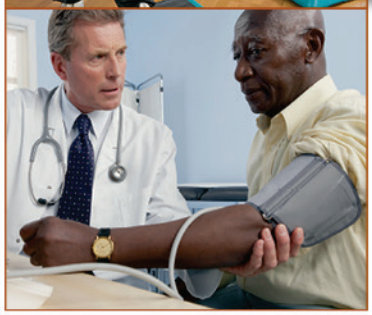
EVIDENCE REPORT



Managing Blood Pressure in Adults

Systematic Evidence Review From the Blood Pressure Expert Panel, 2013

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

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NIH National Heart, Lung, and Blood Institute

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Foreword

In 1977, the National Heart, Lung, and Blood Institute (NHLBI) issued the first of several clinical practice guidelines (CPGs) as part of its core mission, which is to provide global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives. Guidelines from the National High Blood Pressure Education Program, the National Cholesterol Education Program, the Obesity Education Initiative, as well as from other similar programs and initiatives, have addressed a variety of topics, including, but not limited to, cholesterol, blood pressure, obesity, asthma, and von Willebrand disease. Over the years, health care systems and providers have used these guidelines for the prevention, detection, evaluation, and treatment of cardiovascular disease (CVD) risk factors, and lung and blood diseases.

In 2008, NHLBI convened expert panels to update the existing clinical guidelines on cholesterol, blood pressure, and overweight/obesity by conducting rigorous systematic evidence reviews. At the same time, three crosscutting work groups—on lifestyle, risk assessment, and implementation—were convened to develop additional systematic evidence reviews to support the work of the expert panels. The impetus for these guidelines was the recognition that, despite the enormous progress over the last 60 years, CVD remains the leading cause of death in the United States.

While the updates were underway, the Institute of Medicine (IOM) issued two reports that established new "best practice" standards for generating systematic evidence reviews and developing clinical guidelines. The reports underscore that these are two distinct, yet related, activities that require careful intersection and coordination. Accordingly, NHLBI's role in the guidelines updates transitioned to completing a systematic evidence review for each topic and collaborating with other organizations to prepare and issue the related clinical guidelines.

Since implementing the new collaborative partnership model for developing guidelines based upon NHLBI-sponsored systematic evidence reviews, four of the five Expert Panels/Work Groups have worked successfully with the American Heart Association (AHA), the American College of Cardiology (ACC), The Obesity Society (TOS), and other professional societies to develop new CVD prevention CPGs for lifestyle, risk assessment, cholesterol, and obesity. The new guidelines—published in November 2013 by the AHA, ACC, and TOS, and endorsed by other professional societies—provide a valuable updated roadmap to help clinicians and patients manage CVD prevention and treatment challenges.

We appreciate the outstanding work and dedication of the expert panels and work groups that developed the systematic evidence reviews that formed the basis for the guidelines. These systematic evidence reviews are the products of one of the most rigorous evidence-based systematic reviews conducted to date. We look forward to continuing to develop accurate and timely evidence reviews, fueled by our investment in primary research on the prevention and treatment of CVD as well as implementation science, to improve public health.

The following systematic evidence report is available as a public resource.

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Section 1: Background and Description of the NHLBI Cardiovascular Risk Reduction Project

A. Background

Since the 1970s, the National Heart, Lung, and Blood Institute (NHLBI) has sponsored the development of clinical practice guidelines (CPGs) that have helped to accelerate the application of health research to strategies and programs for the prevention, detection, and treatment of cardiovascular, lung, and blood diseases. In 2005, NHLBI recognized the need to update the most recent cardiovascular guidelines, namely those on high blood cholesterol, high blood pressure (BP), and overweight/obesity in adults. NHLBI convened stakeholder groups to provide input on the development process for the next generation of CPGs.

The stakeholders emphasized the following needs:

- Maintain guidelines that focus on specific risk factors.
- Take a standardized and coordinated approach to updating the risk factors.
- Take a more evidence-based approach to development and implementation.
- Give more attention to dissemination and implementation issues.
- Work closely with stakeholders in health care and community systems to translate and disseminate the evidence base.

In 2008, NHLBI established three expert panels that would use a rigorous systematic evidence review process to update the guidelines for high blood cholesterol, high BP, and overweight/obesity. Additionally, three work groups were formed around risk assessment, lifestyle, and implementation to develop reports and provide crosscutting input to the expert panels. The Guidelines Executive Committee (GEC)—comprising co-chairs from the expert panels and work groups and staff from NHLBI—coordinated the work of the expert panels and work groups. Efforts resulted in six topic-specific yet complementary reports: blood cholesterol, BP, overweight/ obesity, lifestyle, risk assessment, and implementation. This report summarizes the evidence review findings of the Blood Pressure Expert Panel.

While the expert panels and work groups were undertaking a rigorous, systematic, evidence-based approach to updating the guidelines, the Institute of Medicine (IOM) convened experts to examine the methodology for developing guidelines. In 2011, the IOM issued two reports that established new "best practices" for generating systematic evidence reviews[1] and developing CPGs.[2] The reports from the IOM stress that these are two distinct but related activities that require careful intersection and coordination.

Because of these developments and the changing approaches to developing guidelines, in June 2012 the NHLBI's Advisory Council recommended that the Institute transition to a new model in accordance with the best practice standards established by the IOM. In mid-2013, NHLBI adopted a new collaborative partnership model whereby it will focus on generating high-quality systematic evidence reviews and developing subsequent CPGs by partnering with professional societies and other organizations.[3] The systematic review components of the five adult CPGs (including this systematic evidence review by the Blood Pressure Expert Panel) will be released as a public resource.

A Lifestyle Work Group was convened by NHLBI to conduct a systematic review to develop crosscutting evidence statements that are applicable to the High Blood Pressure and Cholesterol Panels. The primary intent of the Lifestyle Work Group's review was to focus on the effects of diet and physical activity on CVD risk factors independent of their effects on weight. The Lifestyle Interventions to Reduce Cardiovascular Risk: Systematic Evidence Review From the Lifestyle Work Group, 2013 report is available at: http://www.nhlbi.nih.gov/guidelines/cvd_adult/lifestyle/. The effect of weight loss on CVD risk factors is covered in the Managing Overweight and Obesity in Adults: Systematic Evidence Review from the Obesity Expert Panel, 2013: http://www.nhlbi.nih.gov/guidelines/obesity/ser/index.htm.

Section 2: Process and Methods Overview

A. Evidence-Based Approach

i. Overview of the Evidence-Based Methodology

To continually improve the quality and impact of the evidence reviews sponsored by NHLBI, the evidence review process was updated to ensure rigor and minimize bias. This new effort involved the use of a rigorous evidence-based methodology and the development of evidence statements that are based on a systematic review of the biomedical literature for specific periods of time.

All of the expert panels and work groups followed the same methods aside from variations needed to reflect the evidence in the field. The methodology involved numerous components and followed a prespecified development process. Expert panels and work groups consisting of cardiologists, primary care providers, nutritionists, and other clinical and nonclinical experts were convened to develop the evidence review. Directed by NHLBI, with support from a methodology contractor and a systematic review and general support contractor, the expert panels and work groups

- Constructed critical questions (CQs) most relevant to clinical practice (CQs followed the population, intervention/exposure, comparison group, outcome, timing, and setting format); and
- Identified (a priori) inclusion/exclusion (I/E) criteria for each CQ.

Directed by NHLBI, with input from the expert panels and work groups, the contractor staff

- Developed a search strategy, based on I/E criteria, for each CQ;
- Executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ;
- Screened—by two independent, master's- or doctoral.-level reviewers—thousands of abstracts or full-text articles returned from the search to identify relevant original articles, systematic reviews, and/or meta-analyses. Rigorous validation procedures were applied to ensure that the selected articles met pre-established I/E criteria before being included in the final review;
- Determined—by two independent raters on the methodology team—the quality (good, fair, or poor) of each study. With input from NHLBI, methodology staff adapted study rating instruments and trained study raters on the use of these instruments. Six quality-assessment tools were designed to assist reviewers in the critical appraisal of a study's internal validity;
- Abstracted relevant information from the included studies into an electronic database;
- Supported abstractions by constructing templates with lists of data elements that were pertinent to the I/E criteria;
- Constructed detailed evidence tables as a way of organizing the data from the abstraction database; and
- Analyzed the evidence tables and constructed summary tables, which displayed the evidence in a manageable format to answer specific parts of each CQ.

The expert panels and work groups

- Used summary tables to develop evidence statements for each CQ. The quality of evidence for each evidence statement was graded as high, moderate, or low. The grade was based on scientific methodology, scientific strength, and consistency of results; and
- Drafted a report that was reviewed by external Federal agencies and a group of experts selected by NHLBI.

ii. System for Grading the Body of Evidence

NHLBI adapted a system developed by the U.S. Preventive Services Task Force (USTSPF) to grade the body of evidence. Evidence statements were graded as high, moderate, or low quality (table 1).

