazide-type agents. Thiazide and thiazide-type diuretics are similar to beta blockers for CHD outcomes. There is insufficient evidence for*

thiazide and thiazide-type diuretics versus beta blockers for overall mortality, cerebrovascular outcomes, and kidney outcomes.

#### Thiazide and Thiazide-type Diuretics versus ACE Inhibitors

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Moderate	Diuretic ES6
Cerebrovascular	Diuretic better in blacks Similar in non-blacks	Moderate Low/Moderate	Diuretic ES10 Diuretic ES9
CHD	Similar	Moderate	Diuretic ES8
Heart failure	Diuretic better	Moderate	Diuretic ES15
Kidney	Similar	Moderate	Diuretic ES19
Composite	Diuretic better in blacks Similar in non-blacks	Low Low	Diuretic ES17 Diuretic ES16

**Summary:** In blacks, thiazide and thiazide-type diuretics are better than ACE inhibitors for cerebrovascular outcomes, heart failure outcomes, and composite outcomes but similar for overall mortality, CHD outcomes, and kidney outcomes. In non-blacks, thiazide and thiazide-type diuretics are better than ACE inhibitors for heart failure outcomes but are similar for all the other outcomes.

#### Thiazide and Thiazide-type Diuretics versus Calcium Channel Blockers

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Moderate	Diuretic ES6
Cerebrovascular	Similar	High	Diuretic ES11
CHD	Similar	Moderate	Diuretic ES8
Heart failure	Diuretic better	High	Diuretic ES14
Kidney	Similar	Moderate	Diuretic ES19
Composite	Similar	High	Diuretic ES18

**Summary:** Thiazide and thiazide-type diuretics are better than CCBs for heart failure outcomes but are similar for all other health outcomes.

#### Thiazide and Thiazide-type Diuretics versus ARBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	No trials	N/A	ARB ES3
Cardiovascular	No trials	N/A	ARB ES3
Cerebrovascular	No trials	N/A	ARB ES3
Kidney	No trials	N/A	ARB ES3

**Summary:** No eligible trials compare thiazide and thiazide-type diuretics with ARBs with respect to cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or overall mortality.

#### Thiazide and Thiazide-type Diuretics versus Alpha Blockers

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Moderate	Diuretic ES6
Cerebrovascular	Diuretic better	Moderate	Diuretic ES13

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
CHD	Similar	Moderate	Diuretic ES8
Heart failure	Diuretic better	Moderate	Diuretic ES13
Composite	Diuretic better	Moderate	Diuretic ES13

**Summary:** *Thiazide and thiazide-type diuretics are better than alpha blockers for cerebrovascular outcomes, heart failure outcomes, and composite outcomes but are similar for overall mortality and CHD outcomes.*

### Combination Therapy: ACEI/CCB versus ACEI/diuretic

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Moderate	Combo ES29
Cardiovascular	ACEI/CCB better	Moderate	Combo ES29
Cerebrovascular	Similar	Moderate	Combo ES29
CHD	ACEI/CCB better	Moderate	Combo ES29
Heart failure	Similar	Moderate	Combo ES29
End stage kidney disease	Similar	Moderate	Combo ES29
Doubling of serum creatinine	ACEI/CCB better	Moderate	Combo ES29
Composite	ACEI/CCB better	Moderate	Combo ES29

**Summary:** *A combination of ACEI and CCB is better than a combination of ACEI and diuretic for cardiovascular outcomes, CHD outcomes, doubling of serum creatinine, and composite outcomes. They are similar with respect to overall mortality, cerebrovascular outcomes, heart failure outcomes, and end stage kidney disease.*

### Other Drug Classes

No eligible trials assess the drug classes noted below with respect to cardiovascular or cerebrovascular health outcomes, kidney outcomes, or overall mortality compared to another drug class:

- Dual alpha-1, beta blocking agents (bucindolol, carvedilol, labetalol)
- Central alpha 2 adrenergic agonists (clonidine, methyldopa)
- Direct vasodilators (hydralazine, minoxidil)
- Aldosterone receptor antagonists (spironolactone, eplerenone)
- Peripheral adrenergic neuron antagonists (reserpine)
- Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)
- Nitrate containing agents (extended-release nitrate)
- Direct renin inhibitors (aliskiren)
- Potassium-sparing diuretics used as monotherapy (amiloride, triamterene)

The following evidence statements discuss specific drug classes in alphabetical order and the order does not imply a specific priority to use a give drug class.

### Angiotensin Converting Enzyme Inhibitors versus Other Drugs

Exhibits for Question 3 Evidence Statements for the general population for ACE inhibitors versus other drugs are provided in the Appendix.

- [Exhibit L: Evidence from randomized controlled trials of initial antihypertensive drug therapy with ACE inhibitors versus other drugs](#)

### **Question 3, ACE Inhibitor Evidence Statement 1**

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with an ACE inhibitor reduces the incidence of heart failure, but it has a similar effect on other cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, and overall mortality compared to initial antihypertensive drug therapy with a calcium channel blocker.

Evidence Quality: Moderate

**Rationale/Comments:** Three trials contributed to this evidence statement (ALLHAT, JMIC-B, and STOP-HTN2) [Leenen 2006; Yui, 2004b; Hansson, 1999a]. In ALLHAT, the comparison of the ACE inhibitor and calcium channel blocker was a secondary comparison and was thus rated as Fair. JMIC-B was also rated as Fair, and STOP-HTN2 was rated as Good. All three trials had different primary outcomes: fatal CHD and nonfatal MI in ALLHAT, a composite of cardiac events in JMIC-B, and a composite of cardiovascular death in STOP-HTN2. In two of the three studies (ALLHAT and STOP-HTN2), heart failure events were reduced significantly with the use of an ACE inhibitor compared to the use of a calcium channel blocker. In ALLHAT, heart failure was reduced by 13% (95% CI, 0.78, 0.96; p=0.007). In STOP-HTN2, heart failure was reduced by 24% (95% CI, 0.63, 0.97; p=0.025).

In JMIC-B and STOP-HTN2, there was no difference in stroke with the use of an ACE inhibitor compared to the use of a calcium channel blocker. In ALLHAT, stroke was higher by 23% in the ACE inhibitor group (95% CI, 1.08, 1.41; p=0.003). This difference was driven by a significant 51% increase in blacks, but there was no difference in stroke for non-blacks, which constituted 65% of the trial population (see Question 3, ACE Inhibitor Evidence Statement 2). None of the trials showed a difference in overall mortality or kidney outcomes. In STOP-HTN2, there was a significant 23% (95% CI, 0.61, 0.96; p=0.016) lower occurrence of myocardial infarction in the ACE inhibitor group compared to the calcium channel blocker group, but there was no significant difference in myocardial infarctions in the other two trials. The primary composite cardiovascular outcomes in STOP-HTN2 and JMIC-B were also not significantly different between groups. However, combined cardiovascular disease in ALLHAT was higher by 6% (95% CI, 1.00, 1.12; p=0.047) in the ACE inhibitor group compared to the calcium channel blocker group, but it was only significant in blacks.

### **Question 3, ACE Inhibitor Evidence Statement 2**

In the general black population 55 years of age or older with hypertension, initial antihypertensive drug therapy with an ACE inhibitor is associated with higher incidence of stroke compared to initial antihypertensive drug therapy with a calcium channel blocker.

Evidence Quality: Moderate

**Rationale/Comments:** This evidence statement is based on a pre-specified subgroup analysis of blacks in ALLHAT which constituted 35% of the trial population [Leenen, 2006.]. In ALLHAT, the comparison of the ACE inhibitor and calcium channel blocker was a secondary analysis and was thus rated as Fair. There were 18,102 participants in the ACE inhibitor and calcium channel blocker groups. Stroke increased significantly by 51% (95% CI, 1.22, 1.86; p=not reported) in blacks initially treated with an ACE inhibitor compared to blacks initially treated with a calcium channel blocker. In this trial, the ACE inhibitor was also less effective in reducing blood pressure in blacks compared to the calcium channel blocker with a difference of 2.7/1.6 mm Hg for black men and 3.9/2.1 mm Hg for black women between the ACE

inhibitor and calcium channel arms of the study. The other two trials comparing an ACE inhibitor to a calcium channel blocker did not include blacks (JMIC-B included only Japanese participants and STOP-HTN2 included only Scandinavian participants). Therefore, the consistency of the stroke finding across trials cannot be evaluated.

### Angiotensin Receptor Blockers versus Other Drugs

Exhibits for Question 3 Evidence Statements for the general population for ARBs versus other drugs are provided in the Appendix.

- [Exhibit M: Evidence from randomized controlled trials of initial antihypertensive drug therapy with ARBs versus other drugs](#)

**Question 3, Angiotensin Receptor Blocker Evidence Statement 3:** In the general population with hypertension, there are no randomized controlled trials of any quality to determine whether initial antihypertensive drug therapy with an angiotensin receptor blocker compared to initial antihypertensive drug therapy with a diuretic improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

Evidence Quality: Unable to determine because there is no evidence

**Rationale/Comments:** No additional comments.

**Question 3, Angiotensin Receptor Blocker Evidence Statement 4:** In the general population with hypertension, there are no randomized controlled trials of good or fair quality to determine whether initial antihypertensive drug therapy with an angiotensin receptor blocker compared to initial antihypertensive drug therapy with an angiotensin converting enzyme inhibitor improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

Evidence Quality: Unable to determine because there is no evidence

**Rationale/Comments:** There are no randomized controlled trials of any quality meeting our eligibility criteria that compared initial antihypertensive drug therapy with an angiotensin receptor blocker to initial antihypertensive drug therapy with an angiotensin converting enzyme inhibitor and reported cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

ONTARGET compared an angiotensin receptor blocker to an angiotensin converting enzyme inhibitor to a combination of the two drugs in participants with vascular disease or high-risk diabetes [ONTARGET, 2008]. However, ONTARGET was not eligible for inclusion in our evidence review because the study was not designed to assess the effects of blood pressure lowering in hypertension and not all patients in the study were hypertensive. ONTARGET found no difference between the angiotensin receptor blocker and the angiotensin converting enzyme inhibitor for the primary outcome, which was a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure (risk ratio 1.01, 95% CI 0.94, 1.09).

**Question 3, Angiotensin Receptor Blocker Evidence Statement 5:** In the general population 50 years of age or older with hypertension, initial antihypertensive drug therapy with an angiotensin receptor blocker compared to initial antihypertensive drug therapy with a calcium channel blocker resulted in a 3 to 5 percent absolute lower rate of new onset diabetes.

Evidence Quality: Low

**Rationale/Comments:** Two studies contributed to this evidence statement (VALUE and CASE-J) [Julius, 2004; Ogihara, 2008]. Both studies were rated as Good. VALUE included 15,245 adults age 50 or older (mean age 67.2 years), randomized to valsartan or amlodipine. The mean follow-up was 4.2 years. New onset diabetes, defined by 1999 WHO criteria, was a prespecified secondary endpoint and occurred in 13.1% of the valsartan group (n=690) compared to 16.4% of the amlodipine group (n=845). The relative risk for new onset diabetes with valsartan compared to amlodipine was 0.77 (95% CI, 0.69, 0.86) ( $p < 0.0001$ ), while the absolute difference between the two groups was 3.3%. Despite this increase in new onset diabetes, there was no significant increase in cardiovascular events, cerebrovascular events, kidney events, or overall mortality in the amlodipine group compared to the valsartan group. There was, however, a 19% increase in fatal and non-fatal myocardial infarction in the valsartan group compared to the amlodipine group ( $p = 0.02$ ).

CASE-J included 4,728 participants age 20 to 85, with a mean age of 63.8 years, randomized to candesartan or amlodipine. The mean follow-up was 3.2 years. New onset diabetes was a prespecified secondary outcome. The relative risk of new onset diabetes was 36% lower in the candesartan group compared to the amlodipine group ( $p = 0.033$ ), while the absolute difference for new onset diabetes between the two groups was 4.9%. However, there was no difference in the use of additional diabetes drugs, including insulin, between the two groups ( $p=0.402$ ), and no difference in the primary cardiovascular endpoint (hazard ratio 1.01; 95% CI, 0.79, 1.28;  $p=0.969$ ).

Of note is that in CASE-J, the rate of new onset diabetes in the amlodipine group (13.6 per 1000 patient-years) was one-third the rate seen in the amlodipine group in VALUE (41.1 per 1000 patient-years) possibly indicating a population effect. As noted by Ogihara and colleagues, mean BMI for participants without diabetes in CASE-J was 24.1 compared to 28.0 in VALUE. In addition, 3.5% of the population in VALUE was Asian compared to 100% in CASE-J.

The third trial meeting our inclusion criteria for comparing an angiotensin receptor blocker to a calcium channel blocker was MOSES (Schrader 2005), but MOSES did not report new onset diabetes. It should be noted that our literature review was not designed to answer whether new onset diabetes associated with the use of a particular antihypertensive medication, compared to use of another antihypertensive medication, results in significant changes in important health outcomes.

### **Thiazide and Thiazide-type Diuretics versus Other Drugs**

Exhibits for Question 3 Evidence Statements for the general population for thiazide and thiazide-type diuretics versus other drugs are provided in the Appendix. In these sections, all reference to diuretics refers to thiazide and thiazide-type agents as listed in the drug table. The drug table included the evidence-based diuretic doses we considered. [Exhibit I: Evidence from randomized controlled trials of initial antihypertensive drug therapy with diuretics versus other drugs](#)

### **Question 3, Diuretic Evidence Statement 6:**

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic has a similar benefit on overall mortality compared to initial antihypertensive drug therapy with an ACE inhibitor, calcium channel blocker, or alpha 1- blocking agent.

Evidence Quality: Moderate

**Rationale/Comments:** Six trials contributed to this evidence statement (ALLHAT, INSIGHT, SHELL, VHAS, MIDAS, ANBP2) [ALLHAT, 2002; ALLHAT 2003; Brown, 2000; Malacco, 2003; Rosei 1997; Borhani, 1996; Wing, 2003]. ALLHAT and INSIGHT were rated as Good and included populations of 42,418 and 6,321, respectively. The other four trials were rated as Fair and ranged in size from 883 to 6,083 participants. None of the trials was designed or powered to test for differences between drug classes with regard to overall mortality. Nonetheless, overall mortality was a secondary outcome that did not differ significantly between the diuretic and the other classes in any trial, and the confidence intervals around estimates of effect were narrow. For example, in the largest trial (ALLHAT) the relative risk was 1.00 (95% CI, 0.94, 1.08; p=0.90) for the diuretic-ACE inhibitor comparison, 0.96 (95% CI, 0.89, 1.02; p=0.20) for the diuretic-calcium channel blocker comparison, and 1.03 (95% CI, 0.94, 1.13; p=0.50) for the diuretic-alpha 1-blocking agent comparison. In INSIGHT, also a large study rated as Good, the odds ratio for overall mortality was 1.01 (0.80, 1.27; p=0.95) for the diuretic-calcium channel blocker comparison. Based on the consistent findings across six trials, the Panel determined that there was moderate quality evidence of similar benefit of a diuretic, ACE inhibitor, calcium channel blocker, or alpha 1- blocking agent regarding overall mortality. A grade of Moderate (rather than Strong) was given because overall mortality was a secondary outcome in all six trials.

### **Question 3, Diuretic Evidence Statement 7:**

In the general population with hypertension, the evidence is insufficient to determine whether there is a reduction in all-cause mortality with initial antihypertensive drug therapy with a diuretic compared to initial antihypertensive drug therapy with a beta blocker.

Evidence Quality: Unable to determine because there is insufficient evidence.

**Rationale/Comments:** Three studies contributed to this evidence statement (MRC, HAPPHY and MAPHY) [MRC, 1985; Wilhelmsen, 1987; Wilkstrand, 1988; Olsson, 1991]. All contributing trials were rated as Fair and ranged in size from 3,234 to 17,354 participants. MAPHY was considered “Less than Fair” by some Panel members because of an additional study design concern related to a protocol change in MAPHY allowing additional centers to randomize patients to atenolol or diuretics. The original study protocol did not include atenolol as a beta blocker option. Pooled results from all metoprolol centers, all atenolol centers, and the propranolol center were published separately as HAPPHY.

MAPHY showed a significant 22% increase in total mortality in the diuretic group at 10.8 years (95% CI not reported; p=0.028). However, MRC and HAPPHY found no difference between the beta blocker and diuretic groups. All three trials included participants of similar ages (40 to 64 years for MAPHY and HAPPHY; 35 to 64 years in MRC); however, HAPPHY and MAPHY only included men. It was unclear whether the possible benefit of metoprolol in MAPHY was drug specific or applicable to beta blockers as a class. The evidence was deemed insufficient because of the inconsistent results, differences in event rates across the trials, concern about generalizability because HAPPHY and MAPHY included only white men, and weaknesses of MAPHY due to study design concerns.

### **Question 3, Diuretic Evidence Statement 8:**

In the general population 35 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic has a similar benefit on coronary heart disease outcomes compared to initial treatment with an ACE inhibitor, beta blocker, calcium channel blocker, or alpha-1 blocking agent.

Evidence Quality: Moderate

**Rationale/Comments:** Nine studies contributed to this evidence statement (MRC, ALLHAT, SHELL, VHAS, INSIGHT, MIDAS, HAPPHY, MAPHY, and ANBP2) [MRC, 1985; ALLHAT, 2002; ALLHAT, 2003; Malacco, 2003; Rosei, 1997; Brown, 2000; Borhani, 1996, Wilhelmsen, 1987; Wilkstrand, 1988; Wing, 2003]. Two of the nine studies were rated as Good (ALLHAT and INSIGHT) and the remaining seven were rated as Fair. Coronary heart disease outcomes were primary outcomes in four of the nine trials (MRC, ALLHAT, HAPPHY, and MAPHY). Five trials, including the largest trial (ALLHAT) where coronary heart disease was the primary outcome, showed no significant difference in coronary heart disease outcomes for initial treatment with a diuretic compared to an ACE inhibitor, beta blocker, calcium channel blocker, or an alpha-1 blocking agent (MRC, ALLHAT, SHELL, MIDAS and MAPHY). Three trials showed significant differences between groups for coronary heart disease outcomes; however, results were inconsistent among these three trials (INSIGHT, MAPHY, and ANBP2). Fatal MI was a secondary endpoint in INSIGHT where the odds ratio (95% CI) 3.22 (1.18-8.80;  $p < 0.017$ ) where events were lower with the diuretic compared to the calcium channel blocker. MAPHY included fatal coronary heart disease as a primary outcome (composite of fatal MI and sudden coronary death) and the diuretic did worse than the beta blocker (43 versus 36 events, respectively,  $p = 0.048$ ). ANBP2 included MI as a primary endpoint and there were significantly more events in the diuretic group compared to the ACE inhibitor (HR [95% CI]; 0.68 (0.47, 0.98,  $p = 0.04$ ). However, there was no difference in overall coronary events in ANBP2 (HR [95% CI]; 0.86 (0.70, 1.06,  $p = 0.16$ ). One trial did not report p-values (VHAS), but the number of events was small, and CHD was a secondary outcome.

In INSIGHT, fatal myocardial infarction (a secondary outcome) occurred more frequently in the calcium channel blocker group compared to the diuretic group with an odds ratio of 3.22 (95% CI, 1.18, 8.80;  $p = 0.017$ ); there was no significant difference for non-fatal myocardial infarction. MAPHY showed a significant difference between groups for fatal coronary heart disease, which was a composite of myocardial infarction and sudden coronary death. There were fewer fatal coronary heart disease events in the beta blocker (metoprolol) group compared to the diuretic group at 10.8 years follow-up (36 versus 43 events;  $p = 0.048$ ). However, as described in the rationale for the preceding evidence statement, MAPHY was considered “Less than Fair” by some Panel members because of numerous study design concerns. As one example, there was a protocol change in MAPHY that occurred more than 2 years into the randomization that allowed for additional centers that could randomize patients to atenolol or diuretics (the original protocol included metoprolol). In ANBP2, myocardial infarction was reduced by 32% in the ACE inhibitor group compared to the diuretic group (95% CI, 0.47, 0.98;  $p = 0.04$ ). However, the diuretic doses used in ANBP2 were not stated and there was concern that the doses used in ANBP2 were lower than the doses used in the studies demonstrating the benefits of diuretics (for example, doses of HCTZ 25 to 100 mg, chlorthalidone 12.5 to 25 mg, or bendrofluazide 5 to 10 mg). The drug dosing table above lists the target dose for HCTZ of 25-50 mg based on newer evidence even though older studies used higher doses. Doses from 50-100 mg of HCTZ can be used but the additional blood pressuring lowering effect is modest and the risk of hypokalemia is much greater than with lower dosages.

### **Question 3, Diuretic Evidence Statement 9:**

In the general non-black population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic has similar cerebrovascular outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor.

Evidence Quality: Moderate

**Rationale/Comments:** Two trials contributed to this evidence statement (ALLHAT and ANBP2) [ALLHAT, 2002; Wing, 2003]. In ALLHAT, 15,255 adults aged 55 years or older with at least one risk factor for coronary heart disease were randomized to the diuretic chlorthalidone and compared to 9,054 similar participants randomized to the ACE inhibitor lisinopril. ALLHAT was rated as Good. Non-blacks constituted 65% percent of the trial population and were a prespecified subgroup and there was a treatment by race interaction when considering blacks and non-blacks. ANBP2 was conducted in Australia, and the Panel classified the population as non-black. Separate evidence statements were created for cerebrovascular outcomes for the general non-black and black populations due to significantly different results in the two subgroups. Among non-blacks, the relative risk for stroke was 1.00 (95% CI, 0.85, 1.17; p=not reported). Among blacks, the relative risk was 1.40 (95% CI, 1.17, 1.68; p=not reported) favoring use of the diuretic; this evidence is addressed further in evidence statement 5. For stroke, the p value for the interaction term with race was 0.01, indicating that race significantly affected the comparison between the diuretic and the ACE inhibitor for this outcome. However, stroke was a secondary endpoint.

ANBP2 randomized 6,083 adults age 65 to 84 years to a thiazide diuretic (predominantly hydrochlorothiazide) or ACE inhibitor (predominantly enalapril). It was rated as Fair. There was a significant 91% reduction in the secondary endpoint of fatal stroke among those treated with diuretic therapy (95% CI, 1.04, 3.50; p = 0.04), but the findings were not significant for total stroke (HR, 1.02, 95% CI, 0.78, 1.33; p=0.91) or non-fatal stroke (HR 0.93, 95% CI, 0.70, 1.26; p=0.65). As noted earlier, the doses of diuretics or ACE inhibitors used in ANBP2 were not specified.

The significant benefit for fatal stroke seen in ANBP2 favoring diuretic therapy over ACE inhibitor therapy was not confirmed for nonfatal or total stroke in ANBP2 or in ALLHAT, which had a relative risk of 1.00 with narrow confidence limits. Because ALLHAT was a much larger study, had a better quality rating, and narrow confidence limits, the results of ALLHAT were given greater weight by the Panel.

### **Question 3, Diuretic Evidence Statement 10:**

In the general black population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic improves cerebrovascular outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor.

Evidence Quality: Moderate

**Rationale/Comments:** This evidence statement is based on one trial (ALLHAT) in which race was a pre-specified subgroup and 35% of study subjects were black [ALLHAT, 2002]. ALLHAT was rated as Good, and stroke was a prespecified secondary outcome. In the overall trial results, there was a reduction in strokes in the group initially treated with a diuretic compared to the group initially treated with an ACE inhibitor (RR for use of an ACE inhibitor compared to use of a diuretic, 1.15, 95% CI, 1.02, 1.30; p=0.02). This benefit was driven by the reduction in strokes seen in the black subgroup. Among blacks, stroke increased by 40% in the ACE inhibitor group compared to the diuretic group (95% CI, 1.17, 1.68; p=not reported).

There were differences in the percentage of subjects achieving the blood pressure goal of less than 140/90 mm Hg at each annual visit, with blood pressure significantly higher at five years in the lisinopril group compared to the chlorthalidone group (by 2 mm Hg for all participants and by 4 mm Hg in black participants). Analysis of the relative risk for stroke adjusted for follow-up blood pressures suggests that

the systolic blood pressure difference between the lisinopril and chlorthalidone groups is only partly responsible for the observed differences in stroke.

**Question 3, Diuretic Evidence Statement 11:**

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic has similar cerebrovascular outcomes compared to initial antihypertensive drug therapy with a calcium channel blocker.

Evidence Quality: High

**Rationale/Comments:** Four trials contributed to this evidence statement (ALLHAT, SHELL, INSIGHT, MIDAS) [ALLHAT, 2002; Malacco, 2003; Brown, 2000; Borhani, 1996]. In all four trials, cerebrovascular outcomes were pre-specified secondary outcomes. ALLHAT and INSIGHT were rated as Good with study populations of 33,357 and 6,321, respectively. Reductions in fatal and non-fatal stroke outcomes with the calcium channel blocker compared to the diuretic were similar (ALLHAT OR = 0.93 [95% CI 0.82-1.06], p=0.28) and (INSIGHT OR 0.87 [95% CI 0.61-1.26], p=0.52 for nonfatal and 1.09 [95% CI 0.48-2.48], p=0.84 for fatal stroke). SHELL and MIDAS were rated as Fair with study populations of 1,882 and 883, respectively. Reductions in fatal and non-fatal stroke outcomes were also similar for the calcium channel blocker compared to the diuretic in these two trials (SHELL OR 0.96 [95% CI 0.61-1.51], p=0.87 and MIDAS OR 2.00 [95% CI 0.50-7.93], p=0.32). In each of the four trials, initiation of antihypertensive drug therapy with a diuretic yielded similar cerebrovascular outcomes when compared to initiation of antihypertensive therapy with a calcium channel blocker. The quality of this evidence statement is graded as High because four contributing trials yielded consistent results.

**Question 3, Diuretic Evidence Statement 12:**

In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a diuretic results in different cerebrovascular outcomes compared to initial antihypertensive drug therapy with a beta blocker.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Three trials contributed to this evidence statement (MRC, HAPPHY, and MAPHY) [MRC, 1985; Wilhelmsen, 1987; Wikstrand 1988). All three trials were rated as Fair. MRC was the largest trial with 17,354 participants age 35 to 64 and an approximately equal number of males and females. The population in both HAPPHY and MAPHY was exclusively male, age 40 to 64 years, with 6,569 and 3,234 subjects, respectively. Stroke was a secondary outcome in HAPPHY and MAPHY, and it was one of multiple primary outcomes in MRC.

MRC randomized participants to a placebo, bendrofluazide 10 mg, or propranolol 240 mg. There was a significant difference in the rate of strokes favoring the diuretic (0.8 per 1000 patient years (n =18) versus 1.9 per 1000 patient years (n=42); p=0.002.)

HAPPHY randomized participants to a diuretic (hydrochlorothiazide 50 mg daily or bendroflumethazide 5 mg daily) or a beta blocker (atenolol 100 mg daily or metoprolol 200 mg daily). There was no difference in fatal and nonfatal stroke (OR 1.29, 95% CI, 0.82, 2.04; p >0.20). The difference in fatal stroke trended towards significance, but there were few events overall (10 events in the diuretic group compared with 3 events in the beta blocker group; p = 0.09).

MAPHY was a continuation of the HAPPHY study for the centers using metoprolol. There were more fatal strokes in the diuretic group compared to the beta blocker group; however, there were few events overall (9 events in the diuretic group compared with 2 events in the beta blocker group at 10.8 years of follow-up;  $p=0.043$ ). Total strokes and nonfatal stroke were not reported.

The Panel concluded that the quality of the evidence was insufficient due to the heterogeneity of trial outcomes. However, the largest trial (MRC) did favor the diuretic.

### **Question 3, Diuretic Evidence Statement 13:**

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic improves cerebrovascular outcomes, heart failure outcomes, and combined cardiovascular outcomes compared to initial antihypertensive drug therapy with an alpha 1-blocking agent.

Evidence Quality: Moderate

**Rationale/Comments:** This evidence statement is based on one trial (ALLHAT) rated as Good [ALLHAT, 2000; ALLHAT, 2003]. The alpha blocker (doxazosin) arm of ALLHAT, which included 9,067 participants, was terminated early due to a 25% (95% CI, 1.17, 1.33;  $p<0.001$ ) greater incidence of combined cardiovascular outcomes when compared to the diuretic (chlorthalidone) arm, which included 15,268 participants. Combined cardiovascular outcomes were defined as: coronary heart disease death, nonfatal myocardial infarction, stroke, coronary revascularization procedures, angina, heart failure, and peripheral arterial disease. Stroke increased by 26% (95% CI, 1.10, 1.46;  $p=0.001$ ) and heart failure (including fatal, hospitalized and treated heart failure) increased by 80% (95% CI, 1.61, 2.02;  $p<0.001$ ) in the alpha blocker group compared to the diuretic group. Combined cardiovascular outcomes and stroke were prespecified secondary outcomes. Although ALLHAT was a large study that was rated as Good, the overall evidence quality was graded as Moderate because there was only one contributing trial, and the outcomes were secondary.

### **Question 3, Diuretic Evidence Statement 14:**

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic improves heart failure outcomes compared to initial antihypertensive drug therapy with a calcium channel blocker.

Evidence Quality: High

**Rationale/Comments:** Five trials contributed to this evidence statement (ALLHAT, SHELL, VHAS, INSIGHT, MIDAS) [ALLHAT, 2002; Davis, 2006; Malacco, 2003; Rosei, 1997; Brown, 2000; Borhani, 1997]. Two studies, ALLHAT and INSIGHT, were rated as Good with study populations of 33,357 and 6,321, respectively. SHELL, VHAS and MIDAS were smaller studies rated as Fair with study populations ranging from 883 to 1,882. Heart failure was a secondary outcome in all five trials. Both ALLHAT and INSIGHT had significantly lower rates of heart failure in the diuretic group compared to the calcium channel blocker group; however, in INSIGHT the heart failure event rate was low, so the absolute reduction was small. In ALLHAT, there were 38% more heart failure events in the calcium channel blocker group compared to the diuretic group (95% CI, 1.25, 1.52;  $p<0.001$ ). Second line drugs in ALLHAT, which included atenolol, clonidine and reserpine, were used equally in all treatment groups, allowing for a reasonably straightforward comparison of the first line agents. In INSIGHT, there were more non-fatal heart failure events in the calcium channel blocker group (OR 2.20, 95% CI, 1.07, 4.49;  $p=0.028$ );

however, there were few heart failure events overall (11 in the diuretic group and 24 in the calcium channel blocker group).

Neither SHELL nor MIDAS showed a statistically significant difference in heart failure, and the p value for heart failure was not reported for VHAS. In these three trials, there were few heart failure events, and the number of events in the diuretic group was consistently less than the number of events in the calcium channel blocker group. The evidence quality was graded as High because two large studies rated as Good showed consistent results that were statistically significant; the results from three additional trials rated as Fair trended in the same direction, although they did not reach statistical significance due to the small number of events.

**Question 3, Diuretic Evidence Statement 15:**

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic improves heart failure outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor.

Evidence Quality: Moderate

**Rationale/Comments:** Two trials contributed to this evidence statement (ALLHAT, ANBP2) [ALLHAT, 2002; Wing, 2003]. ALLHAT compared chlorthalidone (dose range 12.5 mg to 25 mg) to lisinopril (dose range 10 mg to 40 mg) and was rated as Good. In ANBP2, hydrochlorothiazide was the recommended diuretic and enalapril was the recommended ACE inhibitor; the dose ranges of the two drugs were not specified. Heart failure was a secondary outcome in both trials. In ALLHAT the incidence of heart failure (including fatal, hospitalized, and treated nonhospitalized heart failure) was 19% higher (95% CI, 1.07, 1.31;  $p < 0.001$ ) among the participants on the ACE inhibitor compared to those on the diuretic. In ANBP2 there was no significant difference in heart failure (HR 0.85, 95% CI, 0.62, 1.18;  $p = 0.33$ ), and the direction of the hazard ratio favored the ACE inhibitor. Investigators did not specify the dose of either medication in ANBP2. The Moderate grading for this evidence statement was driven by the ALLHAT results because of its large study population, Good quality rating, and the large number of heart failure events (1,482 heart failure events in ALLHAT compared to 147 in ANBP2).

**Question 3, Diuretic Evidence Statement 16:**

In the general non-black population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic results in similar combined cardiovascular disease outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor.

Evidence Quality: Low

**Rationale/Comments:** Two trials contributed to this evidence statement (ALLHAT and ANBP2) [ALLHAT, 2002; Wing, 2003]. ALLHAT was rated as Good and ANBP2 was rated as Fair. Non-blacks constituted 65% percent of the ALLHAT population and were a prespecified subgroup. ANBP2 was conducted in Australia, and the Panel classified the population as non-black. Separate evidence statements were created for combined cardiovascular disease outcomes for the general adult non-black and black populations due to different results in the two subgroups.

In ALLHAT among non-blacks, the relative risk for combined cardiovascular disease was 1.06 (95% CI, 1.00, 1.13;  $p = \text{not reported}$ ). Outcomes favored the diuretic, but the confidence interval included 1.00, so it did not quite achieve statistical significance. Among blacks, the relative risk was 1.19, also favoring the diuretic (95% CI, 1.09, 1.30;  $p = \text{not reported}$ ), and in this case the CI does not cross 1, so the result was

statistically significant. This evidence is addressed further in the next evidence statement. For combined cardiovascular disease outcomes, the p value for the interaction term with race was 0.04, indicating that race significantly affected the comparison between the diuretic and the ACE inhibitor for this outcome. Combined cardiovascular disease was a secondary composite endpoint that included coronary heart disease death, nonfatal myocardial infarction, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and hospitalization or revascularization for peripheral arterial disease.

In ANBP2, the primary composite outcome of all cardiovascular events and death from any cause was lowered by 11% in the ACE inhibitor group compared to the diuretic group; however the confidence interval included 1.00 (95% CI, 0.79, 1.00; p=0.05), so it did not quite achieve statistical significance. Cardiovascular events in the primary composite outcome included: coronary events including MI, sudden or rapid death from cardiac causes, other deaths from coronary causes or coronary events associated with therapeutic procedure involving coronary arteries, other cardiovascular events, including heart failure, acute occlusion of a major feeding artery in any vascular bed other than cerebral or coronary, death from non-cardiac causes, dissecting or ruptured aortic aneurysm or death from vascular causes and cerebrovascular events including stroke and TIA.

The evidence quality for this statement was graded as Low because of inconsistent results between the two trials (ALLHAT favored the diuretic while ANBP2 favored the ACE inhibitor) and the fact that the confidence intervals included 1.00 in both trials. In addition, each trial defined composite outcomes differently and included softer endpoints such as angina and revascularization. ALLHAT was given more weight for this evidence statement than ANBP2 because of its substantially larger size and higher quality rating.

### **Question 3, Diuretic Evidence Statement 17:**

In the general black population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic improves combined cardiovascular disease outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor.

Evidence Quality: Low

**Rationale/Comments:** This evidence statement is based on one trial (ALLHAT) in which race was a prespecified subgroup and 35% of study subjects were black [ALLHAT, 2002]. ALLHAT was rated as Good, and combined cardiovascular disease was a prespecified secondary composite endpoint. Among blacks, there was a significant 19% lower occurrence of the combined cardiovascular disease endpoints with the diuretic group compared to the ACE inhibitor group (95% CI, 1.09, 1.30; p<0.001). The quality of the evidence was graded as Low because the evidence statement is based on a subgroup analysis from only one trial and the combined cardiovascular disease endpoint included softer endpoints such as angina and revascularization.

### **Question 3, Diuretic Evidence Statement 18:**

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic results in similar combined cardiovascular disease outcomes compared to initial antihypertensive drug therapy with a calcium channel blocker.

Evidence Quality: High

**Rationale/Comments:** Five studies contributed to this evidence statement (ALLHAT, INSIGHT, MIDAS, SHELL, and VHAS) [ALLHAT, 2002; Brown, 2000; Borhani, 1996; Malacco, 2003; and Rosei, 1997]. Two of these trials (ALLHAT and INSIGHT) were rated as Good. ALLHAT included 24,303 participants in the diuretic and calcium channel blocker arms, and INSIGHT included 6,321 participants. The other three trials (MIDAS, SHELL, and VHAS) were smaller studies rated as Fair that ranged in size from 883 to 1,882 participants. The term ‘combined cardiovascular disease outcomes’ in this evidence statement refers to composite cardiovascular outcomes as reported in each of the contributing trials. In two of the trials (SHELL and INSIGHT) composite cardiovascular outcomes were the primary outcomes. In the other three trials the composite cardiovascular outcomes were secondary outcomes. There were no statistically significant differences in combined cardiovascular disease outcomes between the diuretic and calcium channel blocker groups in any of the five trials. In the largest trial, ALLHAT, there was a 4% lower occurrence of composite cardiovascular events with the diuretic group compared to the calcium channel blocker group, but the result was not significant (HR 1.04, 95% CI, 0.99, 1.09; p=0.12). In INSIGHT, there was an 11% higher occurrence of composite cardiovascular events in the calcium channel blocker group, but it was not significant (95% CI, 0.90, 1.36; p=0.34). In MIDAS, there was a 78% lower occurrence in major vascular events in the diuretic group compared to the calcium channel blocker group (favoring the diuretic group) but it was not significant (RR 1.78, 95% CI, 0.94, 3.38; p=0.07). In SHELL the hazard ratio for the composite primary endpoint was 1.01 (95% CI, 0.75, 1.36; p=0.94). In VHAS no hazard ratio or risk ratio was reported for major cardiovascular events, but the number of major cardiovascular events was nearly the same in both groups (9 in the diuretic group and 8 in the calcium channel blocker group). The evidence quality was graded as High because none of the five studies found a significant difference in composite cardiovascular disease outcomes between groups treated initially with a diuretic compared to a calcium channel blocker.

### **Question 3, Diuretic Evidence Statement 19:**

In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic has similar effects on kidney outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor or calcium channel blocker.

Evidence Quality: Moderate

**Rationale/Comments:** Two trials contributed to this evidence statement (ALLHAT and INSIGHT) [ALLHAT, 2002; Brown 2000]. Although three additional trials compared a diuretic to an ACE inhibitor or calcium channel blocker (MIDAS, SHELL, and VHAS), kidney outcomes prespecified by the Panel for consideration were not reported in these trials. Both ALLHAT and INSIGHT were rated as Good. ALLHAT included 33,357 subjects, and INSIGHT included 6,321 subjects. Kidney outcomes were secondary in both trials. ALLHAT compared a diuretic (chlorthalidone) to an ACE inhibitor (lisinopril) or calcium channel blocker (amlodipine) whereas INSIGHT compared a combination diuretic (hydrochlorothiazide and amiloride) to a calcium channel blocker (nifedipine). The ALLHAT inclusion criteria allowed enrollment of subjects with serum creatinine less than 2.0 mg/dl. INSIGHT did not have study inclusion or exclusion criteria based on serum creatinine levels; 170 subjects (2.7%) had proteinuria at baseline defined as 0.5 gram protein per 24 hours or greater.

Neither trial found a significant difference in kidney outcomes between groups. For ESRD in ALLHAT, defined as dialysis, renal transplant, or death, the relative risk for the diuretic-ACE inhibitor comparison was 1.11 (95% CI, 0.88, 1.38; p=0.38) favoring the diuretic. For the diuretic-calcium channel blocker comparison, the relative risk was 1.12 (95% CI, 0.89, 1.40; p=0.33) and also favored the diuretic. In INSIGHT, the odds ratio for renal failure, which was defined as creatinine greater than 2.94 mg/dl, was

0.62 and favored the diuretic, but it was not statistically significant (OR 0.62, 95% CI, 0.26, 1.49; p=0.38), and there were few renal failure events overall (n=21).

The Panel noted that the diuretics used in these two trials differed. Chlorthalidone and hydrochlorothiazide, although both in the diuretic class, are somewhat different compounds. Additionally, INSIGHT used a combination diuretic that included hydrochlorothiazide and amiloride. These differences in the diuretics used in each study, together with the wide confidence intervals for the kidney endpoints, led to an overall grading of the evidence quality as Moderate.

**Question 3, Diuretic Evidence Statement 20:** In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic results in a 3 to 4 mg/dl increase in fasting blood glucose and a 2 to 4 percent absolute increase in hyperglycemia or incident diabetes compared to initial antihypertensive drug therapy with an ACE inhibitor or calcium channel blocker. Evidence Quality: Moderate

**Rationale/Comments:** Three studies contributed to this evidence statement (ALLHAT, INSIGHT, VHAS) [ALLHAT, 2002; Brown, 2000; Rosei, 1997]. In these studies, initiation of antihypertensive treatment with a diuretic, compared to initiation of treatment with an ACE-inhibitor or calcium channel blocker, resulted in an increase in fasting blood glucose, hyperglycemia or incident diabetes but did not result in an increase in adverse cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality (see Question 3, Diuretic Evidence Statements 6, 8, 9, 10, 11, 14, 15, 16, 17, 18, and 19). It should be noted, however, that our literature review was not designed to answer whether increased fasting blood glucose, hyperglycemia, incident diabetes or other adverse effects associated with the use of a particular antihypertensive medication, compared to use of another antihypertensive medication, results in significant changes in health outcomes.

The evidence quality for this statement is strengthened by the fact that fasting blood glucose, hyperglycemia, or incident diabetes increased in the diuretic arm compared to the ACE-inhibitor or the calcium channel blocker arm in the three trials that assessed these outcomes. However, study quality was downgraded from high to moderate because these outcomes were not prespecified as primary or secondary outcomes, the studies used different outcome measures that were not well defined in all the studies, and our literature review was not designed to evaluate the comparative effects of different antihypertensive medications on these endpoints.

### [Beta Blockers versus Other Drugs](#)

Exhibits for Question 3 Evidence Statements for the general population for beta blockers versus other drugs are provided in the Appendix.

- [Exhibit J: Evidence from randomized controlled trials of initial antihypertensive drug therapy with beta blockers versus other drugs](#)

**Question 3, Beta Blocker Evidence Statement 21:** In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a beta blocker compared to initial antihypertensive drug therapy with a calcium channel blocker improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality. Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** Two trials contributed to this evidence statement (ASCOT and ELSA) [Dahlöf, 2005; Zanchetti, 2002]. These trials were not specifically designed to test whether a beta blocker compared to a calcium channel blocker improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

ASCOT included 19,257 subjects and was rated as Good. Antihypertensive drug therapy was initiated with one drug (either a calcium channel blocker or beta blocker) and a second drug was added (ACE inhibitor to the calcium channel blocker group and diuretic to the beta blocker group) as needed to control blood pressure. The intent was that most study participants would receive at least two antihypertensive drugs, and 78% of participants were taking at least two antihypertensive drugs by the end of the trial. However, the Panel did not consider it a combination drug trial in the same sense as ACCOMPLISH (see Question 3, Combination Therapy Evidence Statement 1) because in ASCOT, treatment was initiated with a single drug and then stepped up with a second drug, whereas in ACCOMPLISH, treatment was initiated with two-drug combination therapy in a single-capsule formulation [Jamerson, 2008; Dahlöf, 2005].

ASCOT showed a significant reduction in events for calcium channel blocker-based therapy compared to beta blocker-based therapy, including a 13% reduction in nonfatal MI plus fatal CHD (95% CI, 0.76, 1.00;  $p=0.0458$ ), 23% reduction in fatal and nonfatal stroke (95% CI, 0.66, 0.89;  $p=0.0003$ ), and 11% reduction in all-cause mortality (95% CI, 0.81, 0.99;  $p=0.0247$ ).

ELSA included 2,334 subjects and was rated as Fair. The primary outcome of ELSA was mean maximum intima media thickness, but the trial was not powered to address cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality. ELSA showed no significant differences in these outcomes.

None of the kidney outcomes prespecified by the Panel (ESRD, doubling of creatinine, halving of eGFR) was reported in ASCOT or ELSA.

Although ASCOT was a large study that showed a benefit in the study arm treated initially with a calcium channel blocker compared to a beta blocker, the study population was comprised of high-risk individuals with hypertension and three or more cardiovascular risk factors. It also was complicated by different background therapy in each arm, which included use of a diuretic and doxazosin in the atenolol arm and use of an ACE inhibitor in the amlodipine arm. Given these issues pertaining to ASCOT and the fact that ELSA did not assess any of the clinical endpoints prespecified by the Panel, it was determined that evidence from these two trials was insufficient to determine whether initial antihypertensive drug therapy with a beta blocker compared to a calcium channel blocker improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

**Question 3, Beta Blocker Evidence Statement 22:** In the general population 55 to 80 years of age with hypertension, initial antihypertensive drug therapy with an angiotensin receptor blocker compared to initial antihypertensive drug therapy with a beta blocker decreases stroke and a primary composite endpoint (consisting of CV death, MI, or stroke), but results in no difference in overall mortality, heart failure or MI.

Evidence Quality: Low

**Rationale/Comments:** One trial contributed to this Evidence Statement (LIFE) [Dahlöf, 2002]. LIFE compared initial antihypertensive drug therapy with an ARB to initial therapy with a beta blocker. LIFE was rated as Good and included 9,193 participants age 55 to 80, all of whom had hypertension and left ventricular hypertrophy (LVH) by electrocardiogram (ECG). Atenolol was the beta blocker and losartan was the ARB. The primary endpoint was a composite of cardiovascular death, MI, and stroke. There was a significant 13% (95% CI, 0.77, 0.98; p=0.021) reduction in the primary composite endpoint in the ARB group compared to the beta blocker group. The trial was designed to test the primary outcome, not the separate components; however, the primary outcome result favoring losartan was largely driven by a 25% decrease in stroke (adjusted HR 0.75, 95% CI, 0.63, 0.89; p=0.001). All-cause mortality, cardiovascular mortality, MI, and heart failure were not significantly different between groups. The quality of the evidence was considered Low because the Evidence Statement was based on only one study with a population limited to those with hypertension and LVH by ECG.

**Question 3, Beta Blocker Evidence Statement 23:** In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive therapy with a beta blocker has an effect on kidney outcomes that is different than the effect of initial antihypertensive therapy with a diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** There are no RCTs in hypertensive patients without kidney disease that compared initial antihypertensive drug therapy with a beta blocker to a diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker and reported the kidney outcomes prespecified by the Panel (ESRD, doubling of creatinine, halving of eGFR). Question 3, Evidence Statement 1 for Chronic Kidney Disease addresses this evidence in those with kidney disease. Several trials reported other kidney outcomes for those with hypertension without kidney disease, but they were all intermediate outcomes that did not meet the Panel's prespecified inclusion criteria. For example, ASCOT reported a significant 15% (95% CI, 0.75, 0.97; p=0.0187) lower rate of renal impairment for calcium channel blocker-based therapy compared to beta blocker-based therapy [Dahlöf, 2005]. IPPPSH reported a lower rate of renal impairment with beta blockers compared to placebo alone or added to other non-beta-blocker antihypertensives [IPPPSH, 1985]. HAPPHY reported a non-significant difference in the change in creatinine between the beta blocker and diuretic groups [Wilhelmsen, 1987]. However renal impairment and change in creatinine were not defined with sufficient rigor to be considered eligible kidney outcomes.

**Question 3, Beta Blocker Evidence Statement 24:** In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a beta blocker compared to initial antihypertensive drug therapy with a calcium channel blocker results in a difference in new onset diabetes.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** One study contributed to this evidence statement (ASCOT) [Dahlöf, 2005]. ASCOT included 19,257 subjects and was rated as Good. Antihypertensive drug therapy in ASCOT was initiated with one drug (a calcium channel blocker or beta blocker) and was then stepped-up to another drug (an ACE inhibitor for the calcium channel blocker group and a diuretic for the beta blocker group) as needed to control blood pressure; the intent was that most participants would receive at least two antihypertensive drugs. Development of diabetes was a prespecified tertiary outcome. The development of diabetes was 30% lower with calcium channel blocker-based therapy compared to beta blocker-based therapy (95% CI, 0.63, 0.78; p<0.0001).

The Panel graded the evidence as insufficient because of the low percentage of study participants who received a beta blocker or a calcium channel blocker as monotherapy prior to the addition of Step 2 agents, the categorization of new onset diabetes as a tertiary endpoint, and because our review was not primarily designed to evaluate the association of different antihypertensive medications with new onset diabetes.

**Question 3, Beta Blocker Evidence Statement 25:** In the general population 55 to 80 years of age with hypertension, initial antihypertensive drug therapy with a beta blocker compared to initial antihypertensive drug therapy with an angiotensin receptor blocker results in a 2 percent absolute increase in new onset diabetes.

Evidence quality: Low

**Rationale/Comments:** One trial contributed to this Evidence Statement (LIFE) [Dahlöf, 2002]. LIFE compared atenolol and losartan in participants age 55 to 80 with essential hypertension and left ventricular hypertrophy on ECG. At baseline, 7,998 patients did not have diabetes mellitus. New-onset diabetes occurred in 241 participants receiving losartan (5.99%) and 319 receiving atenolol (8.01%) for a relative risk of 0.75 (95% CI, 0.63, 0.88,  $P < 0.001$ ). Diabetes was defined according to 1985 World Health Organization criteria. The quality of the evidence was considered Low because the Evidence Statement was based on only one study with a population limited to those with hypertension and LVH by ECG.

**Additional comments relating to dysglycemia and beta blocker use:** UKPDS compared two different blood pressure goals in a population 25 to 65 years of age with hypertension and type 2 diabetes [UKPDS, 1998]. The group of 758 study participants assigned to tight blood pressure control with a target blood pressure of less than 150/85 mm Hg was randomized to captopril or atenolol and followed for 9 years. Two measures of dysglycemia were examined prospectively and defined as treatment effects rather than clinical endpoints. For follow-up years 1 through 4, mean hemoglobin A1C (SD) was 7.0% (1.4%) for captopril versus 7.5% (1.4%) for atenolol ( $p = 0.0044$ ). For follow-up years 1 through 4, 53% of participants in the captopril group received additional glucose lowering treatment compared to 66% in the atenolol group ( $p = 0.0015$ ); for follow-up years 5 through 9, 71% of participants in the captopril group received additional glucose lowering treatment compared to 81% in the atenolol group ( $p = 0.029$ ). The Panel thought that while worth noting, the evidence for increased hyperglycemia associated with initial antihypertensive treatment with atenolol compared to captopril was limited by the fact that UKPDS was a small trial rated as Fair.

### [Calcium Channel Blockers versus Other Drugs](#)

Exhibits for Question 3 Evidence Statements for the general population for calcium channel blockers versus other drugs are provided in the Appendix.

- [Exhibit K: Evidence from randomized controlled trials of initial antihypertensive drug therapy with calcium channel blockers versus other drugs](#)

**Question 3, Calcium Channel Blocker Evidence Statement 26:** In the general population 50 years of age or older with hypertension, initial antihypertensive drug therapy with a calcium channel blocker compared to initial antihypertensive drug therapy with an angiotensin receptor blocker results in no difference in overall mortality.

Evidence Quality: Moderate

**Rationale/Comments:** The contributing clinical trials comparing a calcium channel blocker (CCB) to an angiotensin receptor blocker (ARB) are VALUE, CASE-J, and MOSES, all of which used dihydropyridine CCB [Julius, 2004; Ogihara, 2008; Schrader, 2005]. IDNT [Lewis, 2001] also compared a CCB to an ARB; however, this trial was restricted to participants with diabetic nephropathy, and results for this population are addressed in later Evidence Statements.

VALUE and CASE-J were rated as Good and MOSES was rated as Fair. Overall mortality was a secondary outcome in each study, and each study found no difference between the CCB and ARB groups. VALUE enrolled 15,245 high-risk participants age 50 years or older and compared valsartan and amlodipine; the hazard ratio for overall mortality was 1.04 (95% CI, 0.94, 1.15) (p = 0.49). CASE-J enrolled 4,728 participants with a mean age of 63.8 years and compared candesartan and amlodipine; there were 86 all-cause deaths in the amlodipine group compared to 73 in the candesartan group with no significant difference between groups. MOSES enrolled 1,405 participants and was designed as a secondary prevention hypertension trial comparing eprosartan and nitrendipine in participants who suffered a stroke confirmed by an imaging study within the prior 24 months. All-cause mortality occurred in 109 participants without significant a difference between treatment groups (p=0.725). The Panel graded the evidence as Moderate. Although findings were consistent across the three trials and the confidence interval in the largest trial (VALUE) was narrow, overall mortality was a secondary outcome in each trial.

**Question 3, Calcium Channel Blocker Evidence Statement 27:** In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a calcium channel blocker compared to initial antihypertensive drug therapy with an angiotensin receptor blocker results in a difference in coronary heart disease outcomes, cerebrovascular outcomes, heart failure, or kidney outcomes.

Evidence Quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** These statements are based on the same three trials discussed in Evidence Statement 26 (VALUE, CASE-J, MOSES) [Julius, 2004; Ogihara, 2008; Schrader, 2005]. Coronary heart disease (CHD), cerebrovascular disease (CVD), heart failure (HF), and kidney outcomes were all secondary endpoints. Each trial used a composite endpoint as the primary outcome. VALUE and CASE-J were rated as Good, and MOSES was rated as Fair.

Coronary heart disease outcomes: In VALUE, the hazard ratio for fatal and nonfatal MI was 1.19 (95% CI, 1.02, 1.38) (p = 0.02) favoring amlodipine over valsartan. In CASE-J, there was no difference in cardiac events (defined as heart failure, angina pectoris, or acute myocardial infarction) with a hazard ratio of 0.92 (95% CI, 0.61, 1.39) (p = 0.68). In MOSES, the relative risk for fatal and nonfatal cardiovascular events (defined as any cardiovascular event including myocardial infarction and new cardiac failure) was 0.75 (95% CI, 0.55, 1.02) (p = 0.061) favoring eprosartan over nitrendipine.

Improved coronary heart disease outcomes with the calcium channel blocker in VALUE were not confirmed in CASE-J and MOSES. Moreover, the primary composite outcomes in VALUE and CASE-J, which included CHD outcomes, showed no significant difference. Given the inconsistency in findings across the 3 trials, there is insufficient evidence to suggest a difference in coronary heart disease outcomes comparing a CCB and an ARB.

Cerebrovascular disease outcomes: In VALUE and CASE-J, there was no significant difference in cerebrovascular events between the CCB and ARB treatment groups, but the direction favored the CCB. In VALUE, the hazard ratio for the ARB (valsartan) compared to the CCB (amlodipine) for fatal and nonfatal stroke was 1.15 (95% CI, 0.98, 1.35) ( $p = 0.08$ ). In CASE-J, the hazard ratio for the ARB (candesartan) compared to the CCB (amlodipine) for cerebrovascular events (defined as fatal and nonfatal stroke and TIA) was 1.23 (95% CI, 0.85, 1.78) ( $p = 0.282$ ). In contrast, MOSES showed a 25% (RR 0.75; 95% CI, 0.58, 0.97;  $p = 0.026$ ) reduction in fatal and nonfatal cerebrovascular events (stroke and TIA) with the ARB (eprosartan) compared to the CCB (nitrendipine). However, the results of MOSES may not be generalizable because the study was limited to participants with a prior stroke within 24 months. Given the heterogeneity of results, there is insufficient evidence to determine whether initial treatment with a CCB results in different cerebrovascular outcomes compared to an ARB.

Heart failure: In VALUE, the hazard ratio for fatal and nonfatal heart failure was 0.89 (95% CI, 0.77, 1.03) ( $p = 0.12$ ) favoring the ARB, while in CASE-J, the hazard ratio was 1.25 favoring the CCB (95% CI, 0.65, 2.42) ( $p = 0.498$ ), but neither result was significant. In MOSES there were 30 heart failure events with eprosartan and 46 with nitrendipine. These events were reported as part of the fatal and nonfatal cardiovascular events composite, and there was no significant difference between this composite endpoint in the two treatment groups (relative risk 0.75, 95% CI, 0.55, 1.02,  $p = 0.061$ ). Given the inconsistency of findings across trials and wide confidence intervals, the Panel thought there was insufficient evidence to determine whether there is a difference in heart failure between initial treatment with a CCB compared to an ARB.

Kidney outcomes: In CASE-J, the hazard ratio for kidney events (defined as a composite of serum creatinine of 4.0 mg/dl or higher, doubling of serum creatinine, or end stage kidney disease) was 0.70 with wide confidence intervals (95% CI 0.39, 1.26) ( $p = 0.230$ ). In VALUE and MOSES, kidney outcomes were not reported. Therefore, there was insufficient evidence to determine whether initial treatment with a CCB results in different kidney outcomes compared to initial treatment with an ARB.

**Question 3, Calcium Channel Blocker Evidence Statement 28:** In the general population 50 years of age or older with hypertension, initial antihypertensive therapy with a calcium channel blocker compared to initial antihypertensive therapy with an angiotensin receptor blocker results in no difference in composite outcomes.

Evidence Quality: Low

**Rationale/Comments:** Three trials contributed to this Evidence Statement (VALUE, CASE-J, and MOSES) [Julius, 2004; Ogihara, 2008, Schrader, 2005]. Each trial used a composite endpoint as the primary outcome. In VALUE, the primary outcome was a composite of time to first cardiac event that included sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or coronary bypass graft, death due to heart failure, heart failure requiring hospitalization, nonfatal MI, or emergency procedures to prevent MI. The hazard ratio was 1.04 (95% CI, 0.94, 1.15) ( $p = 0.49$ ). In CASE-J, the primary outcome was a composite that included sudden death, stroke, TIA, heart failure, MI, angina, a kidney event composite, dissecting aortic aneurism, and occlusion of a peripheral artery. The hazard ratio was 1.01 (95% CI, 0.79, 1.28) ( $p = 0.969$ ). In MOSES, the primary outcome was a composite that included all-cause mortality, stroke, TIA, MI, and new heart failure. In MOSES the relative risk was 0.79 (95% CI, 0.66, 0.96) ( $p = 0.014$ ) favoring eprosartan over nitrendipine.

The Panel graded the evidence as Low Quality because the composite outcomes were defined differently across the three trials, and the results were not consistent. The one trial (MOSES) that showed a significant difference was a secondary prevention trial, which limits the applicability of its results.

### Combination Therapy

Exhibits for Question 3 Evidence Statements for combination therapy in the general population are provided in the Appendix.

- [Exhibit N: Evidence from randomized controlled trials of antihypertensive drug therapy with combination drugs](#)

**Question 3, Combination Therapy Evidence Statement 29:** In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with the combination of benazepril and amlodipine reduces fatal and nonfatal MI, coronary revascularization procedures, composite of CV morbidity and mortality, and doubling of serum creatinine, but there was no difference in overall mortality, stroke, heart failure, or ESRD outcomes when compared to initial antihypertensive drug therapy with the combination of benazepril and hydrochlorothiazide.

Evidence Quality: Moderate

**Rationale/Comments:** This evidence statement is based on one trial (ACCOMPLISH) which was rated as Good [Jamerson, 2008; Bakris, 2010]. The primary outcome of ACCOMPLISH was a composite of cardiovascular morbidity and mortality. This trial used a single pill combination that compared initial antihypertensive treatment with benazepril-amlodipine to initial antihypertensive treatment with benazepril-hydrochlorothiazide. The benazepril-amlodipine arm of the study had a significant 20% (95% CI, 0.72, 0.90;  $p < 0.001$ ) decrease in the primary outcome compared to the benazepril-hydrochlorothiazide arm, despite similar BP lowering in both groups (131.6/73.3 mm Hg and 132.5/74.4, respectively). The trial was terminated early after a mean follow-up of 36 months due to this difference favoring the benazepril-amlodipine group in the primary outcome. There were no significant differences in the rates of mortality, ESRD, stroke or heart failure in the two groups. However, if the study had not been stopped early, differences in some of these outcomes may have been significant by the end of the trial. An important consideration with ACCOMPLISH is that the maximum dose of the thiazide diuretic used in the study (25 mg of HCTZ) was less than doses used in many of the studies that showed benefit for this class of antihypertensive medications (50-100 mg/day of HCTZ or equivalent doses of other thiazide-type diuretics). However, the HCTZ dose in ACCOMPLISH is consistent with the dose generally used in contemporary medical practice.

The evidence quality was graded as low because there was only one study comparing these fixed-dose combinations, concerns about the dose of the diuretic used in the study, and conflicting evidence from multiple studies that compared calcium channel blockers and diuretics when used with add-on agents other than ACE inhibitors (see Question 3, Diuretic Evidence Statements 1,3,6,9, 13, and 14). In addition, the methodology team identified the following issues with ACCOMPLISH: criteria for event classification were not explicitly described other than being “standardized”, use of concomitant medications was reported at baseline but not at the end of follow-up, and adherence information was reported at six months and one year but not at the end of follow-up (although reporting adherence at all is a strength).

## Other Drug Classes

**Question 3, Other Drug Classes Evidence Statement 30:** There are drug classes for which there are no randomized controlled trials of good or fair quality in the general population with hypertension to determine whether initial antihypertensive drug therapy with one of these medications improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality compared to initial antihypertensive drug therapy with another antihypertensive medication.

Evidence Quality: Unable to determine because there is no evidence

These drug classes include:

- Dual alpha-1, beta blocking agents
- Vasodilating beta blockers
- Central alpha 2 adrenergic agonists
- Aldosterone receptor antagonists
- Peripheral adrenergic neuron antagonists (reserpine)
- Loop diuretics
- Nitrate containing agents
- Direct renin inhibitors
- Potassium-sparing diuretics used as monotherapy

**Rationale/Comments:** There are no randomized controlled trials of any quality that compared initial antihypertensive drug therapy with one of the above medications to initial antihypertensive drug therapy with another antihypertensive medication and reported cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

The Hypertension-Stroke Cooperative Study, EWPHE, SHEP, VA Cooperative and ANBP tested active treatment arms that included centrally-acting sympatholytics used in addition to diuretics [HSCoop, 1974; Amery, 1985; SHEP, 1991; VACoop, 1970]; however, these active treatment arms were compared to placebo. MRC, EWPHE, STOP-Hypertension, and HDFP tested active treatment arms that included potassium-sparing diuretics used in addition to thiazide-type diuretics [MRC, 1985; Amery, 1985; Dahlöf, 1991; HDFP 1979]; however, these active treatment arms were compared to placebo or usual care.

## Statements for the Population with Chronic Kidney Disease

**Question 3, Chronic Kidney Disease Evidence Statement 31:** In the population 18 to 75 years of age with chronic kidney disease (CKD) and hypertension, treatment with an ACE inhibitor improves kidney outcomes (ESRD, halving of GFR or doubling of serum creatinine) compared to treatment with a calcium channel blocker or a beta blocker.

Evidence Quality: Moderate

**Rationale/Comments:** Three studies contributed to this Evidence Statement (AASK, ESPIRAL, and AVER) [Wright, 2002; Marin, 2001; Esnault, 2008]. AASK was rated as Good and included 1,094 participants followed for 3 to 6.4 years. AASK included a population limited to African Americans who were carefully selected to avoid those with proteinuric kidney disease of greater than 2.5 mg protein/mg creatinine. ESPIRAL was rated as Fair and included 241 participants followed for 3 years. AVER was rated as Fair and included 263 participants followed for a median of 2.9 years. All three studies were conducted in similar age ranges: 18 to 70 years for AASK, 18 to 75 years for ESPIRAL, and 18 to 80 years for AVER.

Three different ACEIs were used across the studies: ramipril in AASK, fosinopril in ESPIRAL, and enalapril in AVER. Two different CCBs were used across the studies: amlodipine in AASK and AVER, and nifedipine in ESPIRAL.

Both AASK and ESPIRAL showed significant improvement in kidney outcomes in the ACEI group compared to the CCB group; AVER found no significant differences between groups. In AASK, there was a 40% (95% CI, 14%, 59%;  $p=0.006$ ) risk reduction for a GFR event or ESRD in the ACEI group compared to the CCB group. GFR events were defined as a reduction in GFR by 50% or more or  $\geq 25$  mL/min per  $1.73\text{ m}^2$  from baseline. AASK used a complex trial design with 2 blood pressure goals for each of 3 different agents with similar add-on treatments for all three study arms. The primary outcome of change in GFR slope was not an outcome prespecified by the Panel for consideration. In ESPIRAL, there was a 53% (95% CI, 0.26, 0.84;  $p=0.01$ ) reduction in the doubling of serum creatinine or need for dialysis in the ACEI group compared to the CCB group. This composite was the primary outcome. In ESPIRAL, participants receiving an ACEI achieved systolic blood pressures 4 to 6 mm Hg lower than participants receiving a CCB. At 3 years of follow-up in AVER, 15.4% of participants in the ACEI group had a secondary composite endpoint compared to 21.1% in the CCB group ( $p=NS$ ). The secondary composite endpoint included: renal replacement therapy, discontinuation due to deterioration of renal function, 50% decrease in GFR, doubling of serum Cr, and hospitalization for transient renal failure. Limitations of this endpoint are that it was a secondary composite consisting of many endpoints, some of which were soft endpoints such as hospitalization for transient kidney failure. Attrition rates were negligible in AASK but 33% for AVER and 32% for ESPIRAL.

**Question 3, Chronic Kidney Disease Evidence Statement 32:** In the population 30 to 70 years of age with chronic kidney disease with proteinuria and hypertension, antihypertensive treatment with an angiotensin receptor blocker improves kidney outcomes compared to antihypertensive treatment with a calcium channel blocker.

Evidence Quality: Low

**Rationale/Comments:** One trial (IDNT) contributed to this Evidence Statement [Lewis, 2001]. IDNT, which was rated a Fair study, included 1,715 participants with diabetic nephropathy, 30 to 70 years of age, followed for a mean of 2.6 years. This trial was restricted to a population with diabetic nephropathy (creatinine between 1 and 3 mg/dL) and proteinuria of at least 900 mg/24 hours (equivalent to a spot urine protein to creatinine of 1g/g) for trial entry. The primary outcome was a composite of doubling of baseline serum creatinine concentration, ESRD onset (as indicated by initiation of dialysis, renal transplantation, or serum creatinine  $\geq 6.0$  mg/dL), and all-cause mortality. There was a 24% (95% CI, 0.63, 0.92;  $p=0.005$ ) reduction in the primary outcome for the ARB group compared to the CCB group. Doubling of serum creatinine was significant with a 39% (95% CI, 0.48, 0.79;  $p<0.001$ ) reduction in the ARB group compared to the CCB group, but the 24% (95% CI, 0.57, 1.02) reduction in ESRD for the ARB group was not quite significant with a  $p$ -value of 0.06. While ARBs, ACEIs or CCBs were washed out prior to the intervention, participants were continued on other drugs and could have other drugs added as second line treatment including diuretics, beta blockers, alpha-1 blockers and alpha-2 agonists. There was no evidence to support this statement for participants without diabetes. Although VALUE also compared an ARB to a CCB, kidney outcomes were not reported for subgroups [Zanchetti, 2006].

**Question 3, Chronic Kidney Disease Evidence Statement 33:** In the population 18 to 70 years of age with chronic kidney disease and hypertension, antihypertensive treatment with an ACE inhibitor does

not improve combined cardiovascular disease outcomes compared to antihypertensive treatment with a calcium channel blocker or beta blocker.

Evidence Quality: Moderate

**Rationale/Comments:** One study (AASK) contributed to this Evidence Statement [Wright, 2002; Norris, 2006]. AASK included 1,094 participants and investigated change in GFR as the primary outcome; the principal results paper was rated as Good. The study population was limited to African Americans who were carefully selected to avoid those with proteinuric kidney disease of greater than 2.5 mg protein /mg creatinine, and the results may not be generalizable to other cohorts including higher risk populations. AASK compared an ACEI (ramipril) to a CCB (amlodipine) to a beta blocker (metoprolol). AASK was not powered for cardiovascular outcomes, but they were prespecified secondary outcomes reported in a subsequent publication rated as Fair. There was no difference between groups in the composite cardiovascular outcome defined as cardiovascular deaths and hospitalizations for myocardial infarction, stroke, heart failure, revascularization procedures, and other hospitalized CV events. Hazard ratios for the composite cardiovascular outcome were: 0.77 (95% CI, 0.48, 1.24; p=0.28) for amlodipine versus metoprolol, 1.27 (95% CI, 0.78, 2.06; p=0.33) for ramipril versus amlodipine, and 0.98 (95% CI, 0.69, 1.39; p=0.90) for ramipril versus metoprolol. There were 149 total cardiovascular events.

**Question 3, Chronic Kidney Disease Evidence Statement 34:** In the population 30 years of age or older with chronic kidney disease and hypertension, antihypertensive treatment with an angiotensin receptor blocker does not improve combined cardiovascular disease outcomes compared to antihypertensive treatment with a calcium channel blocker.

Evidence Quality: Moderate

**Rationale/Comments:** The two trials contributing to this Evidence Statement (IDNT, VALUE) showed no differences between groups [Lewis, 2001; Zanchetti, 2006]. Both trials were rated as Fair. IDNT included 1,715 participants with diabetic nephropathy, 30 to 70 years of age, followed for a mean of 2.6 years. VALUE included 15,245 participants age 50 or older with 9,566 people age 65 years or older, of whom 530 participants had a baseline serum creatinine of greater than 1.7 mg/dl. In IDNT, the ARB used was irbesartan; valsartan was used in VALUE. Both trials used amlodipine for the CCB.

Combined cardiovascular disease was a secondary outcome in IDNT and included death from cardiovascular causes, nonfatal MI, HF resulting in hospitalization, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle. The adjusted relative risk for irbesartan versus amlodipine was 1.03 (95% CI, 0.81, 1.32; p=0.78). However, the mean follow-up duration of 2.6 years may not have been long enough for study participants to experience a sufficient number of cardiovascular events to detect a significant difference. Heart failure is addressed below in Question 3, CKD Evidence Statement 5.

In VALUE, the primary outcome was time to first cardiac event which was a composite of: sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or CABG, death as a result of HF, death associated with recent MI at autopsy, HF requiring hospital management, non-fatal MI, or emergency procedures to prevent MI. Among participants with baseline serum creatinine greater than 1.7 mg/dl, 21.9% in the amlodipine group experienced the primary composite endpoint compared to 19.7% in the valsartan group (p=0.670). A thiazide diuretic was part of stepped treatment escalation for both study arms. Other drugs could be used except for additional ARBs. ACEI or CCB could be added for non-BP related reasons.

**Question 3, Chronic Kidney Disease Evidence Statement 35:** In the population 30 to 70 years of age with chronic kidney disease and hypertension, initial antihypertensive treatment with an angiotensin receptor blocker reduces the incidence of heart failure compared to initial antihypertensive treatment with a calcium channel blocker.

Evidence Quality: Low

**Rationale/Comments:** One trial (IDNT) contributed to this Evidence Statement [Lewis, 2001; Berl, 2003]. IDNT included 1,715 participants and was rated a Fair study. This trial was restricted to a specific population with diabetic nephropathy (creatinine between 1 and 3 mg/dL) and proteinuria of at least 900 mg/24 hours (equivalent to a spot urine protein to creatinine of 1g/g) for trial entry. IDNT compared an ARB (irbesartan) to a CCB (amlodipine) to a placebo. Heart failure was a component of the prespecified secondary cardiovascular composite outcome. Heart failure was reduced by 35% (95% CI, 0.48, 0.87;  $p=0.004$ ) in the ARB group compared to the CCB group. While the analysis for heart failure achieved significance, the secondary cardiovascular composite outcome, which included heart failure, did not (hazard ratio 0.90 (95% CI, 0.74, 1.10;  $p>0.2$ ). The mean follow-up time of 2.6 years may have been too short to see sufficient cardiovascular endpoints.

**Comments on other studies that met the eligibility criteria but were not addressed in the above Evidence Statements:**

ASCOT compared two antihypertensive treatment strategies where different add-on drugs were used in each group; the CCB group received an ACEI as add-on therapy and the BB group received a thiazide as add-on therapy [Dahlöf, 2005]. Although ASCOT met the eligibility criteria for this question, the Panel felt that ASCOT was not designed as a clear study of a single drug versus another drug, and it was therefore difficult to interpret the results. In ASCOT, initial antihypertensive treatment with CCB-based therapy reduced the occurrence of total cardiovascular events and procedures compared to BB-based therapy in study participants with renal dysfunction. Although renal dysfunction was a prespecified subgroup, renal dysfunction was not explicitly defined.

LIFE compared an ARB (losartan) to a BB (atenolol) and met the eligibility criteria for this question [Dahlöf, 2002]. The Panel assessed the LIFE substudy of participants with baseline albuminuria but did not include it as a study contributing to the Question 3 CKD Evidence Statements because of how CKD was defined in the study [Ibsen, 2004]. The Ibsen paper reports cardiovascular outcomes by groups above and below the mean baseline urinary Albumin/Creatinine Ratio (UACR), which was 1.28 mg/mmol but does not qualify for a standard diagnosis of CKD where  $UACR >30$  mg/g is generally considered the standard definition. This was a prespecified subgroup analysis of the primary composite outcome reported in a subsequent paper.

**Statements for the Adult Population with Diabetes**

**Diuretic Evidence Statements in Diabetes**

**Question 3, Diabetes Diuretic Evidence Statement 36:** In the population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a thiazide or thiazide-type diuretic improves heart failure outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor or calcium channel blocker, but there is no difference in overall mortality, coronary heart disease outcomes, cerebrovascular outcomes, or a composite of combined cardiovascular outcomes.

Evidence quality: Moderate

**Rationale/Comments:** Two trials contributed to this evidence statement (ALLHAT and INSIGHT) [ALLHAT, 2002; Whelton, 2005; Mancia, 2003]. Diabetes was a prespecified subgroup in both trials. 12,063 (36%) participants in ALLHAT and 1,302 (20.6%) participants in INSIGHT had diabetes at baseline. Both trials compared a calcium channel blocker with a thiazide-type diuretic. ALLHAT also compared an ACE inhibitor with a thiazide-type diuretic. Several trials (CAPPP, CONVINCe, NORDIL) reported outcomes in diabetes subgroups, but they compared an ACE inhibitor or calcium channel blocker to “conventional therapy” which was an investigator selection of a diuretic or beta-blocker [Niskanen, 2001; Black, 2003; Hansson, 2000]. These trials were not included because the contributing role of the diuretic or beta-blocker could not be evaluated.

Among the diabetes population in ALLHAT, there was a 22% (95% CI, 1.05, 1.42; p=not reported) higher incidence of heart failure in the ACE inhibitor group compared to the diuretic group. There was also an 8% (95% CI, 1.00, 1.17) increase in the composite outcome of combined cardiovascular disease, but it was of borderline significance, and it was driven mainly by the higher incidence of heart failure. There was also a 42% (95% CI, 1.23, 1.64) higher incidence of heart failure in the calcium channel blocker group compared to the diuretic group. For both the ACE inhibitor/chlorthalidone comparison and the calcium channel blocker/chlorthalidone comparison, there were no other significant differences in any of the prespecified outcomes, except in the black population. In the black population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a diuretic improved cerebrovascular outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor.

Among the diabetes population in INSIGHT, there was a non-significant higher incidence of heart failure in the calcium channel blocker group compared to the diuretic group (relative risk, 1.51, 95% CI, 0.54, 4.22), but there were only fifteen events overall (six events in the diuretic group versus nine in the calcium channel blocker group). The primary composite outcome of cardiovascular death, myocardial infarction, heart failure, and stroke, was similar between the two groups with a relative risk of 0.99 (95% CI, 0.69, 1.42; p=1.00).

**Question 3, Diabetes Diuretic Evidence Statement 37:** In the population with diabetes and hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a diuretic has a different effect on kidney outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor, calcium channel blocker, or  $\alpha_1$ -blocker.  
Evidence quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** One trial contributed to this evidence statement (ALLHAT) [Whelton, 2005]. ESRD was reported in a secondary ALLHAT publication rated as Fair which examined 13,101 subjects with diabetes followed for a mean of 4.9 years. The number of participants with diabetes is different in this secondary publication than in the primary publication because the secondary publication used an additional criterion for defining diabetes: presence of a baseline fasting glucose level of 126 mg/dL or greater. ESRD was a secondary outcome and was defined as dialysis, renal transplantation, or death due to kidney disease. The 6-year event rate per 100 subjects (standard error) for ESRD was: 3.5 (0.4) for amlodipine, 3.0 (0.4) for lisinopril and 2.6 (3.0) for chlorthalidone. The relative risk for amlodipine compared to chlorthalidone was 1.27 (95% CI, 0.97, 1.67; p=0.08) and lisinopril compared to chlorthalidone was 1.09 (95% CI, 0.82, 1.46; p=0.55). The Panel concluded the evidence to be insufficient, rather than evidence of no difference, because ESRD was a secondary outcome with wide confidence intervals.

**Question 3, Diabetes Diuretic Evidence Statement 38:** In the population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a thiazide-like diuretic improves heart failure and combined cardiovascular outcomes, but there is no difference in coronary heart disease outcomes and overall mortality compared to initial antihypertensive drug therapy with an  $\alpha_1$ -blocker.  
Evidence quality: Moderate

**Rationale/Comments:** The report from ALLHAT for the early termination of the doxazosin arm contributed to this statement [Barzilay, 2004]. There were 3,220 participants with diabetes in the doxazosin arm and 5,529 participants with diabetes in the chlorthalidone arm. Diabetes was a prespecified subgroup, and this secondary publication for the diabetes subgroup was rated as Fair. The doxazosin arm was stopped early due to a 25% greater incidence of combined cardiovascular disease compared with the chlorthalidone arm. Combined cardiovascular disease was defined as combined coronary heart disease, stroke, treated angina without hospitalization, heart failure, and peripheral arterial disease. Combined coronary heart disease included the primary outcome (combined fatal coronary heart disease or nonfatal MI), coronary revascularization, or angina with hospitalization. In the entire ALLHAT population, the risk for stroke was 26% higher (95% CI, 1.10, 1.46;  $p < 0.001$ ) and the risk for fatal or hospitalized heart failure was 66% higher (95% CI, 1.46, 1.89;  $p < 0.001$ ) in the doxazosin group compared to the chlorthalidone group [ALLHAT, 2003]. However, in the smaller diabetic cohort, the relative risk was significant for only heart failure with a point estimate of 1.85 (95% CI, 1.56, 2.19;  $p < 0.001$ ) and combined cardiovascular disease with a point estimate of 1.22 (95% CI, 1.11, 1.33;  $p < 0.001$ ) for doxazosin compared to chlorthalidone. The differences for coronary heart disease (relative risk 1.07, 95% CI, 0.91, 1.27;  $p = 0.41$ ) and stroke (relative risk 1.21, 95% CI, 0.97, 1.50);  $p = 0.09$ ) were not statistically significant for the diabetes subgroup.

**Question 3, Diabetes Diuretic Evidence Statement 39:** In the population less than 55 years of age with diabetes and hypertension, there are no studies of Good or Fair quality to determine whether initial antihypertensive drug therapy with a diuretic compared to initial antihypertensive drug therapy with an ACE inhibitor, calcium channel blocker, or  $\alpha_1$ -blocker improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes or mortality.  
Evidence quality: Unable to determine because there are no trials

**Rationale/Comments:** There are no randomized controlled trials of any quality that compared initial antihypertensive drug therapy with a diuretic to initial antihypertensive drug therapy with an ACE inhibitor, calcium channel blocker, or alpha-1 blocking agent in a population less than 55 years of age with hypertension and diabetes. ALLHAT compared initial antihypertensive therapy with a diuretic to an ACE inhibitor, calcium channel blocker, and alpha-1 blocking agent, and INSIGHT compared initial antihypertensive therapy with a diuretic to a calcium channel blocker. However, neither ALLHAT nor INSIGHT included participants less than 55 years of age.

### [Beta Blocker Evidence Statements in Diabetes](#)

**Question 3, Diabetes Beta Blocker Evidence Statement 40:** In the population 55 to 80 years of age with diabetes and hypertension, initial antihypertensive drug therapy with an angiotensin receptor blocker improves cardiovascular and total mortality, heart failure, and composite cardiovascular outcomes compared to initial antihypertensive drug therapy with a beta blocker.  
Evidence quality: Low

**Rationale/Comments:** One trial contributed to this evidence statement (LIFE) [Lindholm, 2002]. The LIFE trial had 1,195 participants with diabetes (13% of their study population) at baseline, and diabetes was a prespecified subgroup. The primary publication was rated as Good, but the secondary publication focusing on results in the diabetes subgroup was rated as Fair due to the limitations of the subgroup analyses. LIFE was restricted to participants 55 to 80 years of age with left ventricular hypertrophy on electrocardiogram. Diabetes was defined according to the 1985 World Health Organization criteria. The primary endpoint was a composite of cardiovascular morbidity and mortality which included cardiovascular death, stroke, and myocardial infarction.

In participants with diabetes, there was a significant 24% (95% CI, 0.58, 0.98;  $p=0.031$ ) lower occurrence in the primary composite outcome in the losartan group compared to the atenolol group. Cardiovascular mortality was reduced by 37% (95% CI, 0.42, 0.95;  $p=0.028$ ); total mortality was reduced by 39% (95% CI, 0.45, 0.84;  $p=0.002$ ); and heart failure hospitalizations were reduced by 41% (95% CI, 0.38, 0.92;  $p=0.019$ ). Systolic blood pressure reduction favored losartan with mean achieved blood pressure of 146/79 mmHg compared to 148/79 mmHg in the atenolol arm. This corresponds to attainment of goal blood pressure in 85% of participants in the losartan group compared with 82% in the atenolol group. The evidence quality was graded as Low because it was based on a subgroup analysis of one trial that was limited by the entry criterion of left ventricular hypertrophy on electrocardiogram and rated as Fair.

**Question 3, Diabetes Beta Blocker Evidence Statement 41:** In the population 25 to 65 years of age with diabetes and hypertension, initial antihypertensive drug therapy with an ACE inhibitor has a similar effect on overall mortality, stroke, heart failure, coronary heart disease, and cardiovascular disease outcomes compared to initial antihypertensive drug therapy with a beta blocker.

Evidence quality: Low

**Rationale/Comments:** One trial contributed to this evidence statement (UKPDS) [UKPDS, 1998]. UKPDS randomized 758 participants with diabetes to tight blood pressure control (defined as a target blood pressure less than 150/85 mm Hg) with captopril or atenolol and followed them for 9 years. The trial was rated as Fair. Mean achieved blood pressures were 144/83 mm Hg in the captopril arm and 143/81 mm Hg in the atenolol arm.

The primary outcome was a first clinical endpoint related to diabetes, which included sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation of at least one digit, vitreous hemorrhage, retinal photocoagulation, and blindness in one eye or cataract extraction. The relative risk for the primary outcome in the captopril group compared to the atenolol group was 1.10 (95% CI, 0.86, 1.41;  $p = 0.43$ ).

No differences were seen between groups for overall mortality or any cardiovascular endpoint. For captopril versus atenolol, the relative risk for all-cause mortality was 1.14 (95% CI, 0.81, 1.61;  $p=0.44$ ); for strokes it was 1.12 (95% CI, 0.59, 2.12;  $p = 0.74$ ); for myocardial infarction it was 1.20 (95% CI, 0.82, 1.76;  $p = 0.35$ ); and for heart failure it was 1.21 (99% CI, 0.39, 3.78;  $p = 0.66$ ). The evidence quality was graded as Low because it was based on one small study that was rated as Fair.

**Question 3, Diabetes Beta Blocker Evidence Statement 42:** In the population 40 to 79 years of age with diabetes and hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a beta blocker (followed by a thiazide diuretic) compared to initial antihypertensive drug therapy with a calcium channel blocker (followed by an ACE inhibitor) is

associated with lower occurrences of cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

Evidence quality: Unable to determine because there is insufficient evidence

**Rationale/Comments:** One trial contributed to this evidence statement (ASCOT) [Dahlof, 2005; Ostergren, 2008]. In ASCOT, antihypertensive drug therapy was initiated with one drug (amlodipine or atenolol) and then stepped-up to another drug (perindopril for the amlodipine group and bendroflumethiazide for the atenolol group) as needed to control blood pressure; the intent was that most patients would receive at least two antihypertensive drugs. Participants with diabetes were a prespecified subgroup and accounted for 27% of the trial population. The primary outcome was fatal CHD and nonfatal myocardial infarction. In participants with diabetes, there was no difference between groups for the primary outcome with a hazard ratio of 0.92 (95% CI, 0.74, 1.15; p=0.46), which was similar to the result for the overall population (HR 0.90; 95% CI 0.79, 1.02; p=0.11). However, the trial was terminated early due to a higher number of secondary outcome events in the atenolol group, including overall mortality and stroke.

Among participants with diabetes, there were significant differences for total cardiovascular events and procedures and stroke, all of which were secondary outcomes. The Panel determined the evidence to be insufficient because of study design issues such as: different drugs were used as add-on therapy for each study arm; achieved blood pressures were different in each study arm; and insufficient power due to early trial termination. In addition, the statement is based on only one trial which was rated as Fair due to its many limitations.

### [Angiotensin Converting Enzyme Inhibitors Evidence Statements in Diabetes](#)

**Question 3, ACEI Evidence Statement 43:** In the population with diabetes and hypertension, there are no trials meeting our eligibility criteria comparing initial antihypertensive drug therapy with an ACE inhibitor to initial antihypertensive drug therapy with an angiotensin receptor blocker, alpha-1 adrenergic blocker, or renin inhibitor that assessed cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

Evidence quality: Unable to determine because there are no trials

**Rationale/Comments:** This evidence statement reflects the inclusion criteria used to select the clinical trials that constituted our systematic evidence review. For example, ONTARGET, which demonstrated similar outcomes between ACE-I and ARB in a large group of participants with cardiovascular disease or diabetes, was not eligible for inclusion because the study was not designed to assess the effects of blood pressure lowering in hypertension and not all participants in the study were hypertensive. Similarly, our inclusion criteria restricted kidney outcomes to those used in trials that recorded clinical endpoints, which included doubling of serum creatinine, halving of eGFR, or progression to end stage kidney disease. Although albuminuria is closely associated with progression of kidney disease in diabetes, it is an intermediate outcome measure that has not been used as a primary outcome in many studies and is not accepted by the FDA as a surrogate measure for drug studies.

This statement does not contradict other Evidence Statements describing improved kidney outcomes in participants with hypertension and kidney disease, as it merely states that there were no studies meeting our eligibility criteria that compared this drug class to the other drug classes in head-to-head studies and assessed their effects on our pre-specified health outcomes.

## Calcium Channel Blockers Evidence Statements in Diabetes

**Question 3, Calcium Channel Blocker Evidence Statement 44:** In the population 30 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a calcium channel blocker has a similar benefit on cardiovascular composite outcomes compared to initial antihypertensive drug therapy with an angiotensin receptor blocker.

Evidence quality: Low

**Rationale/Comments:** Two trials contributed to this evidence statement (IDNT, VALUE) [Lewis, 2001; Berl, 2003; Zanchetti, 2006]. Both trials, which were rated as Fair, compared the calcium channel blocker amlodipine with an angiotensin receptor blocker; IDNT used irbesartan while VALUE used valsartan. IDNT included 1,715 participants aged 30 to 70 years with diabetic nephropathy and proteinuria (defined as urinary protein excretion of 900 mg per day or greater). VALUE included 15,245 participants with hypertension at high cardiovascular risk. At baseline, 4,823 (31.6%) participants had diabetes, which was a prespecified subgroup. In both trials, blood pressure differences between the different drug arms were 2 mm Hg or less.

Neither trial showed a significant difference in cardiovascular composite outcomes between groups. The cardiovascular composite in IDNT (a secondary outcome defined as time to cardiovascular death, myocardial infarction, congestive heart failure, stroke and coronary revascularization) had a hazard ratio of 0.90 (95% CI, 0.74, 1.10;  $p>0.2$ ). In the prespecified diabetes subgroup analysis for VALUE, the primary endpoint occurred in 14.6% of the amlodipine group and 14.7% of the valsartan group ( $p=0.528$ ). The primary endpoint in VALUE was time to first cardiac event, which was a composite of: sudden cardiac death, fatal or nonfatal myocardial infarction, death during or after percutaneous coronary intervention or CABG, death as a result of heart failure, heart failure requiring hospital management, death associated with recent MI at autopsy, or emergency procedures to prevent MI.

The Panel discussed whether there should be a separate evidence statement for heart failure in those with diabetes comparing initial antihypertensive drug therapy with a calcium channel blocker to initial antihypertensive drug therapy with an angiotensin receptor blocker. In IDNT, there was a significant 35% (95% CI, 0.48, 0.87;  $p=0.0004$ ) reduction in heart failure in the angiotensin receptor blocker group compared to the calcium channel blocker group; however IDNT was restricted to participants with diabetes and some evidence of nephropathy. VALUE did not report heart failure outcomes for the diabetes subgroup. Because the heart failure finding in IDNT was not confirmed in the larger VALUE trial, the Panel decided that a separate evidence statement was not warranted.

**Question 3, Calcium Channel Blocker Evidence Statement 45:** In the hypertensive population with diabetes, initial antihypertensive drug therapy with a calcium channel blocker has a similar benefit on combined nonfatal MI and fatal CHD compared to initial antihypertensive drug therapy with an ACE inhibitor.

Evidence quality: Low

**Rationale/Comments:** Three trials contributed to this evidence statement (ABCD Hypertensive Cohort, FACET, and ALLHAT) [Estacio 1998; Tatti, 1998; Leenen, 2006]. ABCD and FACET were rated as Fair. Although the primary publication for ALLHAT was rated as Good, the secondary publication for ALLHAT which contributed to this evidence statement was rated as Fair due to the limitations of subgroup analyses and because the ACE inhibitor and calcium channel blocker comparison was secondary.

The hypertensive cohort of ABCD included 470 participants between the ages of 40 to 74 with type 2 diabetes. The trial compared the calcium channel blocker nisoldipine with the ACE inhibitor enalapril. ABCD showed a significantly higher rate of events for the secondary outcome of fatal and nonfatal myocardial infarction in the calcium channel blocker group compared to the ACE inhibitor group with an adjusted risk ratio of 7.0 (95% CI, 2.3, 21.4;  $p = 0.001$ ). However, there were a small number of events (25 cases in the CCB arm versus 5 cases in the ACE-I arm). The level of achieved blood pressures was similar in both arms.

FACET included 380 participants with non-insulin dependent type 2 diabetes and hypertension. This was a single site study comparing the ACE inhibitor fosinopril to the calcium channel blocker amlodipine. This study had several limitations. It was not powered for any vascular outcome since the primary aim of the study was to assess treatment-related differences in serum lipids and diabetes control. Additionally, greater than 25% of participants received both study drugs during the course of the trial to control their blood pressure. Systolic blood pressure was 4 mm Hg lower in the calcium channel blocker arm ( $p < 0.01$ ). The secondary composite outcome of major vascular events was reduced by 51% (95% CI, 0.26, 0.95;  $p = 0.030$ ) in the ACE inhibitor group compared to the calcium channel blocker group. The composite included fatal and non-fatal MI and stroke, and hospitalized angina. However, there were a small number of events (14 cases in the ACE-I arm versus 27 cases in the CCB arm). Fatal and nonfatal MI were not significantly different between the two groups (hazard ratio 0.77, 95% CI, 0.34, 0.1.75;  $p > 0.1$ ).

ALLHAT assessed the effects of treatment with an ACE inhibitor compared to a calcium channel blocker on a prespecified group of 6,535 participants with diabetes at baseline. They found no difference between the ACE inhibitor and calcium channel blocker groups for the primary outcome of fatal coronary disease and nonfatal MI with a hazard ratio of 1.00 (95% CI, 0.87, 1.16). The Panel concluded that the results from the large ALLHAT trial offset the results from ABCD and FACET, two much smaller studies that favored the ACE inhibitor.

### **Combination Therapy in Diabetes**

**Question 3, Combination Therapy Evidence Statement 46:** In the population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with the combination of an ACE inhibitor and a calcium channel blocker reduces the composite outcome of cardiovascular events (defined as nonfatal MI, stroke, hospitalization for unstable angina, coronary revascularization, or resuscitation after sudden cardiac arrest) and death from cardiovascular causes (defined as death attributed to sudden death from cardiac causes, MI, stroke, coronary intervention, CHF, or other CV causes) compared to initial antihypertensive drug therapy with the combination of an ACE inhibitor and a diuretic.

Evidence quality: Low

**Rationale/Comments:** This evidence statement is based on the results of a prespecified subgroup of participants with diabetes in one trial (ACCOMPLISH) [Jamerson, 2008; Weber, 2010]. The primary ACCOMPLISH paper was rated as Good, while the secondary publication that focused on results in the diabetes subgroup was rated as Fair due to the limitations of subgroup analyses. ACCOMPLISH included 11,506 participants, 6,946 (60%) of whom had diabetes at baseline. This trial used single pill combinations comparing initial antihypertensive drug treatment with benazepril-amlodipine to initial antihypertensive drug treatment with benazepril-hydrochlorothiazide.

The primary outcome was time to first event of a composite of cardiovascular events and death from cardiovascular causes as listed in the Evidence Statement. There was a significant 21% (95% CI, 0.68, 0.92; p=0.003) lower occurrence of the primary composite outcome in the benazepril-amlodipine group compared to the benazepril-hydrochlorothiazide group. However, only one component of the primary composite outcome, coronary revascularization, achieved statistical significance. The trial was terminated early after a mean follow-up of 36 months due to the difference between groups in the primary composite outcome.

The evidence quality was graded as Low because it was based on a subgroup analysis of a single study comparing these fixed-dose combinations. There was also concern about the dose of the diuretic used in the study (maximum dose of hydrochlorothiazide was 25 mg/day), which was less than doses used in other studies that showed a benefit for this class of antihypertensive medications (50-100 mg/day of HCTZ or equivalent doses of other thiazide-type diuretics). However, both arms achieved similar mean blood pressures. In addition, evidence from ACCOMPLISH is not consistent with the reductions in heart failure events seen with the use of thiazide-type diuretics compared to calcium channel blockers when used with other add-on agents in studies with participants with diabetes and hypertension (see Question 3, Diabetes Diuretic Evidence Statement 1).

### **Evidence Statements for Blacks with Diabetes**

**Question 3, Blacks with Diabetes Evidence Statement 47:** In the black population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a thiazide-type diuretic is associated with a lower occurrence of heart failure, cerebrovascular, and combined cardiovascular outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor, but there is no difference in overall mortality or coronary heart disease outcomes.

Evidence quality: Low

**Rationale/Comments:** One trial contributed to this evidence statement (ALLHAT) [Wright, 2005]. ALLHAT was a large trial rated as Good. Race and diabetes subgroups were prespecified; however, subgroups by both race and diabetes were not prespecified. In ALLHAT, 46% of black participants had diabetes and more than 50% of black participants had either diabetes or impaired fasting glucose. Among blacks, there were statistically significantly lower occurrences of heart failure, stroke, and combined cardiovascular events in the thiazide group compared with the ACE inhibitor group. In blacks treated with the ACE inhibitor, there was a 30% (95% CI, 1.10, 1.54; p=0.003) higher occurrence of heart failure, a 40% (95% CI, 1.17, 1.68; p<0.001) increase in stroke, and a 19% (95% CI, 1.09, 1.30; p<0.001) increase in combined cardiovascular events. There were no differences for overall mortality or coronary heart disease outcomes.

Supporting evidence for this statement is also provided by a post-hoc analysis of black participants in ALLHAT that met the criteria for the metabolic syndrome, 68% of whom had diabetes and 73% of whom had either diabetes or impaired fasting glucose [Wright, 2008]. Among black participants in ALLHAT with metabolic syndrome treated with an ACE inhibitor, there was a 49% (95% CI, 1.17, 1.90; p=NR) increase in the incidence of heart failure, a 37% (95% CI, 1.07, 1.76; p=NR) increase in stroke, and a 24% (95% CI, 1.09, 1.40; p=NR) higher occurrence of combined cardiovascular events compared to those treated with a diuretic. However, this post-hoc analysis was not eligible for inclusion in our evidence review because the subgroups were not prespecified. As such, this evidence was not formally considered by the Panel in grading the quality of evidence.

**Question 3, Blacks with Diabetes Evidence Statement 48:** In the black population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a calcium channel blocker is associated with fewer cerebrovascular and combined cardiovascular outcomes compared to initial antihypertensive drug therapy with an ACE inhibitor, but there is no difference in heart failure or coronary heart disease outcomes.

Evidence quality: Low

**Rationale/Comments:** One trial contributed to this evidence statement (ALLHAT) [Leenen, 2006]. The primary comparison in ALLHAT was between thiazide-type diuretics and other antihypertensive drug classes, while the calcium channel blocker and ACE inhibitor comparison was secondary. The paper presenting the calcium channel blocker and ACE inhibitor comparison was rated as Fair because of the secondary nature of the comparison. As noted in the rationale/comments of the preceding evidence statement, race and diabetes subgroups were prespecified, but subgroups by both race and diabetes were not prespecified.

There was a significant 51% (95% CI, 1.22, 1.86; p=NR) higher occurrence of stroke and a significant 13% (95% CI, 1.02, 1.24; p=NR) increase in combined cardiovascular events in blacks treated with an ACE inhibitor compared with blacks treated with a calcium channel blocker. There were no differences between drugs for coronary heart disease outcomes or heart failure.

Outcomes for the comparison between initial use of a calcium channel blocker and initial use of an ACE inhibitor in blacks with diabetes were not reported in any of the papers that were eligible for our evidence review. Therefore, this evidence statement is extrapolated from the fact that 46% of black participants in ALLHAT had diabetes and more than 50% of black participants had either diabetes or impaired fasting glucose [Wright, 2008].

# Recommendations

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## RECOMMENDATIONS

### Recommendation 1

**In the general population 60 years of age or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP)  $\geq$ 150 mm Hg or diastolic blood pressure (DBP)  $\geq$ 90 mm Hg and treat to a goal SBP  $<$ 150 mm Hg and goal DBP  $<$ 90 mm Hg.**

**(Strong Recommendation – Grade A)**

**Corollary Recommendation: In the general population 60 years of age or older, if pharmacological treatment for high BP results in lower achieved SBPs (for example,  $<$ 140 mm Hg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)**

Recommendation 1 is based on ESs 1-3 from Question 2 in which there is moderate to high-quality evidence from RCTs that in the general population 60 years of age or older, treating high BP to a goal of  $<$ 150/90 mm Hg reduces stroke, heart failure, and coronary heart disease (CHD). There is also evidence (albeit low quality) from ES 6, Question 2 that setting a goal SBP of  $<$ 140 mm Hg in this age group provides no additional benefit compared to a higher goal SBP of 140-160 mm Hg or 140-149 mm Hg.[JATOS Study Group, 2008; Ogihara, 2010]

In order to answer Question 2 about goal BP, we reviewed all RCTs that met the eligibility criteria and that either: 1) compared treatment to a particular goal versus no treatment or placebo; or 2) compared treatment to one BP goal with treatment to another BP goal. The trials on which these ESs and this Recommendation are based include HYVET, Syst-Eur, SHEP, JATOS, VALISH, and CARDIO-SIS.[Staessen, 1997; Beckett, 2008; SHEP, 1991; JATOS Study Group, 2008; Agihara, 2010; Verdecchia, 2009] Strengths, limitations and other considerations related to this evidence review are presented in the ES narratives and clearly support the benefit of treating to  $<$ 150 mm Hg.

The Corollary to Recommendation 1 reflects the fact that there are many treated hypertensive patients age 60 or older in whom SBP is currently  $<$ 140 mm Hg, based on implementation of previous guideline Recommendations.[Chobanian, 2003] The Committee's opinion is that in these patients, it is not necessary to adjust medication in order to allow BP to rise. In two of the trials that provide evidence supporting a SBP goal  $<$ 150 mm Hg, the average treated SBP was 143-144 mm Hg.[Beckett, 2008; SHEP, 1991] Many participants in those studies achieved a SBP  $<$ 140 mm Hg with treatment that was generally well tolerated. Two other trials suggest there was no benefit for a SBP goal  $<$ 140 mm Hg, but the confidence intervals around the effect sizes were wide and did not exclude the possibility of a clinically important benefit.[JATOS Study Group, 2008; Ogihara, 2010] Therefore, we include a Corollary Recommendation based on expert opinion that treatment for hypertension does not need to be adjusted if it results in SBP  $<$ 140 mm Hg and is not associated with adverse effects on health or quality of life.

While all Committee members agreed that the evidence supporting Recommendation 1 is very strong, the Committee was unable to reach unanimity on the Recommendation of a goal SBP of  $<$ 150 mm Hg. Some members recommended continuing the JNC 7 SBP goal of  $<$ 140 mm Hg for individuals  $>$ 60 years old based on expert opinion.[Chobanian, 2003] These members concluded that the evidence was insufficient to raise the

SBP target from <140 to <150 mm Hg in high risk groups, such as Blacks, those with CVD including stroke, and those with multiple risk factors. The Committee agreed that more research is needed to identify optimal goals of SBP for patients with high BP.

### Recommendation 2

**In the general population less than 60 years of age, initiate pharmacologic treatment to lower BP at DBP  $\geq$ 90 mm Hg and treat to a goal DBP <90 mm Hg. (For ages 30-59 years, Strong Recommendation – Grade A; For ages 18-29 years, Expert Opinion – Grade E)**

### Recommendation 3

**In the general population less than 60 years of age, initiate pharmacologic treatment to lower BP at SBP  $\geq$ 140 mm Hg and treat to a goal SBP <140 mm Hg. (Expert Opinion – Grade E)**

Recommendation 2 is based on high-quality evidence from five DBP trials (HDFP, Hypertension-Stroke Cooperative, MRC, ANBP, and VA Cooperative) which demonstrate improvements in health outcomes among adults 30-69 years of age with elevated BP.[HDFP, 1979; HDFP 1982; HSC, 1974; MRC 1985; ANBP, 1980; VA Cooperative, 1970] Initiation of antihypertensive treatment at a DBP threshold of  $\geq$ 90 mm Hg and treatment to a DBP goal of <90 mm Hg reduces cerebrovascular events, heart failure, and overall mortality (Question 1, ESs 10, 11, 13; Question 2, ES 10). In further support for a DBP goal of <90 mm Hg, the Committee found evidence that there is no benefit in treating patients to a goal of either  $\leq$ 80 mm Hg or  $\leq$ 85 mm Hg compared to  $\leq$ 90 mm Hg based on the HOT trial in which patients were randomized to these 3 goals without statistically significant differences between treatment groups in the primary or secondary outcomes (Question 2, ES 14). [Hansson, 1998 ]

In adults less than 30 years of age, there are no good or fair-quality RCTs that assessed the benefits of treating elevated DBP on health outcomes (Question 1, ES 14). In the absence of such evidence, it is the Committee's opinion that in adults less than 30 years of age, the DBP threshold and goal should be the same as in adults 30-59 years of age.

Recommendation 3 is based on expert opinion. While there is high-quality evidence to support a specific SBP threshold and goal for persons 60 years of age or older (See Recommendation 1), the Committee found insufficient evidence from good or fair-quality RCTs to support a specific SBP threshold or goal for persons under 60 years of age. In the absence of such evidence, the Committee recommends a SBP treatment threshold of  $\geq$ 140 mm Hg and a SBP treatment goal of <140 mm Hg based on several factors. First, in the absence of any RCTs that compared the current SBP standard of 140 mm Hg to another higher or lower standard in this age group, there was no compelling reason to change current Recommendations. Second, in the DBP trials that demonstrated the benefit of treating DBP to <90 mm Hg, many of the study participants who achieved DBPs <90 mm Hg were also likely to have achieved SBPs <140 mm Hg with treatment. It is not possible to determine whether the outcome benefits in these trials were due to lowering DBP, SBP, or both. Lastly, given the recommended SBP goal of <140 mm Hg in adults with diabetes or chronic kidney disease (Recommendations 4 and 5,), a similar SBP goal for the general population less than 60 years of age will facilitate guideline implementation.

### Recommendation 4

**In the population 18 years of age or older with chronic kidney disease, initiate pharmacologic treatment to lower BP at SBP  $\geq$ 140 mm Hg or DBP  $\geq$ 90 mm Hg and treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)**

Based on the inclusion criteria used in the RCTs reviewed by the Committee, this Recommendation applies to individuals less than 70 years of age with an estimated glomerular filtration rate (eGFR) or measured GFR <60 ml/min/1.73 m<sup>2</sup> and in people of any age with albuminuria defined as >30 mg albumin/g creatinine at any level of GFR.

Recommendation 4 is based on ES15-17 from Question 2. In adults less than 70 years of age with CKD, the evidence is insufficient to determine if there is a benefit in mortality, or cardiovascular or cerebrovascular health outcomes with antihypertensive drug therapy to a lower BP goal (for example, <130/80 mm Hg) compared to a goal of <140/90 mm Hg (Question 2, ES 15). There is evidence of moderate quality demonstrating no benefit in slowing the progression of kidney disease from treatment with antihypertensive drug therapy to a lower BP goal (for example, <130/80 mm Hg) compared to a goal of <140/90 mm Hg (Question 2, ES 16).

Three trials that met our criteria for review addressed the effect of antihypertensive drug therapy on change in GFR or time to development of ESRD, but only one addressed cardiovascular disease endpoints. BP goals differed across the trials, with two trials (AASK and MDRD) using mean arterial pressure and different targets by age, and one trial (REIN-2) using only DBP goals. [Wright, 2002; Klahr, 1994; Ruggenti, 2005] None of the trials showed that treatment to a lower BP goal (for example, <130/80 mm Hg) significantly lowered kidney or cardiovascular disease endpoints compared to a goal <140/90 mm Hg.

For patients with proteinuria (>3 gm/24 hours), post-hoc analysis from only one study (MDRD) indicated benefit from treatment to a lower BP goal (<130/80 mm Hg), and this related to kidney outcomes only. [Klahr, 1994] Although post-hoc observational analyses of data from this trial and others suggested benefit from the lower goal at lower levels of proteinuria, this result was not seen in the primary analyses or in AASK or REIN-2 (Question 2, ES 17). [Wright, 2002; Ruggenti, 2005]

Based on available evidence the Committee cannot make a Recommendation on a BP goal for people age 70 years and older with GFR <60 mL/min/1.73m<sup>2</sup>. The commonly used estimating equations for GFR were not developed in populations with significant numbers of people >70 years of age and have not been validated in older adults. No outcome trials reviewed by the Committee included large numbers of adults over age 70 years with CKD. Further, the diagnostic criteria for CKD do not take into account age related decline in kidney function as reflected in eGFR. Thus, when weighing the risks and benefits of a lower BP goal for people 70 years of age and older, with eGFR <60 mL/min/1.73m<sup>2</sup>, antihypertensive treatment should be individualized, taking into consideration factors such as frailty, co-morbidities, and albuminuria.