Table 1. Evidence Quality Grading System

Type of Evidence	Strength of Evidence Grade
■ 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; and ■ Meta-analyses of such studies. ■ *There is high confidence that the evidence reflects the true effect. Further research is unlikely to alter confidence in the estimate of effect.*	**HIGH**
■ RCTs with minor limitations affecting confidence in, or applicability of, the results, including minor flaws in design or execution; ■ Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies; and ■ Meta-analyses of such studies. ■ *There is moderate confidence that the evidence reflects the true effect. Further research may alter confidence in the estimate of effect and may change the estimate.*	**MODERATE**
■ RCTs with major limitations; ■ Nonrandomized intervention studies and observational studies with major limitations affecting confidence in, or applicability of, the results; ■ Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports); ■ Physiological studies in humans; and ■ Meta-analyses of such studies; ■ *There is low confidence that the evidence reflects the true effect. Further research is likely to alter confidence in the estimate of effect and is likely to change the estimate.*	**LOW**

The grades provide guidance to primary care providers, clinicians, and other stakeholders on how much support the evidence provided for the evidence statement. 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. Appendix B describes how four domains of the body of evidence—risk of bias, consistency, directness, and precision—were used to grade the strength of evidence.

iii. Peer-Review Process

A formal peer-review process was undertaken that included inviting several scientific experts and representatives from multiple Federal agencies to review and comment on the draft documents. NHLBI selected scientific experts with diverse perspectives to review the reports. Potential reviewers were asked to sign a confidentiality agreement, but NHLBI did not collect conflict of interest (COI) information because it is not permitted under the Paperwork Reduction Act. Division for the Application of Research Discoveries staff collected reviewers' comments and forwarded them to the respective panels and work groups for consideration. Each comment received was addressed—either by a narrative response and/or a change to the draft document. A compilation of the comments received and the panels' and work groups' responses was submitted to the NHLBI Advisory Council working group; individual reviewers did not receive responses.

B. Critical Question–Based Approach

i. How the Questions Were 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 five questions felt to be of highest priority. The five highest ranked questions were discussed further and prioritized. This report focuses on the three highest ranked questions.

ii. 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 mmHg 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 (CKD), coronary artery disease, stroke, or other comorbidities or at-risk populations, including older adults;
- Concern that having a threshold for initiating treatment that differs from the treatment goal may be confusing to people; and
- Interest in the selection of pharmacologic therapy, including whether treatment to lower BP with a particular drug or drug class improves important health outcomes when compared to another drug or drug class.

Blood Pressure Expert Panel—Critical Questions

No.	Question
CQ1.	In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?
CQ2.	In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?
CQ3.	In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

Section 3: Inclusion/Exclusion Criteria for the Evidence Review

The panel decided to limit its evidence review to RCTs because RCTs are subject to less bias than other types of clinical studies and represent the gold standard for determining efficacy and effectiveness.[1] All of the studies in the evidence review were original publications based on eligible RCTs. These studies were used to create evidence tables and summary tables that served as the basis for panel deliberations. Because the panel conducted its own systematic review using original studies, systematic reviews and meta-analyses 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. The panel also excluded pilot studies, which 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 (PAD), heart failure, previous stroke, CKD, 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 followup period of less than 1 year.

Search dates for the literature review were January 1, 1966, to December 31, 2009. To ensure that no major relevant RCT published after December 31, 2009, was excluded from consideration, panel members could identify newly published RCTs for consideration if they met the following criteria: (1) It was a major RCT in the field (e.g., the ACCORD Study); (2) It had at least 2,000 participants; (3) It was a multicenter study; and (4) It met all the other I/E criteria.

Studies selected in this manner were also rated for quality, using the NHLBI standardized quality rating tool, and were included only 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 felt 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 CKD;
- Myocardial infarction (MI), 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); and
- End-stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of estimated glomerular filtration rate (eGFR).

For CQ1, the panel originally looked for studies that randomized participants into groups where pharmacologic therapy to lower BP was initiated at different BP thresholds. For example, the panel looked for studies where

treatment was initiated at a systolic blood pressure (SBP) of 160 mmHg in one group and compared to treatment initiated at a SBP of 140 mmHg in another group. However, the panel found that no RCTs had been conducted that compared two or more different treatment thresholds. Therefore, they had to broaden the inclusion criteria to encompass RCTs that had a specific criterion for initiating treatment in one group (e.g., initiating treatment if SBP was ≥160 mmHg) and compared it to a group that received placebo, usual care, or no treatment.

A. Literature Search Yield

For CQ1, 1,498 articles were screened. Of these, 1,457 articles were excluded because they did not meet the prespecified inclusion criteria. Of the 41 included articles, 7 were rated as good, 18 as fair, and 16 as poor, resulting in 25 articles abstracted.

For CQ2, 1,980 articles were screened. Of these, 1,915 articles were excluded because they did not meet the prespecified inclusion criteria. Of the 65 included articles, 14 were rated as good, 23 as fair, and 28 as poor, resulting in 37 articles abstracted.

For CQ3, 2,668 articles were screened. Of these, 2,570 articles were excluded because they did not meet the prespecified inclusion criteria. Of the 98 included articles, 17 were rated as good, 47 as fair, and 34 as poor, resulting in 64 articles abstracted.

The detailed search strategy for each question is provided in appendix C.

B. Populations Addressed in This Report

The evidence statements in this report are based on the results of RCTs that were deemed eligible for the evidence review per prespecified I/E 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. However, participants with specific comorbidities 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 comorbidity, such as diabetes, previous MI or stroke, left ventricular hypertrophy (LVH), or dyslipidemia.[4-8] Therefore, for the purposes of this report, 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;[9-12] or hypertension and CKD.[13-18] The panel also reviewed evidence from trials looking at prespecified subgroups with hypertension and diabetes or hypertension and CKD that were part of a larger trial; however, a subgroup analysis of a trial was only included if the diabetes or CKD subgroup analysis was prespecified. The evidence from these trials and analyses formed the basis for the evidence statements (ESs) specific to these populations.

C. Definition of High Blood Pressure or Hypertension

For the purposes of this report, the definition for high BP or hypertension was derived from the studies that were included in the evidence review, which usually defined high BP or hypertension as a SBP ≥140 mmHg, a diastolic blood pressure (DBP) ≥90 mmHg, or both. The panel did not set out to define high BP or hypertension; its task was to take an evidence-based approach to answer the three questions discussed in the

previous sections and to develop evidence statements on BP treatment thresholds and goals based on data from RCTs that demonstrate benefits on important health outcomes.

D. Limitations

There are limitations to this systematic evidence review. The panel was attentive to basing decisions on the evidence as outlined in the methodology section and only reviewing evidence that met the methodological criteria for inclusion. Studies that did not meet the panel's explicit inclusion criteria may have contained useful information that was not incorporated into the ESs. The review does not include observational studies, systematic reviews, or meta-analyses, and the panel did not conduct its own meta-analysis.

Many of the studies were conducted at a time when the clinical context differed significantly from the current context of antihypertensive care; thus, estimates of effect may not reflect current practices. At the time some of the critical studies were conducted, clinical trial design and analysis also differed significantly from current trial standards, and this limited the panel's ability to compare or combine studies from different time periods. High-quality evidence was not available in many cases, forcing the panel to rely on fair-quality evidence or expert opinion.

All of the studies included in this systematic evidence review were based on BP measurements obtained in office settings and therefore may not be applicable to other measurement techniques such as ambulatory or self-measured BP monitoring.

Drug-related side effects and harms that were documented in the RCTs meeting the inclusion criteria were carefully considered; however, this review was not designed to answer whether side effects/harms associated with the use of antihypertensive drug therapies result in significant changes in important health outcomes.

In the DBP studies, many of the participants also had elevated SBP, which makes it difficult, if not impossible, to determine if the benefit was due to lowering the DBP, lowering the SBP, or lowering both.

Section 4: Evidence Statements for Critical Question 1 (Pharmacotherapy and BP Thresholds)

CQ1:

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

ES1. **Initiating treatment with antihypertensive medication to lower BP in adults 60 years of age or older with SBP ≥160 mmHg reduces cerebrovascular morbidity and mortality (including fatal stroke, nonfatal stroke, or a combination of fatal and nonfatal stroke).**

Evidence Quality: ***High***

Rationale/Comments: Four studies (see appendix F for full names of studies) contributed to this evidence statement (EWPHE, HYVET, SHEP, and Syst-Eur).[19-23] 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 SBP ≥160 mmHg decreased cerebrovascular morbidity or mortality. In SHEP and Syst-Eur, combined fatal and nonfatal stroke was reduced by 36 percent (p=.0003) and 42 percent (p=.003), respectively. In HYVET, there was a 30 percent reduction in fatal or nonfatal stroke, but the p-value was .06. However, HYVET was stopped early because of a 21 percent reduction in mortality in the active treatment group. If the study had not been stopped early, the reduction in fatal or nonfatal 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 percent reduction in nonfatal cerebrovascular events at 1 year (p<.05) and a 32 percent nonsignificant decrease (p=.16) in cerebrovascular mortality at the end of the trial, which had a mean followup of 4.6 years.

ES2. **Initiating treatment with antihypertensive medication to lower BP in adults 60 years of age or older with SBP ≥160 mmHg reduces fatal and nonfatal 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.[20,21,23,24] 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 SBP ≥160 mmHg significantly reduced heart failure events. In HYVET and SHEP, fatal and nonfatal heart failure were reduced by 64 percent (p<.001) and 49 percent (p<.001), respectively. EWPHE, a much smaller study, had an 8 percent reduction in heart failure at 1 year (p<.05); however, heart failure events at the end of the trial, which had a mean followup of 4.6 years, were not reported for the intention-to-treat (ITT) analysis.[19,20] For this evidence review, only ITT analyses were considered. Syst-Eur had a 29 percent reduction

in fatal and nonfatal heart failure (p=.12) and a 36 percent reduction in nonfatal heart failure (p=.06), but these reductions were not statistically significant.

ES3. Initiating treatment with antihypertensive medication to lower BP in adults 60 years of age or older with SBP ≥160 mmHg reduces coronary heart disease (CHD), including CHD mortality, fatal MI, and nonfatal 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).[19-23,25,26] Because the studies did not all use the same CHD outcomes, the panel considered CHD to include fatal MI, nonfatal MI, or CHD mortality. CHD was a secondary outcome in all four trials. In three of the trials (EWPHE, SHEP, and Syst-Eur), initiation of antihypertensive medication at a SBP ≥160 mmHg significantly reduced at least one CHD outcome (fatal MI, nonfatal MI, or CHD mortality). In some trials, the difference in fatal events was significant, whereas in others the difference in nonfatal 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, nonfatal MI was lower by 33 percent (95 percent confidence interval [CI]=0.47–0.96), and nonfatal MI or CHD deaths were lower by 27 percent (CI=0.57–0.94). In EWPHE, cardiac mortality was lower by 38 percent (p=.036). In Syst-Eur, there was a 30 percent reduction in fatal and nonfatal MI, but the p-value was 0.12 (CI=−56%–9%); there was also a 56 percent reduction in fatal MI, but the p-value was 0.08 (CI=−82%–9%). Syst-Eur also reported a 29 percent reduction in fatal and nonfatal cardiac endpoints (p<.05); however, this composite outcome included heart failure (which was addressed in evidence statement 2), MI, and sudden death. Reductions in CHD outcomes in HVYET 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 nonsignificant CHD results, and in one study (HYVET), none of the CHD results was significant.

ES4. Initiating treatment with antihypertensive medication to lower BP in adults 80 years of age or older with SBP ≥160 mmHg reduces overall mortality.

***Evidence Quality:* Moderate**

Rationale/Comments: One study (HYVET) contributed to this evidence statement.[21] HYVET was the only RCT conducted exclusively in adults 80 years of age or older where antihypertensive medication was initiated at a SBP ≥160 mmHg. HYVET had 3,845 participants and was rated a good study. It showed a significant 21 percent reduction in overall mortality in the treated group (CI=0.65–0.95; p=.02), 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 percent, but their findings were not significant, and most of their study participants were younger than 80 years of age.[19,22,23]

ES5. **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 between 60 to <80 years of age with SBP ≥160 mmHg.**

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

Rationale/Comments: Three trials contributed to this evidence statement (EWPHE, SHEP, and Syst-Eur).[19,22,23] 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 nonsignificant results were because there was truly no difference in overall mortality between the treatment and comparison groups or because the study was not adequately powered to detect a difference.

A fourth study, Syst-China,[27] met the 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 percent of patients. However, Syst-China did show a significant 39 percent decrease in all-cause mortality (p=.003), but it was a secondary outcome.

ES6. **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 SBP 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 Hypertension Study, meeting the inclusion criteria where antihypertensive medication was initiated at a specific SBP threshold in adults less than 60 years of age.[28] However, it was subsequently excluded because of a poor quality rating. The Oslo study included 785 men 40–49 years of age, and treatment was initiated at a SBP threshold of 150 mmHg. This study was rated poor because it was not blinded, there was a 17 percent 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 vs. 34 in the control; p>.10). The investigator did detect a significant decrease in cerebrovascular events in the treated group (p<.02), but there were only seven events. There was no benefit found in terms of total cardiovascular events, coronary events, or total mortality.

The panel found one other study[29] where antihypertensive medication was initiated at a specific SBP 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.

ES7. **The evidence is insufficient to determine whether initiating treatment with antihypertensive medication at a SBP threshold of 140 mmHg 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 SBP threshold of 140 mmHg improves cardiovascular outcomes, cerebrovascular outcomes, or mortality.[30] It was rated as fair. The study included 452 participants, all of whom had a stroke or transient ischemic attack (TIA) in the previous year, and the primary outcome was recurrent stroke. Of the 16 study end points that met the question's prespecified criteria, the only benefit was a reduction in nonfatal heart failure, which was a secondary outcome with few events (0 events in the treatment group vs. 6 events in the placebo group; p=.012). The panel considered the evidence insufficient because it consisted of only one small study in a secondary prevention population.

ES8. **The evidence is insufficient to determine whether initiating treatment with antihypertensive medication to lower BP in prehypertensive patients (SBP 120–139 mmHg, DBP 80–89 mmHg) 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 *SBP of 130–139 mmHg or a DBP 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 SBP of 130–139 mmHg and/or DBP of 85–89 mmHg.[31] It included 1,008 participants, and the primary outcome was the development of office hypertension (defined as either office-based SBP or DBP or both greater than 140/90 mmHg) 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 *SBP of 130–139 mmHg or a DBP of 80–89 mmHg* prevents or postpones the development of hypertension.[32] TROPHY was conducted in participants with a SBP of 130–139 mmHg and DBP of 89 mmHg or lower or SBP of 139 mmHg or lower and DBP of 85–89 mmHg. However, this trial did not meet the inclusion criteria for this question because it did not report cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality, and the power was low in both studies.

The panel considered the evidence insufficient because there was only one study (PHARAO) that was rated as fair. In addition, cardiovascular outcomes, cerebrovascular outcomes, and mortality were all secondary end points, so it is unclear whether the lack of treatment benefit is real or is due to the study not being 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 SBP* of *130–139 mmHg or a DBP of 80–89 mmHg* improves important health outcomes.

ES9. **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 insufficient evidence***

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

ES10. **Initiating treatment with antihypertensive medication to lower BP in adults 30 years of age or older with DBP ≥90 mmHg reduces cerebrovascular morbidity and mortality (including 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 Study of hypertension).[19-21,30,33-36] 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 DBP threshold ≥90 mmHg decreased cerebrovascular morbidity or mortality. Findings were consistent in direction and magnitude across trials. For fatal and nonfatal stroke, HDFP showed a 35 percent reduction ($p<.01$) and MRC showed a 45 percent reduction ($p=.006$, once-off testing). In HYVET, there was a 30 percent reduction in fatal or nonfatal stroke, but the p-value was .06. However, HYVET was stopped early because of a 21 percent reduction in mortality in the active treatment group. If the study had not been stopped early, the reduction in fatal or nonfatal stroke would likely have been significant by the end of the trial.

For fatal stroke, HYVET showed a 39 percent reduction in the active treatment group ($p=.046$) and EWPHE showed a 32 percent reduction, but it was not significant ($p=.16$). In MRC, active treatment reduced fatal stroke by 34 percent (18 fatal strokes in the active treatment group vs. 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 (29 fatal strokes vs. 52 fatal strokes, respectively), but the p-value was not reported. Active treatment reduced nonfatal stroke in EWPHE by 11 percent at 1 year ($p<.05$). MRC showed a 49 percent decrease in nonfatal stroke (42 nonfatal strokes in the active treatment group vs. 82 in the placebo group); however, the p-value was not reported.

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

ES11. Initiating treatment with antihypertensive medication to lower BP in adults 30 years of age or older with DBP ≥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).[20,21,30,36] 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 DBP threshold of 90 mmHg or greater, but these studies did not report on heart failure outcomes.[33-35]

In three of the trials (EWPHE, Hypertension-Stroke Cooperative, and HYVET), initiation of antihypertensive medication at a DBP ≥90 mmHg significantly reduced heart failure events. In HYVET, fatal or nonfatal heart failure was lower by 64 percent ($p<.001$). EWPHE, a much smaller study, had an 8 percent absolute risk reduction in heart failure at 1 year ($p<.05$). However, heart failure events at the end of the trial, which had a mean followup of 4.6 years, were not reported for the ITT analysis.[19,20] For this evidence review, only ITT analyses were considered. Hypertension-Stroke Cooperative found a significant reduction in heart failure ($p=.012$); 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 four contributing trials showed 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.