## Recommendation 5

**In the population 18 years of age and older, with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)**

Recommendation 5 is based on ESs 18-21 from Question 2, which address BP goals in adults with both diabetes and hypertension. There is moderate quality evidence from three trials (SHEP, Syst-Eur, and UKPDS) that treatment to a SBP goal of <150 mm Hg improves cardiovascular and cerebrovascular health outcomes and lowers mortality (See Question 2, ES 18) in adults with diabetes and hypertension. [Curb, 1996; Tuomilehto, 1999; UKPDS, 1998] No RCTs addressed whether treatment to a SBP goal of < 140 mm Hg

compared with a higher goal (for example, < 150 mm Hg) improves health outcomes in adults with diabetes and hypertension. In the absence of such evidence, the Committee recommends a SBP goal of <140 mm Hg and a DBP goal <90 mm Hg in this population based on expert opinion, consistent with the BP goals in Recommendation 3 for the general population less than 60 years of age with hypertension. Use of a consistent BP goal in the general population less than 60 years of age and in adults with diabetes of any age may facilitate guideline implementation. This Recommendation for a SBP goal <140 mm Hg in patients with diabetes is also supported by the ACCORD-BP trial, in which the control arm used this goal and had similar outcomes compared to a lower goal. [Cushman, 2010]

The Committee recognizes that the ADVANCE trial tested the effects of treatment to lower BP on major macrovascular and microvascular events in adults with diabetes who were at increased risk of CVD, but the study did not meet the Committee's inclusion criteria because participants were eligible irrespective of baseline BP, and there were no randomized BP treatment thresholds or goals.[Patel, 2007]

The Committee also recognizes that a SBP goal <130 mm Hg is commonly recommended for adults with diabetes and hypertension. However, this lower SBP goal is not supported by any RCT that randomized participants into two or more groups in which treatment was initiated at a lower SBP threshold than 140 mm Hg or into treatment groups in which the SBP goal was lower than 140 mm Hg and that assessed the effects of a lower SBP threshold or goal on important health outcomes. The only RCT that compared a SBP treatment goal of <140 mm Hg to a lower SBP goal and assessed the effects on important health outcomes is ACCORD-BP, which compared a SBP treatment goal <120 mm Hg to a goal <140 mm Hg. [Cushman, 2010] There was no difference in the primary outcome, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. There were also no differences in any of the secondary outcomes except for a reduction in stroke. However, the incidence of stroke in the group treated to <140 mm Hg was much lower than expected, so the absolute difference in fatal and non-fatal stroke between the two groups was only 0.21% per year. The Committee concluded that the results from ACCORD-BP did not provide sufficient evidence to recommend a SBP goal <120 mm Hg in adults with diabetes and hypertension.

The Committee similarly recommends the same goal DBP in adults with diabetes and hypertension as in the general population (<90 mm Hg). Despite some existing Recommendations that adults with diabetes and hypertension should be treated to a DBP goal of <80 mm Hg, the Committee did not find sufficient evidence to support such a Recommendation. For example, there are no good or fair quality RCTs with mortality as a primary or secondary pre-specified outcome that compared a DBP goal of <90 mm Hg with a lower goal (ES 21).

In the HOT trial which is frequently cited to support a lower DBP goal, investigators compared a DBP goal  $\leq$ 90 mm Hg to a goal  $\leq$ 80 mm Hg. [Hansson, 1998] The lower goal was associated with a reduction in a composite CVD outcome (Question 2, ES 20), but this was a post-hoc analysis of a small subgroup (8%) of the study population that was not prespecified. As a result, the evidence was graded as low quality.

Another commonly cited study to support a lower DBP goal is UKPDS.[UKPDS1998] UKPDS had a BP goal <150/85 mm Hg in the more intensively treated group compared to a goal of <180/105 mm Hg in the less intensively treated group. UKPDS did show that treatment in the lower goal BP group was associated with a significantly lower rate of stroke, heart failure, diabetes-related endpoints, and deaths related to diabetes. However, the comparison in UKPDS was a DBP goal of <85 mm Hg versus <105 mm Hg; therefore it is not

possible to determine whether treatment to a DBP goal <85 mm Hg improves outcomes compared with treatment to a DBP goal of <90 mm Hg. In addition, UKPDS was a mixed systolic and diastolic BP goal study, so it cannot be determined if the benefits were due to lowering SBP, DBP, or both.

## Recommendation 6

**In the general non-Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)**

For this Recommendation, only RCTs that compared one class of antihypertensive medication to another and assessed the effects on health outcomes were reviewed; placebo-controlled RCTs were not included. However, the evidence review was informed by major placebo-controlled hypertension trials, including three federally funded trials (VA Cooperative Trial, HDFP, and SHEP), which were pivotal in demonstrating that treatment of hypertension with antihypertensive medications reduces cardiovascular or cerebrovascular events and/or mortality. [VA Coop, 1970; HDFP, 1979; SHEP, 1991] These trials all used thiazide-type diuretics compared with placebo or usual care as the basis of therapy. Additional evidence that BP-lowering reduces risk comes from trials of beta-blocker versus placebo [MRC, 1985; IPPPSH, 1985] and calcium channel blocker versus placebo. [Staessen, 1997]

Each of the four drug classes recommended by the Committee in Recommendation 6 yielded comparable effects on overall mortality, cardiovascular, cerebrovascular, and kidney outcomes, with one exception – heart failure. Initial treatment with a thiazide-type diuretic was more effective than a CCB or ACEI (Question 3, Diuretic ESs 14 and 15), and an ACEI was more effective than a CCB (Question 3, ACEI ES 1) in improving heart failure outcomes. While the Committee thought that improved heart failure outcomes was an important finding that should be considered when selecting a drug for initial therapy for hypertension, the Committee did not think it was compelling enough within the context of the overall body of evidence to preclude the use of the other drug classes for initial therapy. The Committee also thought that the evidence supported BP control, rather than a specific agent used to achieve that control, as the most relevant consideration for this Recommendation.

The Committee did not recommend beta blockers (BB) for the initial treatment of hypertension because in one study use of BBs resulted in a higher rate of the primary composite outcome of cardiovascular (CV) death, myocardial infarction (MI), or stroke compared to use of an ARB, a finding that was driven largely by an increase in stroke (Question 3, BB ES 22). [Dahlof, 2002] In the other studies that compared a BB to the four recommended drug classes, the BB performed similarly to the other drugs (Question 3, Diuretic ES 8) or the evidence was insufficient to make a determination (Question 3, Diuretic ESs 7 and 12, BB ESs 21, 23, and 24).

Alpha-blockers were not recommended as first-line therapy because in one study initial treatment with an alpha-blocker resulted in worse cerebrovascular, heart failure, and combined cardiovascular outcomes than initial treatment with a diuretic (Question 3, Diuretic ES 13). [ALLHAT, 2003] There were no RCTs of good or fair quality comparing the following drug classes to the four recommended classes: dual alpha-1-beta blocking agents (e.g., carvedilol), vasodilating beta-blockers (e.g., nebivolol), central alpha-2 adrenergic agonists (e.g., clonidine), direct vasodilators (e.g., hydralazine), aldosterone receptor antagonists (e.g., spironolactone), peripherally acting adrenergic antagonists (reserpine), and loop diuretics (e.g. furosemide) (Question 3, Other

Drug Classes ES 30); hence these drug classes are not recommended as first-line therapy. In addition, no eligible RCTs were identified that compared a diuretic versus an ARB, or an ACEI versus an ARB. ONTARGET was not eligible because hypertension was not required for inclusion in the study. [ONTARGET, 2008]

Similar to the general population, this Recommendation applies to those with diabetes because trials including participants with diabetes showed no differences in major cardiovascular or cerebrovascular outcomes from those in the general population (Question 3, Diabetes ESs 36-48).

The following important points should be noted. First, many people will require treatment with more than one antihypertensive drug to achieve BP control. While this Recommendation applies only to the choice of the initial antihypertensive drug, the Committee believes that any of these four classes would be good choices as add-on agents (Recommendation 9). Second, this Recommendation is specific for thiazide-type diuretics, which include thiazide diuretics, chlorthalidone and indapamide; it does not include loop or potassium-sparing diuretics. Third, it is important that medications be dosed adequately to achieve results similar to those seen in the RCTs (See Table 5). Finally, RCTs that were limited to specific non-hypertensive populations, such as those with coronary artery disease (CAD) or heart failure (HF), were not reviewed for this Recommendation. Therefore, Recommendation 6 should be applied with caution to these populations. Recommendations for those with CKD are addressed in Recommendation 8.

### Recommendation 7

**In the general Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general Black population: Moderate Recommendation – Grade B; for Blacks with diabetes: Weak Recommendation – Grade C)**

### Recommendation 8

**In the population age 18 years or older with chronic kidney disease (CKD) and hypertension, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation – Grade B)**

The evidence is moderate (Question 3, CKD ESs 31-32) that treatment with an ACEI or ARB improves kidney outcomes for patients with CKD. This Recommendation applies to CKD patients with and without proteinuria, as studies using ACEIs or ARBs showed evidence of improved kidney outcomes in both groups.

This Recommendation is based primarily on kidney outcomes since there is less evidence favoring ACEI or ARB for cardiovascular outcomes in patients with CKD. Neither ACEIs nor ARBs improved cardiovascular disease outcomes for CKD patients compared to a BB or CCB (Question 3, CKD ESs 33-34). One trial (IDNT) did show improvement in heart failure outcomes with an ARB compared to a CCB, but it was restricted to a population with diabetic nephropathy and proteinuria (Question 3, CKD ES 5).[Lewis, 2001] There are no head-to-head RCTs in the evidence review that compared ACEI to ARB for any cardiovascular outcome. However, both are RAS inhibitors and have been shown to have similar effects on kidney outcomes (Question 3, CKD ESs 31-32).

Recommendation 8 is specifically directed at those with CKD and hypertension and addresses the potential benefit of specific drugs on kidney outcomes. The AASK study showed the benefit of an ACEI on kidney outcomes in Blacks with CKD and provides additional evidence that supports ACEI use in that population.[Wright, 2002] Additional trials that support the benefits of ACEI or ARB therapy did not meet our

inclusion criteria because they were not restricted to patients with hypertension.[Brenner, 2001; Lewis, 1993] Direct renin inhibitors are not included in this Recommendation in the absence of studies demonstrating their benefits on kidney or cardiovascular outcomes.

The Committee noted the potential conflict between this Recommendation to use an ACEI or ARB in those with CKD and hypertension and the Recommendation to use a diuretic or CCB (Recommendation 7) in Blacks – what if the person is Black and has CKD? To answer this, we must rely on expert opinion. In Blacks with CKD and proteinuria, an ACEI or ARB is recommended as initial therapy because of the higher likelihood of progression to ESRD. [Wright, 2002] In Blacks with CKD but without proteinuria, the choice for initial therapy is less clear and includes a thiazide-type diuretic, CCB, ACEI or ARB. If an ACEI or ARB is not used as the initial drug, then an ACEI or ARB can be added as a second-line drug if necessary to achieve goal BP. Because the majority of those with CKD and hypertension will require more than one drug to achieve goal BP, it is anticipated that an ACEI or ARB will be used either as initial therapy or as a second line drug in addition to a diuretic or CCB in Blacks with CKD.

Recommendation 8 applies to adults age 18 or older with CKD, but there is no evidence to support RAS inhibitor treatment in those over age 75. While there may be benefit of ACEI or ARB treatment for those past age 75, use of a thiazide-type diuretic or CCB is also an option for individuals with CKD in this age group.

Use of an ACEI or an ARB will commonly increase serum creatinine and may produce other metabolic effects such as hyperkalemia, particularly in patients with decreased kidney function. Although a rise in creatinine or potassium does not always require adjusting medication, use of RAS inhibitors in the CKD population requires monitoring of electrolyte and serum creatinine levels, and in some cases, may require reduction in dose or discontinuation for safety reasons.

## Recommendation 9

Recommendation 9 was developed by the Committee in response to a perceived need for further guidance to assist in implementation of Recommendations 1-8. Recommendation 9 is based on strategies used in RCTs that demonstrated improved patient outcomes and the expertise and clinical experience of Committee members. It differs from the other Recommendations because it was not developed in response to the three critical questions using a systematic review of the literature. Figure 1 is an Algorithm summarizing the Recommendations in an easy to read format. It is important to note that this algorithm has not been validated with respect to achieving improved patient outcomes.

**The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in Recommendation 6 (thiazide-type diuretic, CCB, ACEI or ARB). Continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with two drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in Recommendation 6 because of a contraindication or the need to use more than three drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients where additional clinical consultation is needed. (Expert Opinion – Grade E)**

How should clinicians titrate and combine the drugs recommended in JNC 8? There were no RCTs and thus expert opinion is our only guide. Three strategies (See Table 6) have been used in RCTs of high BP treatment

but were not compared to each other. Based on the evidence reviewed for Questions 1-3 and on the expert opinion of the Committee members, it is not known if one of the strategies results in improved cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality compared to an alternative strategy. There is not likely to be evidence from well-designed RCTs that compare these strategies and assess their effects on important health outcomes. There may be evidence that different strategies result in more rapid attainment of BP goal or in improved adherence, but those are intermediate outcomes that were not included in the evidence review. Therefore, each strategy is an acceptable pharmacologic treatment strategy that can be tailored based on individual circumstances, clinician and patient preferences, and drug tolerability. With each strategy, clinicians should regularly assess BP, encourage evidence-based lifestyle and adherence interventions, and adjust treatment until goal BP is attained and maintained. In most cases, adjusting treatment means intensifying therapy by increasing the drug dose or by adding additional drugs to the regimen. In order to avoid unnecessary complexity in this Report, the hypertension management algorithm (See Figure) does not explicitly define all of the potential drug treatment strategies.

Finally, Committee members point out that in specific situations, one antihypertensive drug may be replaced with another if it is perceived not to be effective or if there are adverse effects.

## **ADDITIONAL CONTENT**

The following four sections provide additional content where the Panel did not conduct a formal evidence review but thought that it was important to provide guidance that would help the reader understand and implement the recommendations in this report.

### **Measurement and Monitoring of Blood Pressure**

For the purposes of this report, we recommend that blood pressure be measured using procedures similar to the ones described in JNC 7 [Chobanian, 2003]. Although the auscultatory method of measuring blood pressure using a mercury sphygmomanometer is generally regarded as the gold standard for office blood pressure measurement, a ban on the use of mercury sphygmomanometers because of safety concerns continues to diminish the role of this technique [EPA, 1997]. Due to the phasing out of mercury sphygmomanometers from clinical practices and recent advancements in the technology of blood pressure measurement devices, we recommend the use of the oscillometric method of BP measurement with properly calibrated and validated automated devices or carefully performed manual measurements [Ogedegbe, 2010; Myers, 2010].

We recommend that blood pressure measurements be taken in a quiet and relaxed environment with patients seated comfortably for at least 5 minutes in a chair (rather than on an examination table) with feet flat on the floor, their back supported, and their arm supported at heart level. Blood pressure should be taken on the bare upper arm with an appropriate-sized cuff whose bladder encircles at least 80% of the mid-upper arm circumference, and patients should avoid caffeine, cigarettes and physical activity for at least 30 minutes prior to measurement [Pickering, 2005]. In addition, patients should be queried about the need to empty the bladder (and encouraged to do so if there is a need) because BP rises with the urge to urinate [Ogedegbe, 2010]. To establish the diagnosis of hypertension, and for the purpose of treatment and assessment of whether blood pressure goals are being met, 2-3 measurements should be taken at each visit in the manner outlined above, and the average recorded. At the first visit, blood pressure should be measured in both arms, and the arm with the higher blood pressure should be used for subsequent measurements [Myers, 2010].

This report does not comment on home or ambulatory BP monitoring because they were not used in the RCTs in our evidence review, and conducting a separate evidence-based review to look at this issue was beyond the scope of this report.

### Appropriate Dosing of Antihypertensive Medications

Appropriate dosing of antihypertensive medications is important and should be based on the target doses used in RCTs that were shown to improve health outcomes (see Table 5). This table is not meant to exclude other agents within the classes of antihypertensive medications that have been recommended. The speed of titration must be individualized for each patient, but target doses can often be achieved within 2 to 4 weeks and generally should not take longer than two months.

Treatment is often initiated at a dose that is lower than the target dose and then titrated upwards to the target dose in an effort to minimize adverse effects. This approach is especially important for patients with comorbidity who are taking multiple medications, when starting two antihypertensive medications simultaneously, or in older persons who may be more sensitive to the effects of antihypertensive drugs. However, clinical trials have shown that in the majority of cases, medications can be titrated to achieve the target doses within several months. Table 1 displays doses and dosing frequency used in clinical trials. The initial doses in some cases should be higher or lower than listed in Table 5 based on patient age or co-morbidity. In most cases, the maximum dose achieved in RCTs in the table is reasonable for clinical practice with the exception of hydrochlorothiazide. RCTs used doses of hydrochlorothiazide of 25-100 mg daily but the current recommended evidence-based dose which balances efficacy and safety is 25-50 mg daily. Additionally, it is now known that many antihypertensives do not completely cover a full 24-hour dosing interval when given once daily, especially during sleep or the early morning surge in blood pressure. While it may be reasonable to divide doses twice daily, or give some medications at bedtime, there is no RCT evidence that met the Panel's criteria to support such recommendations.

In some cases, patients may not tolerate the target dose of a particular drug. If use of that drug is desirable because of its proven benefits on health outcomes, the dose often can be reduced with resolution of the adverse effect, thus maintaining the patient on the drug. An example would be a patient who is taking amlodipine 10 mg a day and develops lower extremity edema that is attributed to the medication. The dose could be reduced to 5 mg a day and if the adverse effect resolves, one could continue the patient on the lower dose. If needed, a second antihypertensive medication could be added to achieve BP control. If the adverse effect does not resolve or worsens despite lowering the dose, it may be necessary to discontinue the medication and switch to another class of antihypertensive medication.

When used at target doses, the following antihypertensive medications have been shown to improve cardiovascular outcomes (Table 5). Higher doses, when consistent with product labeling, may be used to achieve goal BP, but effects on health outcomes are only known for doses in Table 1. If the target dose for a medication in Table 1 is listed as a dose range, it is because there were multiple studies that used different target doses. Some of the drugs may not be effective for a full 24-hour period; in such cases it may be preferable to give the drug twice a day, especially when one gets close to the total daily target dose.

## Research Gaps

This Expert Panel recognizes that there are a number of important clinical considerations that this report does not address. These issues warrant further investigation to establish the level of evidence necessary for making additional recommendations. Although a comprehensive research agenda is beyond the scope of this report, we highlight several areas that are of high priority for research to guide clinical care:

1. Although we provide evidence-based guidelines for BP thresholds, goals and medication choices for a range of populations, we do not have a high level of evidence based on health outcomes to inform specific guidelines in important subpopulations, including individuals:

- a. Under 60 years of age (including those who develop high blood pressure in youth or young adulthood) and those over age 60 to evaluate SBP targets below 150 mmHg
- b. With other CVD risk factors basing treatment on global cardiovascular risk as determined by a CV risk assessment tool.
- c. With specific co-morbidities (e.g., heart failure, stroke)
- d. Who have already experienced a cardiovascular or cerebrovascular event
- e. Specific treatment strategies for ethnic subgroups including African Americans, Hispanics, East Asian and South Asian patients

2. This guideline (and all previous JNC) guidelines for selection of antihypertensive agent are based on evidence for first line treatment. Additional evidence is needed to guide selection of the second, third, fourth, or nth drug.

3. Renal denervation is currently being evaluated for severe, treatment-resistant hypertension (and subsequently will be evaluated for less severe hypertension). The effect on long-term outcomes of this treatment approach should be compared to pharmacologic therapy.

4. This guideline does not address the ability of various treatment support strategies to improve hypertension-related outcomes. Additional evidence and comparisons among strategies is needed to guide strategies for the optimal use of:

- a. Home BP monitoring (including the role of ambulatory BP monitoring)
- b. Self-management support
- c. Pharmacist support
- d. Health systems approaches (e.g., decision support through the electronic medical record)

## RECOMMENDATIONS FROM THE LIFESTYLE WORKING GROUP

A Lifestyle Working Group was convened by NHLBI to conduct an evidence review using similar methodology to JNC in order to develop cross-cutting recommendations that are applicable to the Blood Pressure and Lipid Expert Panels. The primary intent of the Lifestyle Working Group's review was to focus on the effects of diet and physical activity on CVD risk factors independent of their effects on weight. Therefore, studies in which the primary outcome was weight loss or in which treatment was associated with more than 3% change in weight were excluded from the review. The effect of weight loss on CVD risk factors is covered in the report of the Overweight and Obesity Expert Panel. However, the Panel recognizes the beneficial blood pressure effect of weight loss in those who are overweight or obese. The following lifestyle recommendations apply to individuals who may benefit from blood pressure lowering, including those who are taking or not taking antihypertensive medications. The Panel supports these lifestyle recommendations (Eckel, 2013).

### Lifestyle Workgroup Diet Recommendations

**Advise adults who may benefit from blood pressure lowering to:**

- 1. Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits intake of sweets, sugar- sweetened beverages and red meats.**
  - Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes).
  - Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the American Heart Association Diet.

Strength: A (strong)

#### **2. Lower sodium intake.**

**(Strong Recommendation – Grade A)**

**3. Consume no more than 2,400 mg of sodium per day and that a further reduction of sodium intake to 1,500 mg can result in even greater reduction in blood pressure. Even without achieving these goals, reducing sodium intake by at least 1,000 mg per day lowers blood pressure.**

**(Moderate Recommendation – Grade B)**

#### **4. Combine the DASH dietary pattern with lower sodium intake.**

**(Strong Recommendation – Grade A)**

### Lifestyle Physical Activity Recommendation

**1. In general, advise adults to engage in aerobic physical activity to lower blood pressure: 3 to 4 sessions a week, lasting on average 40 minutes per session involving moderate-to-vigorous intensity physical activity.**

**(Moderate Recommendation – Grade B)**

## Lifestyle for PREVENTION AND TREATMENT OF HIGH BLOOD PRESSURE

Lifestyle modification (i.e., adhering to a heart healthy dietary pattern, regular physical activity, avoiding tobacco, and achieving/maintaining a healthy weight) remains a critical component of health promotion and CVD risk reduction, both prior to and in concert with the use of blood pressure-lowering medication. The NHLBI Lifestyle Work Group specifically addressed the evidence concerning lifestyle factors that lower blood pressure. That Work Group did not review the blood pressure lowering effect of weight loss in those who are overweight or obese, but this effect is well-established. In endorsing the Lifestyle Work Group recommendations as well as weight control, the Panel recognizes the potential for these lifestyle recommendations to prevent and treat hypertension, and to contribute to achieving blood pressure control in those patients on antihypertensive medications.

The Lifestyle Work Group recommendations address dietary pattern, sodium intake, and physical activity.

With regard to dietary pattern, there is strong and consistent clinical trial evidence that eating a **dietary pattern that emphasizes intake of vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, legumes and nuts, and limits intake of sweets, sugar-sweetened beverages and red meat, as exemplified by the DASH dietary pattern, lowers blood pressure. Similarly, there** is strong and consistent clinical trial evidence that reducing sodium intake lowers blood pressure. The effect of both DASH dietary pattern and reducing sodium intake on blood pressure is independent of changes in weight. The magnitude of effect is sufficient to both prevent hypertension, and to promote non-pharmacologic blood pressure control in those with hypertension. The Lifestyle Work Group recommends combining DASH and reduced sodium intake, based on **evidence that** the blood pressure-lowering effect is even greater when these dietary changes are combined.

**The Lifestyle Work Group also recommends moderate-to-vigorous physical activity (such as a brisk walk) for approximately 160 minutes per week.** This amount of physical activity lowers blood pressure and is consistent with recommendations for improving overall health:.

**A thorough summary of the evidence review and more detailed rationale for the lifestyle recommendations can be found in the report of the Lifestyle Work Group. [Eckel, 2013]**

## HISTORY OF THIS GUIDELINE DEVELOPMENT PROCESS

The Panel was originally constituted as the “Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8).” In March 2008 NHLBI sent letters inviting the Co-Chairs and Panel members to serve on JNC8. The charge to the Panel was: “JNC 8 will review and synthesize the latest available scientific evidence, update existing clinical recommendations, and provide guidance to busy primary care clinicians on the best approaches to manage and control hypertension in order to minimize patients’ risk for cardiovascular and other complications.” JNC 8 was also asked to identify and prioritize the most important questions for the evidence review.

The Panel began its work by prioritizing the most important questions relevant to clinicians managing hypertension. Teleconference meetings occurred among the panel almost weekly during the 5 year span of this project. The first face-to-face meeting of the Panel occurred in September 2008. A second face-to-face meeting occurred in March 2009. However, following this, external methodological support resigned from the project, and a new contract was eventually developed with RTI International to provide methodological support beginning in 2010. This contract lasted until December 2011. Because other cardiovascular prevention guidelines were also under development and required methodological support, the number of high priority questions allowed was limited to the top 3 questions. A third face-to-face meeting occurred in August 2011 where initial Recommendations were crafted following the systematic evidence review of the methodology team for Questions 1 and 2. The final face-to-face meeting of the Panel occurred in February 2012 where Question 3 recommendations were deliberated.

In January 2013, the Guideline was submitted for external peer review to 20 reviewers with expertise in hypertension, primary care, cardiology, nephrology, and other important related fields. Comments were reviewed and discussed by the Panel from March through June 2013 and incorporated into a revised document. In June 2013, NHLBI announced its decision to discontinue developing clinical guidelines including those in process, instead partnering with selected organizations that took the lead in completing and publishing the guidelines.[Gibbons, 2013, Gibbons, 2013] Importantly, these organizations required involvement in producing the final content of the report. The Panel elected to pursue publication as an independent panel to bring the recommendations to the public in a timely manner while maintaining the integrity of the pre-defined process. This report is therefore not an NHLBI sanctioned report and does not reflect the views of NHLBI.

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Pickering, 2005	Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. 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. <i>Circulation.</i> 2005 Feb 8; 111(5):697-716.

# Appendices

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# APPENDIX

## Exhibit A: Evidence from randomized controlled trials on initiating antihypertensive pharmacological therapy at SBP thresholds $\geq 160$ mmHg

**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Colors:** *Green* = Statistically significant where the treated group did better ( $p < 0.05$ ); *Yellow* =  $p \geq 0.05$  and  $\leq 0.10$ ; *Clear* =  $p > 0.10$

Trial, year Population Sample size Trial duration Quality Rating	Overall Mortality	Coronary Heart Disease (includes non-fatal MI, fatal MI, sudden death or combination)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal or combination)	Heart Failure (includes fatal, non-fatal, or combination)
<b>EWPHE, 1985</b>  Adults, ages $\geq 60$ years, SBP 160-239 and DBP 90-119 mmHg  N = 840  Mean 4.6 yrs  Fair	 <b>All-cause mortality:</b> 9% decrease in txt CI (-28,15) p = 0.41	 <b>Cardiac mortality:</b> 38% reduction in txt group per 1000 py, p = 0.036 <b>Fatal cardiac events:</b> at 1 year 11% reduction in txt per 1000 py p < 0.05	 <b>Non-fatal cerebrovascular events,</b> at 1 year: 11% decrease in txt per 1000 py, p < 0.05   <b>Cerebrovascular deaths:</b> 32% decrease in txt CI (-61, 19) p = 0.16	 <b>Severe CHF:</b> at 1 year: 8% decrease in txt per 1000 py p < 0.05
<b>HYVET, 2008</b>  Adults, ages $\geq 80$ years, SBP $\geq 160$ and DBP 90-109 at start of trial but relaxed later to <110 mmHg  N = 3,845  Mean 2.1 years  Good	 <b>Death from any cause:</b> Unadj HR: 0.79 CI (0.65, 0.95) p = 0.02 <i>*study stopped early due to mortality reduction</i>	 <b>Death from cardiac cause:</b> Unadj HR: 0.71 CI (0.42, 1.19) p = 0.19 <b>Fatal and non-fatal MI:</b> Unadj HR: 0.72 CI (0.30, 1.70) p = 0.45	 <b>Death from stroke:</b> Unadj HR: 0.61 CI (0.38, 0.99) p = 0.046   <b>Fatal or non-fatal stroke:</b> Unadj HR: 0.70 CI (0.49, 1.01) p = 0.06	 <b>Death from HF:</b> unadj HR: 0.48 CI (0.18, 1.28) p = 0.14   <b>Fatal or non-fatal HF:</b> Unadj HR: 0.36 CI (0.22, 0.58) p < 0.001

<p><b>SHEP, 1991</b></p> <p>Adults, ages ≥60 years, SBP 160-219 and DBP &lt;90 mmHg</p> <p>N = 4,736</p> <p>Mean 4.5 years</p> <p>Good</p>	 <p><b>Total deaths:</b> RR: 0.87 CI (0.73, 1.05) p = NR</p>	 <p><b>Non-fatal MI:</b> RR: 0.67 CI (0.47, 0.96) p = NR</p> <p><b>Symptomatic MI events:</b> 63 vs 98 (txt vs control) p = 0.005</p> <p><b>CHD RR:</b> 0.75 CI (0.60, 0.94) p = NR</p> <p><b>Non-fatal MI or CHD deaths:</b> RR: 0.73 CI (0.57, 0.94) p = NR</p>  <p><b>MI deaths:</b> RR: 0.57 CI (0.30-1.08) p = NR</p> <p><b>Total CHD deaths:</b> RR: 0.80 CI (0.57, 1.13) p = NR</p> <p><b>Sudden death (&lt;1 hour):</b> RR: 1.00 CI (0.56, 1.78) p = NR</p> <p><b>Rapid deaths (1-24 hours):</b> RR: 0.87 CI (0.48, 1.56) p = NR</p>	 <p><b>Non-fatal plus fatal stroke:</b> RR: 0.64 (0.50, 0.82) p = 0.0003</p>	 <p><b>Fatal and non-fatal HF:</b> RR: 0.51 (0.37, 0.71) p &lt; 0.001</p>
<p><b>Syst-Eur, 1997</b></p> <p>Adults, ages ≥ 60 years, SBP 160-219 and DBP &lt;95 mmHg</p> <p>N = 4,695</p> <p>Median 24 months</p> <p>Good</p>	 <p><b>Total mortality:</b> Adj HR: 0.86 CI (0.67, 1.10) p = NR</p>	 <p><b>Fatal and non-fatal cardiac endpoints:</b> Adj HR: 0.71 CI (0.54, 0.94) p &lt; 0.05</p>  <p><b>Fatal MI:</b> 56% decrease in txt group per 1000 py, CI (-82, 9) p = 0.08</p>  <p><b>Non-fatal MI:</b> 20% decrease in txt group per 1000 py, CI (-53, 34) p = 0.40</p> <p><b>Coronary mortality:</b> 27% decrease in txt group per 1000 py, CI (-54, 15) p = 0.17</p> <p><b>Sudden death:</b> 12% decrease in txt group per 1000 py, CI (-49, 52) p = 0.65</p> <p><b>Fatal and non-fatal MI:</b> 30% decrease in txt group per 1000 py, CI (-56, 9) p = 0.12</p>	 <p><b>Non-fatal stroke:</b> 44% decrease in active (rate/1000 py) CI (-63, -14), p = 0.007</p>  <p><b>Death due to Stroke:</b> 27% decrease in txt group per 1000 py CI (-62, 39), p = 0.33</p>  <p><b>Fatal and non-fatal stroke combined:</b> Adj HR: 0.59 (0.38, 0.79) p &lt; 0.01</p>	 <p><b>Non-fatal HF:</b> 36% decrease in txt group per 1000 py CI (-60, 2) p = 0.06</p>  <p><b>Fatal HF:</b> 24% decrease in active (rate/1000 py) CI (-70, 93) p = 0.57</p> <p><b>Fatal &amp; non-fatal HF:</b> 29% decrease in txt group per 1000 py CI (-53, 10) p = 0.12</p>

## Exhibit B: Evidence from randomized controlled trials on initiating antihypertensive pharmacological therapy at DBP thresholds $\geq 90$ mmHg

### Legend

**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified

**Color:** *Green* = Statistically significant ( $p < 0.05$ ) *Yellow* Color =  $p \geq 0.05$  and  $\leq 0.10$  *Clear* =  $p > 0.10$  *Blue* =  $p$  value not reported

Trial, year Sample characteristics Sample size Duration Quality Rating	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal or combination)	Heart Failure (includes fatal, non-fatal, or combination)	Primary Composite Outcomes
<b>ANBP, 1980</b>  Adults, ages 30 to 69 years, DBPs $\geq 95$ or $< 110$ if SBP $< 200$ mmHg  N = 3,931  4 years  Fair	 <b>Total fatal endpoints</b> Events: 25 vs 35 (txt vs control) p = NR <i>Component of Primary Composite</i>	 <b>Non-fatal MI</b> Events: 28 vs 22 (txt vs control) p = NR <b>Fatal Ischemic Heart Disease</b> Events: 5 vs 11 (txt vs control) p = NR <i>Above are all components of Primary Composite</i> <b>Total Ischemic Heart Disease</b> Events: 98 vs 109 (txt vs control) p = NR	 <b>Non-fatal cerebrovascular event (hemorrhagic or thrombosis)</b> Events: 10 vs 16 (txt vs control) p = NR <b>Non-fatal transient ischemic attacks</b> Events: 4 vs 9 (txt vs control) p = NR <b>Fatal cerebrovascular events</b> Events: 3 vs 6 (txt vs control) p = NR <b>Total cerebrovascular events</b> Events: 17 vs 31 (txt vs control) p = NR <i>Above are all components of Primary Composite</i>	 <b>Non-fatal congestive cardiac failure</b> Events: 3 vs 3 (txt vs control) p = NR <i>Component of Primary Composite</i>	 <b>All Trial End Points</b> Rate/1000 py: 19.7 vs 24.5 (txt vs control) p < 0.05   <b>Fatal CV Trial End Points</b> Rate/1000 py: 1.1 vs 2.6 (txt vs control) p < 0.025  <i>[Death from any cause (CV or other); non-fatal: cerebrovascular disease, TIAs, MIs, congestive cardiac failure, dissecting aneurysm of the aorta, retinal hemorrhages, exudates or papilledema, hypertensive encephalopathy, onset of renal failure with plasma creatinine <math>&gt; 2</math> mg/dl]</i>
<b>EWPHE, 1985</b>  Adults, ages $\geq 60$ years, SBPs 160-239 and DBP 90-119 mmHg  N = 840  Mean 4.6 yrs  Fair	 <b>All-cause mortality:</b> 9% decrease in txt group CI (-28, 15) p = 0.41	 <b>Cardiac mortality:</b> 38% reduction in txt group per 1000 py; p = 0.036 <b>Fatal cardiac events:</b> at 1 year 11% reduction in txt group per 1000 py; p < 0.05	 <b>Non-fatal cerebrovascular events at 1 year:</b> 11% decrease in txt group per 1000 py; p < 0.05   <b>Cerebrovascular deaths:</b> 32% decrease in txt group CI (-61, 19) p = 0.16	 <b>Severe CHF at 1 year:</b> 8% decrease in txt group per 1000 py; p < 0.05	
<b>HDFP Cooperative, 1979</b>  Adults, ages 30-69	 <b>Total Deaths</b>	 <b>Deaths from MI</b>	 <b>Deaths from cerebrovascular diseases</b>		

Trial, year Sample characteristics Sample size Duration Quality Rating	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal or combination)	Heart Failure (includes fatal, non-fatal, or combination)	Primary Composite Outcomes
years, and DBPs ≥ 90 mmHg  N = 10,940  5 years  Fair	Rate per 100: 6.4 vs 7.7 (txt vs control) p < 0.01	Events: 51 vs 69 (txt vs control) p = NR	Events: 29 vs 52 (txt vs control) p = NR   <b>Fatal and non-fatal stroke</b> 34.5% incidence reduction; p < 0.01		
<b>Hypertension Stroke Cooperative, 1974</b>  Adults with a stroke or TIA in previous year, ages < 75 years, SBPs 140-220 and DBP 90-115 mmHg  N = 452  Mean 27.4 months  Fair	 <b>Deaths due to medical endpoints</b> Events: 20 vs 14 (txt vs control) p = NR	 <b>MI</b> Events: 4 vs 4 (txt vs control) p = 0.69 <b>Sudden death</b> Events: 2 vs 2 (txt vs control) p = 0.99  <b>Deaths from MI</b> Events: 1 vs 2 (txt vs control) p = NR	 <b>Total stroke recurrence:</b> Events: 37 vs 42 (txt vs control) (15.9 vs 19.2%) p = 0.42	 <b>CHF</b> Events: 0 vs 6 (txt vs control) p = 0.012  <b>Death due to CHF</b> Events: 0 vs 2 (txt vs control) p = NR	
<b>HYVET, 2008</b>  Adults, ages ≥ 80 yrs, SBP ≥ 160 and DBP 90-109 at start of trial but relaxed later to <110 mmHg  N = 3,845  Mean 2.1 years  Good	 <b>Death from any cause:</b> Unadj HR: 0.79 CI (0.65, 0.95) p = 0.02 <i>*study stopped early due to mortality reduction</i>	 <b>Death from cardiac cause:</b> Unadj HR: 0.71 CI (0.42, 1.19) p = 0.19 <b>Fatal and non-fatal MI:</b> Unadj HR: 0.72 CI (0.30, 1.70) p = 0.45	 <b>Death from stroke:</b> Unadj HR: 0.61 CI (0.38, 0.99) p = 0.046  <b>Fatal or non-fatal stroke:</b> Unadj HR: 0.70 CI (0.49, 1.01) p = 0.06	 <b>Death from HF:</b> Unadj HR: 0.48 CI (0.18, 1.28) p = 0.14  <b>Fatal or non-fatal HF:</b> Unadj HR: 0.36 CI (0.22, 0.58) p < 0.001	
<b>MRC, 1985</b>  Adults, ages 35 to 64 years, SBPs < 200 and DBPs 90-109 mmHg  N = 17,354  Mean 5.5 years  Fair	 <b>All deaths:</b> 2% decrease in txt group, CI (-16, 18) p = NR	 <b>Non-fatal coronary events:</b> 16% decrease in txt group per 1000 py; CI (NR) p = NR <b>Fatal coronary events:</b> 9% increase in txt group, CI (NR) p = NR  <b>Total coronary events:</b> 6% decrease in txt group, CI (-13, 21) p = NS (value not reported)	 <b>Non-fatal stroke:</b> 49% decrease in txt group per 1000 py; CI (NR); p = NR <b>Fatal stroke:</b> 34% decrease in txt group per 1000 py; CI (NR); p = NR  <b>Total stroke:</b> 45% decrease in txt group per 1000 py; CI (25, 60) p = 0.0006 (once off testing)		 <b>All CV events:</b> 19% decrease in txt group per 1000 py; CI (5, 31) p = 0.01 (once off testing)

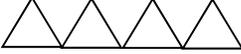
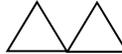
Trial, year Sample characteristics Sample size Duration Quality Rating	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal or combination)	Heart Failure (includes fatal, non-fatal, or combination)	Primary Composite Outcomes
<p><b>VA Cooperative, 1967</b> (initial DBP 115-129 mmHg participants only)</p> <p>Adult males, ages 30 to 73 years, DBPs 115-129 mmHg prior to treatment</p> <p>N = 143</p> <p>Mean 3.2 years</p> <p>Good</p> <p><i>Study terminated early for this group due to high incidence of morbid events in control group</i></p>	 <p><b>Deaths</b> Events: 0 vs 4 (txt vs control) p = NR <i>Primary</i></p>				 <p><b>Total incidence of morbidity and mortality</b> Events: 2 vs 27 (txt vs control) p &lt; 0.001 <i>[Morbidity and mortality]</i></p>
<p><b>VA Cooperative, 1970</b> (initial DBP 90-114 mmHg participants only)</p> <p>Adult males, (mean baseline sample age of 50 years in txt, 52 in control), DBPs of 90-114 mmHg prior to treatment</p> <p>N = 380</p> <p>Mean 3.2 years</p> <p>Good</p>	 <p><b>Total related deaths</b> Events: 8 vs 19 (txt vs control) p = NR <i>Primary</i></p>	 <p><b>Non-fatal MI</b> Events: 5 vs 2 (txt vs control) p = NR <b>Total coronary artery disease</b> Events: 11 vs 13 (txt vs control) p = NR <b>Deaths due to MI</b> Events: 2 vs 3 (txt vs control) p = NR <b>Sudden death</b> Events: 4 vs 8 (txt vs control) p = NR <i>All Primary</i></p>	 <p><b>Cerebrovascular accident (thrombosis or TIA)</b> Events: 4 vs 8 (txt vs control) p = NR <b>Deaths due to cerebrovascular hemorrhage</b> Events: 0 vs 3 (txt vs control) p = NR <b>Deaths due to cerebrovascular thrombosis</b> Events: 1 vs 3 (txt vs control) p = NR <b>Total cerebrovascular accident</b> Events: 5 vs 20 (txt vs control) p = NR <i>All Primary</i></p>	 <p><b>Total CHF</b> Events: 0 vs 11 (txt vs control) p = NR <i>Primary</i></p>	 <p><b>Terminating morbid events</b> (severe, clinically detectable hypertensive damage in optic fundi, brain, heart and kidneys) Events: 9 vs 35 (4.8 vs 18.0%) (txt vs control) p = NR <i>[Morbidity and mortality]</i></p>

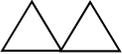
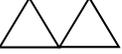
## Exhibit C: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to specified SBP goals

### Legend

Shapes: **Circle** = Primary outcome; **Triangle** = Secondary outcome or not specified

Color: **Green** = Statistically significant ( $p < 0.05$ ); **Yellow** =  $p \geq 0.05$  and  $\leq 0.10$ ; **Clear** =  $p > 0.10$ ; **Blue** =  $p$  value not reported

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes
<b>Systolic Goals &lt; 140 mmHg</b>						
<b>Cardio-Sis, 2009</b>  Adults, ages 55 or older, receiving anti-HTN treatment for $\geq 12$ weeks, with at least one additional risk factor but no diabetes or renal dysfunction  N: 1,111  Median 2 years  Good	SBP Goal: Tight control: <130 Usual control: <140 mmHg  <u>At start of trial</u>  Baseline SBP, mmHg (SD): Tight: 163.3 (11.3) Usual: 163.3 (11.1)  <u>At 2 years</u>  Achieved SBP, mmHg Tight: 131.9 Usual: 135.6 p = NR  SBP reduction, mmHg (SD) Tight: 27.3 (11.0) Usual: 23.5 (10.6) p = NR  SBP differences between groups, mmHg (95% CI) 3.8 (2.4, 5.2) p < 0.0001	 <b>Death from any cause:</b> HR: 0.77 CI (0.21, 2.88) p = 0.70	 <b>MI:</b> HR: 0.66 CI (0.19, 2.34) p = 0.52   <b>Coronary revascularization procedures:</b> HR: 0.33 CI (0.12, 0.91) p = 0.032	 <b>Stroke or TIA:</b> HR: 0.44 CI (0.13, 1.42) p = 0.16	 <b>Admission for HF:</b> HR: 0.42 CI (0.11, 1.63) p = 0.21	
<b>JATOS, 2008</b>  Adults, ages 65 to 85 with essential HTN; SBP $\geq 160$ and DBP < 120  N = 4,418  104 weeks  Good	SBP Goal: Strict txt: <140 Mild txt: $\geq 140$ to <160 mmHg  <u>At start of trial</u>  Baseline SBP, mmHg (SD): Strict: 171.6 (9.7) Mild: 171.5 (9.8)  <u>At 2 years</u>	 <b>Death from any cause</b> Events: 54 vs 42 p = 0.22	 <b>Cardiac and vascular disease:</b> Events: 26 vs 28 p = 0.78  <b>Fatal cardiac and vascular disease:</b> Events: 6 vs 4 p = 0.53  <b>MI:</b> Events: 6 vs 6	 <b>Cerebrovascular disease:</b> Events: 52 vs 49 p = 0.77  <b>Fatal cerebrovascular disease:</b> Events: 3 vs 3 p = 1.00	 <b>CHF:</b> Events: 8 vs 7 p = NS <b>Fatal CHF:</b> Events: 4 vs 1 p = NS	 <b>Composite of cerebrovascular, cardiac and vascular disease and renal failure events and deaths:</b> Events: 86 vs 86 p = 0.99

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes
<p><i>NOTE: all outcomes are strict treatment versus mild treatment</i></p>	<p>Achieved SBP, mmHg (SD) Strict: 135.9 (11.7) Mild: 145.6 (11.1) p = NR</p> <p>SBP differences between groups, mmHg: 9.7 p &lt; 0.001</p>		<p>p = NS <b>Fatal MI:</b> Events: 1 vs 0 p = NS <b>Sudden deaths:</b> Events: 1 vs 1 p = NS</p>			<p> <b>Composite of cerebrovascular, cardiac and vascular disease and renal failure deaths:</b> Events: 9 vs 8 p = 0.81</p>
<p><b>VALISH, 2010</b></p> <p>Adults, ages 70-85 with HTN (SBP ≥ 160 and DBP &lt; 90 mmHg)</p> <p>N = 3,260</p> <p>Mean 2.85 years</p> <p>Good</p>	<p>SBP Goal: Strict control: &lt;140 Moderate control: ≥140 to &lt;150 mmHg</p> <p><u>At start of trial</u></p> <p>Baseline SBP, mmHg (SD): Strict: 169.5 (7.9) Moderate: 169.6 (7.9)</p> <p><u>At mean 2.85 years</u></p> <p>Achieved SBP, mmHg (SD) Strict: 136.6 (13.3) Moderate: 142 (12.5) p &lt; 0.001</p> <p><u>At 36 months</u></p> <p>SBP differences between groups, mmHg 5.6 p &lt; 0.001</p>	<p> <b>All cause death:</b> HR: 0.78 CI (0.46, 1.33) p = 0.362</p>	<p> <b>Fatal and non-fatal MI:</b> HR: 1.23 CI (0.33, 4.56) p = 0.761 <b>Sudden death:</b> HR: 0.73 CI (0.25, 2.11) p = 0.564</p>	<p> <b>Fatal or non-fatal stroke:</b> HR: 0.68 CI (0.36, 1.29) p = 0.237</p>		<p> <b>Composite of CV events:</b> HR: 0.89 CI (0.60, 1.31) p = 0.383</p> <p> <b>CV death:</b> HR: 0.97 CI (0.42, 2.25) p = 0.950</p>
<b>Systolic Goals ≤ 150 mmHg</b>						
<p><b>HVYET, 2008</b></p> <p>Adults, ages ≥ 80 years, SBP ≥ 160 and DBP 90-109 at start of trial but relaxed later to &lt; 110 mmHg</p> <p>N = 3,845</p> <p>Mean 2.1 years</p>	<p>Goal: &lt;150/80 mmHg</p> <p><u>At start of trial</u></p> <p>Baseline SBP, mmHg (SD): Tx: 173 (8.4) Placebo: 173 (8.6)</p> <p><u>At 2 years</u></p> <p>Achieved SBP: NR</p> <p>Mean SBP change since</p>	<p> <b>Death from any cause:</b> unadj HR: 0.79 CI (0.65, 0.95) p = 0.02 <i>*study stopped early due to mortality reduction</i></p>	<p> <b>Death from cardiac cause:</b> unadj HR: 0.71 CI (0.42, 1.19) p = 0.19 <b>Fatal and non-fatal MI:</b> unadj HR: 0.72 CI (0.30, 1.70) p = 0.45</p>	<p> <b>Death from stroke:</b> unadj HR: 0.61 CI (0.38, 0.99) p = 0.046</p> <p> <b>Fatal or non-fatal stroke:</b> unadj HR: 0.70 CI (0.49, 1.01) p = 0.06</p>	<p> <b>Death from HF:</b> unadj HR: 0.48 CI (0.18, 1.28) p = 0.14</p> <p> <b>Fatal or non-fatal HF:</b></p>	

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes
Good	baseline, mmHg (SD) Txt: 29.5 (15.4) Placebo: 14.5 (18.5) p = NR  SBP differences between groups, mmHg: 15.0 p = NR  % reaching BP goal Txt: 48% Placebo: 19.9 % p < 0.001				unadj HR: 0.36 CI (0.22, 0.58) p < 0.001	
<b>Syst-Eur, 1997</b>  Adults, ages ≥ 60 years, SBPs 160-219 and DBPs of < 95 mmHg  N = 4,695  Median 24 months  Good	SBP Goal: <150 and decrease SBP by ≥ 20 mmHg  <u>At start of trial</u>  Baseline SBP, mmHg (SD): Txt: 173.8 (6.7) Placebo: 173.9 (10.1)  <u>At 2 years</u> Achieved SBP: not reported numerically, results illustrated in a figure and showed that drug group had consistently lower SBPs and DBPs versus placebo from year 1 through year 4  Mean fall in sitting SBP, mmHg (SD) Txt: 23 (16) Placebo: 13 (17) p = NR  SBP differences between groups, mmHg (95% CI) 10.1 (8.8, 11.4) p = NR  % at target Txt: 43.5% Placebo: 21.4% p < 0.001  <u>At 4 years</u> Differences between groups, SBP (95% CI) 10.7 (8.8, 12.5) p = NR	 <b>Total mortality:</b> adj HR: 0.86 CI (0.67, 1.10) p = NR	 <b>Fatal and non-fatal cardiac endpoints:</b> adj HR: 0.71 CI (0.54, 0.95) p < 0.05   <b>Fatal MI</b> Rate per 1000 py: 56% ↓ in txt group CI (-82, 9) p = 0.08   <b>Non-fatal MI:</b> Rate per 1000 py: 20% ↓ in txt group CI (-53, 34) p = 0.40 <b>Coronary mortality:</b> Rate per 1000 py: 27% ↓ in txt group CI (-54, 15) p = 0.17 <b>Sudden death:</b> Rate per 1000 py: 12% ↓ in txt group CI (-49, 52) p = 0.65 <b>Fatal and non-fatal MI:</b> Rate per 1000 py: 30% ↓ in txt group CI (-56, 9) p = 0.12	 <b>Non-fatal stroke:</b> Rate per 1000 py: 44% ↓ in txt group CI (-63, -14) p = 0.007   <b>Death due to stroke:</b> Rate per 1000 py: 27% ↓ in txt group CI (-62, 39) p = 0.33   <b>Fatal and non-fatal stroke combined</b> adj HR: 0.59 CI (0.38, 0.79) p < 0.01	 <b>Non-fatal HF:</b> Rate per 1000 py: 36% ↓ in txt group CI (-60, 2) p = 0.06   <b>Fatal HF:</b> Rate per 1000 py: 24% ↓ in txt group CI (-70, 93) p = 0.57 <b>Fatal and non-fatal HF</b> Rate per 1000 py: 29% ↓ in txt group CI (-53, 10) p = 0.12	

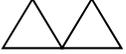
Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes
<b>Systolic Goals &lt; 160 mmHg (also includes lower goals)</b>						
<p><b>SHEP, 1991</b></p> <p>Adults, ages ≥ 60 years, SBPs 160-219 and DBPs of &lt; 90 mmHg</p> <p>N = 4,736</p> <p>Mean 4.5 years</p> <p>Good</p> <p><i>NOTE: Outcome events reported as treatment versus placebo</i></p>	<p>SBP Goal:</p> <ul style="list-style-type: none"> <li>For individuals with SBPs of &gt;180 mmHg: &lt;160</li> <li>For those with SBPs of 160-179: a reduction of at least 20 mmHg</li> </ul> <p><u>At start of trial</u> Baseline SBP, mmHg (SD): Tx: 170.5 (9.5) Placebo: 170.1 (9.2)</p> <p><u>At 5 years</u> Achieved SBP, mmHg (SD) Tx: 144.0 (19.3) Placebo: 155.1 (20.9) p = NR</p> <p>SBP change from baseline, mmHg Tx: -26.5 Placebo: -15 p = NR</p>	 <p><b>Total deaths</b> RR: 0.87 CI (0.73, 1.05)</p>	 <p><b>Non-fatal MI</b> RR: 0.67 CI (0.47, 0.96)</p> <p><b>Symptomatic MI</b> Events: 63 vs 98 p = 0.005</p> <p><b>CHD</b> RR: 0.75 CI (0.60, 0.94)</p> <p><b>Non-fatal MI or CHD deaths</b> RR: 0.73 CI (0.57, 0.94)</p>  <p><b>MI deaths:</b> RR: 0.57 CI (0.30-1.08)</p> <p><b>Total CHD deaths:</b> RR: 0.80 (0.57, 1.13)</p> <p><b>CHD death - sudden (&lt;1 hr)</b> RR: 1.00 CI (0.56, 1.78)</p> <p><b>CHD death - rapid (1-24 hrs)</b> RR: 0.87 CI (0.48, 1.56)</p>	 <p><b>Non-fatal plus fatal stroke</b> RR: 0.64 CI (0.50, 0.82) p = 0.0003</p>	 <p><b>Fatal and non-fatal HF</b> RR: 0.51 CI (0.37, 0.71) p &lt; 0.001</p>	

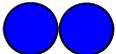
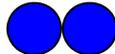
## Exhibit D: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to specified DBP goals

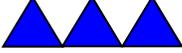
### Legend

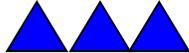
Shapes: **Circle** = Primary outcome; **Triangle** = Secondary outcome or not specified

Color: **Green** = Statistically significant ( $p < 0.05$ ); **Yellow** Color =  $p \geq 0.05$  and  $\leq 0.10$ ; **Clear** =  $p > 0.10$ ; **Blue** =  $p$  value not reported