ES12. The evidence is insufficient to determine whether initiating treatment with antihypertensive medication to lower BP in adults 30 years of age or older with DBP ≥90 mmHg reduces CHD events (including CHD mortality, fatal MI, and nonfatal 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).[19-21,30,33,35,36] 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).

CHD events were the primary outcome in only one trial (MRC). In this trial, coronary events were lower by 6 percent in the active treatment group, but the finding was not significant (CI=–31%–21%; *p*-value not reported). Only one trial (EWPHE) showed a significant decrease in CHD events (38 percent decrease in cardiac mortality at 4.6 years, $p=.036$) when treatment was initiated at a DBP threshold of 90 mmHg or greater.

The panel considered the evidence insufficient because CHD events were the primary outcome in only one (MRC) of the six contributing trials. In the one trial (EWPHE) where a significant difference was found, CHD events were a secondary outcome. Therefore, it is unclear whether the mostly nonsignificant results were due to the lack of differences in CHD events between the treatment and comparison groups or due to the trials not being powered to detect differences in these outcomes.

ES13. Initiating treatment with antihypertensive medication to lower BP in adults 30 years of age or older with DBP ≥90 mmHg 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).[19,21,30,33,35,36] 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 DBP threshold ≥90 mmHg. In HDFP, which included participants 30–69 years of age, the stepped care group experienced a 1.3 percent absolute decrease in mortality at 5 years compared to the usual care group (6.4 percent in stepped care compared to 7.7 percent in usual care, $p<.01$). HYVET, which was conducted in participants 80 years of age or older, showed a significant 21 percent decrease in mortality in the treatment group and was stopped early due to this benefit. In two (EWPHE and MRC) of the other four trials, there was no significant difference in mortality. In the remaining two trials (Hypertension-Stroke Cooperative and 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 vs. 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 vs. 19 deaths in the placebo group).

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

ES14. There are no RCTs of good or fair quality that assessed whether initiating treatment with antihypertensive medication to lower BP at any DBP threshold improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality in adults less than 30 years of age.

***Evidence Quality:* Unable to determine because there is no evidence**

Rationale/Comments: Three trials (Hypertension-Stroke Cooperative, Sprackling, and USPHS) had entry eligibility criteria that allowed for participants less than 30 years of age;[30,37,38] 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 four participants were less than 65 years of age) and USPHS (age range of 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 was not reported whether any of the participants were less than 30 years of age. Because it was a secondary prevention trial in persons who had a stroke or TIA, and the mean age of participants entering the trial was 59, the panel thought that probably very few, if any, participants were less than 30 years of age in the study.

No RCTs of any quality (good, fair, or poor) assessed whether initiating antihypertensive treatment at any DBP threshold improved cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality in adults *exclusively* less than 30 years of age.

Section 5: Evidence Statements for Critical Question 2 (Pharmacotherapy Treatment and BP Goals)

CQ2:

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

A. Statements for the General Population

ES1. **Treatment with antihypertensive medication to lower SBP in adults 60 years of age or older to a SBP goal <150 mmHg 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).[21-23] 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 SBP goals of <150 mmHg. The SBP goal in SHEP was based on baseline BP; the goal for individuals with a SBP >180 mmHg at baseline was <160 mmHg, and the goal for those with SBPs between 160 and 179 mmHg at baseline was a decrease of at least 20 mmHg. Thus, SBP goals in SHEP ranged from 140 mmHg to 159 mmHg, unlike the other two studies, which used a fixed goal of <150 mmHg.

In all three trials, cerebrovascular morbidity or mortality was significantly reduced when participants were treated with antihypertensive medications to a SBP goal of less than 150 mmHg. In SHEP and Syst-Eur, combined fatal and nonfatal stroke were reduced by 36 percent (p=.0003) and 42 percent (p=.003), respectively. In HYVET, there was a 30 percent reduction in fatal or nonfatal stroke, but the p-value was .06. However, HYVET was stopped early because of a 21 percent reduction in mortality in the treatment group.

ES2. **Treatment with antihypertensive medication to lower SBP in adults 60 years of age or older to a SBP goal of <150 mmHg 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).[21,23,24] All three studies were rated as good, and heart failure was a secondary outcome in each trial. In HYVET, fatal and nonfatal heart failure were lower by

64 percent (p<.001) even though the study was stopped early because of a 21 percent reduction in mortality in the treatment group. In SHEP, fatal and nonfatal heart failure were lower by 49 percent (p<.001). Syst-Eur showed a 29 percent reduction in fatal and nonfatal heart failure (p=.12) and a 36 percent reduction in nonfatal heart failure (p=.06), but these results were not statistically significant.

The panel rated the evidence quality as 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.

ES3. Treatment with antihypertensive medication to lower SBP in adults 60 years of age or older to a SBP goal of <150 mmHg reduces CHD (including nonfatal 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).[21-23,25,26,39] Because the studies did not all use the same CHD outcomes, the panel considered CHD to include nonfatal MI, fatal MI, CHD death, or sudden death. CHD was a secondary outcome in all three trials.

In SHEP, treatment with antihypertensive medication reduced CHD events by 25 percent (CI=0.60–0.94), nonfatal MI by 33 percent (CI=0.47–0.96), and nonfatal MI or CHD deaths by 27 percent (CI=0.57–0.94). In Syst-Eur, treatment reduced fatal and nonfatal cardiac end points by 29 percent (CI=0.54–0.94). However, these cardiac end points consisted of heart failure, MI, 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 percent 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 evidence quality as moderate.

ES4. Treatment with antihypertensive medication to lower SBP in adults 80 years of age or older to a SBP goal of <150 mmHg reduces overall mortality.

***Evidence Quality:* Moderate**

Rationale/Comments: One study (HYVET) contributed to this evidence statement.[21] HYVET was the only RCT conducted exclusively in adults 80 years of age or older where participants were treated to a SBP goal of <150 mmHg. HYVET had 3,845 participants and was rated a good study. It showed a significant 21 percent reduction in overall mortality in the treated group (p=.02; 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 percent and 13 percent, respectively, but their findings were not significant, and most of their study participants were younger than 80 years of age.[22,23] In Syst-Eur, 9.3 percent of participants were 80 years of age or older at baseline; in SHEP, the proportion was 13.7 percent. 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 rating the quality of evidence as moderate.

ES5. **In the general population <80 years of age, the evidence is insufficient to determine whether treatment with antihypertensive medication to lower SBP to a goal of <150 mmHg 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.[22,23] Both were large studies rated as good, and overall mortality was a secondary outcome in each trial. Syst-Eur and SHEP showed nonsignificant reductions in overall mortality of 14 percent (CI=0.67–1.09) and 13 percent (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 is uncertain whether the nonsignificant 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.

ES6. **In the general population ≥65 years of age with hypertension, there is evidence that treatment with antihypertensive medication to a SBP goal of <140 mmHg 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.[40,41] Both studies were rated as good, with study populations of 3,260 and 4,418, respectively. JATOS compared a SBP goal of <140 mmHg to a goal of 140–160 mmHg in adults 65 to 85 years of age. VALISH compared a SBP goal of <140 mmHg to a goal of 140–149 mmHg 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 CVD, 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 followup (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.

A few panel members 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 revote, the majority of panel members supported the statement but thought that it represented low-quality evidence.

ES7. **In the general population <65 years of age with hypertension, there are no RCTs that tested whether treatment with antihypertensive drug therapy to a SBP goal of <140 mmHg compared to a higher goal (for example, <150 mmHg) improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.**

Evidence Quality:* *Unable to determine because there is no evidence

Rationale/Comments: No additional comments.

ES8. **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 SBP goal of <140 mmHg compared to a lower goal (for example, <130 mmHg).**

Evidence Quality:* *Unable to determine because there is no evidence

Rationale/Comments: One study contributed to this evidence statement (Cardio-Sis).[42] Cardio-Sis compared a SBP goal of <130 mmHg to a goal of <140 mmHg 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 LVH by electrocardiogram (ECG) at the final 2-year visit. Although the study showed a decrease in LVH by ECG with the lower BP goal, LVH is an intermediate measure, not a health outcome as required by the I/E 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 percent reduction in coronary revascularization (p=.032), which was an outcome of interest. However, the panel placed less emphasis on this outcome compared to the other clinical end points because it is a softer end point with wide practice variation that is frequently performed without appropriate indications. There was also a significant 50 percent 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=.003). The panel also placed less emphasis on this end point because it was a composite made up of so many components, including many softer end points 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 SBP difference of only 3.8 mmHg between groups whereas the intended SBP difference between groups was 10 mmHg. Some panel members also believed that a sample size of 1,111 with median followup of 2 years is not adequate to assess meaningful differences in cardiovascular or cerebrovascular health outcomes or mortality.

ES9. **In the general population <55 years of age with hypertension, there are no RCTs that tested whether treatment with antihypertensive medication to any SBP 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 SBP 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.

ES10. In the general population with hypertension, treatment with antihypertensive medication to a DBP goal of <90 mmHg reduces cerebrovascular morbidity and mortality (including 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).[33-36,43] One study was rated as good (VA Cooperative), and three studies were rated as fair (MRC, ANBP, and HDFP). Cerebrovascular morbidity and/or mortality were primary outcomes in one of the four contributing trials (MRC).

MRC showed a 45 percent 5-year reduction in fatal and nonfatal stroke (p=.006 once-off testing; p<.01 sequential analysis) while HDFP showed a 34.5 percent 5-year reduction in fatal and nonfatal stroke (p<.01). MRC had a DBP goal of <90 mmHg. HDFP had a DBP goal of 90 mmHg for those entering the trial with a DBP of ≥100 mmHg or those who were already receiving antihypertensive medication; it had a goal of a 10 mmHg decrease in DBP for those entering the study with a DBP between 90 and 99 mmHg.

Although p-values and CIs were not reported for cerebrovascular outcomes in the VA Cooperative or ANBP studies, 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.

ES11. In the general population with hypertension, the evidence is insufficient to determine if treatment with antihypertensive medication to a DBP goal of <90 mmHg reduces heart failure.

Evidence Quality: Unable to determine because there is insufficient evidence

Rationale/Comments: Although four trials[33,35,36,43] treated patients to a goal DBP of <90 mmHg, 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 three 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.

ES12. In the general population with hypertension, the evidence is insufficient to determine whether treatment with antihypertensive medication to a DBP goal of <90 mmHg reduces CHD events (including CHD mortality, nonfatal 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.[33,35,36,43] 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 one trial (MRC) reported CIs or *p*-values for CHD outcomes. MRC showed a nonsignificant 6 percent reduction in total coronary events in the treated group, which had a goal DBP of <90 mmHg (CI=–31%–21%; *p*-value not reported).

The other three trials showed inconsistent results for CHD outcomes. For example, in VA Cooperative and ANBP, there were more nonfatal MIs in the treated group (5 vs. 2 in VA Cooperative and 28 vs. 22 in ANBP). However, in both trials, there were fewer total CHD events in the treated group (11 vs. 13 in VA Cooperative and 98 vs. 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 vs. 69 events). However, *p*-values and CIs 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 CHD events were the primary outcome in only one of four contributing trials (MRC). In that trial, the 6 percent reduction in coronary events was not significant. In the other three trials, CIs or *p*-values for CHD 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 the VA Cooperative and ANBP studies between nonfatal and total CHD events, led the panel to conclude that there was insufficient evidence to conclude whether treating patients to a DBP goal of <90 mmHg reduces CHD events.

ES13. In the general population 30 years of age or older with hypertension, the evidence is insufficient to determine whether treatment with antihypertensive drug therapy to a DBP goal of <90 mmHg reduces overall mortality.

***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.[33,35,36,43] 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 percent absolute decrease in mortality at 5 years compared to the usual care group (6.4 percent in stepped care vs. 7.7 percent in usual care, $p<.01$). 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 nonsignificant 2 percent reduction in overall mortality (CI=–16%–18%; *p*-value was not reported). In the other two studies (VA Cooperative and ANBP), there were few events, and significance was not reported. There was a trend toward possible benefit in the treated groups in VA Cooperative (0 vs. 4 deaths) and ANBP (25 vs. 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.

ES14. **In the general population with hypertension, there is evidence of no benefit in cardiovascular outcomes, cerebrovascular outcomes, or mortality with antihypertensive drug therapy to a DBP goal of either ≤80 mmHg or ≤85 mmHg compared to a goal of ≤90 mmHg.**

Evidence Quality: ***Low***

Rationale/Comments: One trial, HOT, contributes to this evidence statement.[44] HOT was rated as fair and included 18,790 participants. HOT compared three goal diastolic pressures: ≤80 mmHg, ≤85 mmHg, and ≤90 mmHg. 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 HOT reached statistical significance. The relative risk for the primary outcome was 0.99 for each DBP goal comparison, and the CIs crossed 1 (CI=0.83–1.19) for the ≤90 versus ≤85 comparison; 1.08 (CI=0.89–1.29) for the ≤85 versus ≤80 comparison; and 1.07 (CI=0.89–1.28) for the ≤90 versus ≤80 comparison. There was a 37 percent increase in MI (a component of the primary composite outcome) that almost reached statistical significance for the ≤90 mmHg group compared to the ≤80 mmHg group, but the CI crossed 1 (CI=0.99–1.91). There were more deaths in the ≤80 mmHg 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 as low quality, as opposed to insufficient, because HOT 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 DBP goals achieved smaller differences in BP than were anticipated based on the study design; for example, the mean achieved DBP difference between the ≤90 group and the ≤80 group was only 4.0 mmHg. The failure to achieve the stated BP goal differences in each group, together with the fact that it was only one study that was rated fair, resulted in the low-quality grade.

B. Statements for the Population With Chronic Kidney Disease

ES15. **(CKD subpopulation): In the population <70 years of age with CKD (without diabetes), the evidence is insufficient to determine if there is a benefit in cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality with antihypertensive drug therapy to a lower BP goal (for example, <130/80 mmHg) compared to a goal of <140/90 mmHg.**

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

Rationale/Comments: Three trials (AASK, MDRD, and REIN-2) contributed to this evidence statement.[13-15,45,46] One trial was rated as good (AASK) with a study population of 1,094, and two trials were rated as fair (REIN-2 and 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 ESRD. All study participants in AASK were Black and had hypertension, while MDRD included White and Black and hypertensive and normotensive participants.

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/1.73 m². MDRD consisted of two studies each with a 2x2 factorial design. Study 1 included subjects with a GFR of 25–55 mL/min/1.73 m² who were randomized to a usual or low-protein diet and to a usual or low BP goal. Study 2 consisted of participants with a GFR of 13–25 mL/min/1.73 m² who were randomized to a low- or very low protein diet and to a usual or

low BP goal. In REIN-2, participants had nondiabetic nephropathy and persistent proteinuria, defined as urinary protein excretion greater than 1 gram per 24 hours for at least 3 months.

Direct comparison of BP goals across trials was not possible because the goals in each trial were different. AASK compared a mean arterial pressure (MAP) goal of ≤92 mmHg to a MAP goal of 102–107 mmHg (as an example, a BP of 140/90 mmHg equals a MAP of 107, and a BP of 120/80 mmHg equals a MAP of 93). In MDRD, BP goals were based on age. In the lower goal group, the MAP goal was ≤92 mmHg 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 mmHg for those aged 18–60 and ≤113 mmHg for those ≥61 years of age. In REIN-2, a BP goal of <130/80 mmHg was compared to a diastolic goal of <90 mmHg, irrespective of SBP.

None of the three trials showed that treatment to a lower BP goal (e.g., 130/80 mmHg) compared to a BP goal of <140/90 mmHg significantly reduced the incidence of ESRD, GFR by 50 percent or by 25 mL/min/1.73 m² from baseline, cardiovascular outcomes, cerebrovascular outcomes, or mortality. 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 (CI=.61–1.64). The secondary clinical composite outcome in AASK (which included ESRD, reduction in GFR by 50 percent or by 25 mL/min/1.73 m² from baseline, and death) showed a nonsignificant 2 percent reduction in the lower goal group (p=.85). MDRD found a nonsignificant 15 percent reduction in ESRD or death in the lower goal group (CI=0.60–1.22).

AASK found no significant differences in major CHD events, stroke, heart failure, death prior to ESRD, 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 BP target was 130/80 mmHg; total followup time including the cohort phase ranged from 8.8 to 12.2 years.[47] As in the trial phase, there were no significant differences in the doubling of serum creatinine, in ESRD, or in deaths during the extended followup period. Because participants were no longer randomized in the cohort phase, this analysis did not meet the study design criterion for this question and thus 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, kidney outcomes, or mortality as primary outcomes. Only one trial, REIN-2, assessed ESRD as a primary outcome. This trial was rated as fair and included only 335 participants followed for a median of 19 months. 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 if the study was not powered to detect a significant difference in these outcomes.

ES16. (CKD subpopulation): In the population with hypertension and CKD (without diabetes), there is evidence of no benefit of treatment with antihypertensive drug therapy to a lower BP goal (for example, <130/80 mmHg) compared to a goal of <140/90 mmHg on the progression of kidney disease.