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes non-fatal MI, fatal MI, sudden death, not HF)	Cerebrovascular morbidity and mortality (includes fatal stroke, non-fatal stroke or a combination of fatal and non-fatal stroke)	Heart Failure (includes fatal or non-fatal)	Primary Composite Outcomes
<b>DBP goals <math>\leq 80</math> mmHg</b>						
<b>HOT, 1998</b>  Adults, ages 50-80, with HTN (DBP 100-115)  N = 18,790  Mean 3.8 years  Fair	DBP goal: $\leq 80$ mmHg $\leq 85$ mmHg $\leq 90$ mmHg  <u>At start of trial</u> Achieved BP, mmHg (SD) $\leq 80$ : 170/105 (14.1/3.4) $\leq 85$ : 170/105 (14.0/3.4) $\leq 90$ : 170/105 (14.4/3.4) p = NR  <u>Mean of 6 months F/U to study end</u> Baseline BP, mmHg (SD) $\leq 80$ : $\leq 85$ : $\leq 90$ : p = NR  BP decrease from baseline, mmHg (SD) $\leq 80$ : 29.9/24.3 (13.6/5.8) $\leq 85$ : 28.0/22.3 (13.2/5.4) $\leq 90$ : 26.2/20.3 (13.0/5.6) p = NR  Mean between group difference in achieved BP, mmHg $\leq 90$ vs $\leq 85$ : 1.8/2.0 $\leq 85$ vs $\leq 80$ : 1.9/2.0 $\leq 90$ vs $\leq 80$ : 3.7/4.0 p = NR	 <b>Total mortality</b> RR (95% CI): $\leq 90$ vs $\leq 85$ : 0.97 (0.79, 1.19) $\leq 85$ vs $\leq 80$ : 0.93 (0.77, 1.14) $\leq 90$ vs $\leq 80$ : 0.91 (0.74, 1.10) p for trend: 0.32	 <b>All MI</b> RR (95% CI): $\leq 90$ vs $\leq 85$ : 1.32 (0.95, 1.82) $\leq 85$ vs $\leq 80$ : 1.05 (0.74, 1.48) $\leq 90$ vs $\leq 80$ : 1.37 (0.99, 1.91) p for trend: 0.05   <b>All MI including silent cases</b> RR (95% CI): $\leq 90$ vs $\leq 85$ : 1.19 (0.92, 1.54) $\leq 85$ vs $\leq 80$ : 1.00 (0.76, 1.3) $\leq 90$ vs $\leq 80$ : 1.19 (0.92, 1.53) p for trend: 0.19	 <b>All stroke</b> RR (95% CI): $\leq 90$ vs $\leq 85$ : 0.85 (0.64, 1.11) $\leq 85$ vs $\leq 80$ : 1.24 (0.94, 1.64) $\leq 90$ vs $\leq 80$ : 1.05 (0.79, 1.41) p for trend: 0.74		 <b>Major CV events (fatal and nonfatal MI, fatal and nonfatal stroke, all other CV death)</b> RR (95% CI): $\leq 90$ vs $\leq 85$ : 0.99 (0.83, 1.19) $\leq 85$ vs $\leq 80$ : 1.08 (0.89, 1.29) $\leq 90$ vs $\leq 80$ : 1.07 (0.89, 1.28) p for trend: 0.50
<b>HYVET, 2008</b>  Adults, ages $\geq 80$ years, SBPs 160	Goal: 150/80 mmHg  <u>At start of trial</u> Baseline DBP, mmHg (SD):	 <b>Death from any</b>	 <b>Death from cardiac cause:</b>	 <b>Death from stroke:</b> unadj HR: 0.61	 <b>Death from HF:</b>	

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes non-fatal MI, fatal MI, sudden death, not HF)	Cerebrovascular morbidity and mortality (includes fatal stroke, non-fatal stroke or a combination of fatal and non-fatal stroke)	Heart Failure (includes fatal or non-fatal)	Primary Composite Outcomes
and DBP 90-109 at start of trial but relaxed later to < 110 mmHg  N = 3,845  Mean 2.1 years  Good	Txt: 90.8 (8.5) Placebo: 90.8 (8.5)  <u>At 2 years</u>  Achieved DBP: NR [For informative purposes Baseline DBP, mmHg (SD): Txt: 90.8 (8.5) Placebo: 90.8 (8.5)]  Mean DBP change since baseline, mmHg (SD): Txt: -12.9 (9.5) Placebo: -6.8 (10.5) p = NR  DBP differences between groups, mmHg: 6.1 p = NR  % reaching BP goal Txt: 48% Placebo: 19.9 % p < 0.001	<b>cause:</b> unadj HR: 0.79 CI (0.65, 0.95) p = 0.02 <i>*study stopped early due to mortality reduction</i>	unadj HR: 0.71 CI (0.42, 1.19) p = 0.19 <b>Fatal and non-fatal MI:</b> unadj HR: 0.72 CI (0.30, 1.70) p = 0.45	CI (0.38, 0.99) p = 0.046    <b>Fatal or non-fatal stroke:</b> unadj HR: 0.70 CI (0.49, 1.01) p = 0.06	unadj HR: 0.48 CI (0.18, 1.28) p = 0.14    <b>Fatal or non-fatal HF:</b> unadj HR: 0.36 CI (0.22, 0.58) p < 0.001	
<b>DBP goals ≤ 90 mmHg</b>						
<b>MRC, 1985</b>  Adults, ages 35 to 64 years, SBPs < 200 and DBPs 90-109 mmHg  N = 17,354  5.5 years  Fair	DBP Goal: < 90 for both txt groups; placebo goal not stated  <u>At start of trial</u> Baseline DBP, mmHg: Txt 1: Men: 98 Women: 99 Txt 2: Men: 98 Women: 99 Placebo: Men: 98 Women: 98  <u>At 5 years</u> Achieved DBP: NR [For informative purposes: Baseline DBPs for men and women combined across txts, mmHg: Men: 98 Women: 99]	 <b>All deaths:</b> % difference in rate per 1000 py: 2% ↓ in txt group CI (-16, 18) p = NR	 <b>Non-fatal coronary events</b> % difference in rate per 1000 py: 16% ↓ in txt group CI (NR) p = NR <b>Fatal coronary events</b> % difference in rate per 1000 py: 9% ↑ in txt group CI (NR) p = NR   <b>Total coronary events</b> % difference in rate per 1000 py: 6% ↓ in txt group CI (-13, 21) p = NS (value not reported)	 <b>Non-fatal stroke</b> % difference in rate per 1000 py: 49% ↓ in txt group CI (NR) p = NR <b>Fatal stroke:</b> % difference in rate per 1000 py: 34% ↓ in txt group CI (NR) p = NR   <b>Total stroke:</b> % difference in rate per 1000 py: 45% ↓ in txt group CI (25, 60) p < 0.01		

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes non-fatal MI, fatal MI, sudden death, not HF)	Cerebrovascular morbidity and mortality (includes fatal stroke, non-fatal stroke or a combination of fatal and non-fatal stroke)	Heart Failure (includes fatal or non-fatal)	Primary Composite Outcomes
	DBP differences between groups reported by sex, mmHG Men Txt 1 vs placebo: 6 Txt 2 vs placebo: 6 p = NR Women Txt 1 vs placebo: 6 Txt 2 vs placebo: 4 p = NR  % reaching BP goal Men Txt 1: 72% Txt 2: 71% Placebo: 43% p = NR Women Txt 1: 78% Txt 2: 76% Placebo: 50%					
<b>VA Cooperative, 1967</b> (initial DBP 115-129 mmHg participants only)  Adult males, ages 30 to 73 years, DBPs 115-129 mmHg prior to treatment  N = 143  Mean 3.2 years  Good  <i>Study terminated early for this group due to high incidence of morbid events in control group</i>	DBP Goal: implied < 90 mmHg, derived from titration  <u>At start of trial</u> Baseline DBP, mmHg (SD): Txt: Hospital: 106.5 (8.4) Clinic: 121.2 (5) Placebo: Hospital: 105.8 (8.4) Clinic: 121.(4.7)  <u>At 24 month followup</u> Achieved DBP, mmHg Txt: 91.5 Placebo: 119.7 p = NR  DBP change from baseline, mmHg Txt: -29.7 Placebo: -1.3 p = NR	 <b>Deaths</b> Events: 0 vs 4 (txt vs placebo) p = NR				 <b>Total incidence of morbidity and mortality</b> Events: 2 vs 27 (txt vs placebo) p < 0.001
<b>VA Cooperative, 1970</b> (DBPs averaging 90 to 114 mmHg participants only)	DBP Goal: implied < 90 mmHg, derived from titration  <u>At start of trial</u> Baseline DBP, mmHg:	 <b>Total related deaths</b>	 <b>Non-fatal MI</b> Events: 5 vs 2	 <b>Cerebrovascular accident (thrombosis or TIA)</b>	 <b>Total CHF</b> Events: 0 vs 11	 <b>Terminating morbid events (severe,</b>

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes non-fatal MI, fatal MI, sudden death, not HF)	Cerebrovascular morbidity and mortality (includes fatal stroke, non-fatal stroke or a combination of fatal and non-fatal stroke)	Heart Failure (includes fatal or non-fatal)	Primary Composite Outcomes
<p>Adult males, (mean baseline sample age of 50 years in txt, 52 in control), DBPs of 90-129 mmHg prior to treatment</p> <p>N = 380</p> <p>Mean 3.2 years</p> <p>Good</p> <p><i>NOTE: all events presented treatment versus placebo with no p values reported</i></p>	<p>Txt: Hospital: 100.2 Clinic: 103.8 Control: Hospital: 101.3 Clinic: 104.7</p> <p>Follow-up Achieved DBP: NR</p>	<p>Events: 8 vs 19 (txt vs control) p = NR</p>	<p><b>Total coronary artery disease</b> Events: 11 vs 13</p> <p><b>Deaths due to MI</b> Events: 2 vs 3</p> <p><b>Sudden death</b> Events: 4 vs 8</p>	<p>Events: 4 vs 8</p> <p><b>Deaths due to cerebrovascular hemorrhage</b> Events: 0 vs 3</p> <p><b>Deaths due to cerebrovascular thrombosis</b> Events: 1 vs 3</p> <p><b>Total cerebrovascular accident</b> Events: 5 vs 20</p>		<p>clinically detectable hypertensive damage in optic fundi, brain, heart and kidneys)</p> <p>Events (%): 9 (4.8) vs 35 (18.0)</p> <p>Effectiveness of treatment: 73%</p>
<p><b>ANBP, 1980</b></p> <p>Adults, ages 30 to 69 years, DBPs <math>\geq</math> 95 and &lt; 110 with SBP &lt; 200 mmHg</p> <p>N = 3,931</p> <p>Mean of 4 years</p> <p>Fair</p> <p><i>NOTE: all events presented treatment versus placebo with no p values reported</i></p>	<p>DBP Goal:</p> <ul style="list-style-type: none"> <li>• reduce to <math>\leq</math> 90 mmHg</li> <li>• after 2 years goal lowered to 80 mmHg</li> </ul> <p><u>At start of trial</u> Baseline DBP, mmHg (SD): Txt: 100.5 (4.0) Placebo: 100.4 (3.8)</p> <p><u>At 4 years followup</u> Achieved DBP, mmHg Txt: 88.3 Placebo: 93.9 p = NR</p> <p>DBP change from baseline, mmHg Txt: -12.2 Placebo: -6.6 p = NR</p>	<p> <b>Total fatal endpoints</b> Events: 25 vs 35</p>	<p> <b>Non-fatal MI</b> Events: 28 vs 22</p> <p><b>Fatal Ischemic Heart Disease</b> Events: 5 vs 11</p> <p><b>Total Ischemic Heart Disease</b> Events: 98 vs 109</p>	<p> <b>Non-fatal cerebrovascular event (hemorrhagic or thrombosis)</b> Events: 10 vs 16</p> <p><b>Non-fatal transient ischemic attacks</b> Events: 4 vs 9</p> <p><b>Fatal cerebrovascular events</b> Events: 3 vs 6</p> <p><b>Total stroke events</b> Events: 17 vs 31</p>	<p> <b>Non-fatal congestive cardiac failures</b> Events: 3 vs 3</p>	<p> <b>All Trial End Points</b> Rate per 1000 py: 19.7 vs 24.5 (txt vs placebo) p &lt; 0.05</p> <p> <b>Fatal CV Trial End Points</b> Rate per 1000 py: 1.1 vs 2.6 (txt vs placebo) p &lt; 0.025</p>
<p><b>HDFP Cooperative, 1979</b></p> <p>Adults, ages 30-69 years, and DBPs <math>\geq</math> 90 mmHg</p> <p>N = 10,940</p>	<p>DBP Goal:</p> <ul style="list-style-type: none"> <li>• 90 mmHg for those entering at <math>\geq</math> 100 or already receiving anti-HTN medication</li> <li>• 10 mmHg decrease for those entering with 90 to 99</li> </ul> <p><u>At start of trial</u> Baseline DBP, mmHg:</p>	<p> <b>Total Deaths</b> Rate per 100: 6.4 vs 7.4 (txt vs control) p &lt; 0.01</p>	<p> <b>Deaths from MI</b> Events: 51 vs 69</p>	<p> <b>Deaths from cerebrovascular diseases</b> Events: 29 vs 52</p> <p></p>		

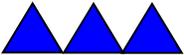
Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes non-fatal MI, fatal MI, sudden death, not HF)	Cerebrovascular morbidity and mortality (includes fatal stroke, non-fatal stroke or a combination of fatal and non-fatal stroke)	Heart Failure (includes fatal or non-fatal)	Primary Composite Outcomes
5 years  Fair  <i>NOTE: all events presented treatment versus placebo with no p values reported</i>	Txt: 101.1 Placebo: 101.1  <u>At 5 years</u>  Achieved DBP, mmHg Txt: 84.1 Placebo: 89.1 p = NR  DBP change from baseline, mmHg Txt: -17.0 Placebo: -12.1 p = NR			<b>Fatal and non-fatal stroke</b> Incidence: 34.5% ↓ in txt group p < 0.01		

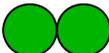
## Exhibit E: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to mixed SBP and DBP goals

### Legend

Shapes: **Circle** = Primary outcome; **Triangle** = Secondary outcome or not specified

Color: **Green** = Statistically significant ( $p < 0.05$ ) **Yellow** Color =  $p \geq 0.05$  and  $\leq 0.10$  **Clear** =  $p > 0.10$  **Blue** =  $p$  value not reported

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes
<b>SCOPE, 2003</b>  Adults, ages 70 to 89, previously treated or untreated with SBPs of 160 to 179 mmHg and/or DBPs of 90 to 99 mmHg and MMSE scores of $\geq 24$  N = 4964  Mean 3.7 years  Fair  <i>NOTE: all rates are treatment versus control with <math>p = NR</math></i>	Goal: Not explicitly stated, drug titration began at SBP > 160 or DBP > 85 or 90 depending upon step  <u>At start of trial</u>  Baseline SBP/DBP, mmHg: Txt: 166.0/90.3 Control: 166.5/90.4  <u>At mean 3.7 years</u>  Difference in achieved SBP and DBP of treatment versus control, mmHg (95% CI) SBP: 3.2 (-4.4, -1.9) P < 0.001 DBP: 1.6 (-2.1, -0.9) p < 0.001	 <b>Total mortality</b> Rate per 1000 py: 27.9 vs 29.0	 <b>Non-fatal MI</b> Rate per 1000 py: 5.9 vs. 5.2 <b>All MI</b> Rate per 1000 py: 7.6 vs. 6.9 <b>Fatal MI</b> Rate per 1000 py: 1.9 vs. 2.0	 <b>Non-fatal stroke</b> Risk reduction (CI): 27.8 (1.3, 47.2)   <b>All stroke</b> Risk reduction (CI): 23.6 (-0.7, 42.1)   <b>Fatal stroke</b> Rate per 1000 py: 2.6 vs. 2.8		  <b>Major CV events composite of CV death, non-fatal stroke, and non-fatal MI</b> Risk reduction (CI): 10.9 (-6, 25.1)
<b>STOP, 1991</b>  Adults, ages 70 to 84 years, treated or untreated for hypertension, with SBPs of 180 to 230 and DBP $\geq 90$ or DBPs of 105 to 120 irrespective of SBP during run-in  N = 1,627  Mean 25 months  Fair	SBP/DBP Goal: <160/95 mmHg  <u>At start of trial</u>  Baseline SBP/DBP, mmHg (SD): Txt: 195/102 (14/7) Control: 195/102 (14/7)  <u>At 4 years followup</u>  Achieved SBP/DBP (SD) Txt: 166/85 (21/10) Placebo: 193/95 (20/11) p = NR  SBP/DBP change from baseline Txt: -29/-17 Placebo: -2/-7	 <b>Total deaths</b> (irrespective of preceding non-fatal endpoint): RR (CI): 0.57 (0.37, 0.87)	 <b>All MI</b> (first endpoint): RR (CI): 0.87 (0.49, 1.56) <b>Fatal MI</b> (first endpoint): RR (CI): 0.98 (0.26, 3.66)	 <b>All stroke</b> (first endpoint): RR (CI): 0.53 (0.33, 0.86) <b>Fatal stroke</b> (first endpoint): RR (CI): 0.24 (0.04, 0.91)	 <b>CHF endpoints:</b> 19 vs. 39 (txt vs placebo) p = NR	 <b>Total primary endpoint</b> [stroke, MI, other CV death] (first to happen): RR (CI): 0.60 (0.43, 0.85)

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes
<p><b>Coope and Warrender, 1986</b></p> <p>Adults, age 60 to 79, SBPs <math>\geq</math> 170 or DBP <math>\geq</math> 105 mmHg</p> <p>N = 884</p> <p>Mean 4.4 years</p> <p>Good</p>	<p>p = NR</p> <p>Goal: Not explicitly stated, however additional therapy added if at the end of 3 months, SBP &gt; 170 or DBP &gt; 105 mmHg</p> <p><u>At start of trial</u></p> <p>Baseline SBP/DBP, mmHg (SD): Ttx: 196.2/99.7 (16.7/12.0) Control: 196.1/98.0 (15.6/11.8)</p> <p><u>During follow-up</u></p> <p>Achieved SBP: NR</p> <p>SBP/DBP achieved differences between groups, mmHg 18/11 p = NR</p> <p>Reduction in SBP/DBP mmHg Ttx: NR Control: 16/10 p = NR</p> <p><u>At 1 year</u></p> <p>% of patients at or below SBP 170 mmHg Ttx: 36% Control: 20% p = NR</p> <p><u>At 8 years</u></p> <p>% of patients at or below SBP 170 mmHg Ttx: 62% Control: 31% p = NR</p>	<p></p> <p><b>All deaths</b> Rate of ttx/rate of control (95% CI): 0.97 (0.70, 1.42) p = NS</p>	<p></p> <p><b>Fatal coronary attacks</b> Rate of ttx/rate of control (95% CI): 1.00 (0.58, 1.71) p = NS</p> <p><b>Non-fatal coronary attacks</b> Rate of ttx/rate of control (95% CI): 1.11 (0.46, 2.68) p = NS</p> <p><b>All coronary attacks</b> Rate of ttx/rate of control (95% CI): 1.03 (0.63, 1.63) p = NS</p>	<p></p> <p><b>Fatal stroke</b> Rate of ttx/rate of control (95% CI): 0.30 (0.11, 0.84) p &lt; 0.025</p> <p><b>All stroke</b> Rate of ttx/rate of control (95% CI): 0.58 (0.35, 0.96) p &lt; 0.03</p>	<p></p> <p><b>Fatal ventricular failure</b> Rate of ttx/rate of control (95% CI): 1.11 (0.28, 4.45) p = NS</p> <p><b>Non-fatal ventricular failure</b> Rate of ttx/rate of control (95% CI): 0.63 (0.35, 1.11) p = NS</p>	

## Exhibit F: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in patients with chronic kidney disease

**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** *Green* = Statistically significant ( $p < 0.05$ ); *Yellow* =  $p \geq 0.05$  and  $\leq 0.10$ ; *Clear* =  $p > 0.10$ ; *Blue* p value NR

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BPs Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or a combination)	Heart Failure (includes fatal, non-fatal, or combination)	Kidney Outcomes
<b>SBP/DBP goal of &lt; 130 mmHg</b>						
<b>REIN-2, 2005</b>  Adults, age 18-70, with non-diabetic nephropathy, persistent proteinuria (> 3 months) not on ACEI in previous 6 weeks  N: 338  Median F/U 19 months (IQR 12-35)  Fair	SBP/DBP Goal: Intensive control: < 130/80 Conventional control: < 90 mmHg irrespective of SBP  <u>At start of trial</u>  Baseline SBP/DBP, mmHg (SD): Intensive: 137.0/84.3 (16.7/9.0) Conventional: 136.4/83.9 (17.0/10.4)  <u>At median 19 months</u>  Achieved SBP/DBP, mmHg Intensive: 129.6/79.5 (10.9/5.3) Conventional: 133.7/82.3 (12.6/7.1) p=0.0019/< 0.0001  Change in SBP/DBP, mmHg Intensive: -7.4/-4.8 Conventional: -2.7/-1.6 p=NR  BP difference between groups, mmHg (95% CI) 4.1/2.8 p = NR					 <b>ESRD</b> HR (95% CI): 1.00 (0.61, 1.64)   <b>GFR decline</b> ml/min/1.73 meters <sup>2</sup> /month (IQR): 0.22 (0.06, 0.55) intensive vs. 0.24 (0.0001, 0.56) conventional p = 0.62
<b>MAP goal of ≤ 92 mmHg</b>						
<b>AASK, 2002</b>  Adult African-Americans (ages 18-70), with HTN and GFRs of 20-65, no diabetes, DBP ≥ 95  N: 1,094	MAP Goal: Low: ≤ 92 Usual: 102 to 107  <u>At start of trial</u>  Baseline MAP, mmHg (SD) Low: 115 (17)	 <b>Death prior to ESRD</b> 38 lower goal vs. 47 usual goal P = NR	 <b>Major CAD events</b> Rate per person year: 0.008 lower vs. 0.010 usual P = NS	 <b>Stroke</b> Rate per person year: 0.011 lower vs. 0.013 usual P = NS	 <b>Heart Failure</b> Rate per person year: 0.012 lower vs. 0.010 usual	 <b>Acute and chronic rate of change in GFR (slope)</b> change rate of lower vs. usual goal groups (SE) First 3 months: -1.82 (0.54)

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BPs Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or a combination)	Heart Failure (includes fatal, non-fatal, or combination)	Kidney Outcomes
3 to 6.4 years  Good	Usual: 113 (15)  <u>Mean of all BPs from 3 months to study end</u>  Achieved MAP, mm Hg (SD) Lower: 95 (8) Usual: 104 (7) p = NR  Change in MAP, mmHg Lower: -20 Usual: -9 p = NR  Achieved MAP difference between groups, mm Hg 11 p = NR				P = NS	<p>p &lt; 0.001            3 months to study end:            0.21 (0.22)            p = 0.33            4 years of follow-up            -0.25 (0.22)            p = 0.24</p>  <p><b>Clinical composite outcome</b>            % Risk Reduction (95% CI): 2 (-22 to 21)            p=0.85  <i>[includes reduction in GFR by 50% or by 25 ml/min/meters<sup>2</sup>, ESRD, death]</i></p>
<p><b>MDRD, 1994</b></p> <p>Adults, ages 18 to 70, with renal insufficiency (serum Cr 1.2 to 7.0 mg/dL in women and 1.4 to 7.0 mg/dL in men or CrCl &lt;70 ml/min per 1.73 meters<sup>2</sup>)</p> <p>Study 1: GFRs 25-55 ml/min randomized to usual protein or low protein diet and BP goals            Study 2: GFRs 13-24 randomized to low protein or very low protein diet and BP goals</p> <p>N: 840</p> <p>Mean F/U 2.2 years</p> <p>Fair</p>	<p>MAP Goal:            For those ages 18 to 60:            Low: ≤ 92            Usual: ≤ 107            For those ages 61 or greater:            Low: ≤ 98            Usual: ≤ 113</p> <p><u>At start of trial</u></p> <p>MAP, mmHg (SD)            Overall population: 98 (11)</p> <p><u>During follow-up</u></p> <p>Achieved MAP difference between groups, mm Hg            4.7            p &lt; 0.001</p>					 <p><b>Rate of decline in GFR, ml/min (95% CI)</b>            Study 1            First 4 months:            3.4 (2.6, 4.1) low goal vs.            1.9 (1.1., 2.7) usual goal            p = 0.010            4 months to study end            2.8 (2.2, 3.3) low goal vs.            3.9 (3.3, 4.5) usual goal            p = 0.006  <b>Note: NS from 0 to 3 yrs</b>            Study 2            Baseline to study end            3.7 (3.1, 4.3) low goal vs.            4.2 (3.6, 4.9) usual goal            p = 0.28</p>  <p><b>ESRD or death</b>            Study 2            RR: 0.85 (0.60, 1.22)            p=NR</p>

## Exhibit G: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in patients with chronic kidney disease by baseline proteinuria subgroups

**Legend**

**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** *Green* = Statistically significant ( $p < 0.05$ ); *Yellow* =  $p \geq 0.05$  and  $\leq 0.10$ ; *Clear* =  $p > 0.10$ ; *Blue* =  $p$  value not reported

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BPs Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or a combination)	Heart Failure (includes fatal, non-fatal, or combination)	Kidney Outcomes
<b>SBP/DBP goal of &lt; 130/80 mmHg</b>						
<p><b>REIN-2, 2005</b></p> <p>Adults, age 18-70, with non-diabetic nephropathy, persistent proteinuria (defined as urinary protein excretion &gt;1 g/24 h for <math>\geq 3</math> months) not on ACEI in previous 6 weeks. Patients with proteinuria 1–3 g/24 h included if CrCl was &lt;45 mL/min/1.73 meters<sup>2</sup>; those with proteinuria <math>\geq 3</math> g/24 h included if CrCl &lt;70 mL/min/1.73 meters<sup>2</sup></p> <p>N: 338</p> <p>Median F/U 19 months (IQR 12-35)</p> <p>Fair</p>	<p>SBP/DBP Goal: Intensive control: &lt; 130/80 Conventional control: &lt; 90 mmHg irrespective of SBP</p> <p><u>At start of trial</u></p> <p>All BP data are for full sample, NR by baseline proteinuria subgroups</p> <p>Baseline SBP/DBP, mmHg (SD): Intensive: 137.0/84.3 (16.7/9.0) Conventional: 136.4/83.9 (17.0/10.4)</p> <p><u>At median 19 months</u></p> <p>Achieved SBP/DBP, mmHg Intensive: 129.6/79.5 (10.9/5.3) Conventional: 133.7/82.3 (12.6/7.1) <math>p=0.0019 &lt; 0.0001</math></p> <p>Change in SBP/DBP, mmHg Intensive: -7.4/-4.8 Conventional: -2.7/-1.6 <math>p=NR</math></p> <p>BP difference between groups, mmHg (95% CI) 4.1/2.8 <math>p = NR</math></p>					<div style="text-align: center;">   <b>ESRD</b>                      Baseline proteinuria 1-3 g/24 h                      HR (95% CI): 1.06 (0.51, 2.20)  <math>p=0.89</math> </div> <div style="text-align: center;">                     Baseline proteinuria <math>\geq 3</math> g/24 h                      HR (95% CI): 1.09 (0.55, 2.19)  <math>p=0.81</math> </div> <div style="text-align: center;">   <b>GFR decline</b>                      Median rate of GFR decline, mL/min/1.73 meters<sup>2</sup>/month (IQR)                 </div> <div style="text-align: center;">                     Baseline proteinuria &lt;3 g/24 h                      0.18 (0.03, 0.49) intensive vs.                      0.21 (-0.03, 0.40) conventional  <math>p = 0.89</math> </div> <div style="text-align: center;">                     Baseline proteinuria <math>\geq 3</math> g/24 h                      0.51 (0.16, 1.05) intensive vs.                      0.39 (0.03, 0.98) conventional  <math>p = 0.39</math> </div>

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BPs Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or a combination)	Heart Failure (includes fatal, non-fatal, or combination)	Kidney Outcomes
<b>MAP goal of <math>\leq 92</math> mmHg</b>						
<p><b>AASK, 2002</b></p> <p>Adult African-Americans (ages 18-70), with HTN and GFRs of 20-65, no diabetes, DBP <math>\geq 95</math></p> <p>N: 1,094</p> <p>3 to 6.4 years</p> <p>Good</p>	<p>MAP Goal: Low: <math>\leq 92</math> Usual: 102 to 107</p> <p><u>At start of trial</u> BP data are for full sample; NR by baseline proteinuria subgroups</p> <p>Baseline MAP, mmHg Low: 115 (17) Usual: 113 (15)</p> <p><u>At 3 months to study end</u></p> <p>Achieved MAP, mm Hg (SD) Lower: 95 (8) Usual: 104 (7) p = NR</p> <p>Change in MAP, mmHg (SD) Lower: -20 Usual: -9 p = NR</p> <p>Achieved MAP difference between groups, mm Hg 11 p = NR</p>					<p style="text-align: center;"></p> <p><b>Acute and chronic rate of change in GFR (slope)</b> NS for chronic and total slope in subgroup analyses by baseline proteinuria strata<sup>1</sup> Acute slope: p=0.08 for interaction Total slope: p=0.04 for interaction Chronic slope: p=0.16 for interaction</p> <p style="text-align: center;"></p> <p><b>Clinical composite outcome</b> <i>[includes reduction in GFR by 50% or by 25 ml/min/meters<sup>2</sup>, ESRD, death]</i> NS in subgroup analyses by baseline proteinuria strata p=0.007 for interaction</p> <p>For above outcomes, trends favored the lower BP goal over the usual goal in participants with higher baseline proteinuria and opposite trends in participants with little or no proteinuria</p>
<p><b>MDRD, 1994</b></p> <p>Adults, ages 18 to 70, with renal insufficiency (serum Cr 1.2 to 7.0 mg/dL in women and 1.4</p>	<p>MAP Goal: For those ages 18 to 60: Low: <math>\leq 92</math> Usual: <math>\leq 107</math> For those ages 61 or greater: Low: <math>\leq 98</math></p>					<p style="text-align: center;"></p> <p><b>Rate of decline in GFR, ml/min (95% CI)</b> Study 1</p>

<sup>1</sup> Pg 2428 states: "with the exception of the acute slope, the BP comparison for the aforementioned outcomes was not significantly different within either the lower (baseline urinary protein to creatinine ratio  $\leq 0.22$ ) or higher (baseline urinary protein to creatinine ratio  $>0.22$ ) proteinuria strata." However page 2429 reports "there was no significant effect of the BP intervention on GFR slope or clinical events in all patients or in subgroup analyses by baseline proteinuria strata."

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BPs Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or a combination)	Heart Failure (includes fatal, non-fatal, or combination)	Kidney Outcomes
<p>to 7.0 mg/dL in men or CrCl &lt; 70 ml/min per 1.73 meters<sup>2</sup> )</p> <p>Study 1: GFRs 25-55 ml/min randomized to usual protein or low protein diet and BP goals Study 2: GFRs 13-24 randomized to low protein or very low protein diet and BP goals</p> <p>N: 840</p> <p>Mean F/U 2.2 years</p> <p>Fair</p>	<p>Usual: <math>\leq 113</math></p> <p><u>At start of trial</u></p> <p>BP data are for full sample, NR by baseline proteunria subgroups</p> <p>MAP, mmHg (SD) Overall population: 98 (11)</p> <p><u>During follow-up</u></p> <p>Achieved MAP difference between groups, mm Hg 4.7 p &lt; 0.001</p>					<p>p for interaction of BP goal and degree of baseline proteinuria: First 4 months: p=0.006 Baseline to 3 years: p=0.02</p> <p>Benefit of low BP intervention greatest in 54 subjects with urinary protein excretion &gt;3 g/day at baseline (statistically significant as indicated by CIs that do not overlap; Figure 3); benefit modest in 104 subjects with urinary protein excretion 1-3 g/day (NS); no benefit in 420 subjects with urinary protein excretion &lt;1 g/day (NS)</p> <p>Study 2 p=0.01 for interaction of baseline protein excretion and BP intervention Benefit of low BP intervention statistically significant as indicated by CIs that do not overlap in group with urinary protein excretion &gt; 3 g/day; NS for other baseline proteinuria subgroups</p>

## Exhibit H: Evidence from randomized controlled trials on treatment with antihypertensive pharmacological therapy to BP goals in patients with diabetes

**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** *Green* = Statistically significant ( $p < 0.05$ ); *Yellow* =  $p \geq 0.05$  and  $\leq 0.10$ ; *Clear* =  $p > 0.10$

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BP Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non-fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes	Kidney Outcomes
<b>Trials with Systolic Goals</b>							
<b>ACCORD, 2010</b>  Adults with type 2 diabetes and glycated hemoglobin $\geq 7.5\%$ and SBP 130-180 mmHg taking $\leq 3$ anti-HTN meds and 24hr protein excretion rate $<1.0$ g; age $\geq 40$ years with CVD or $\geq 55$ years with anatomical evidence of atherosclerosis, albuminuria, LVH, or $\geq 2$ additional risk factors for CVD (dyslipidemia, HTN, smoking, or obesity)  N: 4,733  Mean 4.7 years  Good	SBP goal Intensive txt: $< 120$ Standard txt: $< 140$ mmHg  <u>At start of trial</u>  Baseline SBP/DBP, mmHg (SD): Intensive txt: 139.0/75.9 (16.1/10.6) Standard txt: 139.4/76.0 (15.5/10.2)  <u>Average of BPs from 1 year F/U to end of study</u>  Achieved SBP, mmHg (95% CI) Intensive txt: 119.3 (118.9, 119.7) Standard txt: 133.5 (133.1, 133.8) p = NR  Average SBP difference between groups, mmHg (95% CI): 14.2 (13.7, 14.7) p = NR	 <b>Death from any cause</b> HR (95% CI): 1.07 (0.85, 1.35) p = 0.55	 <b>Non-fatal MI</b> HR (95% CI): 0.87 (0.68, 1.10) p = 0.25   <b>Major coronary disease event</b> HR (95% CI): 0.94 (0.79, 1.12) p = 0.50	 <b>Non-fatal stroke</b> HR (95% CI): 0.63 (0.41, 0.96) p = 0.03   <b>Any stroke</b> HR (95% CI): 0.59 (0.39, 0.89) p = 0.01	 <b>Fatal or non-fatal HF</b> HR (95% CI): 0.94 (0.70, 1.26) p = 0.67	 <b>Composite of first occurrence of major CV event</b> (non-fatal MI, non-fatal stroke, CV death) HR (95% CI): 0.88 (0.73, 1.06) p = 0.20	 <b>Renal failure</b> 5 events (0.2%) Intensive txt vs 1 event (0.04%) Standard txt p=0.12   <b>ESRD or need dialysis</b> 59 events (2.5%) Intensive txt vs 58 events (2.4%) Standard txt p=0.93  <i>[Both outcomes reported as AE; note that definitions for renal failure and ESRD are unclear]</i>

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BP Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non- fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes	Kidney Outcomes
<p><b>SHEP, 1996</b></p> <p>Adults, ages <math>\geq 60</math> years, SBPs 160-219 and DBPs of <math>&lt; 90</math> mmHg</p> <p>N = 4,736 in overall trial population; <b>583 with diabetes at baseline. This exhibit represents only the diabetes subgroup.</b></p> <p>Mean 4.5 years</p> <p>Good (primary paper); Fair (diabetes subgroup analysis). Subgroup analysis downgraded to fair based on reduced power due to a small number of patients with diabetes at baseline and that authors explicitly state that SHEP was not designed to address treatment effects in patients with and without diabetes.</p>	<p>SBP Goal:</p> <ul style="list-style-type: none"> <li>For individuals with SBPs of <math>&gt;180</math> mmHg: Goal was SBP <math>&lt;160</math></li> <li>For those with SBPs of 160-179: goal was reduction of at least 20 mmHg in SBP</li> </ul> <p><u>At start of trial</u> For diabetes subpopulation: Baseline SBP, mmHg (SD): Active: 170.2 (9.2) Placebo: 170.2 (9.2)</p> <p><u>During follow-up</u> For diabetes subpopulation, SBP difference between txt and placebo, mmHg: 9.8 <math>p=NR</math></p> <p>Achieved BP: NR for diabetes subpopulation</p>	 <p><b>All cause mortality</b> RR (95% CI): 0.74 (0.46, 1.18) <math>p=NR</math></p>	 <p><b>Non-fatal MI and fatal CHD</b> RR (95% CI): 0.46 (0.24, 0.88) <math>p=NR</math></p>	 <p><b>Non-fatal and fatal strokes</b> RR (95% CI): 0.78 (0.45, 1.34) <math>p=NR</math></p>			
<p><b>Syst-Eur, 1999</b></p> <p>Adults, ages <math>\geq 60</math> years, SBPs 160-219 and DBPs <math>&lt; 95</math> mmHg</p> <p>N = 4,695 in overall trial population; <b>492 with diabetes at baseline. This exhibit represents only the diabetes subgroup.</b></p>	<p>SBP Goal: <math>&lt;150</math> and decrease SBP by <math>\geq 20</math> mmHg</p> <p><u>At start of trial</u> NR for those with diabetes, Full sample presented below: Baseline SBP, mmHg (SD) Txt: 173.8 (6.7) Placebo: 173.9 (10.1)</p> <p><u>At 2 years</u> Achieved SBP: NR for</p>	 <p><b>Overall mortality:</b> Benefit of treatment* (95% CI): 41% (-9 to 69) <math>p = 0.09</math></p> <p><i>(p for interaction between diabetes status</i></p>	 <p><b>Fatal and nonfatal cardiac events:</b> Benefit of treatment (95% CI): 57% (-6 to 82) <math>p=0.06</math></p> <p><i>(p for interaction between diabetes status and treatment group = 0.12)</i></p>	 <p><b>Fatal and nonfatal stroke</b> Benefit of treatment (95% CI): 69% (14 to 89) <math>p=0.02</math></p> <p><i>(p for interaction between diabetes status and treatment group = 0.13)</i></p>			

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BP Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non- fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes	Kidney Outcomes
<p>Median 24 months</p> <p>Good (primary paper); Fair (diabetes subgroup analysis). Diabetes subgroup analysis downgraded to fair because the analysis was not prespecified and there was reduced power due to a small sample of patients with diabetes at baseline.</p>	<p>diabetes subpopulation (NR as numerical values for full sample though achieved results are graphically illustrated in a figure demonstrating that txt groups had consistently lower SBPs and DBPs versus placebo from year 1 through year 4)</p> <p>Mean fall in SBP/DBP for diabetes subpopulation, mmHg (SD)            Txt: 22.1/6.8 (14.5/8.2)            Placebo: 13.5/2.9 (16.5/7.8)            p = NR</p> <p>SBP/DBP difference between active and placebo groups in patients with diabetes, mmHg            8.6/3.9            p for difference in SBP            0.40            p for difference in DBP            0.44</p>	<p><i>and treatment group = 0.04)</i></p> <p>*Benefit of treatment = % reduction in event rate for active txt group</p>					
<b>Trials with Diastolic Goals</b>							
<p><b>ABCD- HTN Cohort, 2000</b></p> <p>Adults, ages 40 to 74, with Type 2 diabetes and DBPs <math>\geq</math> 90 mmHg</p> <p>N: 470 (HTN Cohort)</p> <p>5 years</p> <p>Fair</p>	<p>Goal:            Intensive txt: DBP: 75            Moderate txt: DBP 80 to 89 mm Hg</p> <p><u>At start of trial</u></p> <p>Baseline SBP/DBP, mmHg (SD):            Intensive txt: 156/98 (16.1/6.4)            Moderate txt: 154/98 (16.9/6.4)</p> <p><u>Average of last 4 years of follow-up</u></p> <p>Achieved SBP/DBP, mmHg</p>	<p>  <b>All-cause mortality</b>            % (intensive vs. moderate txt)            5.5 vs. 10.7%            p = 0.037</p>					

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BP Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non- fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes	Kidney Outcomes
	Intensive txt: 132/78 Moderate txt: 138/86 p = NR  Change in achieved SBP/DBP, mmHg Intensive txt: -24/20 Moderate txt: -16/12 p = NR  Achieved SBP/DBP difference between groups, mmHg 8/8 p < 0.001						
<b>ABCD- Normotensive Cohort, 2002</b>  Adults, ages 40 to 74, with Type 2 diabetes and DBPs 80 to 89 mmHg  N: 480 (Normotensive Cohort)  Mean follow-up 5.3 years  Good	Goal: Intensive Txt: DBP 10 mmHg below baseline DBP Moderate Txt: DBP 80 to 89 mm Hg  <u>At start of trial</u>  Baseline DBP, mmHg (SD): Intensive txt: 84.4 (0.2) Moderate txt: 84.4 (0.2)  <u>Average of last 4 years of follow-up</u>  Achieved DBP, mmHg (SD) Intensive txt: 75 (0.3) Moderate txt: 81 (0.3) p < 0.0001  Achieved DBP difference between groups, mmHg 6 p = NR	 <b>Death</b> OR (95% CI): 1.1 (0.56, 2.12) p = 0.80	 <b>MI</b> OR (95% CI): 0.75 (0.37, 1.52) p = 0.43	 <b>CVA</b> OR (95% CI): 3.29 (1.06, 10.25) 4 events (1.7%) in intensive txt vs 13 events (5.4%) in moderate txt p = 0.03	 <b>CHF</b> OR (95% CI): 0.89 (0.38, 2.06) p = 0.78		
<b>HOT, 1998</b>  Adults, ages 50 to 80, with HTN (DBPs of 100-115)  N: In overall trial population: 19,193 randomized; 18,790 analyzed and followed-up (403)	DBP Goals: ≤ 80 mmHg ≤ 85 mmHg ≤ 90 mmHg  <u>At start of trial</u>  NR for diabetes subpopulation  <u>Mean of all BPs from 6 months F/U to the end of</u>	 <b>Total mortality</b> For goal ≤ 90 vs ≤ 85: RR (95% CI): 1.03 (0.62, 1.71)  	 <b>All MI</b> For goal ≤ 90 vs ≤ 85: RR (95% CI): 1.75 (0.73, 4.17)   <b>All MI</b>	 <b>All stroke</b> For goal ≤ 90 vs ≤ 85: RR (95% CI): 1.30 (0.63, 2.67)   <b>All stroke</b>		 <b>Major CV events</b> (fatal and nonfatal MI, fatal and nonfatal stroke, all other CV deaths) For goal ≤90 vs ≤85: RR (95% CI): 1.32 (0.84-2.06)	

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BP Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non- fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes	Kidney Outcomes
<p>excluded early-on due to incorrect data handling at one center). <b>1501 with diabetes at baseline<sup>2</sup></b></p> <p>Mean 3.8 years for overall population</p> <p>Fair</p>	<p><u>the study</u></p> <p>NR for diabetes subpopulation</p> <p><u>Mean between group difference in achieved SBP/DBP, mmHg</u></p> <p>NR for diabetes subpopulation</p>	<p><b>Total mortality</b> For goal ≤ 85 vs ≤ 80: RR (95% CI): 1.72 (0.95, 3.14)</p>  <p><b>Total mortality</b> For goal ≤ 90 vs ≤ 80: RR (95% CI): 1.77 (0.98, 3.21)</p>	<p>For goal ≤ 85 vs ≤ 80: RR (95% CI): 1.14 (0.41, 3.15)</p>  <p><b>All MI</b> For goal ≤ 90 vs ≤ 80: RR (95% CI): 2.01 (0.81, 4.97)</p>	<p>For goal ≤ 85 vs ≤ 80: RR (95% CI): 1.10 (0.50, 2.40)</p>  <p><b>All stroke</b> For goal ≤ 90 vs ≤ 80: RR (95% CI): 1.43 (0.68, 2.99)</p>		 <p><b>Major CV events</b> For goal ≤85 vs ≤80: RR (95% CI): 1.56 (0.91-2.67)</p>  <p><b>Major CV events</b> For goal ≤90 vs ≤80: RR (95% CI): 2.06 (1.24-3.44)</p> <p>22 events (11.9 events per 1000 p-y) in ≤80 goal group vs 45 events (24.4 events per 1000 p-y) in ≤90 goal group</p>	
<b>Trials with Mixed Goals</b>							
<p><b>UKPDS, 1998</b></p> <p>Adults, ages 25 to 65, with newly diagnosed diabetes and SBP/DBPs ≥ 150/85 for those receiving anti-HTN, or ≥ 160/90 for those not previously receiving anti-HTN,</p>	<p>SBP/DBP Goal: Tight control: &lt; 150/85 Less tight control: &lt; 180/105 mmHg</p> <p><u>At start of trial</u> Baseline SBP/DBP, mmHg (SD): Tight control: 159/94 (20/10) Less tight: 160/94 (18/9)</p>	 <p><b>All cause mortality</b> RR (95% CI): 0.82 (0.62, 1.08) p = 0.17</p>	 <p><b>MI</b> RR (95% CI): 0.79 (0.59, 1.07) p = 0.13</p>  <p><b>Sudden death</b> RR (99% CI): 1.39 (0.31, 6.26)</p>	 <p><b>Stroke</b> RR (95% CI): 0.56 (0.35, 0.89) p = 0.013</p>	 <p><b>HF</b> RR (99% CI): 0.44 (0.20, 0.94) p = 0.0043</p>	 <p><b>Any DM related endpoint</b> RR (95% CI): 0.76 (0.62, 0.92) p = 0.0046 <i>[Note: includes sudden death, death from</i></p>	 <p><b>Death from renal failure</b> RR (99% CI): 0.35 (0.03 to 3.66) p=0.23</p> 

<sup>2</sup> **Notes about HOT diabetes subgroup analysis:** The primary HOT paper does not state whether the diabetes subgroup analysis is prespecified. The 2009 Cochrane review on BP targets states “although not clearly specified, the subgroup analysis of diabetic patients in the HOT trial appears to be a post-hoc analysis, because it was not mentioned in any of the preliminary descriptions or reports of the trial published in 1993, 1994, 1995 and 1997.” However, when staff retrieved the 1993 pretrial paper, the following reference was found in the study aims section: “other analyses will investigate the influence of factors such as age, sex, previous history of myocardial infarction or stroke, diabetes mellitus, and smoking.” Although the term “prespecified” is not used, there is a reference to diabetes in a pre-results paper. Citation for 1993 reference: Hansson L, for the HOT Study Group. The Hypertension Optimal Treatment Study (The HOT Study). *Blood Pressure* 1993;2:62–68.