***Evidence Quality:* Moderate**

Rationale/Comments: Three trials contributed to this evidence statement (AASK, MDRD, REIN-2).[13-15] 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 BP goals across trials was not possible because the goals in each trial were different. AASK compared a MAP goal of ≤92 mmHg to a MAP goal of 102–107 mmHg. In MDRD, BP goals were based on age. In the lower goal group, the MAP goal was ≤92 mmHg 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 mmHg for those 18–60 years of age and ≤113 for those ≥61 years of age. In REIN-2, a BP goal of <130/80 mmHg was compared to a diastolic goal of <90 mmHg, irrespective of SBP.

In AASK, treatment to the lower BP 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. Similarly, the median rate of GFR decline in REIN-2 was not significantly different between the group treated to the lower BP goal of <130/80 mmHg and the group treated to the higher DBP goal of <90 mmHg.

MDRD consisted of two studies. Study 1 randomized participants to a low or usual BP goal (described above) and to a usual or low-protein diet (1.3 or 0.58 grams of protein per kilogram of body weight per day). Study 2 randomized participants to the same low or usual BP goal and to a low- or very-low-protein diet (0.58 or 0.28 grams per kilogram of body weight per day). Study 1 included participants with a GFR of 25–55 mL/min/1.73 m², and study 2 included subjects with a GFR of 13 to 24 mL/min/1.73 m². 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=.006). However, when calculated from baseline to 3 years, the difference was not significant (10.7 compared to 12.3 mL/min, 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).

The panel graded the evidence as moderate because all three trials had consistent findings that showed no benefit of treatment to a lower BP goal compared to a goal of <140/90 mmHg. Additionally, change in GFR was the primary outcome in two of the trials, one of which was rated as good (AASK).

ES17. (proteinuria subpopulation): 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 BP goal (for example, <130/80 mmHg) compared to a goal of <140/90 mmHg 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).[13-15,45] 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 prespecified in each trial.

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 toward a benefit in treating to lower BP goals (for example, 130/80 mmHg) compared to a goal of <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 BP goal was 0.04 for the total GFR slope. 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 in the published figure did not overlap); the *p*-values were significant for the interaction.

There were nonsignificant differences in the clinical composite outcome in AASK, which included a reduction in GFR by 50 percent or by 25 mL/min/1.73 m², ESRD, and death; however, the *p*-value for the interaction was 0.007. REIN-2 found no significant differences in ESRD between the lower goal (130/80 mmHg) and conventional goal (<90 mmHg diastolic) for subgroups of patients analyzed by baseline proteinuria strata of 1–3 grams per 24 hours and >3 grams per 24 hours.

Thus, despite some evidence that suggests patients with proteinuria (particularly >3 grams/day) may benefit from a lower BP goal compared to a goal of <140/90 mmHg, the panel considered it to be insufficient.

C. Statements for the Population With Diabetes

ES18. (diabetes subpopulation): In the population with diabetes and hypertension, treatment to a SBP goal of <150 mmHg improves cardiovascular outcomes, cerebrovascular outcomes, or mortality.

***Evidence Quality:* Moderate**

Rationale/Comments: Three trials (SHEP, Syst-Eur, and UKPDS) contributed to this evidence statement.[9,48,49] 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 percent 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 nonfatal stroke. UKPDS specified three primary end points: The first clinical end point related to diabetes, death related to diabetes, and death from all causes.

Syst-Eur and UKPDS had SBP goals of <150 mmHg. The SBP goal in SHEP was based on baseline BP; the goal for individuals with a SBP >180 mmHg at baseline was <160 mmHg, and the goal for those with SBPs between 160 and 179 mmHg at baseline was a decrease of at least 20 mmHg. Thus, SBP goals in SHEP ranged from 140 mmHg to 159 mmHg, unlike the other two studies, which used a fixed goal of <150 mmHg.

SHEP showed a significant 54 percent reduction in nonfatal MI and fatal CHD in participants with diabetes (CI=0.24–0.88). SHEP also showed a 56 percent reduction in major CHD events (CI=0.25–0.77) and a 34 percent reduction in CVD events (CI=0.46–0.94). Syst-Eur showed a 57 percent reduction in fatal and nonfatal cardiac events in this population, but the *p*-value was 0.06 (CI=–6–82). In UKPDS, participants treated to the lower goal of <150/85 mmHg had a nonsignificant 21 percent reduction in MI (*p*=0.13) (CI=0.59–1.07), but there were more sudden deaths (1.8 vs. 1.3 per 1,000 patient-years) than in those treated to the higher goal of <180/105 mmHg; however, these were secondary outcomes and not significant.

Two of the three trials showed a benefit in cerebrovascular outcomes of treatment to a SBP goal of <150 mmHg. Syst-Eur showed a significant 69 percent reduction in fatal and nonfatal stroke (p=.02; CI=14–89), and UKPDS showed a significant 44 percent reduction in stroke (p=.013; CI=0.35–0.89). In SHEP, however, the incidence of fatal and nonfatal stroke in participants with diabetes was reduced by 22 percent, but this finding was not significant (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 reduced in the three trials. In SHEP, there was a nonsignificant 26 reduction (CI=0.46–1.18); in Syst-Eur, there was a nonsignificant 49 percent reduction (p=.09; CI=–9–69). In UKPDS, there was a nonsignificant 18 percent reduction (p=.17; CI=0.62–1.08). In UKPDS, overall mortality was one of three prespecified primary outcomes. The other two primary end points in UKPDS were any diabetes-related end point and deaths related to diabetes. Both were significantly reduced in the tight-control group treated to a goal BP of <150/85 mmHg; there was a 24 percent reduction in clinical end points related to diabetes (p=.0046; CI=0.62–0.92) and a 32 percent reduction in deaths related to diabetes (p=.019; CI=0.49–0.94). The diabetes-related end points and deaths related to diabetes in UKPDS can be found in the summary table D2k.

The panel graded the evidence as moderate. Although three trials 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.

ES19. (diabetes subpopulation): In the population with diabetes and prehypertension or hypertension, treatment to a SBP goal of <120 mmHg compared to <140 mmHg reduces cerebrovascular events, but there is no evidence of benefit on overall mortality, CHD events, heart failure, or a composite cardiovascular outcome.

***Evidence Quality:* Moderate**

Rationale/Comments: One study (ACCORD) contributed to this evidence statement.[11] ACCORD was rated as good and included 4,733 participants with diabetes. ACCORD compared a SBP goal of <120 mmHg to a SBP goal of <140 mmHg in participants with type 2 diabetes, glycated hemoglobin ≥7.5 percent, and SBP between 130 and 180 mmHg. 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 mmHg) and higher (<140 mmHg) SBP 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 mmHg, total strokes were reduced by 41 percent (p=.01) and nonfatal strokes were reduced by 36 percent (p=.03). There was no difference between groups for the primary composite outcome of major cardiovascular events (hazard ratio [HR] 0.88; CI=0.73–1.06; p=.20) or any of the other secondary outcomes: overall mortality (HR 1.07; CI=0.85–1.35; p=.55), major coronary disease events (HR 0.94; CI=0.79–1.12; p=.50), or heart failure (HR 0.94; CI=0.70–1.26; p=.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 percent less than expected, thereby reducing its power.

ES20. (diabetes subpopulation): In the population 50 years of age or older with diabetes and a SBP of 130–139 mmHg or a DBP of 80–89 mmHg or hypertension, treatment with antihypertensive medication to a DBP goal of ≤80 mmHg compared to ≤90 mmHg reduces a composite of fatal and nonfatal MI, fatal and nonfatal stroke, and all other cardiovascular deaths.

***Evidence Quality:* Low**

Rationale/Comments: One trial (HOT) contributed to this evidence statement.[44] 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 DBP goals: ≤80 mmHg, ≤85 mmHg, and ≤90 mmHg. 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 increased, by 106 percent, in the ≤90 mmHg goal group compared to the ≤80 mmHg group (45 vs. 22 events; HR 2.06; CI=1.24–3.44). The difference was not significant in the ≤90 mmHg group compared to the ≤85 mmHg group (45 vs. 34 events; HR 1.32; CI=0.84–2.06) or the ≤85 mmHg group compared to the ≤80 mmHg group (34 vs. 22 events; HR 1.56; 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 mmHg compared to a goal BP of <180/105 mmHg significantly reduced stroke, heart failure, diabetes-related end points, 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 DBP comparisons than HOT, and UKPDS also included SBP goals. In addition, UKPDS was conducted in a younger population (aged 25–65) compared to participants in HOT (aged 50–80).

The panel graded the quality of evidence as low because it was based on one study, only 8 percent 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 DBP goals.

ES21. (diabetes subpopulation): In the population with diabetes and a SBP of 130–139 mmHg or a DBP of 80–89 mmHg or hypertension, there is insufficient evidence to determine whether treatment with antihypertensive medication to a lower diastolic goal (for example, ≤80 mmHg) compared to a BP goal of ≤90 mmHg 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).[9,12,44] 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 percent (*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 DBP goal to a higher goal, direct comparisons across the three trials were not possible because different BP goals were tested in each study and UKPDS included a SBP goal. The ABCD Hypertensive Cohort compared a DBP goal of 75 mmHg to a goal of 80–89 mmHg. HOT compared

three DBP goals: ≤80 mmHg, ≤85 mmHg, and ≤90 mmHg. UKPDS compared a BP goal of <150/85 mmHg to a goal of <180/105.

ABCD showed a significant reduction in overall mortality in the group treated to a DBP goal of 75 mmHg compared to the group treated to 80–89 mmHg (5.5 percent vs. 10.7 percent, p=.037). In the HOT diabetes subgroup, there was a nonsignificant 56 percent reduction in overall mortality in the group treated to a DBP goal of ≤80 mmHg compared to the group treated to a goal of ≤90 mmHg (HR 0.56; CI=0.31–1.02). In UKPDS, there was a nonsignificant 18 percent reduction in overall mortality in the group treated to <150/85 mmHg compared to the group treated to <180/105 (RR 0.82; CI=0.62–1.08; p=.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 percent of the total study population and was not prespecified.

Section 6: Evidence Statements for Critical Question 3 (Antihypertensive Agents)

CQ3:

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

A. Statements for the General Population

i. Summary of Evidence Statements for the General Population

Tables 2–13 summarize the evidence for the drug comparisons in CQ3. 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.

Table 2. Angiotensin-Converting Enzyme Inhibitors (ACEIs) Versus Calcium Channel Blockers (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 CCBs better in Blacks	Moderate Moderate	ACEI ES1 ACEI ES2
Heart failure	ACEIs better	Moderate	ACEI ES1
Kidney	Similar	Moderate	ACEI ES1

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

Table 3. ACEIs Versus Angiotensin II Receptor Blockers (ARBs)

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	No trials	N/A	ARB ES2
Cardiovascular	No trials	N/A	ARB ES2
Cerebrovascular	No trials	N/A	ARB ES2
Kidney	No trials	N/A	ARB ES2

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

Table 4. Beta Blockers Versus ACEIs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Kidney	Insufficient evidence	Insufficient	BB ES3

Summary: There is insufficient evidence for beta blockers (BB in table 5) compared to ACEIs with respect to kidney outcomes. There are no trials comparing beta blockers to ACEIs for any other outcomes.

Table 5. Beta Blockers Versus CCBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Insufficient evidence	Insufficient	BB ES1
Cardiovascular	Insufficient evidence	Insufficient	BB ES1
Cerebrovascular	Insufficient evidence	Insufficient	BB ES1
Kidney	Insufficient evidence	Insufficient	BB ES1

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

Table 6. Beta Blockers Versus ARBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Low	BB ES2
Cerebrovascular	ARB better	Low	BB ES2
CHD	Similar	Low	BB ES2
Heart failure	Similar	Low	BB ES2
Kidney	Insufficient evidence	Insufficient	BB ES3
Composite	ARB better	Low	BB ES2

Summary: ARBs are better than BBs 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.

Table 7. CCBs versus ARBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	High/moderate	CCB ES1
Cerebrovascular	Insufficient	Insufficient	CCB ES3
CHD	Insufficient	Insufficient	CCB ES2
Heart failure	Insufficient	Insufficient	CCB ES4
Kidney	Insufficient	Insufficient	CCB ES6
Composite	Similar	Low	CCB ES5

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.

Table 8. Thiazide and Thiazide-Type Diuretics Versus Beta Blockers

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Insufficient evidence	Insufficient	Diuretic ES2
Cerebrovascular	Insufficient evidence	Insufficient	Diuretic ES7
CHD	Similar	Moderate	Diuretic ES3
Kidney	Insufficient evidence	Insufficient	BB ES3

Summary: All references to diuretics in these tables refer to thiazide and thiazide-type agents. Thiazide and thiazide-type diuretics are similar to BBs for CHD outcomes. There is insufficient evidence for thiazide and thiazide-type diuretics versus BBs for overall mortality, cerebrovascular outcomes, and kidney outcomes.

Table 9. Thiazide and Thiazide-Type Diuretics Versus ACEIs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Moderate	Diuretic ES1
Cerebrovascular	Diuretic better in Blacks	Moderate	Diuretic ES5
Cerebrovascular	Similar in non-Blacks	Low/moderate	Diuretic ES4
CHD	Similar	Moderate	Diuretic ES3
Heart failure	Diuretic better	Moderate	Diuretic ES10
Kidney	Similar	Moderate	Diuretic ES14
Composite	Diuretic better in Blacks	Low	Diuretic ES12
Composite	Similar in non-Blacks	Low	Diuretic ES11

Summary: In Blacks, thiazide and thiazide-type diuretics are better than ACEIs 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 ACEIs for heart failure outcomes but are similar for all the other outcomes.

Table 10. Thiazide and Thiazide-Type Diuretics Versus CCBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Moderate	Diuretic ES1
Cerebrovascular	Similar	High	Diuretic ES6
CHD	Similar	Moderate	Diuretic ES3
Heart failure	Diuretic better	High	Diuretic ES9
Kidney	Similar	Moderate	Diuretic ES14
Composite	Similar	High	Diuretic ES13

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

Table 11. Thiazide and Thiazide-Type Diuretics Versus ARBs

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	No trials	N/A	ARB ES1
Cardiovascular	No trials	N/A	ARB ES1
Cerebrovascular	No trials	N/A	ARB ES1
Kidney	No trials	N/A	ARB ES1

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

Table 12. Thiazide and Thiazide-Type Diuretics Versus Alpha Blockers

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Moderate	Diuretic ES1
Cerebrovascular	Diuretic better	Moderate	Diuretic ES8
CHD	Similar	Moderate	Diuretic ES3
Heart failure	Diuretic better	Moderate	Diuretic ES8
Composite	Diuretic better	Moderate	Diuretic ES8

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.

Table 13. Combination Therapy: ACEI/CCB Versus ACEI/Diuretic

Outcome	Result of Comparison	Evidence Quality	Evidence Statement
Overall mortality	Similar	Low	Combo ES1
Cardiovascular	ACEI/CCB better	Low	Combo ES1
Cerebrovascular	Similar	Low	Combo ES1
CHD	ACEI/CCB better	Low	Combo ES1
Heart failure	Similar	Low	Combo ES1
ESRD	Similar	Low	Combo ES1
Doubling of serum creatinine	ACEI/CCB better	Low	Combo ES1
Composite	ACEI/CCB better	Low	Combo ES1

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 ESRD.

B. 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; the order does not imply a specific priority to use a given drug class.

i. ACEIs Versus Other Drugs

ES1. **ACEI Evidence Statement 1. In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with an ACEI 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 CCB.**

Evidence Quality: ***Moderate***

Rationale/Comments: Three trials contributed to this evidence statement (ALLHAT, JMIC-B, and STOP-HTN2).[50-52] In ALLHAT, the comparison of the ACEI and CCB 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 significantly reduced with the use of an ACEI compared to the use of a CCB. In ALLHAT, heart failure was reduced by 13 percent (CI=0.78–0.96; p=.007). In STOP-HTN2, heart failure was reduced by 24 percent (CI=0.63–0.97; p=.025).

In JMIC-B and STOP-HTN2, there was no difference in stroke with the use of an ACEI compared to a CCB. In ALLHAT, stroke was 23 percent higher in the ACEI group (CI=1.08–1.41; p=.003). This difference was driven by a significant 51 percent increase in Blacks, but there was no difference in stroke for non-Blacks, which comprised 65 percent of the trial population (see CQ3, ACEI Evidence Statement 2). None of the trials showed a difference in overall mortality or kidney outcomes. In STOP-HTN2, there was a significant 23 percent (CI=0.61–0.96; p=.016) lower occurrence of MI in the ACEI group compared to the CCB group, but there was no significant difference in MIs 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 CVD in ALLHAT was higher by 6 percent (CI=1.00–1.12; p=.047) in the ACEI group compared to the CCB group, but it was only significant in Blacks.

ES2. **ACEI Evidence Statement 2. In the general Black population 55 years of age or older with hypertension, initial antihypertensive drug therapy with an ACEI is associated with higher incidence of stroke compared to initial antihypertensive drug therapy with a CCB.**

Evidence Quality: ***Moderate***

Rationale/Comments: This evidence statement is based on a prespecified subgroup analysis of Blacks in ALLHAT; they comprised 35 percent of the trial population.[50] In ALLHAT, comparison of the ACEI and CCB was a secondary analysis and was thus rated as fair. There were 18,102 participants in the ACEI and CCB groups. Stroke increased significantly by 51 percent (CI=1.22–1.86; p-value not reported) in Blacks initially treated with an ACEI compared to Blacks initially treated with a CCB. In this trial, the ACEI was also less effective in reducing BP in Blacks compared to the CCB with a difference of 2.7/1.6 mmHg for Black men and 3.9/2.1 mmHg for Black women between the ACEI and CCB arms of the study. The other two trials comparing an ACEI to a CCB 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.

ii. ARBs Versus Other Drugs

ES1. **ARB Evidence Statement 1: In the general population with hypertension, there are no RCTs of any quality to determine whether initial antihypertensive drug therapy with an ARB 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.