Trial, year Sample characteristics Sample size Duration Quality Rating	BP Goal Baseline BP Achieved BP Differences between groups	Overall Mortality	Coronary Heart Disease (includes fatal MI, non- fatal MI, sudden death, or combinations)	Cerebrovascular morbidity and mortality (includes fatal, non-fatal, or combination)	Heart Failure (includes fatal, non-fatal or combination)	Primary Composite Outcomes	Kidney Outcomes
<p>and fasting plasma glucose &gt; 6 mmol/l</p> <p>N: 1,148</p> <p>Mean 8.4 years</p> <p>Fair</p>	<p><u>At 9 years</u></p> <p>Achieved SBP, mmHg (SD)</p> <p>Tight control: 144/ 82 (14/7)</p> <p>Less tight control: 154/87 (16/7)</p> <p>p &lt; 0.0001/ p &lt; 0.0001</p> <p>SBP change, mmHg</p> <p>Tight: -15</p> <p>Less tight: -6</p> <p>p=NR</p> <p>DBP change, mmHg</p> <p>Tight: -12</p> <p>Less tight: -7</p> <p>p=NR</p>		<p>p = 0.57</p>			<p><i>hyperglycemia or hypoglycemia, fatal or non-fatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction]</i></p> <p></p> <p><b>Death related to DM</b></p> <p>RR (95% CI): 0.68 (0.49, 0.94)</p> <p>p = 0.019</p> <p><i>[Note: includes sudden death or death due to stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia]</i></p>	<p><b>Renal failure</b></p> <p>RR (99% CI): 0.58 (0.15-2.21)</p> <p>p= 0.29</p>

## Exhibit I: Evidence from randomized controlled trials of initial antihypertensive drug therapy with diuretics versus other drugs

**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** *Green* = Statistically significant where the diuretic did better ( $p < 0.05$ ) *Red* = Statistically significant where the diuretic did worse *Yellow* =  $p \geq 0.05$  and  $\leq 0.10$  *Clear* =  $p > 0.10$   
*Blue* =  $p$  value not reported

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<b>MRC, 1985</b>  Adults, ages 35-64 years, with mild to moderate HTN  BEN: Bendrofluzide: 10 mg QD PRO: Propranolol: 240 mg QD  N: 17,354  5.5 years  Fair	 <b>All deaths</b> 6.0 per 1000 py BEN vs 5.5 per 1000 py PRO p=0.71	 <b>Coronary events</b> 5.6 per 1000 py BEN vs 4.8 per 1000 py PRO p=0.24	 <b>Stroke</b> 0.8 per 1000 py BEN vs 1.9 per 1000 py PRO p=0.002		 <b>All CV events</b> 6.6 per 1000 py BEN vs 6.7 per 1000 py PRO p=0.76		
<b>ALLHAT, 2002</b>  Adults, $\geq 55$ years of age with at least one additional risk factor for CHD  CHL: Chlorthalidone: 12.5, 25 mg QD LIS: Lisinopril: 10, 20, and 40 mg QD AML: Amlodipine: 2.5, 5, and 10 mg QD  N: 33,357  Mean 4.9 years  Good	 <b>All-cause mortality</b> LIS vs. CHL: RR (95% CI): 1.00 (0.94, 1.08) p = 0.90   <b>All-cause mortality</b> AML vs CHL: RR (95% CI): 0.96 (0.89, 1.02) p = 0.20	 <b>CHD (combined fatal CHD and nonfatal MI)</b> LIS vs. CHL: RR (95% CI): 0.99 (0.91, 1.08) p = 0.81   <b>CHD (combined fatal CHD and nonfatal MI)</b> AML vs CHL: RR (95% CI): 0.98 (0.90, 1.07) p = 0.65	 <b>Stroke</b> LIS vs. CHL: RR (95% CI): 1.15 (1.02, 1.30) p = 0.02   <b>Stroke</b> AML vs. CHL: RR (95% CI): 0.93 (0.82, 1.06) p = 0.28	 <b>HF</b> LIS vs. CHL: RR (95% CI): 1.19 (1.07, 1.31) p < 0.001   <b>HF</b> AML vs. CHL: RR (95% CI): 1.38 (1.25, 1.52) p < 0.001	 <b>Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)</b> LIS vs. CHL: RR (95% CI): 1.10 (1.05, 1.16) p < 0.001	 <b>Kidney disease death</b> LIS vs. CHL: 0.5 per 100 persons LIS vs 0.4 per 100 persons CHL RR (95% CI): NR p = 0.37   <b>Kidney disease death</b> AML vs CHL: 0.5 per 100 persons AML vs 0.4 per 100 persons CHL RR (95% CI): NR	 <b>Fasting glucose progressing to <math>\geq 126</math> mg/dL among non-DM with baseline fasting glucose &lt;126 mg/dL:</b> LIS vs. CHL: 8.1% LIS vs 11.6% CHL p < 0.001   <b>Fasting glucose progressing to <math>\geq 126</math> mg/dL among non-DM with baseline fasting glucose</b>

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		 <b>Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)</b> LIS vs. CHL: RR (95% CI): 1.05 (0.98, 1.11) p = 0.18   <b>Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)</b> AML vs. CHL: RR (95% CI): 1.00 (0.94, 1.07) p = 0.97   <b>Coronary revascularization</b> LIS vs. CHL: RR (95% CI): 1.10 (1.00, 1.21) p = 0.05   <b>Coronary revascularization</b> AML vs. CHL:	 <b>Death from stroke</b> LIS vs. CHL: 1.7 per 100 persons LIS vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.06   <b>Death from stroke</b> AML vs. CHL: 1.4 per 100 persons AML vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.71	 <b>Hospitalized/ Fatal HF</b> LIS vs. CHL: RR (95% CI): 1.10 (0.98, 1.23) p = 0.11   <b>Hospitalized/ Fatal HF</b> AML vs. CHL: RR (95% CI): 1.35 (1.21, 1.50) p < 0.001   <b>HF death</b> LIS vs. CHL: 1.1 per 100 persons LIS vs 1.0 per 100 persons CHL RR (95% CI): NR P = 0.98   <b>HF death</b> AML vs CHL: 1.4 per 100 persons AML vs 1.0 per 100 persons CHL RR (95% CI): NR p = 0.17	 <b>Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)</b> AML vs. CHL: RR (95% CI): 1.04 (0.99, 1.09) p = 0.12   <b>Cardiovascular death</b> LIS vs. CHL: 8.5 per 100 persons LIS vs 8.0 per 100 persons CHL RR (95% CI): NR p = 0.39   <b>Cardiovascular death</b> AML vs. CHL: 8.5 per 100 persons AML vs 8.0 per 100 persons CHL RR (95% CI): NR p = 0.76   <b>Other CVD death</b>	<p>p = 0.68</p>  <b>ESRD</b> LIS vs CHL: RR (95% CI): 1.11 (0.88, 1.38) p = 0.38   <b>ESRD</b> AML vs. CHL: RR (95% CI): 1.12 (0.89, 1.40) p = 0.33	<p>&lt;126 mg/dL:            AML vs. CHL:            9.8% AML vs            11.6% CHL            p = 0.04</p>  <b>Angioedema</b> AML vs. CHL <0.1% AML vs 0.1% CHL p = NR   <b>Angioedema</b> LIS vs. CHL 0.4% LIS vs 0.1% CHL p < 0.001

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		<p>RR (95% CI): 1.09 (1.00, 1.20) p = 0.06</p>  <p><b>MI death</b> LIS vs. CHL 2.2 per 100 persons LIS vs 2.4 per 100 persons CHL RR (95% CI): NR p = 0.25</p>  <p><b>MI death</b> AML vs. CHL 2.3 per 100 persons AML vs 2.4 per 100 persons CHL RR (95% CI): NR p = 0.66</p>  <p><b>Definite CHD death</b> LIS vs. CHL 1.0 per 100 persons LIS vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.52</p>  <p><b>Definite CHD death</b> AML vs. CHL 1.2 per 100 persons AML vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.88</p>  <p><b>Possible CHD</b></p>			<p>LIS vs. CHL: 1.5 per 100 persons LIS vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.66</p>  <p><b>Other CVD death</b> AML vs. CHL: 1.7 per 100 persons AML vs 1.4 per 100 persons CHL RR (95% CI): NR p = 0.46</p>		

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		<p><b>death</b> LIS vs. CHL 1.4 per 100 persons LIS vs 1.1 vs 100 per persons CHL RR (95% CI): NR p = 0.10</p> <p> <b>Possible CHD death</b> AML vs. CHL 1.1 per 100 persons AML vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.62</p>					
<p><b>ALLHAT, 2003</b></p> <p>Adults, ages ≥ 55 years, with at least one additional risk factor for CHD</p> <p>CHL: Chlorthalidone: 12.5, 25 mg QD DOX: Doxazosin: 2, 4, or 8 mg QD</p> <p>N: 24,316</p> <p>Mean 3.2 years</p> <p>Good</p> <p><i>Doxazosin arm terminated early because of a 25% greater incidence of combined CVD events compared with chlorthalidone</i></p>	<p> <b>All-cause mortality</b> RR (95% CI): 1.03 (0.94, 1.13) p = 0.50</p>	<p> <b>Non-fatal MI and fatal CHD</b> RR (95% CI): 1.03 (0.92, 1.15) p = 0.62</p> <p> <b>Death from MI</b> RR (95% CI): 0.96 (0.76, 1.22) p = 0.75</p> <p> <b>Death from definite CHD</b> RR (95% CI): 1.16 (0.77, 1.74) p = 0.49</p> <p> <b>Coronary revascularization</b></p>	<p> <b>Stroke</b> 4.08 per 100 CHL vs 5.49 per 100 DOX RR (95% CI): 1.26 (1.10, 1.46) p = 0.001</p> <p> <b>Death from stroke</b> 0.79 per 100 CHL vs 1.25 per 100 DOX RR (95% CI): 1.39 (1.03, 1.89) p = 0.03</p>	<p> <b>Fatal, hospitalized, treated CHF</b> 5.35 per 100 CHL vs 8.89 per 100 DOX RR (95% CI): 1.80 (1.61, 2.02) p &lt; 0.001</p> <p> <b>Fatal, hospitalized CHF</b> 4.41 per 100 CHL vs 6.63 per 100 DOX RR (95% CI): 1.66 (1.46, 1.89) p &lt; 0.001</p> <p> <b>Death from CHF</b> RR (95% CI): 1.20 (0.81, 1.78) p = 0.36</p>	<p> <b>Combined CHD</b> 14.87 per 100 CHL vs 16.00 per 100 DOX RR (95% CI): 1.07 (0.99, 1.66) p = 0.07</p> <p> <b>Combined CVD</b> 25.09 per 100 CHL vs 28.56 per 100 DOX RR (95% CI): 1.20 (1.13, 1.27) p &lt; 0.001</p> <p> <b>CV mortality</b> 4.74 per 100 CHL vs 5.60 per 100 DOX RR (95% CI): 1.15 (1.01, 1.32) p = 0.03</p>	<p> <b>Kidney disease death</b> RR (95% CI): 1.69 (0.76, 3.77) p = 0.20</p> <p> <b>ESRD</b> RR (95% CI): 1.04 (0.76, 1.42) p = 0.80</p> <p> <b>Doubling of serum Cr from baseline:</b> 0.8% CHL vs 0.5% DOX p = 0.02</p>	

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		7.08 per 100 CHL vs 8.02 per 100 DOX RR (95% CI): 1.12 (1.00, 1.25) p = 0.05   <b>Lower extremity PAD</b> RR (95% CI): 0.97 (0.82, 1.15) p = 0.76			 <b>Other CV death</b> RR (95% CI): 1.25 (0.92, 1.70) p = 0.15		
<b>SHELL, 2003</b>  Adults ≥ 60 years with isolated systolic HTN  CHL: Chlorthalidone: 12.5, 25 mg QD LAC: Lacidipine: 4, 6 mg QD  N: 1,882  Fair	 <b>All-cause mortality</b> 122 events CHL vs 145 events LAC HR (95% CI): 1.23 (0.97, 1.57) p = 0.09	 <b>Fatal and non-fatal MI</b> HR (95% CI): 0.85 (0.39-1.83) p = 0.67   <b>Sudden death</b> HR (95% CI): 1.22 (0.58, 2.53) p = 0.60   <b>Revascularization</b> HR (95% CI): 0.50 (0.09, 2.70) p = 0.41	 <b>Fatal and non-fatal stroke</b> HR (95% CI): 0.96 (0.61, 1.51) p = 0.87   <b>TIA</b> HR (95% CI): 1.14 (0.54-2.40) p = 0.72	 <b>Fatal and non-fatal HF</b> HR (95% CI): 1.20 (0.65, 2.20) p = 0.56	 <b>Composite primary endpoint</b> (fatal and non-fatal stroke, sudden death, fatal and non-fatal MI, fatal and non-fatal CHF, myocardial revascularization and carotid endarterectomy) HR (95% CI): 1.01 (0.75, 1.36) p = 0.94		 <b>Orthostatic hypotension</b> 2.5% CHL vs 1.9% LAC p = NR   <b>Edema</b> 4.9% CHL vs 14.3% LAC p = NR   <b>Cough</b> 4.0% CHL vs 3.5% LAC p = NR   <b>Dizziness</b> 12.4% CHL 12.7% LAC p = NR   <b>Fatigue</b> 20.5% CHL

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>VHAS, 1997</b></p> <p>Adults, ages 40-65 years, with HTN</p> <p>CHL: Chlorthalidone: 25 mg QD VER: Verapamil: slow release 240 mg QD</p> <p>N: 1,414</p> <p>2 years</p> <p>Fair</p>	 <b>Death by any cause</b> 4 events CHL vs 5 events VER p = NR	 <b>MI</b> 5 events CHL vs 5 events VER p = NR   <b>Revascularization procedures</b> 3 events CHL vs 4 events VER p = NR   <b>Cardiac deaths</b> 4 events CHL vs 3 events VER p = NR	 <b>Strokes</b> 4 events CHL vs 3 events VER p = NR   <b>TIA</b> 7 events CHL vs 7 events VER p = NR   <b>Cerebrovascular deaths</b> 0 events CHL vs 2 events VER p = NR	 <b>CHF</b> 0 events CHL vs 2 events VER p = NR	 <b>Non-fatal CV events</b> 39 events CHL vs 37 events VER p = NR   <b>Major CV events</b> 9 events CHL vs 8 events VER p = NR   <b>Minor CV events</b> 30 events CHL vs 29 events VER p = NR   <b>CV deaths</b> 4 events CHL vs 5 events VER p = NR		<p>13.7% LAC p = NR</p>  <b>Hypokalemia</b> 24.6% CHL vs 4.4% VER p < 0.01   <b>Hyperuricemia</b> 10.8% CHL vs 3.9% VER p < 0.01   <b>Glucose, mg/dl (SD)</b> +1.8 change CHL vs -1.2 change VER p = 0.01   <b>Severe hypokalemia</b> 8 events CHL vs 4 events VER p = NR   <b>Constipation</b> 3.1% CHL vs 13.7% VER p = NR
<p><b>INSIGHT, 2000</b></p> <p>Men and women age 55-80 years, high risk patients with HTN; one additional CV risk factor</p>	 <b>All deaths (first event)</b> OR (95% CI): OR (95% CI):	 <b>Non-fatal MI</b> OR (95% CI): 1.09 (0.76-1.58)	 <b>Non-fatal stroke</b> OR (95% CI): 0.87 (0.61-1.26)	 <b>Non-fatal HF</b> OR (95% CI): 2.20 (1.07-4.49)	 <b>Primary composite</b> (death from any CV or cerebrovascular)	 <b>Renal Failure (defined as creatinine &gt;2.94)</b>	 <b>Serious AEs</b> 28% Co-am vs 25% NIFE

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>Co-am: Co-amilozide: HCTZ 25 mg and amloride 2.5 mg QD or doubling the dose of both drugs to HCTZ 50 mg QD and amloride 5 mg QD NIFE: Nifedipine: 30, 60 mg QD</p> <p>N: 6,321</p> <p>Maximum 51 months F/U</p> <p>Good</p>	<p>1.01 (0.80-1.27) p = 0.95</p>	<p>p = 0.52</p>  <p><b>Fatal MI</b> OR (95% CI): 3.22 (1.18-8.80) p = 0.017</p>	<p>P= 0.52</p>  <p><b>Fatal stroke</b> OR (95% CI): 1.09 (0.48-2.48) p = 0.84</p>  <p><b>TIA</b> OR (95% CI): 1.00 (0.57-1.75) p = 1.0</p>	<p>p = 0.028</p>  <p><b>Fatal HF</b> OR (95% CI): 2.01 (0.18-22.13) p = 0.63</p>	<p>cause, together with non-fatal stroke, MI and HF) OR (95% CI): 1.11 (0.90-1.36) p = 0.34</p>  <p><b>Secondary composite</b> (primary outcome plus non-CV deaths, renal failure, angina and TIA) OR (95% CI): 0.96 (0.83-1.12) p = 0.62</p>  <p><b>Other CV death</b> OR (95% CI): 1.09 (0.50-2.38) p = 0.85</p>  <p><b>CV Deaths</b> OR (95% CI): 1.16 (0.80-1.69) p = 0.45</p>  <p><b>Non-fatal primary CV events</b> OR (95% CI): 1.08 (0.85-1.38) p = 0.53</p>  <p><b>Non-fatal CV events</b> OR (95% CI): 0.94 (0.78-1.13) p = 0.50</p>	<p><b>mg/dl)</b> OR (95% CI): 0.62 (0.26-1.49) p = 0.38</p>	<p>p &lt; 0.02</p>  <p><b>DM reported as AE</b> 4.3% Co-am vs 3.0% NIFE p = 0.01</p>  <p><b>New onset DM reported as an outcome</b> 5.6% Co-am vs 4.3% NIFE p = 0.02</p>  <p><b>Impaired renal function as an adverse event</b> 4.6% Co-am vs 1.8% NIFE p &lt; 0.0001</p>  <p><b>Hyperglycemia,</b> 7.7% Co-am vs 5.6% NIFE p = 0.001</p>  <p><b>Hypokalemia</b> 6.2% Co-am vs 1.9% NIFE p &lt; 0.0001</p>  <p><b>Hyponatremia</b> 61 events Co-am</p>

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
							vs 8 events NIFE $p < 0.0001$  <b>Dizziness</b> 10% Co-am vs 8% NIFE $p < 0.006$   <b>GFR, mL/min</b> Co-am vs. NIFE (95% CI): -2.3 (-3.8, 1.9) Co-am lower than NIFE $p = \text{NR}$   <b>All AEs</b> 42% Co-am vs 49% NIFE $p < 0.0001$   <b>Peripheral edema</b> 4.3% Co-am vs 28% NIFE $p < 0.0001$   <b>Headache</b> 9.2% Co-am vs 12% NIFE $p < 0.0002$
<b>MIDAS, 1996</b> Adults, ages $\geq 40$ years, without hyperlipidemia, and presence of IMT 1.3-	 <b>All-cause mortality</b>	 <b>MI</b>	 <b>Stroke</b>	 <b>CHF</b>	 <b>Any major vascular</b>		 <b>CV-related</b>

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>3.5 mm in the carotid artery; fasting TC and LDL-C <math>\leq</math> 6.21 and 4.14 mmol/L (240 and 160 mg/dL) respectively</p> <p>HCTZ: Hydrochlorothiazide: 12.5 to 25 mg BID ISR: Isradipine: 2.5 to 5.0 mg BID</p> <p>N: 883</p> <p>3 years</p> <p>Fair</p>	<p>RR (95% CI): 0.89 (0.35-2.28) p = 0.81</p>	<p>RR (95% CI): 1.20 (0.37, 3.89) p = 0.77</p> <p> <b>CABG</b> RR (95% CI): 1.00 (0.32, 3.07) p = 0.97</p> <p> <b>Coronary angioplasty</b> 0.22 n per 100 HCTZ vs 1.13 n per 100 ISR RR (95% CI): 4.99 (0.59, 42.53) p = 0.10</p> <p> <b>Sudden death</b> RR (95% CI): 1.00 (0.14, 7.05) p &gt; 0.99</p>	<p>RR (95% CI): 2.00 (0.50, 7.93) p = 0.32</p>	<p>0.0 n per 100 HCTZ vs 0.45 n per 100 ISR RR (95% CI): NR p = 0.16</p>	<p><b>event</b> 3.17 n per 100 HCTZ vs 5.65 n per 100 ISR RR (95% CI): 1.78 (0.94, 3.38) P = 0.07</p> <p> <b>Major vascular events and procedures</b> 4.31 n per 100 HCTZ vs 6.78 n per 100 ISR RR (95% CI): 1.58 (0.90, 2.76) p = 0.10</p> <p> <b>Other CVD death</b> RR (95% CI): 1.00 (0.06, 15.90) p &gt; 0.99</p>		<p><b>adverse reactions</b> 0.9% HCTZ vs 3.0% ISR p = NR</p>
<p><b>HAPPHY, 1987</b></p> <p>Adult men, ages 40-64 years, with mild to moderate HTN</p> <p>DIUR: Diuretic: 50-100 mg HCTZ or 5-10 mg bendroflumethazide BB: Beta Blocker: 100 mg atenolol or 200 mg QD metoprolol</p> <p>N: 6,569</p> <p>Mean 45.1 months</p> <p>Fair</p>	<p> <b>All deaths</b> OR (95% CI): 1.06 (0.80, 1.41) p &gt; 0.20</p>	<p> <b>Non-fatal MI</b> OR (95% CI): 0.90 (0.66, 1.23) p &gt; 0.20</p> <p> <b>Fatal and/or non-fatal CHD</b> OR (95% CI): 0.88 (0.68, 1.14) p &gt; 0.20</p> <p></p>	<p> <b>Non-fatal stroke</b> OR (95% CI): 1.11 (0.68, 1.83) p &gt; 0.20</p> <p> <b>Fatal and/or non-fatal stroke</b> OR (95% CI): 1.29 (0.82, 2.04) p &gt; 0.20</p> <p></p>	<p> <b>Heart failure</b> 1.8 per 1000 py DIUR vs 2.6 per 1000 py BB p = NS (value NR)</p>	<p> <b>Patients with an endpoint of death, non-fatal MI, or non-fatal stroke</b> OR (95% CI): 0.98 (0.80, 1.20) p &gt; 0.20</p> <p> <b>Total endpoints of death, non-fatal MI, or non-fatal stroke</b> OR (95% CI): 1.00 (0.83, 1.21)</p>	<p> <b>Change in serum Cr from baseline, (<math>\mu</math>mol/l)</b> +4.2 DIUR vs +4.0 BB p = NS (value NR)</p>	<p> <b>Dry mouth</b> 15.4% DIUR vs 12.5% BB p &lt; 0.002</p> <p> <b>Developed DM</b> 6.1 per 1000 py vs 6.9 per 1000 py BB p = NS (value NR)</p> <p></p>

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		<b>Fatal CHD</b> OR (95% CI): 0.93 (0.64, 1.37) p > 0.20	<b>Fatal stroke</b> OR (95% CI): 3.37 (0.96, 9.53) p = 0.09		p > 0.20   <b>Other deaths</b> OR (95% CI): 1.06 (0.69, 1.64) p > 0.20		<b>Reporting any symptoms related to drug at 12 month visit</b> 16.8% DIUR vs 19.1% BB p < 0.001   <b>Cold hands and feet</b> 12.7% DIUR vs 21.4% BB p < 0.001   <b>Unusual tiredness</b> 15.4% DIUR vs 18.2% BB p < 0.005
<b>MAPHY, 1988</b>  Adult males, ages 40 to 64, either previously treated patients or newly detected and untreated HTN  DIUR: Diuretic: HCTZ 50-100 mg/d or benfroflumethiazide 5-10 mg/d MET: Metoprolol: 200 mg/d  N: 3,234  Median 4.16 years  Fair  <i>There was a protocol change in MAPHY that occurred more than 2 years after the first patient was randomized that allowed for additional centers that could randomize patients to atenolol or diuretics. The original study protocol did</i>	 <b>Total mortality at median 4.16 years</b> 9.3 per 1000 py DIUR vs 4.8 per 1000 py MET % difference (95% CI): -48 (-68, -17)   <b>Total mortality at 10.8 years (end of study)</b> 10.3 per 1000 py DIUR vs 8.0 per 1000 py MET % difference: -22 p = 0.028  	 <b>Fatal CHD (composite of MI or sudden coronary death) at 10.8 years</b> 43 events DIUR vs 36 events MET p = 0.048	 <b>Fatal stroke at 10.8 years</b> 9 events DIUR vs 2 events MET p = 0.043	 <b>Fatal HF at 10.8 years</b> 0 events DIUR vs 3 events MET p = NR	 <b>CV mortality at median 4.16 years</b> 6.2 per 1000 py DIUR vs 2.6 per 1000 py MET % difference: -58 p = NR   <b>CV mortality at 10.8 years (end of study)</b> 7.1 per 1000 py DIUR vs 5.2 per 1000 py MET % difference: -27 p = 0.012  		

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><i>not include atenolol as an optional BB. Pooled results from all metoprolol centers, all atenolol centers, and the propranolol center are published separately as HAPPHY (see row above)</i></p>	<p><b>Total sudden mortality at end of study</b> 45 events DIUR vs 32 events MET p = 0.017</p>				<p><b>Sudden CV mortality at 10.8 years (end of study)</b> 5.6 per 1000 py DIUR vs 3.9 per 1000 py MET % difference: -30 p = 0.017</p> <p style="text-align: center;">△</p> <p><b>Non-sudden CV mortality at 10.8 years (end of study)</b> 3.2 per 1000 py DIUR vs 2.8 per 1000 py MET % difference: -13 p = NS (value NR)</p>		
<p><b>ANBP2, 2003</b></p> <p>Adults, ages 65 to 84, with absence of recent CV events</p> <p>DIU: Diuretic: HCTZ recommended; dose not specified ACE: ACE Inhibitor: Enalapril recommended; dose not specified</p> <p>N: 6,083</p> <p>Median 4.1 years</p> <p>Fair</p>	<p style="text-align: center;">△</p> <p><b>Death from any cause</b> HR (95% CI): 0.90 (0.75, 1.09) p = 0.27</p>	<p style="text-align: center;">▲</p> <p><b>Non-fatal MI</b> 5.8 per 1000 py DIUR vs 4.1 per 1000 py ACE HR (95% CI): 0.68 (0.47, 0.99) p = 0.05</p> <p style="text-align: center;">▲</p> <p><b>MI</b> 6.7 per 1000 py DIUR vs 4.7 per 1000 py ACE HR (95% CI): 0.68 (0.47, 0.98) p = 0.04</p> <p style="text-align: center;">△</p> <p><b>Coronary event</b> HR (95% CI):</p>	<p style="text-align: center;">△</p> <p><b>Non-fatal Stroke</b> HR (95% CI): 0.93 (0.70, 1.26) p = 0.65</p> <p style="text-align: center;">△</p> <p><b>Stroke</b> HR (95% CI): 1.02 (0.78, 1.33) p = 0.91</p> <p style="text-align: center;">△</p> <p><b>Cerebrovascular event</b> HR (95% CI): 0.90 (0.73, 1.12) p = 0.35</p>	<p style="text-align: center;">△</p> <p><b>Non-fatal HF</b> HR (95% CI): 0.85 (0.62, 1.17) p = 0.32</p> <p style="text-align: center;">△</p> <p><b>HF</b> HR (95% CI): 0.85 (0.62, 1.18) p = 0.33</p> <p style="text-align: center;">△</p> <p><b>Fatal HF events</b> HR (95% CI): 0.24 (0.03, 1.94) p = 0.18</p>	<p style="text-align: center;">▲</p> <p><b>Non-fatal CV event</b> 32.8 per 1000 py DIUR vs 28.9 per 1000 py ACE HR (95% CI): 0.86 (0.74, 0.99) p = 0.03</p> <p style="text-align: center;">△</p> <p><b>Non-fatal other CV</b> HR (95% CI): 0.84 (0.66, 1.07) p = 0.17</p> <p style="text-align: center;">●</p> <p><b>All CV events or death from any cause</b> 59.8 per 1000 py DIUR vs 56.1 per 1000 py ACE</p>		

Study Characteristics (Trial, Year, Population, Interventions, N, Duration and Quality Rating)	Overall Mortality	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		<p>0.86 (0.70, 1.06) p = 0.16</p>  <p><b>Fatal MI events</b> HR (95% CI): 0.79 (0.31, 1.99) p = 0.61</p>  <p><b>Fatal coronary events</b> HR (95% CI): 0.74 (0.49, 1.11) p = 0.14</p>	 <p><b>Fatal stroke events</b> 1.2 per 1000 py DIUR vs 2.3 per 1000 py ACE HR (95% CI): 1.91 (1.04, 3.50) p = 0.04</p>		<p>HR (95% CI): 0.89 (0.79, 1.00) p = 0.05</p>  <p><b>First CV event or death from any cause</b> 45.7 per 1000 py DIUR vs 41.9 per 1000 py ACE HR (95% CI): 0.89 (0.79, 1.01) p = 0.06</p>  <p><b>First CV event</b> 37.1 per 1000 py DIUR vs 33.7 per 1000 py ACE HR (95% CI): 0.88 (0.77, 1.01) p = 0.07</p>  <p><b>Other CV event</b> HR (95% CI): 0.90 (0.71, 1.14) p = 0.36</p>  <p><b>Fatal CV events</b> HR (95% CI): 0.99 (0.72, 1.35) p = 0.94</p>  <p><b>Other fatal CV events</b> HR (95% CI): 0.95 (0.46, 1.96) p = 0.89</p>		



## Exhibit J: Evidence from randomized controlled trials of initial antihypertensive drug therapy with beta blockers versus other drugs

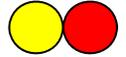
**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** *Green* = Statistically significant where the BB did better ( $p < 0.05$ ) *Red* = Statistically significant where the BB did worse ( $p \geq 0.05$  and  $\leq 0.10$ ) *Yellow* =  $p > 0.10$  *Blue* =  $p$  value not reported

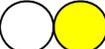
Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>ASCOT-BPLA, 2005</b></p> <p>Adults, age 40-79 years, with HTN and at least 3 CV risk factors</p> <p>ATN: Atenolol-based regimen: atenolol 50, 100 mg adding bendroflumethiazide 1.25, 2.5 mg + potassium and doxazosin GITS 4, 8 mg in steps                      AML: Amlodipine based regimen: amlodipine 5, 10 mg adding perindopril 4, 8 mg and doxazosin GITS 4, 8 mg in steps</p> <p>N: 19,342</p> <p>Median 5.5 years</p> <p>Good</p>	<p style="text-align: center;"></p> <p><b>All-cause mortality</b>                      15.5 per 1000 pts                      ATN vs 13.9 per 1000 pts AML                      HR for AML (95% CI): 0.89 (0.81, 0.99)  <math>p = 0.0247</math></p>	<p style="text-align: center;"></p> <p><b>Total coronary endpoint</b>                      16.8 per 1000 pts                      ATN vs 14.6 per 1000 pts AML                      HR (95% CI) for AML: 0.87 (0.79, 0.96)  <math>p = 0.0070</math></p> <p style="text-align: center;"></p> <p><b>Silent MI</b>                      0.6 per 1000 pts                      ATN vs 0.8 per 1000 pts AML                      HR (95% CI) for AML: 1.27 (0.80, 2.00)  <math>p = 0.3089</math></p> <p style="text-align: center;"></p> <p><b>PAD</b>                      3.9 per 1000 pts                      ATN vs 2.5 per 1000 pts AML                      HR (95% CI) for AML: 0.65 (0.52, 0.81)  <math>p = 0.0001</math></p>	<p style="text-align: center;"></p> <p><b>Fatal and non-fatal stroke</b>                      8.1 per 1000 pts                      ATN vs 6.2 per 1000 pts AML                      HR (95% CI) for AML: 0.77 (0.66, 0.89)  <math>p = 0.0003</math></p>	<p style="text-align: center;"></p> <p><b>Fatal and non-fatal HF</b>                      3.0 per 1000 pts                      ATN vs 2.5 per 1000 pts AML                      HR (95% CI) for AML: 0.84 (0.66, 1.05)  <math>p = 0.1257</math></p>	<p style="text-align: center;"></p> <p><b>Non-fatal MI (including silent MI) and fatal CHD</b>                      9.1 per 1000 pts ATN vs 8.2 per 1000 pts AML                      HR (95% CI) for AML: 0.90 (0.79, 1.02)  <math>p = 0.1052</math></p> <p style="text-align: center;"></p> <p><b>Non-fatal MI (excluding silent MI) and fatal CHD</b>                      8.5 per 1000 pts ATN vs 7.4 per 1000 pts AML                      HR (95% CI) for AML: 0.87 (0.76, 1.00)  <math>p = 0.0458</math></p> <p style="text-align: center;"></p> <p><b>Total CV events and procedures</b>                      32.8 per 1000 pts                      ATN vs 27.4 per 1000 pts AML                      HR (95% CI) for AML: 0.84 (0.78, 0.90)  <math>p &lt; 0.0001</math></p> <p style="text-align: center;"></p> <p><b>Composite of</b></p>		<p style="text-align: center;"></p> <p><b>Development of DM</b>                      15.9 per 1000 pts                      ATN vs 11.0 per 1000 pts AML                      HR (95% CI) for AML: 0.70 (0.63, 0.78)  <math>p &lt; 0.0001</math></p> <p style="text-align: center;"></p> <p><b>Dizziness</b>                      16% ATN vs 12% AML  <math>p &lt; 0.0001</math></p> <p style="text-align: center;"></p> <p><b>Dyspnea</b>                      10% ATN vs 6% AML  <math>p &lt; 0.0001</math></p> <p style="text-align: center;"></p> <p><b>Fatigue</b>                      16% ATN vs 8% AML  <math>p &lt; 0.0001</math></p> <p style="text-align: center;"></p> <p><b>Cough</b>                      8% ATN vs 19%</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
					<p><b>primary endpoints of non-fatal MI including silent MI and fatal CHD plus coronary revascularization procedures</b>  13.4 per 1000 pts ATN vs 11.5 per 1000 pts AML  HR (95% CI) for AML: 0.86 (0.77, 0.96)  p = 0.0058</p> <p> <b>CV death, MI and stroke</b>  18.4 per 1000 pts ATN vs 15.4 per 1000 pts AML (796)  HR (95% CI) for AML: 0.84 (0.76, 0.92)  p = 0.0003</p> <p> <b>CV mortality</b>  6.5 per 1000 pts ATN vs 4.9 per 1000 pts AML  HR (95% CI) for AML: 0.76 (0.65, 0.90)  p = 0.0010</p>		<p>AML  p &lt; 0.0001</p> <p> <b>Peripheral edema</b>  6% ATN vs 23% AML  p &lt; 0.0001</p> <p> <b>Joint swelling</b>  3% ATN vs 14% AML  p &lt; 0.0001</p>
<p><b>ELSA, 2002</b></p> <p>Adults, age 45 to 75 years, with fasting serum total cholesterol ≤320 mg/dl, fasting serum triglycerides ≤300 mg/dl, serum Cr ≤1.7 mg/dl, and a readable ultrasound carotid artery scan with maximum IMT no greater than 4.0 mm</p> <p>ATN: Atenolol: 50, 100 mg/day  LAC: Lacidipine: 4, 6 mg/day</p> <p>N: 2,334</p>	<p> <b>All death</b>  4.68 per 1000 py ATN vs 3.59 per 1000 py LAC  p = NS</p>	<p> <b>Fatal and non-fatal MI</b>  4.68 per 1000 py ATN vs 4.97 per 1000 py LAC  p = NS</p>	<p> <b>Fatal and non-fatal stroke</b>  3.86 per 1000 py ATN vs 2.49 per 1000 py LAC  p = NS</p>		<p> <b>Major CV events</b>  9.09 per 1000 py ATN vs 7.46 per 1000 py LAC  p = NS</p> <p> <b>Minor CV events</b>  11.59 per 1000 py</p>		<p> <b>All serious AEs</b>  55.37% ATN vs 51.38% LAC  p = NS</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
Fair					ATN vs 12.42 vs 1000 py LAC p = NS  <b>All (major and minor) CV events</b> 19.85 per 1000 py ATN vs 19.04 per 1000 py LAC p = NS  <b>CV death</b> 2.20 per 1000 py ATN vs 1.10 per 1000 py LAC p = NS		
<b>LIFE, 2002</b> Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG  ATN: Atenolol: Atenolol 50 mg; Atenolol 50 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) LOS: Losartan: Losartan 50 mg; Losartan 50 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB)  N: 9,222  Mean 4.8 years  Good  Note: HR adjusted for degree of LVH and Framingham risk score at randomization	  <b>Total mortality</b> 19.6 per 1000 py ATN vs 17.3 per 1000 py LOS AdjHR (95% CI) for LOS: 0.90 (0.78, 1.03) p = 0.128 UnadjHR (95% CI) for LOS: 0.88 (0.77, 1.01) p = 0.077	 <b>MI</b> 8.7 per 1000 py ATN vs 9.2 per 1000 py LOS AdjHR (95% CI) for LOS: 1.07 (0.88, 1.31) p = 0.491 UnadjHR (95%CI) for LOS: 1.05 (0.86, 1.28) p = 0.628   <b>Revascularization</b> 13.3 per 1000 py ATN vs 12.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.94 (0.79, 1.11) p = 0.441 UnadjHR (95%CI)	 <b>Stroke</b> 14.5 per 1000 py ATN vs 10.8 per 1000 py LOS AdjHR (95% CI) for LOS: 0.75 (0.63, 0.89) p = 0.001 UnadjHR (95% CI) for LOS: 0.74 (0.63, 0.88) p = 0.0006	 <b>Heart Failure</b> 7.5 per 1000 py ATN vs 7.1 per 1000 py LOS AdjHR (95% CI) for LOS: 0.97 (0.78, 1.21) p = 0.765 UnadjHR (95% CI) for LOS: 0.95 (0.76, 1.18) p = 0.622	 <b>Primary composite endpoint of CV death, MI or stroke</b> 27.9 per 1000 py ATN vs 23.8 per 1000 py LOS AdjHR (95% CI) for LOS: 0.87 (0.77, 0.98) p = 0.021 UnadjHR (95% CI) for LOS: 0.85 (0.76, 0.96) p = 0.009   <b>CV mortality</b> 10.6 per 1000 py ATN vs 9.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.89 (0.73, 1.07) p = 0.206 UnadjHR (95% CI) for LOS: 0.87 (0.72, 1.05)	 <b>New diabetes</b> 17.4 per 1000 py ATN vs 13.0 per 1000 py LOS AdjHR (95% CI) for LOS: 0.75 (0.63, 0.88) p = 0.001 UnadjHR (95% CI) for LOS: 0.75 (0.63, 0.88) p = 0.001   <b>Lower extremity</b> 14% ATN vs 12% LOS p = 0.002   <b>Albuminuria</b> 6% ATN vs 5%	

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		for LOS: 0.91 (0.77, 1.08) p = 0.292			p = 0.136		LOS p = 0.0002  <b>Hyperglycemia</b> 7% ATN vs 5% LOS p = 0.007  <b>Asthenia/Fatigue</b> 17% ATN vs 15% LOS p = 0.001  <b>Dyspnea</b> 14% ATN vs 10% LOS p < 0.0001  <b>Angioedema</b> 0.2% ATN vs 0.1% LOS p = 0.237  <b>Cough</b> 2% ATN vs 3% LOS p = 0.220  <b>Dizziness</b> 16% ATN vs 17% LOS p = 0.247  <b>Chest pain</b>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
							10% ATN vs 11% LOS $p = 0.068$  <b>Hypotension</b> 2% ATN vs 3% LOS $p = 0.001$  <b>Back pain</b> 10% ATN vs 12% LOS $p = 0.004$
<b>LIFE, 2002</b>  <i>Subanalysis of Isolated Systolic Hypertension</i> Kjeldsen et al, 2002  Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG; included in subanalysis if trough sitting SBP 160-200 mmHg with DBP <90 mmHg after 1 and 2 weeks placebo  ATN: Atenolol: Atenolol 50 mg; Atenolol 50 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) LOS: Losartan: Losartan 50 mg; Losartan 50 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB)  N: 9,222 in full trial (1,326 with isolated systolic hypertension)  Mean 4.7 years	<i>Subanalysis of patients with Isolated Systolic Hypertension</i>  <b>Total mortality</b> 30.2 per 1000 py ATN vs 21.2 per 1000 py LOS AdjRR (95% CI) for LOS: 0.72 (0.53, 1.00) $p = 0.046$ UnadjRR (95% CI) for LOS: 0.70 (0.51, 0.96) $p = 0.03$	<i>Subanalysis of patients with Isolated Systolic Hypertension</i>  <b>MI</b> 11.9 per 1000 py ATN vs 10.2 per 1000 py LOS AdjRR (95% CI) for LOS: 0.89 (0.55, 1.44) $p = 0.64$ UnadjRR (95% CI) for LOS: 0.86 (0.53, 1.39) $p = 0.54$   <b>Revascularization</b> 14.4 per 1000 py ATN vs 16.4 per 1000 py LOS AdjRR (95% CI) for LOS: 1.17 (0.78, 1.77) $p = 0.45$	<i>Subanalysis of patients with Isolated Systolic Hypertension</i>  <b>Stroke</b> 18.9 per 1000 py ATN vs 10.6 per 1000 py LOS AdjRR (95% CI) for LOS: 0.60 (0.38, 0.92) $p = 0.02$ UnadjRR (95% CI) for LOS: 0.56 (0.36, 0.86) $p = 0.008$	<i>Subanalysis of patients with Isolated Systolic Hypertension</i>  <b>Hospitalization for Heart Failure</b> 13.3 per 1000 py ATN vs 8.5 per 1000 py LOS AdjRR (95% CI) for LOS: 0.66 (0.40, 1.09) $p = 0.11$ UnadjRR (95% CI) for LOS: 0.64 (0.39, 1.05) $p = 0.08$	<i>Subanalysis of patients with Isolated Systolic Hypertension</i>  <b>Primary composite endpoint of CV death, MI or stroke</b> 35.4 per 1000 py ATN vs 25.1 per 1000 py LOS AdjRR (95% CI) for LOS: 0.75 (0.56, 1.01) $p = 0.06$ UnadjRR (95% CI) for LOS: 0.71 (0.53, 0.95) $p = 0.02$   <b>CV mortality</b> 16.9 per 1000 py ATN vs 8.7 per 1000 py LOS AdjRR (95% CI) for LOS: 0.54 (0.34, 0.87)	 <b>Bradycardia</b> 14.6% ATN vs 3.0% LOS $p < 0.001$   <b>Cold extremities</b> 6.6% ATN vs 4.1% LOS $p = 0.05$   <b>Angioedema</b> 0.3% ATN vs 0.3% LOS $p = 0.99$   <b>Cough</b> 2.9% ATN vs 4.1% LOS $p = 0.23$	

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>Fair</p> <p>NOTE: Adjusted RRs are adjusted for degree of LVH and Framingham risk score at randomization Interaction between treatment and ISH status was not statistically significant</p>	<p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>Total mortality</b> 17.9 per 1000 py ATN vs 16.7 per 1000 py LOS AdjRR (95% CI) for LOS: 0.95 (0.82, 1.11) p = 0.51 UnadjRR (95%CI) for LOS: 0.93 (0.80, 1.09) p = 0.38</p>	<p>UnadjRR (95% CI) for LOS: 1.14 (0.76, 1.72) p = 0.53</p> <p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>MI</b> 8.2 per 1000 py ATN vs 9.0 per 1000 py LOS AdjRR (95% CI) for LOS: 1.12 (0.90, 1.40) p = 0.30 UnadjRR (95% CI) for LOS: 1.10 (0.88, 1.36) p = 0.41</p>  <p><b>Revascularization</b> 13.2 per 1000 py ATN vs 11.5 per 1000 py LOS AdjRR (95% CI) for LOS: 0.89 (0.74, 1.08) p = 0.23 UnadjRR (95% CI) for LOS: 0.87 (0.73, 1.05) p = 0.15</p>	<p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>Stroke</b> 13.8 per 1000 py ATN vs 10.8 per 1000 py LOS AdjRR (95% CI) for LOS: 0.79 (0.66, 0.95) p = 0.01 UnadjRR (95%CI) for LOS: 0.78 (0.65, 0.94) p = 0.01</p>	<p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>Hospitalization for Heart Failure</b> 6.5 per 1000 py ATN vs 6.8 per 1000 py LOS AdjRR (95% CI) for LOS: 1.06 (0.83, 1.36) p = 0.65 UnadjRR (95% CI) for LOS: 1.05 (0.82, 1.34) p = 0.72</p>	<p>p = 0.01 UnadjRR (95%CI) for LOS: 0.51 (0.32, 0.81) p = 0.004</p> <p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>Primary composite endpoint of CV death, MI or stroke</b> 26.7 per 1000 py ATN vs 23.6 per 1000 py LOS AdjRR (95% CI) for LOS: 0.90 (0.79, 1.02) p = 0.11 UnadjRR (95%CI) for LOS: 0.88 (0.78, 1.01) p = 0.06</p>  <p><b>CV mortality</b> 9.6 per 1000 py ATN vs 9.3 per 1000 py LOS AdjRR (95% CI) for LOS: 0.99 (0.80, 1.22) p = 0.90 UnadjRR (95%CI) for LOS: 0.97 (0.79, 1.19) p = 0.77</p>		<p><i>Subanalysis of patients with Isolated Systolic Hypertension</i></p>  <p><b>New diabetes</b> 20.1 per 1000 py ATN vs 12.6 per 1000 py LOS AdjHR (95% CI) for LOS: 0.62 (0.40, 0.97) p = 0.04 UnadjHR (95%CI) for LOS: 0.63 (0.40, 0.99) p = 0.04</p> <p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>New diabetes</b> 17.0 per 1000 py ATN vs 13.1 per 1000 py LOS AdjRR (95% CI) for LOS: 0.77 (0.64, 0.92) p = 0.005 UnadjRR (95%CI) for LOS: 0.77 (0.64, 0.92) p = 0.004</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>LIFE, 2003</b></p> <p><i>Subanalysis of subjects with and without clinically evident vascular disease</i> Devereux et al, 2003</p> <p>Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG</p> <p>ATN: Atenolol: Atenolol 50 mg; Atenolol 50 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5 mg; Atenolol 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB) LOS: Losartan: Losartan 50 mg; Losartan 50 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5 mg; Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (no ACE, angiotensin II type-1 receptor antagonists or BB)</p> <p>N: 9,222 in full trial (6,886 without clinically evident vascular disease at baseline)</p> <p>Mean 4.8 years</p> <p>Fair</p> <p>NOTE: Adjusted HRs are adjusted for degree of LVH and Framingham risk score at randomization Interaction between treatment and presence or absence of arterial disease was not statistically significant for primary endpoint</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>Total mortality</b> 15.9 per 1000 py ATN vs 13.5 per 1000 py LOS AdjHR (95% CI) for LOS: 0.85 (0.71, 1.02) p = 0.080</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>Total mortality</b> 31.7 per 1000 py ATN vs 28.5 per 1000 py LOS AdjHR (95% CI) for LOS: 0.94 (0.75, 1.16) p &gt; 0.2</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>MI</b> 6.0 per 1000 py ATN vs 6.8 per 1000 py LOS AdjHR (95% CI) for LOS: 1.14 (0.87, 1.49) p &gt; 0.2</p> <p></p> <p><b>Revascularization</b> 9.0 per 1000 py ATN vs 7.6 per 1000 py LOS AdjHR (95% CI) for LOS: 0.85 (0.67, 1.08) p = 0.18</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>MI</b> 17.7 per 1000 py ATN vs 16.3 per 1000 py LOS AdjHR (95% CI) for LOS: 0.97 (0.72, 1.31) p &gt; 0.2</p> <p></p> <p><b>Revascularization</b> 28.4 per 1000 py ATN vs 26.3 per</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>Stroke</b> 11.8 per 1000 py ATN vs 7.7 per 1000 py LOS AdjHR (95% CI) for LOS: 0.66 (0.53, 0.82) p &lt; 0.001</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>Stroke</b> 23.7 per 1000 py ATN vs 20.0 per 1000 py LOS AdjHR (95% CI) for LOS: 0.87 (0.67, 1.13) p &gt; 0.2</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>Hospitalization for Heart Failure</b> 4.4 per 1000 py ATN vs 4.7 per 1000 py LOS AdjHR (95% CI) for LOS: 1.06 (0.77, 1.46) p &gt; 0.2</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>Hospitalization for Heart Failure</b> 17.7 per 1000 py ATN vs 14.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.84 (0.62, 1.14) p &gt; 0.2</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>Primary composite endpoint of CV death, MI or stroke</b> 21.8 per 1000 py ATN vs 17.5 per 1000 py LOS AdjHR (95% CI) for LOS: 0.81 (0.69, 0.95) p = 0.008</p> <p></p> <p><b>CV mortality</b> 7.8 per 1000 py ATN vs 6.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.80 (0.62, 1.04) p = 0.092</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>Primary composite endpoint of CV death, MI or stroke</b> 48.6 per 1000 py ATN vs 43.0 per 1000 py LOS AdjHR (95% CI) for LOS: 0.93 (0.77, 1.11) p &gt; 0.2</p>		<p></p> <p><b>Patients with at least one adverse event of any type</b> 17.3% ATN vs 12.7% LOS p &lt; 0.001</p> <p></p> <p><b>Patients with at least one drug related adverse event</b> 10.2% ATN vs 6.0% LOS p &lt; 0.001</p> <p></p> <p><b>Patients with at least one serious drug related adverse event</b> 1.0% ATN vs 0.5% LOS p = 0.018</p> <p></p> <p><b>Asthenia or fatigue</b> 16.9% ATN vs 14.2% LOS p &lt; 0.002</p> <p></p> <p><b>Lower extremity edema</b> 13.6% ATN vs 11.5% LOS p &lt; 0.008</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		<p>1000 py LOS AdjHR (95% CI) for LOS: 0.98 (0.78, 1.25) p &gt; 0.2</p>			<p> <b>CV mortality</b> 19.8 per 1000 py ATN vs 18.0 per 1000 py LOS AdjHR (95% CI) for LOS: 0.95 (0.72, 1.25) p &gt; 0.2</p>		<p> <b>Dyspnea</b> 13.6% ATN vs 8.8% LOS p &lt; 0.001</p> <p> <b>Hyperglycemia</b> 6.7% ATN vs 5.4% LOS p = 0.023</p> <p> <b>Patients with at least one serious adverse event</b> 4.4% ATN vs 3.8% LOS p &gt; 0.2</p> <p> <b>Back pain</b> 10.0% ATN vs 12.0% LOS p = 0.009</p> <p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p> <b>New diabetes</b> 17.7 per 1000 py ATN vs 12.2 per 1000 py LOS AdjHR (95% CI) for LOS: 0.69 (0.57, 0.84) p &lt; 0.001</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
							<i>Subanalysis of subjects with clinically evident vascular disease</i>  <b>New diabetes</b> 16.4 per 1000 py ATN vs 15.5 per 1000 py LOS AdjHR (95% CI) for LOS: 0.97(0.69, 1.36) p > 0.2
<b>MAPHY</b>  Wilkstrand et al, 1988 Olsson et al, 1991 Wilkstrand et al, 1991  Adult males, ages 40 to 64, either previously treated patients or newly detected and untreated HTN  MET: Metoprolol: 200 mg/d DIUR: Diuretic: HCTZ 50 mg/d or bendroflumethiazide 5 mg/d  N: 3,234  Median 4.16 years  Fair  <i>There was a protocol change in MAPHY that occurred more than 2 years after the first patient was randomized that allowed for additional centers that could randomize patients to atenolol or diuretics. The original study protocol did not include atenolol as an optional BB. Pooled results from all metoprolol centers, all atenolol centers, and the propranolol center are published separately as HAPPHY</i>	At median 4.16 years  <b>Total mortality</b> 4.8 per 1000 py MET vs 9.3 per 1000 py DIUR % difference (95% CI): -48 (-68, -17) p=NR  At end of study (10.8 years)  <b>Total mortality</b> 8.0 per 1000 py MET vs 10.3 per 1000 py DIUR % difference: -22 p=0.028   <b>Total sudden mortality</b> 32 events MET vs 45 events DIUR p= 0.017	At 10.8 years  <b>Fatal CHD (composite of MI or sudden coronary death)</b> 36 events MET vs 43 events DIUR p = 0.048	At 10.8 years  <b>Fatal stroke</b> 2 events MET vs 9 events DIUR p = 0.043	At 10.8 years  <b>Fatal Heart Failure</b> 3 events MET vs 0 events DIUR p = NR	At median 4.16 years  <b>First CV event: definite non-fatal acute MI</b> 5.7 per 1000 py MET vs 7.0 per 1000 py DIUR p = NR   <b>First CV event: definite non-fatal silent MI</b> 4.8 per 1000 py MET vs 7.1 per 1000 py DIUR p = NR   <b>First CV event: definite non-fatal stroke</b> 2.7 per 1000 py MET vs 2.4 per 1000 py DIUR p = NR		

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
					 <b>First CV event, all definite events</b> 17.3 per 1000 py MET vs 22.3 per 1000 py DIUR RR (95% CI): 0.60 (0.44, 0.81) p = 0.0009   <b>First CV event, all definite and possible events</b> 23.3 per 1000 py MET vs 30.5 per 1000 py DIUR p = 0.0011   <b>First CV event: fatal coronary event</b> 3.7 per 1000 py MET vs 4.5 per 1000 py DIUR p = NR   <b>First CV event: fatal other CV event</b> 0.1 per 1000 py MET vs 0.5 per 1000 py DIUR p = NR   <b>First CV event: fatal stroke</b> 0.3 per 1000 py MET vs 0.9 per 1000 py DIUR p = NR		

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
					 <p><b>CV mortality</b> 2.6 per 1000 py MET vs 6.2 per 1000 py DIUR % difference: -58 p = NR</p>  <p><b>Sudden CV mortality</b> 2.1 per 1000 py MET vs 4.8 per 1000 py DIUR % difference: -56 p = NR</p> <p>At end of study (10.8 years)</p>  <p><b>First CV event, all definite events</b> MET vs. DIUR: RR (95% CI): 0.77 (0.61, 0.98) p=NR</p>  <p><b>CV mortality</b> 5.2 per 1000 py MET vs 7.1 per 1000 py DIUR % difference: -27 p = 0.012</p>  <p><b>Sudden CV mortality</b> 3.9 per 1000 py MET vs 5.6 per 1000 py DIUR % difference: -30 p = 0.017</p>		

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>IPPPSH, 1985</b></p> <p>Adults, age 40 to 64 years with seated DBPs of 100 to 125 mmHg, either untreated or receiving anti-HTN at study entry</p> <p>BB: Slow-release oxprenolol 160 mg QD Non-BB: placebo as sole anti-HTN treatment given or initial step in otherwise open anti-HTN regimen</p> <p>N: 6,708</p> <p>3 to 5 years (mean NR)</p> <p>Fair</p>	 <p><b>Total mortality</b> 8.3 per 1000 py BB vs 8.8 per 1000 py Non-BB RR (95% CI): 0.95 (0.73, 1.24) p = NR</p>	 <p><b>Non-fatal MI</b> 4.4 per 1000 py BB vs 5.2 per 1000 py Non-BB RR (95% CI): 0.84 (0.59, 1.20) p = NR</p>  <p><b>All MI</b> 4.7 per 1000 py BB vs 5.7 per 1000 py Non-BB RR (95% CI): 0.83 (0.59, 1.16) p = NR</p>  <p><b>All cardiac events</b> 7.6 per 1000 py BB vs 8.4 per 1000 py Non-BB RR (95% CI): 0.91 (0.69, 1.20) p = NR</p>  <p><b>Fatal MI</b> (first event analysis) 0.3 per 1000 py BB vs 0.5 per 1000 py Non-BB RR (95% CI): 0.66 (0.19, 2.34) p = NR</p>  <p><b>Fatal MI</b> (includes deaths following non-fatal events)</p>	 <p><b>Non-fatal CVA</b> 3.1 per 1000 py BB vs 3.0 per 1000 py Non-BB RR (95% CI): 1.04 (0.67, 1.63) p = NR</p>  <p><b>All stroke (CVA)</b> 3.5 per 1000 py BB vs 3.6 per 1000 py Non-BB RR (95% CI): 0.97 (0.64, 1.47) p = NR</p>  <p><b>Fatal CVA</b> (first event analysis) 0.4 per 1000 py BB vs 0.6 per 1000 py Non-BB RR (95% CI): 0.62 (0.20, 1.90) p = NR</p>  <p><b>Fatal CVA</b> (includes deaths following non-fatal events) 0.4 per 1000 py BB vs 0.8 per 1000 py Non-BB RR (95% CI): 0.50 (0.17, 1.47) p = NR</p>		 <p><b>Critical events of sudden cardiac death, fatal or non-fatal definite MI and cerebrovascular accidents</b> 11.1 per 1000 py BB vs 12.0 per 1000 py Non-BB RR (95% CI): 0.99 (0.79, 1.24) p = NR</p>	 <p><b>Impaired renal function (creatinine &gt;177 µmol/l and urea &gt;10 mmol/l)</b> 15 events BB vs 23 events Non-BB p = NR</p>	 <p><b>Cold extremities</b> 35.8 per 1000 patients BB vs 19.2 per 1000 patients Non-BB p &lt; 0.01</p>  <p><b>Dyspepsia</b> 114.9 per 1000 patients BB vs 101.5 per 1000 patients Non-BB p &lt; 0.05</p>  <p><b>Constipation</b> 349.4 per 1000 patients BB vs 324.3 per 1000 patients Non-BB p &lt; 0.05</p>  <p><b>Increased sweating</b> 494.6 per 1000 patients BB vs 464.2 per 1000 py Non-BB p &lt; 0.05</p>  <p><b>Serum potassium &lt;3.0 mmol/l on at least 1 occasion during study</b> 2.6% BB vs 4.7% Non-BB p = NR</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		<p>0.3 per 1000 py BB vs 0.8 per 1000 py Non-BB RR (95% CI): 0.40 (0.13, 1.29) p = NR</p> <p> <b>Sudden death</b> (first event analysis) 2.9 per 1000 py BB vs 2.7 per 1000 py Non-BB RR (95% CI): 1.08 (0.68, 1.72) p = NR</p> <p> <b>Sudden death</b> (includes deaths following non-fatal events) 2.8 per 1000 py BB vs 2.8 per 1000 py Non-BB RR (95% CI): 1.01 (0.63, 1.60) p = NR</p>					<p> <b>Serum potassium &lt;3.5 mmol/l on at least 1 occasion during study</b> 18% BB vs 29% Non-BB p &lt; 0.001</p> <p> <b>Impotence and libido decrease</b> 79.8 per 1000 patients BB vs 100.1 per 1000 patients Non-BB p &lt; 0.05</p> <p> <b>Anxiety, depression, other emotional disorders</b> 148.5 per 1000 patients BB vs 176.5 per 1000 patients Non-BB p &lt; 0.01</p> <p> <b>Headache</b> 260.3 per 1000 patients BB vs 312.1 per 1000 patients Non-BB p &lt; 0.01</p> <p> <b>Dizziness</b> 142.5 per 1000 patients BB vs</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
							154.8 per 1000 patients Non-BB $p < 0.05$  <b>Dry mouth</b> 423.2 per 1000 patients BB vs 478.3 per 1000 patients Non-BB $p < 0.01$  <b>Frequency and nocturia</b> 544.9 per 1000 patients BB vs 593.3 per 1000 patients Non-BB $p < 0.01$
<b>MRC, 1985</b> Adults, ages 35-64 years, with mild to moderate HTN PRO: Propranolol: 240 mg QD BEN: Bendrofluazide: 10 mg QD N: 17,354 5.5 years Fair	 <b>All deaths</b> 5.5 per 1000 py PRO vs 6.0 per 1000 py BEN $p = 0.71$	 <b>Coronary events</b> 4.8 per 1000 py PRO vs 5.6 per 1000 py BEN $p = 0.24$	 <b>Strokes</b> 1.9 per 1000 py PRO vs 0.8 per 1000 py BEN $p = 0.002$		 <b>All CV events</b> 6.7 per 1000 py PRO vs 6.6 per 1000 py BEN $p = 0.76$		
<b>HAPPY, 1987</b> Adult men, ages 40-64 years, with mild to moderate HTN BB: Beta Blocker: 100 mg atenolol or 200 mg QD metoprolol DIUR: Diuretic: 50 mg HCTZ or 5 mg bendroflumethazide N: 6,569	 <b>All deaths</b> OR (95% CI) for DIUR: 1.06 (0.80, 1.41) $p > 0.20$	 <b>Non-fatal MI</b> OR (95% CI) for DIUR: 0.90 (0.66, 1.23) $p > 0.20$	 <b>Non-fatal stroke</b> OR (95% CI) for DIUR: 1.11 (0.68, 1.83) $p > 0.20$	 <b>Heart failure</b> 2.6 per 1000 py BB vs 1.8 per 1000 py DIUR $p = \text{NS (value NR)}$	 <b>Patients with an endpoint of death, non-fatal MI, or non-fatal stroke</b> OR (95% CI) for DIUR: 0.98 (0.80, 1.20) $p > 0.20$	 <b>Change in serum Cr from baseline, (<math>\mu\text{mol/l}</math>)</b> +4.0 BB vs +4.2 DIUR $p = \text{NS (value NR)}$	 <b>Reporting any symptoms related to drug at 12 month visit</b> 19.1% BB vs 16.8% DIUR $p < 0.001$

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>Mean 45.1 months</p> <p>Fair</p>		<p>  <b>Fatal and/or non-fatal CHD</b>  OR (95% CI) for DIUR:  0.88 (0.68, 1.14)  p &gt; 0.20</p> <p>  <b>Fatal CHD</b>  OR (95% CI) for DIUR:  0.93 (0.64, 1.37)  p &gt; 0.20</p>	<p>  <b>Fatal and/or non-fatal stroke</b>  OR (95% CI) for DIUR:  1.29 (0.82, 2.04)  p &gt; 0.20</p> <p>  <b>Fatal stroke</b>  0.24 per 1000 py BB vs 0.82 per 1000 py DIUR  OR (95% CI) for DIUR:  3.37 (0.96, 9.53)  p = 0.09</p>		<p>  <b>Total endpoints of death, non-fatal MI, or non-fatal stroke</b>  OR (95% CI) for DIUR:  1.00 (0.83, 1.21)  p &gt; 0.20</p> <p>  <b>Other deaths</b>  OR (95% CI) for DIUR:  1.06 (0.69, 1.64)  p &gt; 0.20</p>		<p>  <b>Cold hands and feet</b>  21.4% BB vs 12.7% DIUR  p &lt; 0.001</p> <p>  <b>Unusual tiredness</b>  18.2% BB vs 15.4% DIUR  p &lt; 0.005</p> <p>  <b>Developed DM</b>  6.9 per 1000 py BB vs 6.1 per 1000 py DIUR  p = NS</p> <p>  <b>Dry mouth</b>  12.5% BB vs 15.4% DIUR  p &lt; 0.002</p>

## Exhibit K: Evidence from randomized controlled trials of initial antihypertensive drug therapy with calcium channel blockers versus other drugs

**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** *Green* = Statistically significant where the CCB did better ( $p < 0.05$ ) *Red* = Statistically significant where the CBB did worse *Yellow* =  $p \geq 0.05$  and  $\leq 0.10$  *Clear* =  $p > 0.10$  *Blue* =  $p$  value not reported

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>ALLHAT, 2002</b></p> <p>Adults, <math>\geq 55</math> years of age with at least one additional risk factor for CHD</p> <p>AML: Amlodipine: 2.5, 5, and 10 mg QD                      LIS: Lisinopril: 10, 20, and 40 mg QD                      CHL: Chlorthalidone: 12.5, 25 mg QD</p> <p>N: 33,357</p> <p>Mean 4.9 years</p> <p>Good</p>	<p>  <b>All-cause mortality</b>                      AML vs CHL:                      RR (95% CI) for AML:                      0.96 (0.89, 1.02)  <math>p = 0.20</math></p>	<p>  <b>CHD (fatal CHD and nonfatal MI)</b>                      AML vs CHL:                      RR (95% CI) for AML:                      0.98 (0.90, 1.07)  <math>p = 0.65</math></p> <p>  <b>Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)</b>                      AML vs. CHL:                      RR (95% CI) for AML:                      1.00 (0.94, 1.07)  <math>p = 0.97</math></p> <p>  <b>Coronary revascularization</b>                      AML vs. CHL:                      RR (95% CI) for AML:                      1.09 (1.00, 1.20)  <math>p = 0.06</math></p> <p></p>	<p>  <b>Stroke</b>                      AML vs. CHL:                      RR (95% CI) for AML:                      0.93 (0.82, 1.06)  <math>p = 0.28</math></p> <p>  <b>Death from stroke</b>                      AML vs. CHL:                      1.4 per 100 persons AML vs 1.4 per 100 persons CHL                      RR (95% CI): NR  <math>p = 0.71</math></p>	<p>  <b>HF</b>                      AML vs. CHL:                      RR (95% CI) for AML:                      1.38 (1.25, 1.52)  <math>p &lt; 0.001</math></p> <p>  <b>Hospitalized/fatal HF</b>                      AML vs. CHL:                      RR (95% CI) for AML:                      1.35 (1.21, 1.50)  <math>p &lt; 0.001</math></p> <p>  <b>HF death</b>                      AML vs CHL:                      1.4 per 100 persons AML vs 1.0 per 100 persons CHL                      RR (95% CI): NR  <math>p = 0.17</math></p>	<p>  <b>Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)</b>                      AML vs. CHL:                      RR (95% CI) for AML:                      1.04 (0.99, 1.09)  <math>p = 0.12</math></p> <p>  <b>Cardiovascular death</b>                      AML vs. CHL:                      8.5 per 100 persons AML vs 8.0 per 100 persons CHL                      RR (95% CI): NR  <math>p = 0.76</math></p> <p>  <b>Other CVD death</b>                      AML vs. CHL:                      1.7 per 100 persons AML vs 1.4 per 100 persons CHL                      RR (95% CI): NR  <math>p = 0.46</math></p>	<p>  <b>ESRD</b>                      AML vs. CHL:                      RR (95% CI) for AML:                      1.12 (0.89, 1.40)  <math>p = 0.33</math></p> <p>  <b>Kidney disease death</b>                      AML vs. CHL:                      0.5 per 100 persons AML vs 0.4 per 100 persons CHL                      RR (95% CI): NR  <math>p = 0.68</math></p>	<p>  <b>Angioedema</b>  <math>&lt;0.1\%</math> AML vs <math>0.4\%</math> LIS vs <math>0.1\%</math> CHL  <math>p = \text{NR}</math></p> <p>At 4 years</p> <p>  <b>Fasting glucose progressing to <math>\geq 126</math> mg/dL among non-DM with baseline fasting glucose <math>&lt; 126</math> mg/dL:</b>  <math>9.8\%</math> AML vs <math>11.6\%</math> CHL  <math>p = 0.04</math></p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		<p><b>Hospitalized or treated PAD</b> AML vs. CHL: RR (95% CI) for AML: 0.87 (0.75, 1.01) p = 0.06</p>  <p><b>MI death</b> AML vs. CHL: 2.3 per 100 persons AML vs 2.4 per 100 persons CHL RR (95% CI): NR p = 0.66</p>  <p><b>Definite CHD death</b> AML vs. CHL: 1.2 per 100 persons AML vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.88</p>  <p><b>Possible CHD death</b> AML vs. CHL: 1.1 per 100 persons AML vs 1.1 per 100 persons CHL RR (95% CI): NR p = 0.62</p>					
<p><b>ALLHAT, 2006</b> Adults, ≥ 55 years of age with at least one additional risk factor for CHD AML: Amlodipine: 2.5, 5, and 10 mg QD LIS: Lisinopril: 10, 20, and 40 mg QD N: 18, 102</p>	 <p><b>All-cause mortality</b> LIS vs AML: RR (95% CI): 1.05 (0.97, 1.13) p = 0.214</p>	 <p><b>CHD (fatal CHD and nonfatal MI)</b> LIS vs AML: RR (95% CI): 1.01 (0.91, 1.11) p = 0.854</p>	 <p><b>Stroke</b> LIS vs AML: RR (95% CI): 1.23 (1.08, 1.41) p = 0.003</p>	 <p><b>HF</b> LIS vs AML: RR (95% CI): 0.87 (0.78, 0.96) P = 0.007</p>	 <p><b>Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina,</b></p>	 <p><b>ESRD</b> LIS vs AML: RR (95% CI): 0.99 (0.77, 1.26) p = 0.929</p>	 <p><b>Angioedema</b> 0.03% AML vs 0.42% LIS p &lt;0.001</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>Mean 4.9 years</p> <p>Fair</p>		<p></p> <p><b>Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)</b>            LIS vs AML:            RR (95% CI):            1.04 (0.97, 1.12)            p = 0.243</p> <p></p> <p><b>Coronary revascularization</b>            LIS vs AML:            RR (95% CI):            1.00 (0.91, 1.11)            p = 0.943</p> <p></p> <p><b>Hospitalized or fatal PAD</b>            LIS vs AML:            RR (95% CI):            1.19 (1.01, 1.40)            p = 0.036</p>		<p></p> <p><b>Hospitalized/fatal HF</b>            LIS vs AML:            RR (95% CI):            0.81 (0.72, 0.92)            p &lt;0.001</p>	<p><b>treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)</b>            LIS vs AML:            RR (95% CI): 1.06 (1.00, 1.12)            p = 0.047</p>		<p></p> <p><b>Hospitalization for GI bleeding</b>            8.0 per 100 AML vs 9.6 per 100 LIS            p = 0.04</p> <p>At 4 years</p> <p></p> <p><b>DM (&gt;=7.0 mmol/L) if no DM at baseline</b>            10.4% AML vs 9.4% LIS            p = 0.30</p>
<p><b>CASE-J, 2008</b></p> <p>Adults with high CVD risk</p> <p>AML: Amlodipine 2.5-10 mg/day            CAN: Candesartan 4-12 mg/day</p> <p>N: 4,728</p> <p>Mean 3.2 years</p> <p>Good</p>	<p></p> <p><b>All-cause death</b>            11.1 per 1000 p-y            AML vs 9.4 per 1000 p-y CAN            HR (95% CI): NR            p = NS</p>	<p></p> <p><b>Acute MI</b>            HR (95% CI) for CAN:            0.95 (0.49, 1.84)            p = 0.870</p> <p></p> <p><b>Sudden death</b>            HR (95% CI) for</p>	<p></p> <p><b>Cerebrovascular events</b>            HR (95% CI) for CAN:            1.23 (0.85, 1.78)            p = 0.282</p> <p></p> <p><b>Stroke</b></p>	<p></p> <p><b>Heart Failure</b>            HR (95% CI) for CAN:            1.25 (0.65, 2.42)            p = 0.498</p>	<p></p> <p><b>Primary composite endpoint</b>            HR (95% CI) for CAN:            1.01 (0.79, 1.28)            p = 0.969</p> <p></p> <p><b>Cardiac events</b>            HR (95% CI) for CAN:</p>	<p></p> <p><b>Renal events</b>            HR (95% CI) for CAN:            0.70 (0.39, 1.26)            p = 0.230</p> <p></p> <p><b>Creatinine abnormality</b></p>	<p></p> <p><b>New onset diabetes</b>            HR (95% CI) for CAN:            0.64 (0.43, 0.97)            p=0.033</p> <p></p> <p><b>Hyperkalemia</b></p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		CAN: 0.73 (0.34, 1.60) p = 0.434	HR (95% CI) for CAN: 1.28 (0.88, 1.88) p = 0.198  <b>TIA</b> HR (95% CI) for CAN: 0.50 (0.09, 2.73) p = 0.414		0.92 (0.61, 1.39) p = 0.680  <b>Peripheral vascular events</b> HR (95% CI) for CAN: 1.57 (0.61, 4.05) p = 0.348	HR (95% CI) for CAN: 0.73 (0.40, 1.31) p = 0.287  <b>ESRD</b> HR (95% CI) for CAN: 0.40 (0.13, 1.29) p = 0.112	0.3% AML vs 1.0% CAN p = NR
<b>ASCOT-BPLA, 2005</b>  Adults, age 40-79 years, with HTN and at least 3 CV risk factors  AML: Amlodipine based regimen: Step 1: Amlodipine 5 mg Step 2: Amlodipine 10 mg Step 3: Amlodipine 10 mg + perindopril 4 mg Step 4: Amlodipine 10 mg + perindopril 8 mg (2 x 4 mg) Step 5: Amlodipine 10 mg + perindopril 8 mg + doxazosin GITS 4 mg Step 6: Amlodipine 10 mg + perindopril 8 mg + doxazosin GITS 8 mg  ATN: Atenolol-based regimen: Step 1: Atenolol 50 mg Step 2: Atenolol 100 mg Step 3: Atenolol 100 mg + bendroflumethiazide 1.25 mg + potassium Step 4: Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium Step 5: Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium + doxazosin GITS 4 mg Step 6: Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium + doxazosin GITS 8 mg  N: 19,342  Median 5.5 years	 <b>All-cause mortality</b> HR (95% CI) for AML: 0.89 (0.81, 0.99) p = 0.0247	 <b>Total coronary endpoint</b> HR (95% CI) for AML: 0.87 (0.79, 0.96) p = 0.0070  <b>Silent MI</b> HR (95% CI) for AML: 1.27 (0.80, 2.00) p = 0.3089  <b>PAD</b> HR (95% CI) for AML: 0.65 (0.52, 0.81) p = 0.0001	 <b>Fatal and non-fatal stroke</b> HR (95% CI) for AML: 0.77 (0.66, 0.89) p = 0.0003	 <b>Fatal and non-fatal HF</b> HR (95% CI) for AML: 0.84 (0.66, 1.05) p = 0.1257	 <b>Non-fatal MI (including silent MI) and fatal CHD</b> HR (95% CI) for AML: 0.90 (0.79, 1.02) p = 0.1052  <b>Non-fatal MI (excluding silent MI) and fatal CHD</b> HR (95% CI) for AML: 0.87 (0.76, 1.00) p = 0.0458  <b>Total CV events and procedures</b> HR (95% CI) for AML: 0.84 (0.78, 0.90) p < 0.0001  <b>Composite of primary endpoints of non-fatal MI including silent MI and fatal CHD plus coronary revascularization</b>	 <b>Cough</b> 19% AML vs 8% ATN p < 0.0001  <b>Peripheral edema</b> 23% AML vs 6% ATN p < 0.0001  <b>Joint swelling</b> 14% AML vs 3% ATN p < 0.0001  <b>Development of DM</b> HR (95% CI) for AML: 0.70 (0.63, 0.78) p < 0.0001  <b>Dizziness</b>	

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
Good					<p><b>procedures</b> HR (95% CI) for AML: 0.86 (0.77, 0.96) p = 0.0058</p> <p> <b>CV death, MI and stroke</b> HR (95% CI) for AML: 0.84 (0.76, 0.92) p = 0.0003</p> <p> <b>CV mortality</b> HR (95% CI) for AML: 0.76 (0.65, 0.90) p = 0.0010</p>		<p>12% AML vs 16% ATN p &lt; 0.0001</p> <p> <b>Dyspnea</b> 6% AML vs 10% ATN p &lt; 0.0001</p> <p> <b>Fatigue</b> 8% AML vs 16% ATN p &lt; 0.0001</p>
<p><b>VALUE, 2004</b></p> <p>Adults, ≥50 years with treated or untreated HTN and predefined combinations of CV risk factors or CVD</p> <p>AML: Amlodipine step-up therapy Step 1: amlodipine 5 mg Step 2: amlodipine 10 mg Step 3: amlodipine 10 mg + HCTZ 12.5 mg Step 4: amlodipine 10 mg + HCTZ 25 mg Step 5: other HTN drugs</p> <p>VAL: Valsartan step-up therapy Step 1: valsartan 80 mg Step 2: valsartan 160 mg Step 3: valsartan 160 mg + HCTZ 12.5 mg Step 4: valsartan 160 mg + HCTZ 25 mg Step 5: other HTN drugs</p> <p>N: 15,313</p> <p>Mean exposure to study medication of 3.6 years; mean 4.2 years F/U</p> <p>Good</p>	<p> <b>All-cause death</b> HR (95% CI) for VAL: 1.04 (0.94, 1.14) p = 0.45</p>	<p> <b>Fatal and non-fatal MI</b> HR (95% CI) for VAL: 1.19 (1.02, 1.38) p = 0.02</p>	<p> <b>Fatal and non-fatal stroke</b> HR (95% CI) for VAL: 1.15 (0.98, 1.35) p = 0.08</p>	<p> <b>Fatal and non-fatal HF</b> HR (95% CI) for VAL: 0.89 (0.77, 1.03) p = 0.12</p>	<p> <b>Primary composite of time to first cardiac event</b> HR (95% CI) for VAL: 1.04 (0.94, 1.15) p = 0.49</p> <p> <b>Cardiac morbidity</b> HR (95% CI) for VAL: 1.02 (0.91, 1.15) p = 0.71</p> <p> <b>Cardiac mortality</b> HR (95% CI) for VAL: 1.01 (0.86, 1.18) p = 0.90</p>	<p> <b>New onset DM</b> OR (95% CI) for VAL: 0.77 (0.69, 0.86) p &lt; 0.0001</p>	

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>NORDIL, 2000</b></p> <p>Adults 50-74 years old with previously treated or untreated primary HTN</p> <p>DIL: Diltiazem 180-360 mg daily DIUR or BB: Thiazide diuretic or BB (dose NR) in first step; diuretic and BB combined in second step</p> <p>N: 10,916</p> <p>Mean 4.5 years</p> <p>Good</p>	 <b>Total mortality</b> RR (95% CI) for DIL: 1.00 (0.83, 1.20) p = 0.99	 <b>All MI</b> RR (95% CI) for DIL: 1.16 (0.94, 1.44) p = 0.17   <b>Fatal MI</b> RR (95% CI) for DIL: 1.10 (0.64, 1.88) p = 0.74   <b>All Cardiac Events</b> RR (95% CI) for DIL: 1.04 (0.91, 1.18) p = 0.57	 <b>All Stroke</b> RR (95% CI) for DIL: 0.80 (0.65, 0.99) p = 0.04   <b>Fatal Stroke</b> RR (95% CI) for DIL: 0.96 (0.52, 1.74) p = 0.89   <b>All Stroke plus TIA</b> RR (95% CI) for DIL: 0.84 (0.70, 1.01) p = 0.07	 <b>CHF</b> RR (95% CI) for DIL: 1.16 (0.81, 1.67) p = 0.42	 <b>Primary endpoint (composite of fatal and nonfatal stroke, fatal and nonfatal MI, and other CV death)</b> RR (95% CI) for DIL: 1.00 (0.87, 1.15) p = 0.97   <b>CV Death</b> RR (95% CI) for DIL: 1.11 (0.87, 1.43) p = 0.41		 <b>Headaches</b> 8.5% DIL vs 5.7% DIUR or BB p < 0.001   <b>Diabetes</b> RR (95% CI) for DIL: 0.87 (0.73, 1.04) p = 0.14   <b>Fatigue</b> 4.4% DIL vs 6.5% DIUR or BB p < 0.001   <b>Dyspnea</b> 2.9% DIL vs 3.9% DIUR or BB p = 0.006   <b>Impotence</b> 2.3% DIL vs 3.7% DIUR or BB p < 0.001
<p><b>STOP Hypertension-2, 1999</b></p> <p>Adults 70-84 years old with HTN</p> <p>CCB: Calcium channel blockers: felodipine 2.5 mg QD or isradipine 2.5 mg QD ACE: ACE inhibitors: enalapril 10 mg, or</p>	 <b>Total mortality</b> ACE vs. CCB: RR (95% CI) for ACE: 1.03 (0.69, 1.19) p = 0.71	 <b>All MI</b> ACE vs CCB: RR (95% CI) for ACE: 0.77 (0.61, 0.96)	 <b>All stroke</b> ACE vs CCB: RR (95% CI) for ACE: 1.02 (0.64, 1.24)	 <b>Frequency CHF</b> ACE vs CCB: RR (95% CI) for ACE: 0.76 (0.63, 0.97)	 <b>All major CV events</b> ACE vs. CCB: RR (95% CI) for ACE: 0.95 (0.63, 1.06) p = 0.42		 <b>Frequency of DM</b> ACE vs. CCB: RR (95% CI) for ACE: 0.96 (0.74, 1.31)

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>lisinopril 10 mg BB or DIUR: atenolol 50 mg, or metoprolol 100 mg, or pindolol 5 mg, or fixed ratio HCTZ 25 mg plus amiloride 2.5 mg</p> <p>N: 6,614</p> <p>Mean F/U unclear; authors report study duration of 60 months; max BP measurement reported is 54 months, and Kaplan-Meier curves extend to 6 years</p> <p>Good</p>	 <b>Total mortality</b> CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.99 (0.66, 1.15) p = 0.90	<p>p = 0.016</p>  <b>All MI</b> CCB vs. BB or DIUR: RR (95% CI) for CCB: 1.18 (0.95, 1.47) p = 0.13  <b>Sudden death</b> 4.7 per 1000 p-y CCB vs 5.3 per 1000 p-y ACE vs 4.8 per 1000 p-y BB or DIUR p = NR  <b>Fatal MI</b> 5.3 per 1000 p-y CCB vs 4.3 per 1000 p-y ACE vs 4.9 per 1000 p-y BB or DIUR p = NR	<p>p = 0.64</p>  <b>All stroke</b> CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.66 (0.73, 1.06) p = 0.16  <b>Fatal stroke</b> 4.2 per 1000 p-y CCB vs 4.5 per 1000 p-y ACE vs 4.6 per 1000 p-y BB or DIUR p = NR	<p>p = 0.025</p>  <b>Frequency CHF</b> CCB vs BB or DIUR: RR (95% CI) for CCB: 1.06 (0.67, 1.31) p = 0.56	 <b>All major CV events</b> CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.99 (0.67, 1.12) p = 0.65  <b>CV mortality</b> ACE vs CCB RR (95% CI) for ACE: 1.04 (0.66, 1.26) p = 0.67  <b>CV mortality</b> CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.97 (0.60, 1.17) p = 0.72  <b>Other CV mortality</b> 5.0 per 1000 p-y vs 6.2 per 1000 p-y vs BB or DIUR: 5.6 per 1000 p-y p = NR		<p>p = 0.91</p>  <b>Frequency of DM</b> CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.97 (0.73, 1.29) p = 0.63  <b>Ankle edema</b> 25.5% CCB vs 8.7% ACE vs 8.5% BB or DIUR p = NR  <b>Dry cough</b> 30.1% ACE vs 5.7% CCB vs 3.7% BB or DIUR p = NR  <b>Dizziness</b> 24.5% CCB vs 27.7% ACE vs 27.8% BB or DIUR p = NR
<p><b>MIDAS, 1996</b></p> <p>Adults, ages ≥ 40 years, without hyperlipidemia, and presence of IMT 1.3-3.5 mm in the carotid artery; fasting TC and LDL-C ≤6.21 and 4.14 mmol/L (240 and 160 mg/dL) respectively</p> <p>ISR: Isradipine: 2.5 to 5.0 mg BID HCTZ: Hydrochlorothiazide: 12.5 to 25 mg BID</p> <p>N: 883</p>	 <b>All-cause mortality</b> RR (95% CI) for ISR: 0.89 (0.35, 2.28) p = 0.81	 <b>MI</b> RR (95% CI) for ISR: 1.20 (0.37, 3.89) p = 0.77 	 <b>Stroke</b> RR (95% CI) for ISR: 2.00 (0.50, 7.93) p = 0.32	 <b>CHF</b> RR (95% CI) for ISR: NR p = 0.16	 <b>Any major vascular event</b> RR (95% CI) for ISR: 1.78 (0.94, 3.38) P = 0.07 		 <b>CV-related adverse reactions</b> 3.0% ISR vs 0.9% HCTZ p = NR

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>3 years</p> <p>Fair</p>		<p><b>CABG</b> RR (95% CI) for ISR: 1.00 (0.32, 3.07) p = 0.97</p> <p></p> <p><b>Coronary angioplasty</b> RR (95% CI) for ISR: 4.99 (0.59, 42.53) p = 0.10</p> <p></p> <p><b>Sudden death</b> RR (95% CI) for ISR: 1.00 (0.14, 7.05) p &gt; 0.99</p>			<p><b>Major vascular events and procedures</b> RR (95% CI) for ISR: 1.58 (0.90, 2.76) p = 0.10</p> <p></p> <p><b>Other CVD death</b> HCTZ: 1 (0.22) RR (95% CI) for ISR: 1.00 (0.06, 15.90) p &gt; 0.99</p>		
<p><b>ELSA, 2002</b></p> <p>Adults, age 45 to 75 years, with fasting serum total cholesterol <math>\leq</math>320 mg/dl, fasting serum triglycerides <math>\leq</math>300 mg/dl, serum Cr <math>\leq</math>1.7 mg/dl, and a readable ultrasound carotid artery scan with maximum IMT no greater than 4.0 mm</p> <p>LAC: Lacidipine 4-6 mg/day ATN: Atenolol 50-100 mg/day</p> <p>N: 2,334</p> <p>Mean 3.75 years</p> <p>Fair</p>	<p></p> <p><b>All death</b> 3.59 per 1000 p-y LAC vs 4.68 per 1000 p-y ATN p = NS</p>	<p></p> <p><b>Fatal and non-fatal MI</b> 4.97 per 1000 p-y LAC vs 4.68 per 1000 p-y ATN p = NS</p>	<p></p> <p><b>Fatal and non-fatal Stroke</b> 2.49 per 1000 p-y LAC vs 3.86 per 1000 p-y ATN p = NS</p>		<p></p> <p><b>Major CV events</b> 7.46 per 1000 p-y LAC vs 9.09 per 1000 p-y ATN p = NS</p> <p></p> <p><b>Minor CV events</b> 12.42 per 1000 p-y LAC vs 11.59 per 1000 p-y ATN p = NS</p> <p></p> <p><b>All major and minor CV events</b> 19.04 per 1000 p-y LAC vs 19.85 per 1000 p-y ATN p = NS</p> <p></p>		

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
					<b>CV death</b> 1.10 per 1000 p-y LAC vs 2.20 per 1000 p-y ATN p = NS		
<b>SHELL, 2003</b>  Adults ≥ 60 years with isolated systolic HTN  LAC: Lacidipine: 4, 6 mg QD CHL: Chlorthalidone: 12.5, 25 mg QD  N: 1,882  Median 32 months (95% CI, 30-33 months)  Fair  Panel Comments: Trial underpowered, 4800 needed over 5 years to achieve 80% power for primary outcome, but only 1882 patients randomized	 <b>All-cause mortality</b> HR (95% CI) for LAC: 1.23 (0.97, 1.57) p = 0.09	 <b>Fatal and non-fatal MI</b> HR (95% CI) for LAC: 0.85 (0.39, 1.83) p = 0.67   <b>Sudden death</b> HR (95% CI) for LAC: 1.22 (0.58, 2.53) p = 0.60   <b>Revascularization</b> HR (95% CI) for LAC: 0.50 (0.09, 2.70) p = 0.41	 <b>Fatal and non-fatal stroke</b> HR (95% CI) for LAC: 0.96 (0.61, 1.51) p = 0.87   <b>TIA</b> HR (95% CI) for LAC: 1.14 (0.54, 2.40) p = 0.72	 <b>Fatal and non-fatal HF</b> HR (95% CI) for LAC: 1.20 (0.65, 2.20) p = 0.56	 <b>Composite primary endpoint</b> HR (95% CI) for LAC: 1.01 (0.75, 1.36) p = 0.94		 <b>Orthostatic hypotension</b> 1.9% LAC vs 2.5% CHL p = NR   <b>Edema</b> 14.3% LAC vs 4.9% CHL p = NR   <b>Cough</b> 3.5% LAC vs 4.0% CHL p = NR   <b>Dizziness</b> 12.7% LAC vs 12.4% CHL p = NR   <b>Fatigue</b> 13.7% LAC vs 20.5% CHL p = NR
<b>JMIC-B, 2004</b>  Adults, ages <75 years with HTN and CAD	 <b>Totally mortality</b> RR (95% CI) for NIF:	 <b>MI</b> RR (95% CI) for NIF:	 <b>Cerebrovascular accidents</b>	 <b>HF requiring hospitalization</b>	 <b>Cardiac events</b> RR (95% CI) for NIF:	 <b>Worsening of renal dysfunction</b>	<i>Withdrawals by AE</i> 

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>NIF: Nifedipine long-acting 10-20 mg BID ACE: ACE inhibitor: enalapril, 5-10 mg, or imidapril 5-10 mg, or lisinopril 10-20 mg</p> <p>N: 1,650</p> <p>Median 35.7 months</p> <p>Fair</p>	0.76 (0.35, 1.63) p = 0.48	<p>1.31 (0.63, 2.74) p = 0.47</p> <p> <b>Coronary intervention</b> RR (95% CI) for NIF: 1.04 (0.76, 1.43) p = 0.81</p> <p> <b>Sudden death/cardiac death</b> RR (95% CI) for NIF: 0.96 (0.31, 3.04) p = 0.95</p> <p> <b>Non-cardiac death</b> RR (95% CI) for NIF: 0.64 (0.23, 1.81) p = 0.40</p>	RR (95% CI) for NIF: 1.00 (0.50, 2.02) p = 0.99	RR (95% CI) for NIF: 1.25 (0.52, 2.98) p = 0.62	1.05 (0.81, 1.37) p = 0.75	<p><b>(serum Cr &gt;353.6 μmol/l)</b> RR (95% CI) for NIF: 2.70 (0.54, 13.49) p = 0.23</p>	<p><b>Hypotension</b> 1.0% NIF vs 0.2% ACE p &lt; 0.01</p> <p> <b>Edema</b> 0.8% NIF vs 0% ACE p &lt; 0.01</p> <p> <b>Facial erythema, hot flushes</b> 0.7% NIF vs 0% ACE p &lt; 0.05</p> <p> <b>Dry cough</b> 0% NIF vs 7.3% ACE p &lt; 0.01</p>
<p><b>INSIGHT, 2000</b></p> <p>Men and women age 55-80 years, high risk patients with HTN; one additional CV risk factor</p> <p>NIF: Nifedipine: 30, 60 mg QD Co-am: Co-amilozide: HCTZ 25 mg and amloride 2.5 mg QD or doubling the dose of both drugs to HCTZ 50 mg QD and amloride 5 mg QD</p> <p>N: 6,321</p> <p>Maximum of 51 months F/U; BP outcomes reported at 48 months</p>	<p> <b>All deaths (first event)</b> OR (95% CI): 1.01 (0.80, 1.27) p = 0.95</p>	<p> <b>Non-fatal MI</b> OR (95% CI): 1.09 (0.76, 1.58) p = 0.52</p> <p> <b>Fatal MI</b> OR (95% CI): 3.22 (1.18, 8.80) p = 0.017</p>	<p> <b>Non-fatal stroke</b> OR (95% CI): 0.87 (0.61, 1.26) p = 0.52</p> <p> <b>Fatal stroke</b> OR (95% CI): 1.09 (0.48, 2.48) p = 0.84</p>	<p> <b>Non-fatal HF</b> OR (95% CI): 2.20 (1.07, 4.49) p = 0.028</p> <p> <b>Fatal HF</b> OR (95% CI): 2.01 (0.18, 22.13) p = 0.63</p>	<p> <b>Primary outcome composite: death from any CV or cerebrovascular cause, together with non-fatal stroke, MI and HF</b> OR (95% CI): 1.11 (0.90, 1.36) p = 0.34</p>	<p> <b>Renal Failure</b> OR (95% CI): 0.62 (0.26, 1.49) p = 0.38</p>	<p> <b>All AEs</b> 49% NIF vs 42% Co-am p &lt; 0.0001</p> <p> <b>Peripheral edema</b> 28% NIF vs 4.3% Co-am p &lt; 0.0001</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
Good		<p><b>Sudden death</b> OR (95% CI): 0.74 (0.39, 1.39) p = 0.43</p>	<p><b>TIA</b> OR (95% CI): 1.00 (0.57, 1.75) p = 1.0</p>		<p> <b>Composite secondary outcomes: Primary outcomes plus non-CV deaths, renal failure, angina and TIA</b> OR (95% CI): 0.96 (0.83, 1.12) p = 0.62</p> <p> <b>Other CV death</b> OR (95% CI): 1.09 (0.50, 2.38) p = 0.85</p> <p> <b>CV Deaths</b> OR (95% CI): 1.16 (0.80, 1.69) p = 0.45</p> <p> <b>Non-fatal primary CV events</b> OR (95% CI): 1.08 (0.85, 1.38) p = 0.53</p> <p> <b>Non-fatal CV events</b> OR (95% CI):</p>		<p><b>Headache</b> 12% NIF vs 9.2% Co-am p &lt; 0.0002</p> <p> <b>GFR, mL/min</b> Co-am vs. NIF (95% CI): -2.3 (-3.8, 1.9) Co-amilozide lower than nifedipine p = NR</p> <p> <b>Serious adverse events</b> 25% NIF vs 28% Co-am p &lt; 0.02</p> <p> <b>Impaired renal function as an adverse event</b> 1.8% NIF vs 4.6% Co-am p &lt; 0.0001</p> <p> <b>DM reported as an adverse event</b> 3.0% NIF vs 4.3% Co-am p = 0.01</p> <p> <b>New onset DM</b></p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
					0.94 (0.78, 1.13) p = 0.50		<p><b>reported as an outcome, n (%)</b> 4.3% NIF vs 5.6% Co-am p = 0.02</p> <p> <b>Hyperglycemia</b> 5.6% NIF vs 7.7% Co-am p = 0.001</p> <p> <b>Hypokalemia</b> 1.9% NIF vs 6.2% Co-am p &lt; 0.0001</p> <p> <b>Hyponatremia</b> 8 events NIF vs 61 events Co-am p &lt; 0.0001</p> <p> <b>Dizziness</b> 8% NIF vs 10% Co-am p &lt; 0.006</p>
<p><b>MOSES, 2005</b></p> <p>Adults with HTN and history of a cerebrovascular event</p> <p>NIT: Nitrendipine 10 mg/day EPR: Eprosartan 600 mg/day</p> <p>N: 1,405</p> <p>Mean 2.5 years</p> <p>Fair</p> <p>Notes: IDR: incidence density ratio</p>	<p> <b>All cause death</b> HR (95% CI) for EPR: 1.07 (0.73, 1.56) p = 0.725</p>		<p> <b>Fatal and non-fatal cerebrovascular events (including recurrent events)</b> IDR (95% CI): 0.75 (0.58, 0.97) p = 0.026</p> <p> <b>First time occurrence of cerebrovascular</b></p>		<p> <b>Primary combined endpoint: cerebrovascular and CV events and non-CV death (including recurrent events)</b> IDR (95% CI): 0.79 (0.66, 0.96) p = 0.014</p> <p> <b>Fatal and non-fatal</b></p>		<p> <b>Dizziness /hypotension</b> 10.6% NIT vs 12.9% EPR p = NR</p> <p> <b>Pneumonia</b> 11.4% NIT vs 10.8% EPR p = NR</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
			<p><b>event</b> HR (95% CI) for EPR: 0.88 (0.65, 1.20) p = 0.425</p>		<p><b>CV events (including recurrent events)</b> IDR (95% CI): 0.75 (0.55, 1.02) p = 0.061</p> <p> <b>First time occurrence of CV event</b> HR (95% CI) for EPR: 0.69 (0.50, 0.97) p = 0.031</p>		<p> <b>Metabolic disorder</b> 5.9% NIT vs 5.5% EPR p = NR</p>
<p><b>CONVINCE, 2003</b></p> <p>Adults age &gt;55 with HTN and 1 or more additional risk factor for CVD</p> <p>VER: Controlled-onset extended-release verapamil 180-360 mg ATN or HCTZ: atenolol 50-100 mg QD or HCTZ 12.5-25 mg QD</p> <p>N:16,602</p> <p>Median F/U 3 years</p> <p>Fair</p> <p>Panel Comments: Sponsor closed study 2 years earlier than planned for "commercial reasons"</p>	<p> <b>Death</b> HR (95% CI) for VER: 1.08 (0.93, 1.26) p = 0.32</p>	<p> <b>Fatal or nonfatal MI</b> HR (95% CI) for VER: 0.82 (0.65, 1.03) p = 0.09</p> <p> <b>Cardiac revascularization/ cardiac transplant</b> HR (95% CI) for VER: 1.01 (0.82, 1.26) p = 0.91</p>	<p> <b>Fatal or nonfatal stroke</b> HR (95% CI) for VER: 1.15 (0.90, 1.48) p = 0.26</p> <p> <b>TIA or carotid endarterectomy</b> HR (95% CI) for VER: 0.87 (0.66, 1.15) p = 0.33</p>	<p> <b>Heart failure</b> HR (95% CI) for VER: 1.30 (1.00, 1.69) p = 0.05</p>	<p> <b>Primary composite outcome</b> HR (95% CI) for VER: 1.02 (0.88, 1.18) p = 0.77</p> <p> <b>Primary event or CV hospitalization</b> HR (95% CI) for VER: 1.05 (0.95, 1.16) p = 0.31</p> <p> <b>CVD-related death</b> HR (95% CI) for VER: 1.09 (0.87, 1.37) p = 0.47</p>	<p> <b>Renal failure (acute/chronic)</b> HR (95% CI) for VER: 0.81 (0.49, 1.35) p = 0.43</p>	<p> <b>Withdrawals due to constipation</b> 216 events VER vs 28 events ATN or HCTZ p = NR</p> <p> <b>Death or hospitalization due to serious adverse event</b> HR (95% CI) for VER: 1.04 (0.97, 1.12) p = 0.29</p> <p> <b>Hospitalization for serious adverse event</b> HR (95% CI) for VER:</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
							1.03 (0.95, 1.12) p = 0.44  <b>Withdrawals due to poor BP control</b> 115 events VER vs 207 events ATN or HCTZ p < 0.001
<b>VHAS, 1997</b> Adults, ages 40-65 years with HTN VER: Verapamil: slow release 240 mg QD CHL: Chlorthalidone: 25 mg QD N: 1,414 2 years Fair	 <b>Death by any cause</b> 5 events VER vs 4 events CHL p = NR	 <b>MI</b> 5 events VER vs 5 events CHL p = NR  <b>Revascularization procedures</b> 4 events VER vs 3 events CHL p = NR  <b>Cardiac deaths</b> 3 events VER vs 4 events CHL p = NR	 <b>Strokes</b> 3 events VER vs 4 events CHL p = NR  <b>TIA</b> 7 events VER vs 7 events CHL p = NR  <b>Cerebrovascular deaths</b> 2 events VER vs 0 events CHL p = NR	 <b>CHF</b> 2 events VER vs 0 events CHL p = NR	 <b>Non-fatal CV events</b> 37 events VER vs 39 events CHL p = NR  <b>Major CV events</b> 8 events VER vs 9 events CHL p = NR  <b>Minor CV events</b> 29 events VER vs 30 events CHL p = NR  <b>CV deaths</b> 5 events VER vs 4 events CHL p = NR		 <b>Constipation</b> 13.7% VER vs 3.1% CHL p = NR  <b>Severe hypokalemia</b> 4 events VER vs 8 events CHL p = NR  <b>Hyperuricemia</b> 3.9% VER vs 10.8% CHL p < 0.01  <b>Hypokalemia</b> 4.4% VER vs 24.6% CHL p < 0.01  <b>Glucose, mg/dl (SD)</b> -1.2 change VER vs +1.8 change CHL

<b>Study Criteria and Characteristics</b>	<b>Mortality Outcomes</b>	<b>Coronary Heart Disease Outcomes</b>	<b>Cerebrovascular Outcomes</b>	<b>Heart Failure Outcomes</b>	<b>Composite Outcomes</b>	<b>Kidney Outcomes</b>	<b>Adverse Events</b>
							p = 0.01

## Exhibit L: Evidence from randomized controlled trials of initial antihypertensive drug therapy with ACE inhibitors versus other drugs

**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** **Green** = Statistically significant where the ACE inhibitor did better ( $p < 0.05$ ) **Red** = Statistically significant where the ACE inhibitor did worse **Yellow** =  $p \geq 0.05$  and  $\leq 0.10$  **Clear** =  $p > 0.10$  **Blue** = p value not reported

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>CAPPP, 1999</b></p> <p>Adults, ages 25 to 66 years, with treated or untreated primary HTN</p> <p>CAP: Captopril 50 mg QD – 100 BID                      BB or DIUR: atenolol 50-100 mg QD; metoprolol 50-100 mg QD; HCTZ 25 mg QD; bendrofluazide 2.5 mg QD</p> <p>N: 10,985</p> <p>Mean 6.1 years</p> <p>Fair</p>	 <p><b>All fatal events</b>                      RR (95% CI) for CAP:                      0.93 (0.76, 1.14)                      p = 0.49</p>	 <p><b>Non-fatal MI</b>                      137 events CAP vs                      128 events BB or                      DIUR                      p = NR</p>  <p><b>Ischemic heart disease</b>                      258 events CAP vs                      251 events BB or                      DIUR                      p = NR</p>  <p><b>MI, fatal and non-fatal</b>                      RR (95% CI) for                      CAP:                      0.96 (0.77, 1.19)                      p = 0.68</p>  <p><b>Fatal MI</b>                      27 events CAP vs                      35 events BB or                      DIUR                      p = NR</p>	 <p><b>Non-fatal stroke</b>                      173 events CAP vs                      127 events BB or                      DIUR                      p = NR</p>  <p><b>Stroke, fatal and non-fatal</b>                      RR (95% CI) for                      CAP:                      1.25 (1.01, 1.55)                      p = 0.044</p>  <p><b>TIA</b>                      31 events CAP vs                      25 events BB or                      DIUR                      p = NR</p>  <p><b>Fatal stroke</b>                      20 events CAP vs                      22 events BB or                      DIUR                      p = NR</p>	 <p><b>CHF</b>                      75 events CAP vs                      66 events BB or                      DIUR                      p = NR</p>	 <p><b>Combination of fatal and non-fatal MI and stroke, and other CV deaths</b>                      RR (95% CI) for CAP:                      1.05 (0.90, 1.22)                      p = 0.52</p>  <p><b>All cardiac events</b>                      RR (95% CI) for CAP:                      0.94 (0.83, 1.06)                      p = 0.30</p>  <p><b>Fatal CV events</b>                      RR (95% CI) for CAP:                      0.77 (0.57, 1.04)                      p = 0.092</p>  <p><b>Other CV deaths</b>                      23 events CAP vs 24                      events BB or DIUR                      p = NR</p>		 <p><b>New onset DM</b>                      RR (95% CI) for                      CAP:                      0.86 (0.74, 0.99)                      p = 0.039                      Hansson et al                      1999</p> <p><i>Reported as:                      RR (95% CI) for                      CAP:                      0.79 (NR)                      p=0.001 in                      Niskanen 2001</i></p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		 <b>Sudden death</b> 6 events CAP vs 14 events BB or DIUR p = NR					
<b>ANBP2, 2003</b>  Adults, ages 65 to 84, with absence of recent CV events  ACE: ACE Inhibitor: Enalapril recommended; dose not specified DIU: Diuretic: HCTZ recommended; dose not specified  N: 6,083  Median 4.1 years  Fair	 <b>Death from any cause</b> HR (95% CI) for ACE: 0.90 (0.75, 1.09) p = 0.27	 <b>Non-fatal MI</b> HR (95% CI) for ACE: 0.68 (0.47, 0.99) p = 0.05   <b>Non-fatal coronary event</b> HR (95% CI) for ACE: 0.92 (0.73, 1.16) p = 0.49   <b>MI</b> HR (95% CI) for ACE: 0.68 (0.47, 0.98) p = 0.04   <b>Coronary event</b> HR (95% CI) for ACE: 0.86 (0.70, 1.06) p = 0.16   <b>Fatal MI events</b> HR (95% CI) for ACE:	 <b>Non-fatal stroke</b> HR (95% CI) for ACE: 0.93 (0.70, 1.26) p = 0.65   <b>Stroke</b> HR (95% CI) for ACE: 1.02 (0.78, 1.33) p = 0.91   <b>Cerebrovascular event</b> HR (95% CI) for ACE: 0.90 (0.73, 1.12) p = 0.35   <b>Fatal stroke events</b> HR (95% CI) for ACE: 1.91 (1.04, 3.50) p = 0.04	 <b>Non-fatal HF</b> HR (95% CI) for ACE: 0.85 (0.62, 1.17) p = 0.32   <b>HF</b> HR (95% CI) for ACE: 0.85 (0.62, 1.18) p = 0.33   <b>Fatal HF events</b> HR (95% CI) for ACE: 0.24 (0.03, 1.94) p = 0.18	 <b>Non-fatal CV event</b> HR (95% CI) for ACE: 0.86 (0.74, 0.99) p = 0.03   <b>Non-fatal other CV event</b> HR (95% CI) for ACE: 0.84 (0.66, 1.07) p = 0.17   <b>All CV events or death from any cause</b> HR (95% CI) for ACE: 0.89 (0.79, 1.00) p = 0.05   <b>First CV event or death from any cause</b> HR (95% CI) for ACE: 0.89 (0.79, 1.01) p = 0.06   <b>First CV event</b> HR (95% CI) for ACE: 0.88 (0.77, 1.01)		

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		0.79 (0.31, 1.99) $p = 0.61$  <b>Fatal coronary events</b> HR (95% CI) for ACE: 0.74 (0.49, 1.11) $p = 0.14$			$p = 0.07$  <b>Other CV event</b> HR (95% CI) for ACE: 0.90 (0.71, 1.14) $p = 0.36$  <b>Fatal CV events</b> HR (95% CI) for ACE: 0.99 (0.72, 1.35) $p = 0.94$  <b>Fatal other CV events</b> HR (95% CI) for ACE: 0.95 (0.46, 1.96) $p = 0.89$		
<b>ALLHAT, 2002</b> Adults, $\geq 55$ years of age with at least one additional risk factor for CHD LIS: Lisinopril: 10, 20, and 40 mg QD CHL: Chlorthalidone: 12.5 or 25 mg QD AML: Amlodipine: 2.5, 5, and 10 mg QD N: 33,357 Mean 4.9 years Good	 <b>All-cause mortality</b> LIS vs. CHL: RR (95% CI): 1.00 (0.94, 1.08) $p = 0.90$	 <b>CHD (combined fatal CHD and nonfatal MI)</b> LIS vs. CHL: RR (95% CI): 0.99 (0.91, 1.08) $p = 0.81$  <b>Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)</b> LIS vs. CHL: RR (95% CI): 1.05 (0.98, 1.11)	 <b>Stroke</b> LIS vs. CHL: RR (95% CI): 1.15 (1.02, 1.30) $p = 0.02$  <b>Death from stroke</b> 1.7 per 100 persons LIS vs 1.4 per 100 persons CHL vs 1.4 per 100 persons AML LIS vs. CHL: RR (95% CI): NR $p = 0.06$	 <b>HF</b> LIS vs. CHL: RR (95% CI): 1.19 (1.07, 1.31) $p < 0.001$  <b>Hospitalized/fatal HF</b> LIS vs. CHL: RR (95% CI) for LIS: 1.10 (0.98, 1.23) $p = 0.11$  <b>HF death</b> 1.1 per 100 persons LIS vs 1.0 per 100 persons CHL vs 1.4	 <b>Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)</b> LIS vs. CHL: RR (95% CI): 1.10 (1.05, 1.16) $p < 0.001$  <b>Cardiovascular death</b>	 <b>ESRD</b> LIS vs CHL: RR (95% CI): 1.11 (0.88, 1.38) $p = 0.38$  <b>Kidney disease death</b> 0.5 per 100 persons LIS vs 0.4 per 100 persons CHL vs 0.5 per 100 persons AML LIS vs. CHL: RR (95% CI): NR $p = 0.37$	At 6 years  <b>Angioedema</b> 0.4% LIS vs 0.1% CHL vs <0.1% AML LIS vs. CHL: RR (95% CI): NR $p < 0.001$ At 4 years  <b>Fasting glucose progressing to <math>\geq 126</math> mg/dL among non-DM with baseline fasting glucose <math>&lt; 126</math> mg/dL</b> 8.1% LIS vs

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		<p>p = 0.18</p>  <p><b>Coronary revascularization</b> LIS vs. CHL: RR (95% CI) for LIS: 1.10 (1.00, 1.21) p = 0.05</p>  <p><b>Hospitalized or treated PAD</b> LIS vs. CHL: RR (95% CI): 1.04 (0.90, 1.19) p = 0.63</p>  <p><b>MI death</b> 2.2 per 100 persons LIS vs 2.4 per 100 persons CHL vs 2.3 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.25</p>  <p><b>Definite CHD death</b> 1.0 per 100 persons LIS vs 1.1 per 100 persons CHL vs 1.2 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.52</p>		<p>per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.98</p>	<p>8.5 per 100 persons LIS vs 8.0 per 100 persons CHL vs 8.5 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.39</p>  <p><b>Other CVD death</b> 1.5 per 100 persons LIS vs 1.4 per 100 persons CHL vs 1.7 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.66</p>		<p>11.6% CHL vs 9.8% AML LIS vs. CHL: p &lt; 0.001</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		 <p><b>Possible CHD death</b> 1.4 per 100 persons LIS vs 1.1 per 100 persons CHL vs 1.1 per 100 persons AML LIS vs. CHL: RR (95% CI): NR p = 0.10</p>					
<p><b>ALLHAT, 2006</b></p> <p>Adults, ≥ 55 years of age with at least one additional risk factor for CHD</p> <p>LIS: Lisinopril: 10, 20, and 40 mg QD AML: Amlodipine: 2.5, 5, and 10 mg QD</p> <p>N: 18, 102</p> <p>Mean 4.9 years</p> <p>Fair</p>	 <p><b>All-cause mortality</b> LIS vs AML: RR (95% CI): 1.05 (0.97, 1.13) p = 0.214</p>	 <p><b>CHD (fatal CHD and nonfatal MI)</b> LIS vs AML: RR (95% CI): 1.01 (0.91, 1.11) p = 0.854</p>  <p><b>Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina)</b> LIS vs AML: RR (95% CI): 1.04 (0.97, 1.12) p = 0.243</p>  <p><b>Coronary revascularization</b> LIS vs AML: RR (95% CI): 1.00 (0.91, 1.11) p = 0.943</p>	 <p><b>Stroke</b> LIS vs AML: RR (95% CI): 1.23 (1.08, 1.41) p = 0.003</p>	 <p><b>HF</b> LIS vs AML: RR (95% CI): 0.87 (0.78, 0.96) P = 0.007</p>  <p><b>Hospitalized/fatal HF</b> LIS vs AML: RR (95% CI): 0.81 (0.72, 0.92) p &lt;0.001</p>	 <p><b>Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization)</b> LIS vs AML: RR (95% CI): 1.06 (1.00, 1.12) p = 0.047</p>	 <p><b>ESRD</b> LIS vs AML: RR (95% CI): 0.99 (0.77, 1.26) p = 0.929</p>	 <p><b>Angioedema</b> 0.42% LIS vs 0.03% AML p &lt;0.001</p>  <p><b>Hospitalization for GI bleeding</b> 9.6 per 100 LIS vs 8.0 per 100 AML p = 0.04</p> <p>At 4 years</p>  <p><b>DM (&gt;=7.0 mmol/L) if no DM at baseline</b> 9.4% LIS vs 10.4% AML p = 0.30</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
		 <b>Hospitalized or fatal PAD</b> <b>LIS vs AML:</b> RR (95% CI): 1.19 (1.01, 1.40) p = 0.036					
<b>JMIC-B, 2004</b>  Adults, ages <75 years with HTN and CAD  ACE: ACE inhibitor: enalapril 5-10 mg, or imidapril 5-10 mg, or lisinopril 10-20 mg NIF: Nifedipine long acting 10-20 mg BID  N: 1,650  Median 35.7 months  Fair	 <b>Total mortality</b> RR (95% CI) for NIF: 0.76 (0.35, 1.63) p = 0.48	 <b>MI</b> RR (95% CI) for NIF: 1.31 (0.63, 2.74) p = 0.47   <b>Coronary intervention of PTCA, CABG, stenting</b> RR (95% CI) for NIF: 1.04 (0.76, 1.43) p = 0.81   <b>Sudden death/ cardiac death</b> RR (95% CI) for NIF: 0.96 (0.31, 3.04) p = 0.95	 <b>Cerebrovascular accidents</b> RR (95% CI) for NIF: 1.00 (0.50, 2.02) p = 0.99	 <b>HF requiring hospitalization</b> RR (95% CI) for NIF: 1.25 (0.52, 2.98) p = 0.62	 <b>Cardiac events (composite of cardiac or sudden death, MI, angina pectoris requiring hospitalization, HF requiring hospitalization, serious arrhythmia, coronary interventions)</b> RR (95% CI) for NIF: 1.05 (0.81, 1.37) p = 0.75   <b>Non-cardiac death</b> RR (95% CI) for NIF: 0.64 (0.23, 1.81) p = 0.40	 <b>Worsening of renal dysfunction with serum Cr &gt;353.6 μmol/l</b> RR (95% CI) for NIF: 2.70 (0.54, 13.49) p = 0.23	<i>Withdrawals by AE</i>  <b>Dry cough</b> 7.3% ACE vs 0% NIF NIF: 0 p < 0.01   <b>Hypotension</b> 0.2% ACE vs 1.0% NIF p < 0.01   <b>Edema</b> 0% ACE vs 0.8% NIF p < 0.01   <b>Facial erythema, hot flushes</b> 0% ACE vs 0.7% NIF p < 0.05
<b>STOP Hypertension-2 , 1999</b>  Adults 70-84 years old with HTN  ACE: ACE inhibitors: enalapril 10 mg, or	 <b>Total mortality</b> ACE vs CCB:	 <b>All MI</b> ACE vs CCB:	 <b>All stroke</b> ACE vs. CCB:	 <b>Frequency of CHF</b> ACE vs. CCB:	 <b>All major CV events</b> ACE vs. CCB:		 <b>Frequency of DM</b> ACE vs. CCB:

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>lisinopril 10 mg CCB: Calcium channel blockers: felodipine 2.5 mg QD or isradipine 2.5 mg QD BB or DIUR: atenolol 50 mg, or metoprolol 100 mg, or pindolol 5 mg, or fixed ratio HCTZ 25 mg plus amiloride 2.5 mg</p> <p>N: 6,614</p> <p>Duration: Mean F/U unclear; authors report study duration of 60 months; max BP measurement reported is 54 months, and Kaplan-Meier curves extend to 6 years</p> <p>Good</p>	<p>RR (95%CI) for ACE: 1.03 (0.69, 1.19) p = 0.71</p>  <p><b>Total mortality</b> ACE vs. BB or DIUR: RR (95% CI) for ACE: 1.02 (0.69, 1.16) p = 0.76</p>	<p>RR (95% CI) for ACE: 0.77 (0.61, 0.96) p = 0.016</p>  <p><b>All MI</b> ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.90 (0.72, 1.13) p = 0.36</p>  <p><b>Sudden death</b> 5.3 per 1000 p-y ACE vs 4.7 per 1000 p-y CCB vs 4.8 per 1000 p-y BB or DIUR p = NR</p>  <p><b>Fatal MI</b> 4.3 per 1000 p-y ACE vs 5.3 per 1000 p-y CCB vs 4.9 per 1000 p-y BB or DIUR p = NR</p>	<p>RR (95% CI) for ACE: 1.02 (0.64, 1.24) p = 0.64</p>  <p><b>All stroke</b> ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.90 (0.74, 1.06) p = 0.24</p>  <p><b>Fatal stroke</b> 4.5 per 1000 p-y ACE vs 4.2 per 1000 p-y CCB vs 4.6 per 1000 p-y p = NR</p>	<p>RR (95% CI) for ACE: 0.76 (0.63, 0.97) p = 0.025</p>  <p><b>Frequency of CHF</b> ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.63 (0.67, 1.03) p = 0.095</p>	<p>RR (95% CI) for ACE: 0.95 (0.63, 1.06) p = 0.42</p>  <p><b>All major CV events</b> ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.94 (0.62, 1.07) p = 0.32</p>  <p><b>CV mortality</b> ACE vs. CCB: RR (95% CI) for ACE: 1.04 (0.66, 1.26) p = 0.67</p>  <p><b>CV mortality</b> ACE vs. BB or DIUR: RR (95% CI) for ACE: 1.01 (0.64, 1.22) p = 0.69</p>  <p><b>Other CV mortality</b> 6.2 per 1000 p-y ACE vs 5.0 per 1000 p-y CCB vs 5.6 per 1000 p-y BB or DIUR p = NR</p>		<p>RR (95% CI) for ACE: 0.96 (0.74, 1.31) p = 0.91</p>  <p><b>Frequency of DM</b> ACE vs. BB or DIUR: RR (95% CI) for ACE: 0.96 (0.72, 1.27) p = 0.77</p>  <p><b>Ankle edema</b> 8.7% ACE vs 25.5% CCB vs 8.5% BB or DIUR p = NR</p>  <p><b>Dry cough</b> 30.1% ACE vs 5.7% CCB vs 3.7% BB or DIUR p = NR</p>  <p><b>Dizziness</b> 27.7% ACE vs 24.5% CCB vs 27.8% BB or DIUR p = NR</p>

## Exhibit M: Evidence from randomized controlled trials of initial antihypertensive drug therapy with ARBs versus other drugs

**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** *Green* = Statistically significant where the ARB did better ( $p < 0.05$ ) *Red* = Statistically significant where the ARB did worse ( $p < 0.05$ ) *Yellow* =  $p \geq 0.05$  and  $\leq 0.10$  *Clear* =  $p > 0.10$  *Blue* =  $p$  value not reported

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>CASE-J, 2008</b></p> <p>Adults with high CVD risk</p> <p>CAN: Candesartan 4-12 mg/day                      AML: Amlodipine 2.5-10 mg/day</p> <p>N: 4,728</p> <p>Mean 3.2 years</p> <p>Primary outcome: composite of sudden death, cerebrovascular events, cardiac events, renal events vascular events</p> <p>Good</p>	 <p><b>All-cause death</b>                      9.4 per 1000 p-y CAN vs 11.1 per 1000 p-y AML                      HR (95% CI): NR                      p = NS</p>	 <p><b>Acute MI</b>                      HR (95% CI) for CAN:                      0.95 (0.49, 1.84)                      p = 0.870</p>  <p><b>Sudden death</b>                      HR (95% CI) for CAN:                      0.73 (0.34, 1.60)                      p = 0.434</p>	 <p><b>Cerebrovascular events</b>                      HR (95% CI) for CAN:                      1.23 (0.85, 1.78)                      p = 0.282</p>  <p><b>Stroke</b>                      HR (95% CI) for CAN:                      1.28 (0.88, 1.88)                      p = 0.198</p>  <p><b>TIA</b>                      HR (95% CI) for CAN:                      0.50 (0.09, 2.73)                      p = 0.414</p>	 <p><b>Heart failure</b>                      HR (95% CI) for CAN:                      1.25 (0.65, 2.42)                      p = 0.498</p>	 <p><b>Primary composite endpoint of sudden death, cerebrovascular events, cardiac events, renal events and vascular events</b>                      HR (95% CI) for CAN:                      1.01 (0.79, 1.28)                      p = 0.969</p>  <p><b>Cardiac events</b>                      HR (95% CI) for CAN:                      0.92 (0.61, 1.39)                      p = 0.680</p>  <p><b>Peripheral vascular events</b>                      HR (95% CI) for CAN:                      1.57 (0.61, 4.05)                      p = 0.348</p>	 <p><b>Renal events</b>                      HR (95% CI) for CAN:                      0.70 (0.39, 1.26)                      p = 0.230</p>  <p><b>Creatinine abnormality</b>                      HR (95% CI) for CAN:                      0.73 (0.40, 1.31)                      p = 0.287</p>  <p><b>ESRD</b>                      HR (95% CI) for CAN:                      0.40 (0.13, 1.29)                      p = 0.112</p>	 <p><b>Hyperkalemia</b>                      1.0% CAN vs 0.3% AML                      p = NR</p>  <p><b>New onset DM</b>                      HR (95% CI) for CAN:                      0.64 (0.43, 0.97)                      p = 0.033</p>
<p><b>SCOPE, 2003</b></p> <p>Adults, 70-89 years old with treated or untreated HTN and MMSE <math>\geq</math> 24</p> <p>CAN: Candesartan:                      Step 1: Candesartan 8 mg QD                      Step 2: If SBP &gt;160 mmHg or reduction in SBP &lt;10 mmHg or DBP &gt;85, dose doubled                      Step 3: If SBP remained <math>\geq</math>160 mmHg or</p>	 <p><b>Total mortality</b>                      27.9 per 1000 p-y CAN vs 29.0 per 1000 p-y CTL                      Risk Reduction (95% CI): NR                      p = NS</p>	 <p><b>Non-fatal MI</b>                      5.9 per 1000 p-y CAN vs 5.2 per 1000 p-y CTL                      Risk Reduction (95% CI): NR                      p = NS</p>	 <p><b>Non-fatal stroke</b>                      Risk Reduction (95% CI) for CAN:                      27.8 (1.3, 47.2)                      p = 0.04</p>		 <p><b>Major CV events</b>                      Risk Reduction (95% CI) for CAN:                      10.9 (-6.0, 25.1)                      p = 0.19</p>	 <p><b>Change in mean serum Cr, <math>\mu</math>mol/l</b>                      CAN: +9.6                      CTL: +5.3                      p = NR</p>	 <p><b>Dizziness/vertigo</b>                      20.9% CAN vs 20.0% CTL                      p = NR</p>  <p><b>Accident/injury</b>                      18.4% CAN vs 18.4% CTL</p>



250



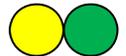
Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>DBP ≥90 mmHg, other anti-HTN drug added (ARB or ACE not allowed); recommendation was to start with HCTZ 12.5 mg QD</p> <p>CTL: Control: Step 1: Placebo QD Step 2: If SBP &gt;160 mmHg or reduction in SBP &lt;10 mmHg or DBP &gt;85, dose doubled Step 3: If SBP remained ≥160 mmHg or DBP ≥90 mmHg, other anti-HTN drug added (ARB or ACE not allowed); recommendation was to start with HCTZ 12.5 mg QD</p> <p>N: 4,964</p> <p>Mean 3.7 years</p> <p>Fair</p> <p>Panel Comments: Authors note that during the recruitment period it became necessary to recommend open-label active anti-HTN therapy in both treatment groups for patients whose BP remained high. Thus, the trial actually compared a candesartan-based regimen to usual treatment without candesartan. However, the initial intent was to compare candesartan to placebo.</p>		<p><b>All MI</b> 7.6 per 1000 p-y CAN vs 6.9 per 1000 p-y CTL Risk Reduction (95% CI): NR p = NS</p>	<p><b>All stroke</b> Risk Reduction (95% CI) for CAN: 23.6 (-0.7, 42.1) p = 0.056</p> <p> <b>Fatal stroke</b> 2.6 per 1000 p-y CAN vs 2.8 per 1000 p-y CTL Risk Reduction (95% CI): NR p = NS</p>		<p><b>CV deaths</b> 15.6 per 1000 p-y CAN vs 16.6 per 1000 p-y CTL Risk Reduction (95% CI): NR p = NS</p>		<p>p = NR</p> <p> <b>Back pain</b> 19.2% CAN vs 17.1% CTL p = NR</p> <p> <b>Bronchitis</b> 15.9% CAN vs 16.0% CTL p = NR</p> <p> <b>AEs indicating possible hypotension</b> 24.6% CAN vs 23.4% CTL p = NR</p> <p> <b>New Onset DM</b> 4.3% CAN vs 5.3% CTL p = 0.09</p>
<p><b>MOSES, 2005</b></p> <p>Patients with HTN and history of a cerebrovascular event</p> <p>EPR: Eprosartan 600 mg/day NIT: Nitrendipine 10 mg/day</p> <p>N: 1,405</p> <p>Mean 2.5 years</p> <p>Fair</p> <p>Panel Comments: IDR: incidence density ratio</p>	<p> <b>All cause death</b> HR (95% CI) for EPR: 1.07 (0.73, 1.56) p = 0.725</p>		<p> <b>Fatal and non-fatal cerebrovascular events</b> IDR (95% CI): 0.75 (0.58, 0.97) p = 0.026</p> <p></p>		<p> <b>Primary combined endpoint: cerebrovascular and CV events and non-CV death</b> IDR (95% CI): 0.79 (0.66, 0.96) p = 0.014</p> <p></p>		<p> <b>Metabolic disorder</b> 5.5% EPR vs 5.9% NIT p = NR</p> <p> <b>Dizziness/hypotension</b> 12.9% EPR vs 10.6% NIT p = NR</p>

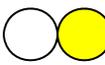
Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
			<p><b>First time occurrence of cerebrovascular event</b> HR (95% CI) for EPR: 0.88 (0.65, 1.20) p = 0.425</p>		<p><b>Fatal and non-fatal CV events</b> IDR (95% CI): 0.75 (0.55, 1.02) p = 0.061</p> <p><b>First time occurrence of CV event</b> HR (95% CI) for EPR: 0.69 (0.50, 0.97) p = 0.031</p>		<p> <b>Pneumonia</b> 10.8% EPR vs 11.4% NIT p = NR</p>
<p><b>LIFE, 2002</b></p> <p>Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG</p> <p>LOS: Losartan, titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg Step 1: Losartan 50 mg Step 2 (Month 2): Losartan 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Losartan 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)</p> <p>ATN: Atenolol, titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg Step 1: Atenolol 50 mg Step 2 (Month 2): Atenolol 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Atenolol 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Atenolol 100 mg + HCTZ 12.5-25 mg + other anti-HTN</p>	<p> <b>Total mortality</b> 17.3 per 1000 py LOS vs 19.6 per 1000 py ATN Adj HR (95% CI) for LOS: 0.90 (0.78, 1.03) p = 0.128 Unadj HR (95% CI) for LOS: 0.88 (0.77, 1.01) p = 0.077</p>	<p> <b>MI</b> 9.2 per 1000 py LOS vs 8.7 per 1000 py ATN Adj HR (95% CI) for LOS: 1.07 (0.88, 1.31) p = 0.491 Unadj HR (95% CI) for LOS: 1.05 (0.86, 1.28) p = 0.628</p> <p> <b>Resuscitated cardiac arrest</b> 0.4 per 1000 py LOS vs 0.2 per 1000 py ATN Adj HR (95% CI) for LOS: 1.91 (0.64, 5.72) p = 0.250 Unadj HR (95% CI) for LOS: 1.80 (0.60, 5.36) p = 0.294</p>	<p> <b>Stroke</b> 10.8 per 1000 py LOS vs 14.5 per 1000 py ATN Adj HR (95% CI) for LOS: 0.75 (0.63, 0.89) p = 0.001 Unadj HR (95% CI) for LOS: 0.74 (0.63, 0.88) p = 0.0006</p>	<p> <b>Heart failure</b> 7.1 per 1000 py LOS vs 7.5 per 1000 py ATN Adj HR (95% CI) for LOS: 0.97 (0.78, 1.21) p = 0.765 Unadj HR (95% CI) for LOS: 0.95 (0.76, 1.18) p = 0.622</p>	<p> <b>Primary composite endpoint of CV death, MI, and stroke</b> 23.8 per 1000 py LOS vs 27.9 per 1000 py ATN Adj HR (95% CI) for LOS: 0.87 (0.77, 0.98) p = 0.021 Unadj HR (95% CI) for LOS: 0.85 (0.76, 0.96) p = 0.009</p> <p> <b>CV mortality</b> 9.2 per 1000 py LOS vs 10.6 per 1000 py ATN Adj HR (95% CI) for LOS: 0.89 (0.73, 1.07) p = 0.206 Unadj HR (95% CI) for LOS: 0.87 (0.72, 1.05) p = 0.136</p>	<p> <b>Change in creatinine, mmol/L (SD)</b> LOS: +11.2 (20.4) ATN: +11.0 (19.7) p = NR</p>	<p> <b>Hypotension</b> 3% LOS vs 2% ATN p = 0.001</p> <p> <b>Back pain</b> 12% LOS vs 10% ATN p = 0.004</p> <p> <b>Chest pain</b> 11% LOS vs 10% ATN p = 0.068</p> <p> <b>Angioedema</b> 0.1% LOS vs 0.2% ATN p = 0.237</p>



Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)</p> <p>N: 9,222</p> <p>Mean 4.8 years</p> <p>Good</p> <p>Panel Comments: Hazard ratios adjusted for degree of LVH and Framingham risk score</p>		<p style="text-align: center;"></p> <p><b>Revascularization</b>  12.2 per 1000 py  LOS vs 13.3 per  1000 py ATN  ATN vs. LOS  Adj HR (95% CI) for  LOS:  0.94 (0.79, 1.11)  p = 0.441  Unadj HR (95% CI)  for LOS:  0.91 (0.77, 1.08)  p = 0.292</p>					<p><b>Cough</b>  3% LOS vs  2% ATN  p = 0.220</p> <p style="text-align: center;"></p> <p><b>Dizziness</b>  17% LOS vs  16% ATN  p = 0.247</p> <p style="text-align: center;"></p> <p><b>New DM</b>  13.0 per 1000 py  LOS vs 17.4 per  1000 py ATN  Adj HR (95% CI)  for LOS:  0.75 (0.63, 0.88)  p = 0.001  Unadj HR (95%  CI) for LOS:  0.75 (0.63, 0.88)  p = 0.001</p> <p style="text-align: center;"></p> <p><b>Lower extremity edema</b>  12% LOS vs  14% ATN  p = 0.002</p> <p style="text-align: center;"></p> <p><b>Albuminuria</b>  5% LOS vs  6% ATN  p = 0.0002</p>



Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
							<p><b>Hyperglycemia</b> 5% LOS vs 7% ATN p = 0.007</p>  <p><b>Dyspnea</b> 10% LOS vs 14% ATN p &lt; 0.0001</p>  <p><b>Asthenia/ Fatigue</b> 15% LOS vs 17% ATN p = 0.001</p>
<p><b>LIFE, 2002</b></p> <p><i>Subanalyses on those with Isolated Systolic Hypertension</i></p> <p>Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG; included in subanalysis if trough sitting SBP 160-200 mmHg with DBP &lt;90 mmHg after 1 and 2 weeks placebo</p> <p>LOS: Losartan, titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg Step 1: Losartan 50 mg Step 2 (Month 2): Losartan 50 mg + HCTZ 12.5 mg Step 3 (Month 4): Losartan 100 mg + HCTZ 12.5 mg Step 4 (Month 6): Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)</p>	<p><i>Subanalysis of patients with Isolated Systolic Hypertension</i></p>  <p><b>Total mortality</b> 21.2 per 1000 py LOS vs 30.2 per 1000 py ATN AdjRR (95% CI) for LOS: 0.72 (0.53, 1.00) p = 0.046 UnadjRR (95% CI) for LOS: 0.70 (0.51, 0.96) p = 0.03</p> <p><i>Subanalysis of</i></p>	<p><i>Subanalysis of patients with Isolated Systolic Hypertension</i></p>  <p><b>MI</b> 10.2 per 1000 py LOS vs 11.9 per 1000 py ATN AdjRR (95% CI) for LOS: 0.89 (0.55, 1.44) p = 0.64 UnadjRR (95% CI) for LOS: 0.86 (0.53, 1.39) p = 0.54</p>  <p><b>Revascularization</b> 16.4 per 1000 py LOS vs 14.4 per</p>	<p><i>Subanalysis of patients with Isolated Systolic Hypertension</i></p>  <p><b>Stroke</b> 10.6 per 1000 py LOS vs 18.9 per 1000 py ATN AdjRR (95% CI) for LOS: 0.60 (0.38, 0.92) p = 0.02 UnadjRR (95% CI) for LOS: 0.56 (0.36, 0.86) p = 0.008</p> <p><i>Subanalysis of</i></p>	<p><i>Subanalysis of patients with Isolated Systolic Hypertension</i></p>  <p><b>Hospitalization for Heart Failure</b> 8.5 per 1000 py LOS vs 13.3 per 1000 py ATN AdjRR (95% CI) for LOS: 0.66 (0.40, 1.09) p = 0.11 UnadjRR (95% CI) for LOS: 0.64 (0.39, 1.05) p = 0.08</p> <p><i>Subanalysis of</i></p>	<p><i>Subanalysis of patients with Isolated Systolic Hypertension</i></p>  <p><b>Primary composite endpoint of CV death, MI or stroke</b> 25.1 per 1000 py LOS vs 35.4 per 1000 py ATN AdjRR (95% CI) for LOS: 0.75 (0.56, 1.01) p = 0.06 UnadjRR (95% CI) for LOS: 0.71 (0.53, 0.95) p = 0.02</p>  <p><b>CV mortality</b> 8.7 per 1000 py LOS vs 16.9 per 1000 py ATN</p>	 <p><b>Angioedema</b> 0.3% LOS vs 0.3% ATN p = 0.99</p>  <p><b>Cough</b> 4.1% LOS vs 2.9% ATN p = 0.23</p>  <p><b>Cold extremities</b> 4.1% LOS vs 6.6% ATN p = 0.05</p> 	

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>ATN: Atenolol, titration upward if sitting DBP <math>\geq</math>90 mmHg or sitting SBP <math>\geq</math>140 mmHg  Step 1: Atenolol 50 mg  Step 2 (Month 2): Atenolol 50 mg + HCTZ 12.5 mg  Step 3 (Month 4): Atenolol 100 mg + HCTZ 12.5 mg  Step 4 (Month 6): Atenolol 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)</p> <p>N: 9,222 randomized (1,326 with isolated hypertension)</p> <p>Mean 4.7 years</p> <p>Fair</p> <p>NOTE: Adjusted RRs are adjusted for degree of LVH and Framingham risk score at randomization  Interaction between treatment and ISH status was not statistically significant</p>	<p><i>patients without Isolated Systolic Hypertension</i></p>  <p><b>Total mortality</b>  16.7 per 1000 py LOS vs 17.9 per 1000 py ATN  AdjRR (95% CI) for LOS: 0.95 (0.82, 1.11)  p = 0.51  UnadjRR (95% CI) for LOS: 0.93 (0.80, 1.09)  p = 0.38</p>	<p>1000 py ATN  AdjRR (95% CI) for LOS:  1.17 (0.78, 1.77)  p = 0.45  UnadjRR (95% CI) for LOS:  1.14 (0.76, 1.72)  p = 0.53</p> <p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>MI</b>  9.0 per 1000 py LOS vs 8.2 per 1000 py ATN  AdjRR (95% CI) for LOS:  1.12 (0.90, 1.40)  p = 0.30  UnadjRR (95% CI) for LOS:  1.10 (0.88, 1.36)  p = 0.41</p> <p><b>Revascularization</b>  11.5 per 1000 py LOS vs 13.2 per 1000 py ATN  AdjRR (95% CI) for LOS:  0.89 (0.74, 1.08)  p = 0.23  UnadjRR (95% CI) for LOS:  0.87 (0.73, 1.05)  p = 0.15</p>	<p><i>patients without Isolated Systolic Hypertension</i></p>  <p><b>Stroke</b>  10.8 per 1000 py LOS vs 13.8 per 1000 py ATN  AdjRR (95% CI) for LOS:  0.79 (0.66, 0.95)  p = 0.01  UnadjRR (95% CI) for LOS:  0.78 (0.65, 0.94)  p = 0.01</p>	<p><i>patients without Isolated Systolic Hypertension</i></p>  <p><b>Hospitalization for Heart Failure</b>  6.8 per 1000 py LOS vs 6.5 per 1000 py ATN  AdjRR (95% CI) for LOS:  1.06 (0.83, 1.36)  p = 0.65  UnadjRR (95% CI) for LOS:  1.05 (0.82, 1.34)  p = 0.72</p>	<p>AdjRR (95% CI) for LOS:  0.54 (0.34, 0.87)  p = 0.01  UnadjRR (95% CI) for LOS:  0.51 (0.32, 0.81)  p = 0.004</p> <p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>Primary composite endpoint of CV death, MI or stroke</b>  23.6 per 1000 py LOS vs 26.7 per 1000 py ATN  AdjRR (95% CI) for LOS: 0.90 (0.79, 1.02)  p = 0.11  UnadjRR (95% CI) for LOS: 0.88 (0.78, 1.01)  p = 0.06</p> <p><b>CV mortality</b>  9.3 per 1000 py LOS vs 9.6 per 1000 py ATN  AdjRR (95% CI) for LOS: 0.99 (0.80, 1.22)  p = 0.90  UnadjRR (95% CI) for LOS: 0.97 (0.79, 1.19)  p = 0.77</p>		<p><b>Bradycardia</b>  3.0% LOS vs 14.6% ATN  p &lt; 0.001</p> <p><i>Subanalysis of patients with Isolated Systolic Hypertension</i></p>  <p><b>New diabetes</b>  12.6 per 1000 py LOS vs 20.1 per 1000 py ATN  AdjHR (95% CI) for LOS:  0.62 (0.40, 0.97)  p = 0.04  UnadjHR (95% CI) for LOS:  0.63 (0.40, 0.99)  p = 0.04</p> <p><i>Subanalysis of patients without Isolated Systolic Hypertension</i></p>  <p><b>New diabetes</b>  13.1 per 1000 py LOS vs 17.0 per 1000 py ATN  AdjRR (95% CI) for LOS:  0.77 (0.64, 0.92)  p = 0.005  UnadjRR (95% CI) for LOS:  0.77 (0.64, 0.92)  p = 0.004</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>LIFE, 2003</b></p> <p><i>Subanalysis of subjects with and without clinically evident vascular disease</i></p> <p>Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG</p> <p>LOS: Losartan: titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg  Step 1: Losartan 50 mg  Step 2 (Month 2): Losartan 50 mg + HCTZ 12.5 mg  Step 3 (Month 4): Losartan 100 mg + HCTZ 12.5 mg  Step 4 (Month 6): Losartan 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)</p> <p>ATN: Atenolol: titration upward if sitting DBP ≥90 mmHg or sitting SBP ≥140 mmHg  Step 1: Atenolol 50 mg  Step 2 (Month 2): Atenolol 50 mg + HCTZ 12.5 mg  Step 3 (Month 4): Atenolol 100 mg + HCTZ 12.5 mg  Step 4 (Month 6): Atenolol 100 mg + HCTZ 12.5-25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)</p> <p>N: 9,222 (6,886 without clinically evident vascular disease at baseline)</p> <p>Mean 4.8 years</p> <p>Fair</p> <p>NOTE: Adjusted HRs are adjusted for degree of LVH and Framingham risk score at randomization  Interaction between treatment and</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>Total mortality</b>  13.5 per 1000 py LOS vs 15.9 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.85 (0.71, 1.02)  p = 0.080</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>Total mortality</b>  28.5 per 1000 py LOS vs 31.7 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.94 (0.75, 1.16)  p &gt; 0.2</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>MI</b>  6.8 per 1000 py LOS vs 6.0 per 1000 py ATN  AdjHR (95% CI) for LOS: 1.14 (0.87, 1.49)  p &gt; 0.2</p> <p></p> <p><b>Revascularization</b>  7.6 per 1000 py LOS vs 9.0 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.85 (0.67, 1.08)  p = 0.18</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>MI</b>  16.3 per 1000 py LOS vs 17.7 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.97 (0.72, 1.31)  p &gt; 0.2</p> <p></p> <p><b>Revascularization</b>  26.3 per 1000 py</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>Stroke</b>  7.7 per 1000 py LOS vs 11.8 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.66 (0.53, 0.82)  p &lt; 0.001</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>Stroke</b>  20.0 per 1000 py LOS vs 23.7 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.87 (0.67, 1.13)  p &gt; 0.2</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>Hospitalization for Heart Failure</b>  4.7 per 1000 py LOS vs 4.4 per 1000 py ATN  AdjHR (95% CI) for LOS: 1.06 (0.77, 1.46)  p &gt; 0.2</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>Hospitalization for Heart Failure</b>  14.2 per 1000 py LOS vs 17.7 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.84 (0.62, 1.14)  p &gt; 0.2</p>	<p><i>Subanalysis of subjects without clinically evident vascular disease</i></p> <p></p> <p><b>Primary composite endpoint of CV death, MI or stroke</b>  17.5 per 1000 py LOS vs 21.8 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.81 (0.69, 0.95)  p = 0.008</p> <p></p> <p><b>CV mortality</b>  6.2 per 1000 py LOS vs 7.8 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.80 (0.62, 1.04)  p = 0.092</p> <p><i>Subanalysis of subjects with clinically evident vascular disease</i></p> <p></p> <p><b>Primary composite endpoint of CV death, MI or stroke</b>  43.0 per 1000 py LOS vs 48.6 per 1000 py ATN  AdjHR (95% CI) for LOS: 0.93 (0.77, 1.11)  p &gt; 0.2</p>		<p></p> <p><b>Back pain</b>  12.0% LOS vs 10.0% ATN  p = 0.009</p> <p></p> <p><b>Patients with at least one serious adverse event</b>  3.8% LOS vs 4.4% ATN  p &gt; 0.2</p> <p></p> <p><b>Patients with at least one adverse event of any type</b>  12.7% LOS vs 17.3% ATN  p &lt; 0.001</p> <p></p> <p><b>Patients with at least one drug related adverse event</b>  6.0% LOS vs 10.2% ATN  p &lt; 0.001</p> <p></p> <p><b>Patients with at least one serious drug related adverse event</b>  0.5% LOS vs 1.0% ATN  p = 0.018</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
presence or absence of arterial disease was not statistically significant for primary endpoint		LOS vs 28.4 per 1000 py ATN AdjHR (95% CI) for LOS: 0.98 (0.78, 1.25) p > 0.2			 <b>CV mortality</b> 18.0 per 1000 py LOS vs 19.8 per 1000 py ATN AdjHR (95% CI) for LOS: 0.95 (0.72, 1.25) p > 0.2		 <b>Asthenia or fatigue</b> 14.2% LOS vs 16.9% ATN p < 0.002   <b>Lower extremity edema</b> 11.5% LOS vs 13.6% ATN p < 0.008   <b>Dyspnea</b> 8.8% LOS vs 13.6% ATN p < 0.001   <b>Hyperglycemia</b> 5.4% LOS vs 6.7% ATN p = 0.023  <i>Subanalysis of subjects without clinically evident vascular disease</i>   <b>New diabetes</b> 12.2 per 1000 py LOS vs 17.7 per 1000 py ATN AdjHR (95% CI) for LOS: 0.69 (0.57, 0.84) p < 0.001

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
							<p>Subanalysis of subjects with clinically evident vascular disease</p>  <p><b>New diabetes</b> 15.5 per 1000 py LOS vs 16.4 per 1000 py ATN AdjHR (95% CI) for LOS: 0.97 (0.69, 1.36) p &gt; 0.2</p>
<p><b>Jikei Heart Study, 2007</b></p> <p>Adults, 20-79 years of age with HTN, CHD, HF, or a combination of these CV disorders</p> <p>VAL: Valsartan 80 mg daily; flexibly adjusted to 40-160 mg per day as needed to control BP; patients with HF or CHD started on 40 mg QD and uptitrated as tolerated; non-ARB treatment could be added to achieve BP goal</p> <p>CT: Conventional therapy; given either an increased dose of their existing treatment or an additional conventional treatment to achieve BP goal</p> <p>N: 3,081</p> <p>Median 3.1 years</p> <p>Good</p> <p>Panel Comments: Study terminated early after DSMB recommended that the study should be stopped for ethical reasons because additional valsartan treatment was associated with a reduction in the primary endpoint (p&lt;0.001, adjusted for three interim analyses).</p>	 <p><b>All-cause mortality</b> HR (95% CI) for VAL: 1.09 (0.64, 1.85) p = 0.7537</p>	 <p><b>New or recurrent MI</b> HR (95% CI) for VAL: 0.90 (0.47, 1.74) p = 0.7545</p>  <p><b>Dissecting aneurysm of the aorta</b> HR (95% CI) for VAL: 0.19 (0.04, 0.88) p = 0.0340</p>	 <p><b>Stroke or TIA</b> HR (95% CI) for VAL: 0.60 (0.38, 0.95) p = 0.0280</p>	 <p><b>New occurrence or exacerbation of HF needing hospitalization</b> HR (95% CI) for VAL: 0.53 (0.31, 0.94) p = 0.0293</p>	 <p><b>Composite of CV mortality and morbidity (hospital admissions for stroke or TIA; MI; admission for CHF; admission for angina pectoris; dissecting aneurysm of the aorta; doubling of serum Cr; or transition to dialysis)</b> HR (95% CI) for VAL: 0.61 (0.47, 0.79) p = 0.0002</p>  <p><b>CV mortality</b> HR (95% CI) for VAL: 1.03 (0.41, 2.60) p = 0.9545</p>	 <p><b>Transition to dialysis, doubling of serum Cr levels</b> HR (95% CI) for VAL: 0.93 (0.34, 2.61) p = 0.8966</p>	 <p><b>Any adverse event</b> 2.7% VAL vs 2.3% CT p = NS</p>  <p><b>Elevated serum potassium</b> 2 events VAL vs 0 events CT p = NR</p>  <p><b>Dry Cough</b> 1 event VAL vs 1 event CT p = NR</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>VALUE, 2004</b></p> <p>Adults, ≥50 years with treated or untreated HTN and predefined combinations of CV risk factors or CVD</p> <p>VAL: Valsartan step-up therapy  Step 1: valsartan 80 mg  Step 2: valsartan 160 mg  Step 3: valsartan 160 mg + HCTZ 12.5 mg  Step 4: valsartan 160 mg + HCTZ 25 mg  Step 5: other HTN drugs</p> <p>AML: Amlodipine step-up therapy  Step 1: amlodipine 5 mg  Step 2: amlodipine 10 mg  Step 3: amlodipine 10 mg + HCTZ 12.5 mg  Step 4: amlodipine 10 mg + HCTZ 25 mg  Step 5: other HTN drugs</p> <p>N: 15,313</p> <p>Mean exposure to study medication 3.6 years; mean 4.2 years F/U</p> <p>Good</p>	 <b>All-cause death</b> HR (95% CI) for VAL: 1.04 (0.94, 1.14) p = 0.45	 <b>Fatal and non-fatal MI</b> HR (95% CI) for VAL: 1.19 (1.02, 1.38) p = 0.02	 <b>Fatal and non-fatal stroke</b> HR (95% CI) for VAL: 1.15 (0.98, 1.35) p = 0.08	 <b>Fatal and non-fatal HF</b> HR (95% CI) for VAL: 0.89 (0.77, 1.03) p = 0.12	 <b>Primary composite of time to first cardiac event</b> HR (95% CI) for VAL: 1.04 (0.94, 1.15) p = 0.49   <b>Cardiac morbidity</b> HR (95% CI) for VAL: 1.02 (0.91, 1.15) p = 0.71   <b>Cardiac mortality</b> HR (95% CI) for VAL: 1.01 (0.86, 1.18) p = 0.90		 <b>Dizziness</b> 16.5% VAL vs 14.3% AML p <0.0001   <b>Headaches</b> 14.7% VAL vs 12.5% AML p <0.0001   <b>New onset DM</b> OR (95% CI) for VAL: 0.77 (0.69, 0.86) p < 0.0001   <b>Hypokalemia</b> 3.5% VAL vs 6.2% AML p <0.0001   <b>Peripheral edema</b> 14.9% VAL vs 32.9% AML p <0.0001
<p><b>Kyoto Heart Study, 2009</b></p> <p>Adults, ages ≥20 years, with uncontrolled HTN for at least 4 weeks and one or more CV risk factors</p> <p>VAL: Valsartan 80 mg daily; flexibly adjusted to a dose of 40-80 mg as needed to control BP; dose doubled after</p>	 <b>All-cause mortality</b> HR (95% CI) for VAL: 0.76 (0.4, 1.3) p = 0.32851	 <b>Acute MI</b> HR (95% CI) for VAL: 0.65 (0.2, 1.8) p = 0.39466	 <b>Stroke</b> HR (95% CI) for VAL: 0.55 (0.3, 0.9) p = 0.01488	 <b>Heart failure</b> HR (95% CI) for VAL: 0.65 (0.3, 1.3) p = 0.20857	 <b>Composite of fatal and non-fatal CV events (stroke, TIA, MI, new occurrence or exacerbation of angina pectoris, new occurrence or</b>	 <b>Transition to dialysis or doubling serum Cr</b> HR (95% CI) for VAL: 0.43 (0.2, 1.1) p = 0.34666	 <b>New onset DM</b> HR (95% CI) for VAL: 0.67 (0.5, 0.9) p = 0.02817

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p>4 weeks if initial dose could not achieve BP goal; after 8 weeks, anti-HTN drugs other than ARBs or ACE allowed if necessary</p> <p>CT: conventional therapy; anti-HTN drugs other than ARB and ACE provided to patients to reach target BP; "usual" dosage administered for first 4 weeks and titrated upward to "high" dosage if BP not controlled; other anti-HTN drugs (excluding ACE and ARBs) added at 8 weeks if necessary.</p> <p>N: 3,031</p> <p>3.27 years</p> <p>Fair</p>		<p style="text-align: center;"></p> <p style="text-align: center;"><b>Dissecting aneurysm of aorta</b> HR (95% CI) for VAL: 0.60 (0.1, 2.5) p = 0.69987</p>			<p><b>exacerbation of HF, dissecting aneurysm of the aorta, lower limb arterial obstruction, emergency thrombosis, transition to dialysis, and doubling of plasma Cr levels)</b> HR (95% CI) for VAL: 0.55 (0.4, 0.7) P = 0.00001</p> <p style="text-align: center;"></p> <p><b>CV death</b> HR (95% CI) for VAL: 0.66 (0.3, 1.6) p = 0.37121</p>		<p style="text-align: center;"></p> <p style="text-align: center;"><b>Dry cough</b> 0.1% VAL vs 0.3% CT p = NS</p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Elevated serum potassium</b> 0.3% VAL vs 0.1% CT p = NS</p>

## Exhibit N: Evidence from randomized controlled trials of antihypertensive drug therapy with combination drugs

**Legend**  
**Shapes:** *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified  
**Color:** **Green** = Statistically significant where the diuretic combination did better ( $p < 0.05$ ) **Red** = Statistically significant where the diuretic combination did worse **Yellow** =  $p \geq 0.05$  and  $\leq 0.10$  **Clear** =  $p > 0.10$   
**Blue** =  $p$  value not reported

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
<p><b>ACCOMPLISH, 2008</b></p> <p>Adults, ages <math>\geq 60</math> with one risk factor or 55 to 59 with 2 or more risk factors</p> <p>BEN-HCTZ: Benazepril-HCTZ single pill formulation: 20/12.5 mg QD (max: 40/25)</p> <p>BEN-AML: Benazepril-Amlodipine single pill formulation: 20/5 mg QD (max: 40/10)</p> <p>N: 11,506</p> <p>Mean 36 months</p> <p>Good</p> <p>Panel Comments: After mean 30 months treatment exposure, the DSMB observed a difference between the two treatment groups that exceeded the boundary of the prespecified stopping rule and recommended early termination of the study</p>	<p style="text-align: center;"></p> <p style="text-align: center;"><b>Death from any cause</b></p> <p>HR (95% CI) for BEN-AML: 0.90 (0.76, 1.07)  <math>p = 0.24</math></p>	<p style="text-align: center;"></p> <p style="text-align: center;"><b>Fatal and non-fatal MI</b></p> <p>HR (95% CI) for BEN-AML: 0.78 (0.62, 0.99)  <math>p = 0.04</math></p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Coronary revascularization procedure</b></p> <p>HR (95% CI) for BEN-AML: 0.86 (0.74, 1.00)  <math>p = 0.04</math></p>	<p style="text-align: center;"></p> <p style="text-align: center;"><b>Fatal and non-fatal stroke</b></p> <p>HR (95% CI) for BEN-AML: 0.84 (0.65, 1.08)  <math>p = 0.17</math></p>	<p style="text-align: center;"></p> <p style="text-align: center;"><b>Hospitalization for CHF</b></p> <p>HR (95% CI) for BEN-AML: 1.04 (0.79, 1.38)  <math>p = 0.77</math></p>	<p style="text-align: center;"></p> <p style="text-align: center;"><b>Composite of CV events</b></p> <p>HR (95% CI) for BEN-AML: 0.83 (0.73, 0.93)  <math>p = 0.002</math></p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Primary end point plus hospitalization for CHF</b></p> <p>HR (95% CI) for BEN-AML: 0.83 (0.74, 0.92)  <math>p = 0.0005</math></p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Composite of CV events and death from CV causes</b></p> <p>HR (95% CI) for BEN-AML: 0.80 (0.72, 0.90)  <math>p &lt; 0.001</math></p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Composite of death from CV events, non-fatal MI, and non-fatal stroke</b></p> <p>HR (95% CI) BEN-</p>		<p style="text-align: center;"></p> <p style="text-align: center;"><b>Any adverse event of dizziness</b></p> <p>25.4% BEN-HCTZ vs 20.7% BEN-AML  <math>p = \text{NR}</math></p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Any adverse event of peripheral edema</b></p> <p>13.4% BEN-HCTZ vs 31.2% BEN-AML  <math>p = \text{NR}</math></p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Serious adverse event of peripheral edema</b></p> <p>0.1% BEN-HCTZ vs 0.2% BEN-AML  <math>p = \text{NR}</math></p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Drug-related serious adverse event of peripheral edema</b></p> <p>&lt;0.1% BEN-HCTZ vs 0.1% BEN-AML  <math>p = \text{NR}</math></p> <p style="text-align: center;"></p> <p style="text-align: center;"><b>Any adverse event of dry cough</b></p> <p>21.2% BEN-HCTZ vs 20.5% BEN-AML  <math>p = \text{NR}</math></p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
					<p>AML: 0.79 (0.67, 0.92) p = 0.002</p>  <p><b>Death from CV causes</b> HR (95% CI) for BEN-AML: 0.80 (0.62, 1.03) p = 0.08</p>		 <p><b>Serious adverse event of dry cough</b> 0.1% BEN-HCTZ vs 0.1% BEN-AML p = NR</p>  <p><b>Drug-related serious adverse event of dry cough</b> 0.1% BEN-HCTZ vs 0.1% BEN-AML p = NR</p>  <p><b>Any adverse event of hyperkalemia</b> 0.6% BEN-HCTZ vs 0.6% BEN-AML p = NR</p>  <p><b>Serious adverse event of hyperkalemia</b> 0.2% BEN-HCTZ vs 0.2% BEN-AML p = NR</p>  <p><b>Drug-related serious adverse event of hyperkalemia</b> 0.1% BEN-HCTZ vs 0.1% BEN-AML p = NR</p>  <p><b>Any adverse event of hypokalemia</b> 0.3% BEN-HCTZ vs 0.1% BEN-AML</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
							<p>p = NR</p> <p></p> <p><b>Serious adverse event of hypokalemia</b> 0.2% BEN-HCTZ vs &lt;0.1% BEN-AML p = NR</p> <p></p> <p><b>Drug-related serious adverse event of hypokalemia</b> 0.0% BEN-HCTZ vs &lt;0.1% BEN-AML p = NR</p> <p></p> <p><b>Any adverse event of hypotension</b> 3.6% BEN-HCTZ vs 2.5% BEN-AML p = NR</p> <p></p> <p><b>Serious adverse event of hypotension</b> 0.5% BEN-HCTZ vs 0.4% BEN-AML p = NR</p> <p></p> <p><b>Drug-related serious adverse event of hypotension</b> 0.2% BEN-HCTZ vs 0.1% BEN-AML p = NR</p> <p></p> <p><b>Drug-related serious adverse event of angioedema</b></p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events			
							0.1% BEN-HCTZ vs <0.1% BEN-AML p = NR			
<p><b>ACCOMPLISH, 2010</b></p> <p><i>Prespecified secondary analysis of kidney outcomes</i> Bakris et al., 2010</p> <p>Adults, ages ≥ 60 with one risk factor or 55 to 59 with 2 or more risk factors</p> <p>BEN-HCTZ: Benazepril-HCTZ single pill formulation: 20/12.5 mg QD (max: 40/25) BEN-AML: Benazepril-Amlodipine single pill formulation: 20/5 mg QD (max: 40/10)</p> <p>N: 11,506</p> <p>Mean F/U 2.9 years</p> <p>Fair</p> <p>Panel Comments: Trial stopped early because of 20% reduction in CV risk recorded in BEN-AML group</p>					<p> <b>Progression of CKD and CV death</b> HR (95% CI) for BEN-AML: 0.63 (0.53, 0.74) p &lt;0.0001</p> <p> <b>Progression of CKD and all-cause mortality</b> HR (95% CI) for BEN-AML: 0.73 (0.64, 0.84) p &lt; 0.0001</p> <p><i>In patients aged ≥65 years</i></p> <p> <b>Progression of CKD and CV death</b> HR (95% CI) for BEN-AML: 0.68 (0.55, 0.83) p = 0.0002</p> <p> <b>Progression of CKD and all-cause mortality</b> HR (95% CI) for BEN-AML: 0.81 (0.68, 0.95) p = 0.010</p>				<p> <b>Progression of CKD</b> HR (95% CI) for BEN-AML: 0.52 (0.41, 0.65) p &lt;0.0001</p> <p> <b>Doubling of serum Cr</b> HR (95% CI) for BEN-AML: 0.51 (0.39, 0.63) p &lt;0.0001</p> <p> <b>Dialysis</b> HR (95% CI) for BEN-AML: 0.53 (0.21, 1.35) p = 0.180</p> <p> <b>eGFR &lt;15 mL/min/1.73m<sup>2</sup></b> BEN-AML: 1.06 (0.54, 2.05) p = 0.868</p> <p> <b>GFR decline, mL/min/1.73m<sup>2</sup> (SD)</b> -4.22 (16.3) BEN-HCTZ vs -0.88 (15.6) BEN-AML p = 0.01</p>	<p><i>Patients without CKD at baseline</i></p> <p> <b>Hypotension</b> 3.4% BEN-HCTZ vs 2.3% BEN-AML p = 0.0005</p> <p> <b>Hypokalemia</b> 0.3% BEN-HCTZ vs 0.1% BEN-AML p = 0.003</p> <p> <b>Dizziness</b> 25.5% BEN-HCTZ vs 20.3% BEN-AML p &lt;0.0001</p> <p> <b>Dry cough</b> 21.6% BEN-HCTZ vs 20.4% BEN-AML p = 0.14</p> <p> <b>Hyperkalemia</b> 0.4% BEN-HCTZ vs 0.4% BEN-AML p = 0.85</p> <p> <b>Angioedema</b> 0.6% BEN-HCTZ vs 0.9% BEN-AML p = 0.15</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
						<p><i>In patients aged ≥65 years</i></p>  <p><b>Progression of CKD</b> HR (95% CI) for BEN-AML: 0.50 (0.37, 0.67) p &lt;0.0001</p>  <p><b>Doubling of serum Cr</b> HR (95% CI) for BEN-AML: 0.49 (0.37, 0.67) p &lt;0.0001</p>  <p><b>Dialysis</b> HR (95% CI) for BEN-AML: 0.30 (0.08, 1.09) p = 0.053</p>  <p><b>eGFR &lt;15 mL/min/1.73m<sup>2</sup></b> HR (95% CI) for BEN-AML: 1.00 (0.43, 2.31) p = 0.99</p> <p><i>In patients with CKD at baseline</i></p> 	 <p><b>Peripheral edema</b> 13.1% BEN-HCTZ vs 31.0% BEN-AML p &lt;0.0001</p> <p><i>Patients with CKD at baseline</i></p>  <p><b>Hypotension</b> 5.5% BEN-HCTZ vs 4.3% BEN-AML p = 0.36</p>  <p><b>Hyperkalemia</b> 2.3% BEN-HCTZ vs 2.1% BEN-AML p = 0.89</p>  <p><b>Hypokalemia</b> 0.2% BEK-HCTZ vs 0% BEN-AML p = 0.30</p>  <p><b>Dizziness</b> 24.2% BEN-HCTZ vs 25.1% BEN-AML p = 0.73</p>  <p><b>Dry cough</b> 17.5% BEN-HCTZ vs 21.4% BEN-AML p = 0.10</p>

Study Criteria and Characteristics	Mortality Outcomes	Coronary Heart Disease Outcomes	Cerebrovascular Outcomes	Heart Failure Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
						<p>GFR decline, mL/min/1.73m<sup>2</sup> (SD)            -2.3 (10.6) BEN-HCTZ vs 1.6 (12.7) BEN-AML            p = 0.001</p>	<p>  <b>Angioedema</b>            0.4% BEN-HCTZ vs 1.6% BEN-AML            p = 0.04</p> <p>  <b>Peripheral edema</b>            16.0% BEN-HCTZ vs 33.7% BEN-AML            p &lt; 0.0001</p>

## SEARCH STRATEGY OVERVIEW AND SYNTAX OF QUERIES

This section provides a description of the search strategies. A search strategy is an expression of conditions connected by the logical operators AND, OR, and NOT.

Parentheses are used to group conditions. Each condition is described by attributes, operators, and values. Table 1 shows examples of queries and a description of results. A complete list of attributes used in search strategies with their explanation is listed in Table 2. Commonly used macro queries are defined in Table 3.

Table 1. Examples of simple queries

Query	Results
title=blood pressure	Articles with phrase “blood pressure” in article title
title,abstract=blood pressure	Articles with phrase “blood pressure” in article title or its abstract
blood pressure	When attribute name is skipped, “title, abstract” is assumed, therefore, the results are equivalent to query: title,abstract=blood pressure
title=(blood pressure or cholesterol)	Articles with phrases “blood pressure” or “cholesterol” in article title
title=blood pressure and abstract=(mortality or morbidity)	Articles with “blood pressure” in the title and words mortality or morbidity in the abstract.
((subject=Cardiovascular Diseases) with (qualifier=(prevention or epidemiology)))	Articles with MeSH heading “Cardiovascular Diseases” and subheadings ‘prevention’ or ‘epidemiology’
qualifier=mortality	Articles with MeSH subheading ‘mortality’
title,abstract,genre,subject=random?	Articles that include any word starting with ‘random’, e.g. ‘randomized’, ‘randomised’, random, etc.
abstract=?cholesterol?	Articles with abstracts including any word that includes subword ‘cholesterol’, e.g. hypocholesterolemia
not journalTitle=“ACP journal club”	Exclude articles from “ACP journal club”
publicationYear > 1997 and publicationYear < 2010	Articles from 1998 to 2009
(CVD %2 event?)	Articles with ‘CVD’ word in proximity of two words from word stem ‘event’

Table 2. Attributes, their values, and explanation

Attribute	Values
abstract	Text of abstract
title	Text of title
<no attribute specified>	Combined text of title and abstract

journalTitle	Journal name (as in PubMed)
publicationYear	Year of the publication, e.g. 2000
genre	Publication type (as in Pubmed)
language	eng for English
subject	MeSH subject headings
majorSubject	MeSH major subject headings
qualifier	MeSH subheadings
substance	MeSH substances
RecordContentSource	e.g. 'Pubmed', 'embase', 'cinahl'
recordStatus	e.g. 'delete'
pubmedid	Pubmed identifier
uuid	Internal unique identifier

Table 3. Common Macro Queries used in Search Strategies

Macro Name	Query
{RCT}	(((RecordContentSource=pubmed AND (genre=randomized controlled trial OR subject=random allocation OR subject=double-blind method OR subject=single-blind method OR (subject="Randomized Controlled Trials as Topic" and abstract=? and (title=trial or ((title=study or subject,genre=stud?) and subject=outcome?) )) )) OR ((? NOT RecordContentSource=pubmed) AND (genre=randomized OR (title,abstract=randomized AND title,abstract=controlled AND title,abstract=trial) OR title,abstract=random? OR subject=random allocation OR title,abstract=placebo OR subject=double-blind method OR subject=single-blind method))) AND language=eng?) NOT (title=(case report or commentary) OR genre=(letter or abstract or newspaper article or comment?))
{Systematic Review}	(((title=systematic review OR genre=meta-analysis OR title=meta-analysis OR title=systematic literature review OR (title,abstract=systematic review AND genre=review) OR genre=consensus development conference OR genre=practice guideline OR journalTitle=("Cochrane Database of Systematic Reviews" OR "Health technology assessment" OR "Evidence report/technology assessment (Summary)")) OR ((title=evidence based OR subject=evidence-based medicine OR title=best practice? OR title,abstract=evidence synthesis) AND (genre=review OR subject=diseases category OR subject=behavior and behavior mechanisms OR subject=therapeutics OR genre=evaluation studies OR genre=validation studies OR genre=guideline)) OR ((systematic OR systematically OR title,abstract=critical OR (study selection) OR (predetermined OR inclusion AND criteri?) OR exclusion criteri? OR "main outcome measures" OR "standard of care" OR "standards of care") AND (title,abstract=survey OR title,abstract=surveys OR overview? OR title,abstract=review OR title,abstract=reviews OR search? OR handsearch OR title,abstract=analysis OR title,abstract=critique OR appraisal OR (reduction

	AND risk AND (death OR recurrence))) AND (title,abstract=literature OR title,abstract=articles OR title,abstract=publications OR title,abstract=publication OR title,abstract=bibliography OR title,abstract=bibliographies OR title,abstract=published OR unpublished OR citation OR citations OR title,abstract=database OR title,abstract=internet OR title,abstract=textbooks OR references OR scales OR papers OR datasets OR title,abstract=trials OR meta-analy? OR (title,abstract=clinical AND title,abstract=studies) OR subject,title,abstract=treatment outcome))) AND language=eng?) NOT (title=(case report or commentary) OR genre=(letter or abstract or newspaper article or comment?))
{Cardiovascular Diseases}	Term in parentheses is MeSH-exploded and matched against subject headings, titles, and abstracts

In order to increase the readability of search strategies, conditions are grouped in meaningful components. There are three major types of components: study type query, Boolean search, and Boolean filter. These three components are connected with the AND operator, thus a citation must satisfy all three component queries in order to be retrieved. The inclusion/exclusion criteria for each question, which was defined using the PICOTSS structure (population, intervention, comparator, outcomes, timing, study design, and setting), are implemented in search strategies using the study type query, Boolean search, and Boolean filter.

- Study type query: consists of expressions that retrieve the study designs that are eligible for inclusion in the body of evidence as defined in the criteria (i.e., RCTs, systematic reviews, prospective cohort studies, etc.)
- Boolean search: implements expressions for population, intervention, outcomes, timing, and settings
- Boolean filter: implements an extension of search or comparator criterion.

Each of the components may use NOT queries to implement exceptions.

In addition to the strict Boolean strategy, results are ranked using keywords specified for integrated ranking of the TeraText Rank Engine and Content Analyst Conceptual Engine). Ranking helps to identify the most relevant citations first, as the titles and abstracts are analyzed for the presence and frequency of the keywords.

### Question 1 Search Strategy

**Question 1: Among adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?**

- Population: Adults age 18 or older with hypertension
- Intervention: Initiating antihypertensive pharmacologic therapy at a specific BP threshold identified in the study (i.e., the study has to have some BP entry criteria for starting patients on antihypertensive pharmacologic therapy).

- Comparator: Whatever the comparator group is in studies with the above intervention. It could be a group in which antihypertensive pharmacological therapy is initiated at a different BP threshold (we conducted this search and no studies were found), or it could be a control group that received placebo, usual care, or no treatment.
- Outcomes: Overall mortality, CVD-related mortality, CKD-related mortality, myocardial infarction (MI), heart failure (HF), hospitalization for heart failure, stroke, coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), peripheral revascularization (includes carotid, renal, and lower extremity revascularization), end stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of eGFR

### Study Type Query

Study Types eligible for this Question: RCT, Systematic Review

- {RCT} OR {Systematic Review}

### Boolean Search

- (
- (subject,title,abstract=(hypertension or hypertensive?))
  - AND (subject,title,abstract=(blood pressure? or systole? or diastole? or systolic pressure? or diastolic pressure? or arterial pressure?) or BP or DBP or (SBP not spontaneous bacterial peritonitis) or ((systol? or diastol?) and (pressure? or mmHg or mm Hg)) )
  - AND (subject,qualifier,title,abstract=mortality or death? or subject="Cause of Death" or subject=(Fatal Outcome) or ((subject=(Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders or Stroke or Kidney)) with (qualifier=(prevention or epidemiology or etiology or physiopathology))) or (myocardial infarction or heart failure or stroke or cerebrovascular disorder? or cerebrovascular event? or kidney failure or chronic kidney disease? or CKD) or subject,title,abstract=(Myocardial Revascularization) or subject,title,abstract=Creatinine or subject,title,abstract=(Glomerular Filtration Rate) or GFR or hospitalization or coronary revascularization or angioplasty or stent? or peripheral revascularization or carotid or extremity revascularization or end stage renal disease or ESRD or ("aggressive therapy" and (goal? or target?) and (mmHg or "mm Hg"))) or morbidity )
  - AND ( ((subject=Antihypertensive) with (qualifier="therapeutic use")) or ((subject=Hypertension) with (qualifier="drug therapy")) or ((antihypertensive or anti-hypertensive) and ("drug therapy" or "drug treatment")) or ("pharmacologic therapy" or "pharmacologic lowering of blood pressure") or ((subject=("Sodium Chloride Symporter Inhibitors" or "Adrenergic alpha-Antagonists" or "Adrenergic beta-Antagonists" or "Angiotensin-Converting Enzyme Inhibitors" or "Calcium

Channel Blockers" or Ganglionic Blockers or Chlorisondamine or Hexamethonium or Hexamethonium Compounds or Mecamylamine or Pempidine or Pentolinium Tartrate or Trimethaphan or "Vasodilator Agents" or "Endothelium-Dependent Relaxing Factors" or "Receptors, Angiotensin" or "Angiotensin II Type 1 Receptor Blockers" or Renin or Aldosterone or Mineralocorticoids or Endothelin?)) with (qualifier="therapeutic use")) or ((subject="Renin-Angiotensin System") with (qualifier="drug effects")) or (Subject,substance=("1-0-octadecyl 2-0-acetyl sn-glycero-3-phosphorylcholine" or "1-hexadecyl-2-acetyl-glycero-3-phosphocholine" or "1-Sarcosine-8-Isoleucine Angiotensin II" or "3,4-Dichloro-N-methyl-N-(2-(1-pyrrolidiny) cyclohexyl) benzeneacetamide, (trans) Isomer" or "3-morpholino-sydnonimine" or "3-nitropropionic acid" or "5-(dimethylamino)(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide" or "Acebutolol" or "Adrenomedullin" or "AE0047" or "alfuzosin" or "Alprenolol" or "Amlodipine" or "amlodipine-valsartan" or "amosulalol" or "angiotensin I (1-7)" or "aprikalim" or "Atenolol" or "atenolol, chlortalidone drug combinations" or "atrial natriuretic factor prohormone (103-126)" or "B-HT 933" or "BAYI 5240" or "benazepril" or "bendazole" or "Bendigon" or "Bendroflumethiazide" or "benoxathian" or "Bepridil" or "berbamine" or "Betaxolol" or "Bethanidine" or "bimakalim" or "bimatoprost" or "bis(p-chlorophenyl)acetic acid" or "Bisoprolol" or "bisoprolol, hydrochlorothiazide drug combination" or "bosentan" or "BQ 22-708" or "BQ 788" or "Bretylum Tosylate" or "brimonidine" or "Bupranolol" or "cadralazine" or "candesartan" or "candesartan cilexetil" or "candoxatril" or "Captopril" or "Carteolol" or "carvedilol" or "Celiprolol" or "CGS 21680" or "Chlorisondamine" or "Chlorothiazide" or "Chlorthalidone" or "Cilazapril" or "clentiazem" or "Clonidine" or "clonidine, chlorthalidone drug combination" or "Cromakalim" or "cycletanide" or "cyclo(Trp-Asp-Pro-Val-Leu)" or "Cyclopenthiiazide" or "cyclothiazide" or "dauricine" or "Debrisoquin" or "diallyl disulfide" or "Diazoxide" or "Dihydralazine" or "Dihydroalprenolol" or "Diltiazem" or "dimentiapramine" or "dorzolamide" or "Doxazosin" or "efonidipine" or "Enalapril" or "Enalaprilat" or "epanolol" or "Epoprostenol" or "eprosartan" or "essential 303 forte" or "etozolin" or "EXP3174" or "Felodipine" or "Fenoldopam" or "ferulic acid" or "FK 409" or "flesinoxan" or "Fosinopril" or "fosinoprilic acid" or "grayanotoxin I" or "Guanabenz" or "guanadrel" or "Guanethidine" or "Guanfacine" or "Hexamethonium" or "Hexamethonium Compounds" or "Hydralazine" or "Hydrochlorothiazide" or "hydrochlorothiazide-triamterene" or "Hydroflumethiazide" or "imidapril" or "Indapamide" or "indapamide, perindopril drug combination" or "indenolol" or "Indoramin" or "indorenate" or "irbesartan" or "isopropyl unoprostone" or "Isradipine" or "K 351" or "Kallidin" or "Ketanserin" or "L 158809" or "Labetalol" or "lacidipine" or "latanoprost" or "lercanidipine" or "Lisinopril" or "lofexidine" or "Losartan" or "manidipine" or "Mecamylamine" or "medroxalol" or "medullipin I" or "Methyldopa" or "Metipranolol" or "Metolazone" or "Metoprolol" or "Mibefradil" or "Minoxidil" or "monatepil" or "moxonidine" or "Muzolimine" or "N(1),N(11) diethylnorspermine" or "N(1),N(14) bis(ethyl)homospermine" or "N,N-di-n-propyldopamine" or "N-cyano-N'-(2-nitroxyethyl)-3-pyridinecarboximidamide methanesulfonate" or "Nadolol" or "naftopidil" or "nebivolol" or "Nicardipine" or "Nicorandil" or "niguldipine" or "nilvadipine" or "Nimodipine" or "NIP 121" or "Nisoldipine" or "Nitrendipine" or "Nitroprusside" or "oleuropein" or "olmesartan medoxomil" or "omapatrilat" or "Oxprenolol" or "parathyroid hormone-related protein (1-34)" or "Pargyline" or "Pempidine" or "Penbutolol" or "Pentolinium Tartrate" or "Perindopril" or "Phenoxybenzamine" or "Phentolamine" or "Pinacidil" or "Pindolol" or "Piperoxan" or "Polythiazide" or "Prazosin" or

"Propranolol" or "Protoveratrines" or "quinapril" or "Ramipril" or "remikiren" or "rentiapril" or "Reserpine" or "rilmenidine" or "ryodipine" or "Saralasin" or "scoparone" or "sesamin" or "talinolol" or "temocapril hydrochloride" or "Teprotide" or "terlipressin" or "tetrahydropalmatine" or "tibolone" or "Ticrynafen" or "Timolol" or "tobanum" or "tocopherylquinone" or "Todalazine" or "Tolazoline" or "torseamide" or "trandolapril" or "travoprost" or "treprostinil" or "Trichlormethiazide" or "trimazosin" or "Trimethaphan" or "urapidil" or "valsartan" or "Veratrum Alkaloids" or "Vincamine" or "viprostol" or "Viskaldix" or "Xipamide" or "Y 26763" or "Y 27632" or "zofenopril" or Spironolactone or Eplerenone or aliskiren or telmisartan) and subject,abstract,title,qualifier=("drug therapy" or "drug treatment" or "drug effects" or "therapeutic use")) )

- AND (publicationYear>1965 and publicationYear<2010)
- AND language=eng)
- NOT genre=(comment? or abstract)
- NOT journalTitle="ACP journal club"
- NOT (journalTitle="Current Hypertension Reports" not abstract=?)
- NOT (subject,title,abstract=angioplasty and subject,title,abstract=(renal artery obstruction or renal artery stenosis))
- NOT title=(summar? for patients)
- NOT genre="practice guideline"
- NOT recordStatus=delete

### Boolean Filter

- title,abstract,subject,substance=(placebo?)
- or "no treatment" or ((without or no) %3 medication) or "control group" or (("effects of" or "impact of" or decreased or reduced) %2 treatment)
- or title=(study or trial or investigators)
- or genre="meta-analysis"
- or (RecordContentSource=pubmed NOT author=?)

### Question 1 Search Strategy Results and PRISMA Diagram

The following databases were searched for RCTs and systematic reviews and meta-analyses (SR/MA) of RCTs to answer Question 1:

- PubMed from January 1966 to December 2009
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycInfo from January 1998 to July 2008
- EBM (Evidence-based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

Because we conducted our own systematic review using original publications dating back to 1966, SR/MA of RCTs conducted and published by others were not used as part of the formal evidence review (i.e., they were not abstracted and included in the Evidence and Summary Tables). However, SR/MA

identified in the search that met the criteria were eligible for use as reference material in the report. Evidence and Summary Tables consisted only of data from the original publications of eligible RCTs, and these tables formed the basis for panel deliberations.

Duplicate citations which arise from the same citation being found in more than one database were removed from the Central Repository prior to screening. More information on the Central Repository is available in the Appendix Section for Literature search infrastructure, search strategy development and validation. The search produced 1495 citations. Three additional citations were added for review. Two of these citations were for the ACCORD [ACCORD Study Group, 2010] and ROADMAP [Haller, 2011] studies which were published after December 2009. Per NHLBI policy, these citations could be formally reviewed for inclusion after the search cut-off date because they met the criteria of being a multi-center RCT of greater than 2,000 participants. The third citation was a secondary publication of the HDFP trial [Borhani, 1986] which was not identified in the initial search.

The titles and abstracts of these 1498 publications were screened against the inclusion/exclusion criteria independently by two reviewers which resulted in the retrieval of 304 full-text papers. These papers were independently screened by two reviewers and 263 of these publications were excluded on one or more of the inclusion/exclusion criteria. An additional 16 publications were excluded because they were rated as poor quality using the NHLBI Quality Assessment Tool for Controlled Intervention Studies. 25 RCTs were included in the Question 1 Evidence Base.

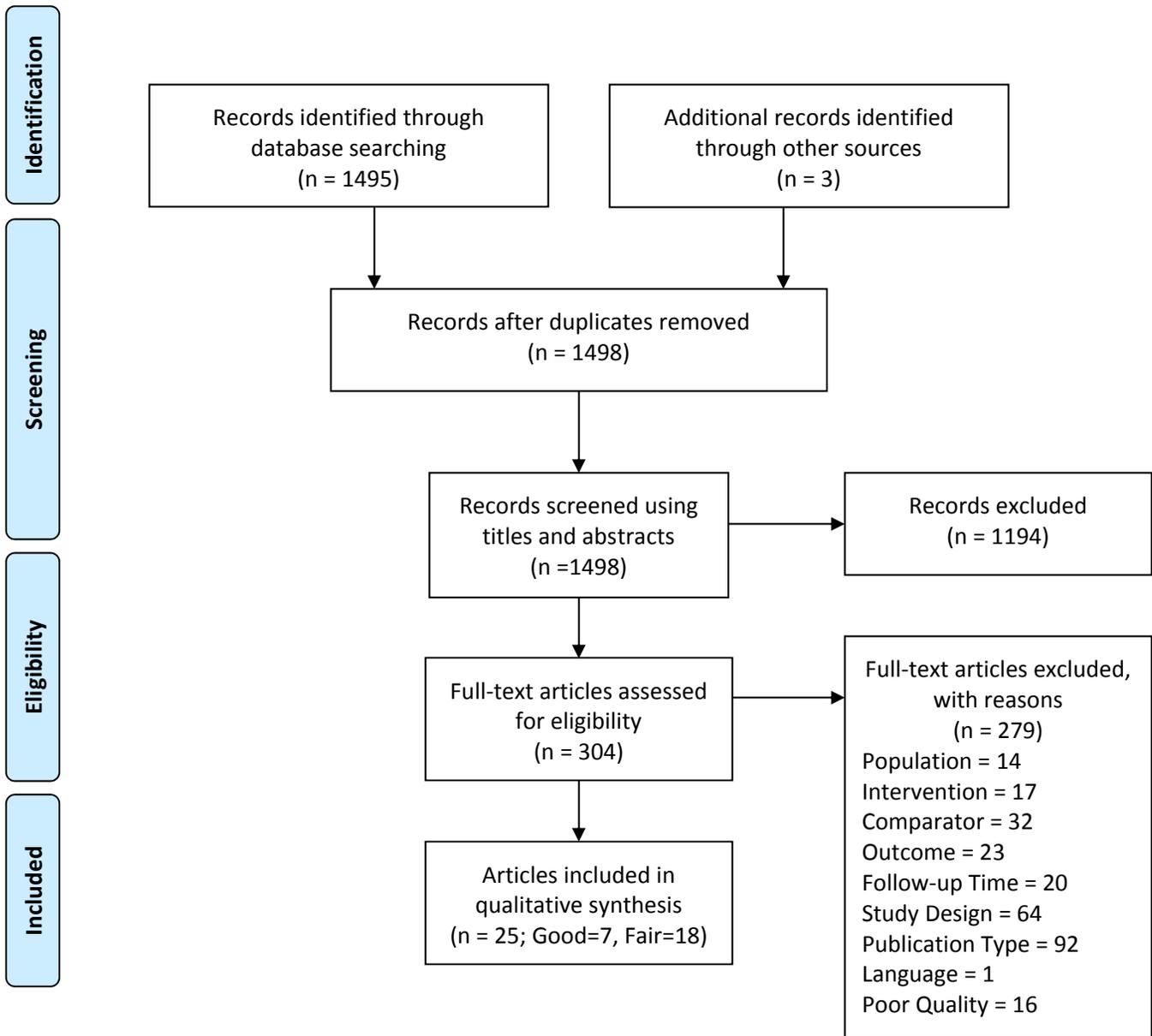


Figure 1: PRISMA Diagram for Question 1

## Question 2 Search Strategy

### Question 2: Among adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?

- Population: Adults age 18 or older with hypertension
- Intervention: Antihypertensive pharmacologic therapy to a specified BP goal. If the primary intent of the treatment was not specifically to treat/lower BP (e.g. use of an ACE/ARB to treat or prevent heart failure; use of a beta blocker to treat angina or MI), it should be excluded.
- Comparator: Comparator: Comparator group has a different BP goal than the intervention group, or the comparator group has no stated BP goal while the intervention group has a specific BP goal. At least one study arm must have a BP goal and the other study arms cannot have the same goal unless the comparator is a placebo. If the comparator is a placebo, the BP goal of the placebo group can be the same as the BP goal of the intervention group because the assumption is that the goal for the placebo group is a sham goal for blinding purposes, with the expectation that most participants on placebo will not reach the goal because they are not on active therapy.
- Outcomes: Included studies must report BP and at least one of these outcomes: Overall mortality, CVD-related mortality, CKD-related mortality, myocardial infarction (MI), heart failure (HF), hospitalization for heart failure, stroke, coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), peripheral revascularization (includes carotid, renal, and lower extremity revascularization), end stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of eGFR

### Study Type Query

Study Types eligible for this Question: RCT, Systematic Review

- {RCT} OR {Systematic Review}

### Boolean Search

- (
- (subject,qualifier,title,abstract=mortality or death? or morbidity or subject="Cause of Death" or subject="Fatal Outcome"
  - or ((subject=(Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders or Stroke or Kidney)) with (qualifier=(prevention or epidemiology or etiology or physiopathology)))
  - or (myocardial infarction or heart failure or stroke or cerebrovascular disorder? or cerebrovascular event? or kidney failure or chronic kidney disease? or CKD)
  - or subject,title,abstract=(Myocardial Revascularization)
  - or subject,title,abstract=Creatinine
  - or subject,title,abstract=(Glomerular Filtration Rate) or GFR or eGFR or estGFR
  - or hospitalization or coronary revascularization or angioplasty or stent?
  - or peripheral revascularization or carotid or extremity revascularization or end stage renal disease or ESRD
  - or ("aggressive therapy" and (goal? or target?) and (mmHg or "mm Hg")) or morbidity

)

- AND** ( ((subject=Antihypertensive) with (qualifier=("therapeutic use" or "administration & dosage"))) )
- or ((subject=Hypertension) with (qualifier="drug therapy"))
  - or ((antihypertensive or anti-hypertensive) and ("drug therapy" or "drug treatment" or dose or dosage))
  - or (?pharmacologic %2 (therapy or intervention or lowering or treatment))
  - or ((subject=("Sodium Chloride Symporter Inhibitors" or "Adrenergic alpha-Antagonists" or "Adrenergic beta-Antagonists" or "Angiotensin-Converting Enzyme Inhibitors" or "Calcium Channel Blockers" or Ganglionic Blockers or Chlorisondamine or Hexamethonium or Hexamethonium Compounds or Mecamylamine or Pempidine or Pentolinium Tartrate or Trimethaphan or "Vasodilator Agents" or "Endothelium-Dependent Relaxing Factors" or "Receptors, Angiotensin" or "Angiotensin II Type 1 Receptor Blockers" or Renin or Aldosterone or Mineralocorticoids or Endothelin?)) with (qualifier=("therapeutic use" or "administration & dosage"))) )
  - or ((subject="Renin-Angiotensin System") with (qualifier="drug effects"))
  - or (Subject,substance=("1-0-octadecyl 2-0-acetyl sn-glycero-3-phosphorylcholine" or "1-hexadecyl-2-acetyl-glycero-3-phosphocholine" or "1-Sarcosine-8-Isoleucine Angiotensin II" or "3,4-Dichloro-N-methyl-N-(2-(1-pyrrolidinyl) cyclohexyl) benzeneacetamide, (trans) Isomer" or "3-morpholino-sydnominine" or "3-nitropropionic acid" or "5-(dimethylamino)(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide" or "Acebutolol" or "Adrenomedullin" or "AE0047" or "alfuzosin" or "Alprenolol" or "Amlodipine" or "amlodipine-valsartan" or "amosulalol" or "angiotensin I (1-7)" or "aprikalim" or "Atenolol" or "atenolol, chlortalidone drug combinations" or "atrial natriuretic factor prohormone (103-126)" or "B-HT 933" or "BAYI 5240" or "benazepril" or "bendazole" or "Bendigon" or "Bendroflumethiazide" or "benoxathian" or "Bepridil" or "berbamine" or "Betaxolol" or "Bethanidine" or "bimakalim" or "bimatoprost" or "bis(p-chlorophenyl)acetic acid" or "Bisoprolol" or "bisoprolol, hydrochlorothiazide drug combination" or "bosentan" or "BQ 22-708" or "BQ 788" or "Bretylum Tosylate" or "brimonidine" or "Bupranolol" or "cadralazine" or "candesartan" or "candesartan cilexetil" or "candoxatril" or "Captopril" or "Carteolol" or "carvedilol" or "Celiprolol" or "CGS 21680" or "Chlorisondamine" or "Chlorothiazide" or "Chlorthalidone" or "Cilazapril" or "clentiazem" or "Clonidine" or "clonidine, chlorthalidone drug combination" or "Cromakalim" or "cycletanide" or "cyclo(Trp-Asp-Pro-Val-Leu)" or "Cyclopenthiiazide" or "cyclothiazide" or "dauricine" or "Debrisoquin" or "diallyl disulfide" or "Diazoxide" or "Dihydralazine" or "Dihydroalprenolol" or "Diltiazem" or "dimedtiapramine" or "dorzolamide" or "Doxazosin" or "efonidipine" or "Enalapril" or "Enalaprilat" or "epanolol" or "Epoprostenol" or "eprosartan" or "essential 303 forte" or "etozolin" or "EXP3174" or "Felodipine" or "Fenoldopam" or "ferulic acid" or "FK 409" or "flesinoxan" or "Fosinopril" or "fosinoprilic acid" or "grayanotoxin I" or "Guanabenz" or "guanadrel" or "Guanethidine" or "Guanfacine" or "Hexamethonium" or "Hexamethonium Compounds" or "Hydralazine" or "Hydrochlorothiazide" or "hydrochlorothiazide-triamterene" or "Hydroflumethiazide" or "imidapril" or "Indapamide" or "indapamide, perindopril drug combination" or "indenolol" or "Indoramin" or "indorenate" or "irbesartan" or "isopropyl unoprostone" or "Isradipine" or "K 351" or "Kallidin" or "Ketanserin" or "L 158809" or "Labetalol" or "lacidipine" or "latanoprost" or "lercanidipine" or "Lisinopril" or "lofexidine" or "Losartan" or

"manidipine" or "Mecamylamine" or "medroxalol" or "medullipin I" or "Methyldopa" or "Metipranolol" or "Metolazone" or "Metoprolol" or "Mibefradil" or "Minoxidil" or "monatepil" or "moxonidine" or "Muzolimine" or "N(1),N(11) diethylnorspermine" or "N(1),N(14) bis(ethyl)homospermine" or "N,N-di-n-propyldopamine" or "N-cyano-N'-(2-nitroxyethyl)-3-pyridinecarboximidamide methanesulfonate" or "Nadolol" or "naftopidil" or "nebivolol" or "Nicardipine" or "Nicorandil" or "niguldipine" or "nilvadipine" or "Nimodipine" or "NIP 121" or "Nisoldipine" or "Nitrendipine" or "Nitroprusside" or "oleuropein" or "olmesartan medoxomil" or "omapatrilat" or "Oxprenolol" or "parathyroid hormone-related protein (1-34)" or "Pargyline" or "Pempidine" or "Penbutolol" or "Pentolinium Tartrate" or "Perindopril" or "Phenoxybenzamine" or "Phentolamine" or "Pinacidil" or "Pindolol" or "Piperoxan" or "Polythiazide" or "Prazosin" or "Propranolol" or "Protoveratrine" or "quinapril" or "Ramipril" or "remikiren" or "rentiapril" or "Reserpine" or "rilmenidine" or "ryodipine" or "Saralasin" or "scoparone" or "sesamin" or "talinolol" or "temocapril hydrochloride" or "Teprotide" or "terlipressin" or "tetrahydropalmatine" or "tibolone" or "Ticrynafen" or "Timolol" or "tobanum" or "tocopherylquinone" or "Todalazine" or "Tolazoline" or "torseamide" or "trandolapril" or "travoprost" or "treprostinil" or "Trichlormethiazide" or "trimazosin" or "Trimethaphan" or "urapidil" or "valsartan" or "Veratrum Alkaloids" or "Vincamine" or "viprostol" or "Viskaldix" or "Xipamide" or "Y 26763" or "Y 27632" or "zofenopril" or Spironolactone or Eplerenone or aliskiren or telmisartan) and subject,abstract,title,qualifier=("drug therapy" or "drug treatment" or "drug effects" or "therapeutic use" or "administration & dosage" or dose or dosage)) )

AND (publicationYear>1965 and publicationYear<2010) and language=eng)

NOT genre=(comment? or abstract)

NOT journalTitle="ACP journal club"

NOT (journalTitle="Current Hypertension Reports" not abstract=?)

NOT title=(summar? for patients)

NOT genre="practice guideline"

NOT (subject,title,abstract=angioplasty and subject,title,abstract=(renal artery obstruction or renal artery stenosis))

NOT subject="ocular hypertension"

NOT recordStatus=delete

### **Boolean Filter**

title,abstract,subject,substance=(placebo?)

or "no treatment" or ((without or no) %3 medication) or "control group"

or (("effects of" or "impact of" or decreased or reduced or allocation) %2 treatment)

or title=(study or trial or investigators) or genre="Multicenter Study"

or (genre="Comparative Study" and subject="Drug Combinations")

or Subject=(Prognosis or "Severity of Illness Index" or Clinical Trials as Topic)

or ((blood pressure or BP or low) %2 (goal? or target?))

or ((intensive or aggressive or moderate or usual or conventional or strict or standard or rigorous or immediate or delayed) %5 (versus or group))

or (genre="meta-analysis")

or (((subject=Hypertension) with (qualifier=drug therapy)) and (? not abstract=?))  
or (RecordContentSource=pubmed NOT author=?)

### Question 2 Search Strategy Results and PRISMA Diagram

The following databases were searched for RCTs and systematic reviews and meta-analyses (SR/MA) of RCTs to answer Question 2:

- PubMed from January 1966 to December 2009
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycInfo from January 1998 to July 2008
- EBM (Evidence-based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

As in Question 1, systematic reviews and meta-analyses were not used as part of the formal evidence review (i.e., they were not abstracted and included in the Evidence and Summary Tables). However, SR/MAs identified in the search that met the criteria were eligible for use as reference materials in the report.

Duplicate citations which arise from the same citation being found in more than one database were removed from the Central Repository prior to screening. The search produced 4015 citations. Three additional citations were added for review. These citations were for the ACCORD [ACCORD Study Group, 2010], VALISH [Ogihara, 2010] and ROADMAP [Haller, 2011] studies which were published after December 2009. Per NHLBI policy, these citations could be formally reviewed for inclusion after the search cut-off date because they met the criteria of being an RCT of greater than 2,000 participants. ACCORD and VALISH met the eligibility criteria and were included in the evidence review. ROADMAP did not meet the criteria because subjects in both the intervention and comparison groups were treated to the same blood pressure goal.

A natural language processing (NLP) filter was used to identify studies with sample sizes less than 100. The NLP filter was executed against titles and abstracts. 2,038 publications were automatically excluded using the NLP filter because they were of studies with sample sizes less than 100. The titles and abstracts of the 1980 remaining publications were screened against the inclusion/exclusion criteria independently by two reviewers which resulted in the retrieval of 585 full-text papers. These papers were independently screened by two reviewers and 519 of these publications were excluded on one or more of the inclusion/exclusion criteria. An additional 29 publications were excluded because they were rated as poor quality using the NHLBI Quality Assessment Tool for Controlled Intervention Studies. 37 RCTs were included in the Question 2 Evidence Base.

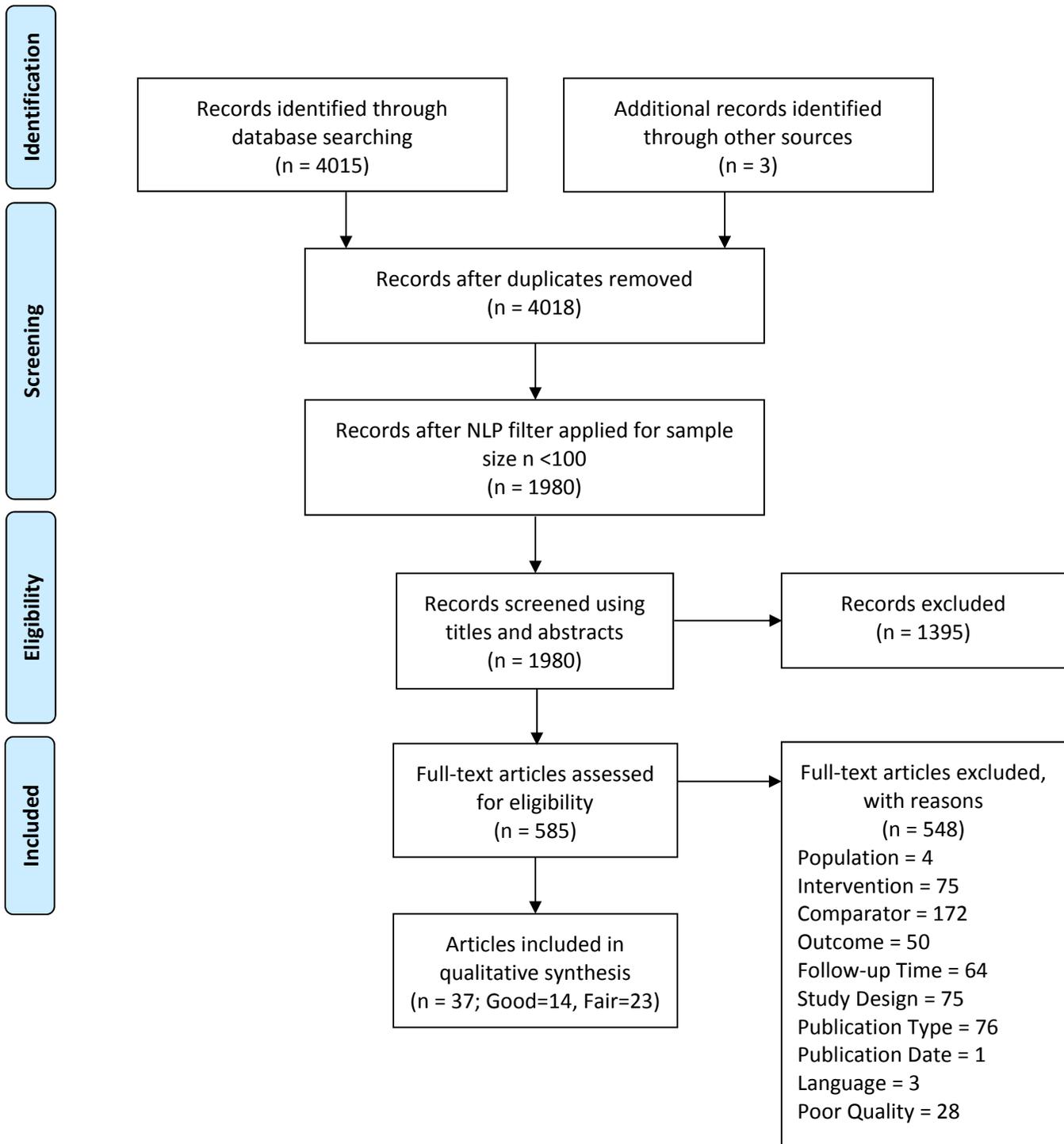


Figure 2: PRISMA Diagram for Question 2

### Question 3 Search Strategy

#### Question 3: In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

- Population: Adults age 18 or older with hypertension
- Intervention: Antihypertensive drug or drug class that is specified in the study
- Comparator: Different antihypertensive drug or drug class that is compared in the study to the intervention drug or drug class
- Outcomes: Overall mortality, CVD-related mortality, CKD-related mortality, myocardial infarction (MI), heart failure (HF), hospitalization for heart failure, stroke, coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), peripheral revascularization (includes carotid, renal, and lower extremity revascularization), end stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of eGFR

#### Study Type Query

Study Types eligible for this Question: RCT, Systematic Review

- {RCT} OR {Systematic Review}

#### Boolean Search

(

- (subject,title,abstract=(hypertension or ?hypertensive?))
- AND (subject,qualifier,title,abstract=mortality or death? or died or subject=("Cause of Death" or "Fatal Outcome" or "Survival Rate"))
  - or ((subject=(Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders or Stroke or Kidney)) with (qualifier=(prevention or epidemiology or etiology or physiopathology)))
  - or (myocardial infarction? or heart failure? or stroke? or cerebrovascular disorder? or cerebrovascular event? or kidney failure? or chronic kidney disease? or CKD)
  - or subject,title,abstract="Renal Dialysis"
  - or subject,title,abstract="Myocardial Revascularization" or coronary revascularization
  - or subject,title,abstract=Creatinine
  - or subject,title,abstract="Glomerular Filtration Rate" or GFR
  - or subject,title,abstract="Internal Mammary-Coronary Artery Anastomosis"
  - or subject,title,abstract="Angioplasty, Transluminal, Percutaneous Coronary" or angioplasty or stent?
  - or hospitalization
  - or peripheral revascularization or carotid or extremity revascularization or end stage renal disease or ESRD
  - or (subject,qualifier,title,abstract=(complications or morbidity))
  - )
- AND ( ((subject=Antihypertensive) with (qualifier=("therapeutic use" or "adverse effects"))) )

- or ((subject=Hypertension) with (qualifier=("drug therapy" or "adverse effects"))) )
- or (subject="Drug Therapy, Combination")
- or ((antihypertensive or anti-hypertensive) and ("drug therapy" or "drug treatment" or "adverse effects" or harm? or drug? or safety or efficacy))
- or ("pharmacologic therapy" or "pharmacologic lowering of blood pressure")
- or ((subject=("Sodium Chloride Symporter Inhibitors" or "Adrenergic alpha-Antagonists" or "Adrenergic beta-Antagonists" or "Angiotensin-Converting Enzyme Inhibitors" or "Calcium Channel Blockers" or Diuretics or Ganglionic Blockers or Chlorisondamine or Hexamethonium or Hexamethonium Compounds or Mecamylamine or Pempidine or Pentolinium Tartrate or Trimethaphan or "Vasodilator Agents" or "Endothelium-Dependent Relaxing Factors" or "Receptors, Angiotensin" or "Angiotensin II Type 1 Receptor Blockers" or Renin or Aldosterone or Mineralocorticoids or Endothelin?)) with (qualifier="therapeutic use"))
- or ((subject="Renin-Angiotensin System") with (qualifier="drug effects"))
- or (Subject,substance=("1-0-octadecyl 2-0-acetyl sn-glycero-3-phosphorylcholine" or "1-hexadecyl-2-acetyl-glycero-3-phosphocholine" or "1-Sarcosine-8-Isoleucine Angiotensin II" or "3,4-Dichloro-N-methyl-N-(2-(1-pyrrolidiny) cyclohexyl) benzeneacetamide, (trans) Isomer" or "3-morpholino-sydnonimine" or "3-nitropropionic acid" or "5-(dimethylamino)(3,4-dimethyl-5-isoxazolyl)-1-naphthalenesulfonamide" or "Acebutolol" or "Adrenomedullin" or "AE0047" or "alfuzosin" or "Alprenolol" or "Amlodipine" or "amlodipine-valsartan" or "amosulalol" or "angiotensin I (1-7)" or "aprikalim" or "Atenolol" or "atenolol, chlortalidone drug combinations" or "atrial natriuretic factor prohormone (103-126)" or "B-HT 933" or "BAYI 5240" or "benazepril" or "bendazole" or "Bendigon" or "Bendroflumethiazide" or "benoxathian" or "Bepridil" or "berbamine" or "Betaxolol" or "Bethanidine" or "bimakalim" or "bimatoprost" or "bis(p-chlorophenyl)acetic acid" or "Bisoprolol" or "bisoprolol, hydrochlorothiazide drug combination" or "bosentan" or "BQ 22-708" or "BQ 788" or "Bretylum Tosylate" or "brimonidine" or "Bupranolol" or "cadralazine" or "candesartan" or "candesartan cilexetil" or "candoxatril" or "Captopril" or "Carteolol" or "carvedilol" or "Celiprolol" or "CGS 21680" or "Chlorisondamine" or "Chlorothiazide" or "Chlorthalidone" or "Cilazapril" or "clentiazem" or "Clonidine" or "clonidine, chlorthalidone drug combination" or "Cromakalim" or "cycletanide" or "cyclo(Trp-Asp-Pro-Val-Leu)" or "Cyclopentiazide" or "cyclothiazide" or "dauricine" or "Debrisoquin" or "diallyl disulfide" or "Diazoxide" or "Dihydralazine" or "Dihydroalprenolol" or "Diltiazem" or "dimeditiapramine" or "dorzolamide" or "Doxazosin" or "efonidipine" or "Enalapril" or "Enalaprilat" or "epanolol" or "Epoprostenol" or "eprosartan" or "essential 303 forte" or "etozolin" or "EXP3174" or "Felodipine" or "Fenoldopam" or "ferulic acid" or "FK 409" or "flesinoxan" or "Fosinopril" or "fosinoprilic acid" or "grayanotoxin I" or "Guanabenz" or "guanadrel" or "Guanethidine" or "Guanfacine" or "Hexamethonium" or "Hexamethonium Compounds" or "Hydralazine" or "Hydrochlorothiazide" or "hydrochlorothiazide-triamterene" or "Hydroflumethiazide" or "imidapril" or "Indapamide" or "indapamide, perindopril drug combination" or "indenolol" or "Indoramin" or "indorenate" or "irbesartan" or "isopropyl unoprostone" or "Isradipine" or "K 351" or "Kallidin" or "Ketanserin" or "L 158809" or "Labetalol" or "lacidipine" or "latanoprost" or "lercanidipine" or "Lisinopril" or "lofexidine" or "Losartan" or "manidipine" or "Mecamylamine" or "medroxalol" or "medullipin I" or "Methyldopa" or "Metipranolol" or "Metolazone" or "Metoprolol" or "Mibefradil" or "Minoxidil" or "monatepil" or "moxonidine" or

"Muzolimine" or "N(1),N(11) diethylnorspermine" or "N(1),N(14) bis(ethyl)homospermine" or "N,N-di-n-propyldopamine" or "N-cyano-N'-(2-nitroxyethyl)-3-pyridinecarboximidamide methanesulfonate" or "Nadolol" or "naftopidil" or "nebivolol" or "Nicardipine" or "Nicorandil" or "niguldipine" or "nilvadipine" or "Nimodipine" or "NIP 121" or "Nisoldipine" or "Nitrendipine" or "Nitroprusside" or "oleuropein" or "olmesartan medoxomil" or "omapatrilat" or "Oxprenolol" or "parathyroid hormone-related protein (1-34)" or "Pargyline" or "Pempidine" or "Penbutolol" or "Pentolinium Tartrate" or "Perindopril" or "Phenoxybenzamine" or "Phentolamine" or "Pinacidil" or "Pindolol" or "Piperoxan" or "Polythiazide" or "Prazosin" or "Propranolol" or "Protoveratrine" or "quinapril" or "Ramipril" or "remikiren" or "rentiapril" or "Reserpine" or "rilmenidine" or "ryodipine" or "Saralasin" or "scoparone" or "sesamin" or "talinolol" or "temocapril hydrochloride" or "Teprotide" or "terlipressin" or "tetrahydropalmatine" or "tibolone" or "Ticrynafen" or "Timolol" or "tobanum" or "tocopherylquinone" or "Todralazine" or "Tolazoline" or "torsemide" or "trandolapril" or "travoprost" or "treprostinil" or "Trichlormethiazide" or "trimazosin" or "Trimethaphan" or "urapidil" or "valsartan" or "Veratrum Alkaloids" or "Vincamine" or "viprostol" or "Viskaldix" or "Xipamide" or "Y 26763" or "Y 27632" or "zofenopril" or Spironolactone or Eplerenone or aliskiren or telmisartan) and subject,abstract,title,qualifier=("drug therapy" or "drug treatment" or "drug effects" or "therapeutic use"))

- AND (genre="Comparative Study" or subject="Drug Therapy, Combination" or (compar? %5 (effect? or group? or safety or efficacy or outcomes or treatment)) or reproducibility or superior? or "more effective" or conventional or standard medication or "study medications" or "significant difference" or "head-to-head comparisons" or "statistical significance" or (between-group %2 difference? ) )
- AND (language=eng)
- AND (publicationYear>1965 and publicationYear<2010)
- NOT subject,title="ocular hypertension"
- NOT subject="Hypertension, Portal"
- NOT genre=(comment? or abstract)
- NOT journalTitle="ACP journal club"
- NOT (journalTitle="Current Hypertension Reports" not abstract=?)
- NOT (subject,title,abstract=angioplasty and subject,title,abstract=(renal artery obstruction or renal artery stenosis))
- NOT title=(summar? for patients)
- NOT genre="practice guideline"
- NOT recordStatus=delete

### Boolean Filter

- (
- ((subject=Hypertension) with (qualifier=("drug therapy" or pharmacology) ))
  - or ((subject="Blood Pressure") with (qualifier="drug effects"))
  - or ((subject="Antihypertensive Agents") with (qualifier="therapeutic use"))

- or antihypertensive? or anti-hypertensive? or blood pressure

)

### Question 3 Search Strategy Results and PRISMA Diagram

The following databases were searched for RCTs and systematic reviews and meta-analyses (SR/MA) of RCTs to answer Question 3:

- PubMed from January 1966 to December 2009
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycInfo from January 1998 to July 2008
- EBM (Evidence-based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

As in Question 1 and Question 2, systematic reviews and meta-analyses were not used as part of the formal evidence review (i.e., they were not abstracted and included in the Evidence and Summary Tables). However, SR/MAs identified in the search that met the criteria were eligible for use as reference materials in the report.

Duplicate citations which arise from the same citation being found in more than one database were removed from the Central Repository prior to screening. The search produced 2663 citations. Five additional citations published after December 2009 were added for review. Per NHLBI policy, these citations could be formally reviewed for inclusion after the search cut-off date because they met the criteria of being an RCT of greater than 2,000 participants. Two of the five citations met the eligibility criteria; both were related to the ACCOMPLISH trial [Bakris, 2010; Weber 2010].

The titles and abstracts of these 2668 publications were screened against the inclusion/exclusion criteria independently by two reviewers which resulted in the retrieval of 702 full-text papers. These papers were independently screened by two reviewers and 604 of these publications were excluded on one or more of the inclusion/exclusion criteria. An additional 34 publications were excluded because they were rated as poor quality using the NHLBI Quality Assessment Tool for Controlled Intervention Studies. 64 RCTs were included in the Question 3 Evidence Base.

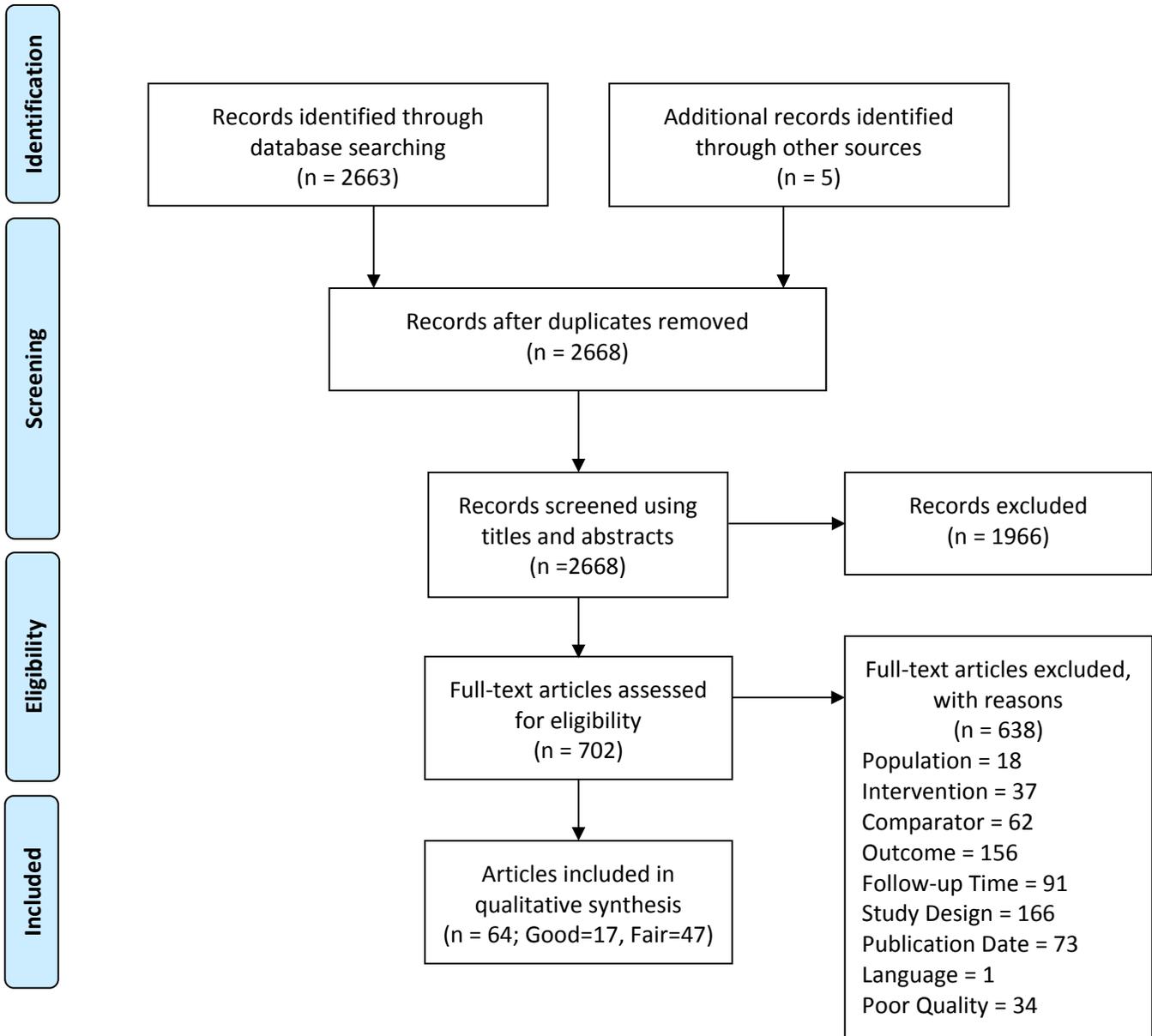


Figure 3: PRISMA Diagram for Question 3

## CRITICAL QUESTIONS IDENTIFIED BY THE PANEL

QUESTIONS 1 THROUGH 3 ARE THE QUESTIONS THAT FORM THE BASIS OF THIS REPORT.

QUESTIONS FOR WHICH SEARCH CRITERIA WERE DEVELOPED, BUT A LITERATURE SEARCH AND EVIDENCE REVIEW WERE NOT CONDUCTED INCLUDE QUESTIONS 4 AND 5:

### Question 4

**In adults with hypertension, does initiating treatment with antihypertensive pharmacological monotherapy versus initiating treatment with two or more drugs (including fixed-dose combination therapy), either of which may be followed by the addition of sequential drugs, differ in comparative benefits and harms on specific health outcomes?**

Population: Adults (age 18 and older) with hypertension

Intervention: Initiating antihypertensive pharmacological treatment with two or more drugs (including fixed-dose combination therapy)

Comparator: Initiating treatment with monotherapy

Outcomes: Change in blood pressure, time to achieve BP goal, or percentage of patients at goal BP within a defined time period

The following additional outcomes are of interest and will be abstracted if reported in the study, but they are not required for the study to be included: Overall mortality, CVD-related mortality, CKD-related mortality, myocardial infarction (MI), heart failure (HF), hospitalization for heart failure, stroke, coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), peripheral revascularization (includes carotid, renal, and lower extremity revascularization), end stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of eGFR

### Question 4 Inclusion/Exclusion Criteria

**Population:**

Adults (age 18 and older) with hypertension

**Outcomes of interest:**

*Intermediate Outcomes (Minimum study duration 3 months)*

- Change in blood pressure
- Time to achieve BP goal
- Percentage of patients at goal BP within a defined time period

*Long-Term Health Outcomes (Not required for study inclusion, but will be abstracted if they are reported)*

- Overall mortality, CVD-related mortality, CKD-related mortality
- Myocardial infarction
- Heart failure, hospitalization for heart failure
- Stroke
- Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement)
- Peripheral revascularization (includes carotid, renal, and lower extremity revascularization)
- End stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of eGFR

*Adverse events / harms (To be abstracted and included in the evidence table but not required for study inclusion)*

SAIC will abstract all data related to adverse events. However, they will look specifically for:

- Total withdrawals from a study and withdrawals attributed to adverse events
- Hypotension resulting in an intervention (such as hospitalization, ER visit, clinic visit identified as hypotension-related, discontinuation of medication, etc.).

**Interventions:** Initiating antihypertensive pharmacological treatment with two or more drugs (including fixed-dose combination therapy)

**Comparator:** Initiating treatment with monotherapy

**Study duration:** Minimum follow-up period of 3 months for intermediate outcomes.

**Publication period:** 1966 to current.

**Study designs:** RCTs and systematic reviews of RCTs for efficacy, effectiveness, and safety

### Question 5

**Among adults, how does self-directed blood pressure measurement/monitoring (e.g., home blood pressure measurement/monitoring) compare with clinic/office-based blood pressure measurement/monitoring and ambulatory blood pressure measurement/monitoring in terms of the following outcomes: accuracy and reliability of BP measurements; changes in BP or BP control; benefits and harms?**

Population: Adults (age 18 and older)

Intervention: Self-directed blood pressure measurement/monitoring, such as use of a home blood pressure measurement/monitoring device or a device in the workplace, grocery store, pharmacy, etc.

Comparator: Clinic or office-based blood pressure measurement/monitoring such as that taken in a physician's office by a physician, nurse, or other health care provider and ambulatory blood pressure measurement/monitoring

Outcomes: Accuracy and reliability of BP measurements (e.g., comparability of BP measurements); changes in BP or BP control; any of the following health outcomes (unlikely to be reported, but if they are, we are interested in them, and they would be abstracted): overall mortality, CVD-related mortality, CKD-related mortality, myocardial infarction (MI), heart failure (HF), hospitalization for heart failure, stroke, coronary revascularization (includes coronary angioplasty and stents), peripheral revascularization (includes carotid, renal, and lower extremity revascularization), end stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of eGFR; any harms reported in a study

## Question 5 Inclusion/Exclusion Criteria

**Population:** Adults age 18 and older (the search will not restrict to any subgroups; however subgroup data will be abstracted if available)

### Outcomes

1. Required Outcome: BP and changes in BP. (We will calculate the changes in BP ourselves if not calculated in the paper; however, included papers must include before and after BPs).
2. Not a required outcome, but will be abstracted if presented in the paper: Comparability of BP measurements across settings or devices - i.e., how does a BP obtained via HBPM (e.g., 138/88) compare to a BP obtained by OBPM or by ABPM - i.e., what would be its equivalent value?
3. Not a required outcome, but will be abstracted if presented in the paper: BP control. The definitions of BP control that are used in the paper will be abstracted.
4. Not a required outcome, but will be abstracted if presented in the paper: Adherence. The definitions of adherence that are used in the paper will be abstracted (e.g., medication adherence, adherence to a treatment protocol, adherence to F/U care, etc.).

5. Not a required outcome, but will be abstracted if presented in the paper: Important health outcomes as defined below (the same outcomes used in the other 4 questions):

Overall mortality, CVD-related mortality, CKD-related mortality, myocardial infarction (MI), heart failure (HF), hospitalization for heart failure, stroke, coronary revascularization (includes coronary angioplasty and stents), peripheral revascularization (includes carotid, renal, and lower extremity revascularization), end stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of eGFR

### **Settings**

- Out-of-Office (i.e., home, workplace, community). We will abstract information on whatever settings are included in the study. Our main focus is on HBPM, but if other settings have been studied (e.g., use of BP devices in local grocery stores and pharmacies), we will abstract them as well.
- Outpatient office setting

Excluded settings: ER, inpatient, nursing home, institutional, urgent care, outpatient surgical

**Intervention/Comparator:** HBPM and other forms of self-measurement / self-monitoring as compared to office-based blood pressure monitoring and/or 24-hour ambulatory blood pressure monitoring

**Study Design:** RCTs and prospective cohort studies; systematic reviews of RCTs and prospective cohort studies

**Follow-up interval:** No minimum period.

**Search period:** 1966 to present.

## **QUESTIONS FOR WHICH NO SEARCH CRITERIA WAS DEVELOPED:**

### **Question 6**

**How should hypertension be defined?**

### **Question 7**

**Does identifying a patient with prehypertension (and its subsequent treatment) improve blood pressure or reduce CVD morbidity and mortality (CVD-related death, overall death, myocardial infarctions, cerebrovascular accidents, heart failure, renal failure, nephropathy, retinopathy or other important health outcomes)?**

### **Question 8**

**What are the roles of home blood pressure monitoring, office-based blood pressure monitoring and 24-hour ambulatory blood pressure monitoring in the diagnosis and management of hypertension?**

### **Question 9**

**Is self-monitored, home-based BP monitoring for patients who are well controlled + as needed office-based follow-up just as good as regularly scheduled office-based follow-up for BP management?**

### **Question 10**

**How frequently should blood pressure be monitored in patients diagnosed and treated for high blood pressure, both controlled and poorly controlled?**

### **Question 11**

**Should systolic blood pressure, diastolic blood pressure, or both be included in CVD risk assessment? Should interventions and target goals be set using systolic blood pressure, diastolic blood pressure, or both?**

### **Question 12**

**What is the blood pressure threshold for initiating treatment for high blood pressure, including treatment thresholds for individuals based on overall CVD risk and treatment thresholds for individuals with specific CVD risk factors or co-morbidities?**

### **Question 13**

**What are the treatment goals of BP management, including treatment goals for individuals based on overall CVD risk and/or treatment thresholds for individuals with specific CVD risk factors or co-morbidities?**

### **Question 14**

**When should one start with single drug therapy and step up the dose (and how high should one go) versus switching to a new drug versus addition of a new drug versus starting with two or more drugs versus using fixed-dose combination drug formulations? Do these choices depend on:**

- Level of initial BP?**
- Other risk factors and overall CVD risk?**
- Other co-morbid conditions?**
- Sex, race, or age?**

### Question 15

What drug should one start with and under what circumstances? An important subquestion that will need to be addressed is: Are diuretics still the preferred first-line agents in the treatment of hypertension?

### Question 16

What specific drugs for hypertension should be used and avoided in various patient subgroups, which include:

- A. CAD
- B. Diabetes
- C. Chronic Kidney Disease
- D. Cerebrovascular disease
- E. Overweight/Obesity
- F. Hyperlipidemia
- G. Metabolic Syndrome
- H. Pregnancy
- I. Caucasians, African-Americans, Hispanics, Native Americans, Asians
- J. Elderly ( $\geq 65$  years of age) and very elderly ( $\geq 80$  years of age)

### Question 17

What is "resistant hypertension"?

### Question 18

What is the most cost-effective way of evaluating patients with resistant hypertension, and does it vary depending on the suspected etiology?

### Question 19

How are hypertensive urgency and hypertensive emergency defined?

### Question 20

What is the most cost-effective way of evaluating and treating patients who present with hypertensive urgency or hypertensive emergency?

### **Question 21**

**When should a patient be referred to a hypertension specialist and what is the long-term role of a hypertension specialist in the management of a patient with hypertension - i.e., Are there differences in blood pressure control or health outcomes between patients managed by primary care providers versus hypertension specialists?**

### **Question 22**

**What are the adverse effects of BP diagnosis and treatment?**

### **Question 23**

**What is the recommended approach for initiating and stepping up pharmacotherapy?**