ES2. **ARB Evidence Statement 2: In the general population with hypertension, there are no RCTs of good or fair quality to determine whether initial antihypertensive drug therapy with an ARB compared to initial antihypertensive drug therapy with an ACEI 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 meeting this review's eligibility criteria that compared initial antihypertensive drug therapy with an ARB to initial antihypertensive drug therapy with an ACEI and reported cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

ONTARGET compared an ARB to an ACEI to a combination of the two drugs in participants with vascular disease or high-risk diabetes.[53] However, ONTARGET was not eligible for inclusion in this evidence review because the study was not designed to assess the effects of BP lowering in hypertension and not all patients in the study were hypertensive. ONTARGET found no difference between the ARB and the ACEI for the primary outcome, which was a composite of death from cardiovascular causes, MI, stroke, or hospitalization for heart failure (risk ratio 1.01; CI=0.94–1.09).

ES3. **ARB Evidence Statement 3: In the general population 50 years of age or older with hypertension, initial antihypertensive drug therapy with an ARB compared to initial antihypertensive drug therapy with a CCB resulted in a 3–5 percent lower absolute rate of new-onset diabetes.**

Evidence Quality:* *Low

Rationale/Comments: Two studies contributed to this evidence statement (VALUE and CASE-J).[54,55] 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 followup was 4.2 years. New-onset diabetes, defined by 1999 World Health Organization (WHO) criteria, was a prespecified secondary end point and occurred in 13.1 percent of the valsartan group (n=690) compared to 16.4 percent of the amlodipine group (n=845). The relative risk for new-onset diabetes with valsartan compared to amlodipine was 0.77 (CI=0.69–0.86; p<.0001) while the absolute difference between the two groups was 3.3 percent. 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 percent increase in fatal and nonfatal MI in the valsartan group compared to the amlodipine group (p=.02).

CASE-J included 4,728 participants ages 20 to 85, with a mean age of 63.8 years, randomized to candesartan or amlodipine. The mean followup was 3.2 years. New-onset diabetes was a prespecified secondary outcome. The relative risk of new-onset diabetes was 36 percent lower in the candesartan group compared to the

amlodipine group (p= .033) while the absolute difference for new-onset diabetes between the two groups was 4.9 percent. However, there was no difference in the use of additional diabetes drugs, including insulin, between the two groups (p=.402) and no difference in the primary cardiovascular end point (HR 1.01; CI=0.79–1.28; p=.969).

Of note is that in CASE-J, the rate of new-onset diabetes in the amlodipine group (13.6 per 1,000 patient-years) was one-third the rate seen in the amlodipine group in VALUE (41.1 per 1,000 patient-years), possibly indicating a population effect. As noted by Ogihara and colleagues,[55] mean body mass index for participants without diabetes in CASE-J was 24.1 compared to 28.0 in VALUE. In addition, 3.5 percent of the population in VALUE was Asian compared to 100 percent in CASE-J.

The third trial meeting the inclusion criteria for comparing an ARB to a CCB was MOSES,[56] but MOSES did not report new-onset diabetes. It should be noted that this 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.

iii. Thiazide and Thiazide-Type Diuretics Versus Other Drugs

ES1. Diuretic Evidence Statement 1: 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 ACEI, CCB, or alpha-1 blocking agent.

***Evidence Quality:* Moderate**

Rationale/Comments: Six trials contributed to this evidence statement (ALLHAT, INSIGHT, SHELL, VHAS, MIDAS, and ANBP2).[5,6,57-61] 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 groups treated with the diuretic and the other drug classes in any trial, and the CIs around estimates of effect were narrow. For example, in the largest trial (ALLHAT) the relative risk was 1.00 (CI=0.94–1.08; p=.90) for the diuretic–ACEI comparison, 0.96 (CI=0.89–1.02; p=.20) for the diuretic–CCB comparison, and 1.03 (CI=0.94–1.13; p=.50) for the diuretic–alpha-1 blocking agent comparison. In INSIGHT, also a large study rated as good, the odds ratio (OR) for overall mortality was 1.01 (CI=0.80–1.27; p=.95) for the diuretic–CCB comparison. Based on the consistent findings across six trials, the panel determined that there was moderate quality evidence of similar benefit of a diuretic, ACEI, CCB, or alpha-1 blocking agent regarding overall mortality. A grade of moderate (rather than high) was given because overall mortality was a secondary outcome in all six trials.

ES2. Diuretic Evidence Statement 2: 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).[35,62-64] 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 BB option. Pooled results from all metoprolol centers, all atenolol centers, and the propranolol center were published separately as HAPPHY.

MAPHY showed a significant 22 percent increase in total mortality in the diuretic group at 10.8 years (CI not reported; p=.028). However, MRC and HAPPHY found no difference between the BB and diuretic groups. All three trials included participants of similar ages (40–64 years for MAPHY and HAPPHY; 35–64 years in MRC); however, HAPPHY and MAPHY included only men. It is unclear whether the possible benefit of metoprolol in MAPHY was drug specific or applicable to BBs 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.

ES3. Diuretic Evidence Statement 3: In the general population 35 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic has a similar benefit on CHD outcomes compared to initial treatment with an ACE inhibitor, BB, CCB, 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).[5,6,35,57-63] Two of the nine studies were rated as good (ALLHAT and INSIGHT), and the remaining seven were rated as fair. CHD outcomes were primary outcomes in four of the nine trials (MRC, ALLHAT, HAPPHY, and MAPHY). Five trials, including the largest trial (ALLHAT) where CHD was the primary outcome, showed no significant difference in CHD outcomes for initial treatment with a diuretic compared to an ACEI, BB, CCB, or an alpha-1 blocking agent (MRC, ALLHAT, SHELL, MIDAS, and MAPHY). Three trials showed significant differences between groups for CHD outcomes; however, results were inconsistent among these three trials (INSIGHT, MAPHY, and ANBP2). Fatal MI was a secondary end point in INSIGHT where the OR was 3.22 (CI=1.18–8.80; p<.017) and events were lower with the diuretic compared to the CCB. MAPHY included fatal CHD as a primary outcome (composite of fatal MI and sudden coronary death), and the diuretic did worse than the BB (43 vs. 36 events, respectively, p=.048). ANBP2 included MI as a primary end point, and there were significantly more events in the diuretic group compared to the ACEI group (HR 0.68; CI=0.47–0.98; p=.04). However, there was no difference in overall coronary events in ANBP2 (HR 0.86; CI=0.70–1.06; p=.16). One trial (VHAS) did not report p-values, but the number of events was small and CHD was a secondary outcome.

In INSIGHT, fatal MI (a secondary outcome) occurred more frequently in the CCB group compared to the diuretic group with an OR of 3.22 (CI=1.18–8.80; p=.017); there was no significant difference for nonfatal MI. MAPHY showed a significant difference between groups for fatal CHD, which was a composite of MI and sudden coronary death. There were fewer fatal CHD events in the BB (metoprolol) group compared to the diuretic group at 10.8 years of followup (36 vs. 43 events; p=.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, MI was reduced by 32 percent in the ACEI group compared to the diuretic group (CI=0.47–0.98; p=.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 hydrochlorothiazide [HCTZ] 25–100 mg, chlorthalidone 12.5–25 mg, or bendrofluazide 5–10 mg).

ES4. Diuretic Evidence Statement 4: 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 ACEI.

***Evidence Quality:* Moderate**

Rationale/Comments: Two trials contributed to this evidence statement (ALLHAT and ANBP2).[5,61] In ALLHAT, 15,255 adults ages 55 years or older with at least one risk factor for CHD were randomized to the diuretic chlorthalidone and compared to 9,054 similar participants randomized to the ACEI lisinopril. ALLHAT was rated as good. Non-Blacks, a prespecified subgroup, constituted 65 percent of the trial population, 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 (CI=0.85–1.17; *p*-value not reported). Among Blacks, the relative risk was 1.40 (CI=1.17–1.68; *p*-value 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 ACEI for this outcome. However, stroke was a secondary end point.

ANBP2 randomized 6,083 adults aged 65–84 years to a thiazide diuretic (predominantly HCTZ) or ACEI (predominantly enalapril). It was rated as fair. There was a significant 91 percent reduction in the secondary end point of fatal stroke among those treated with diuretic therapy (CI=1.04–3.50; *p*=.04), but the findings were not significant for total stroke (HR 1.02; CI=0.78–1.33; *p*=.91) or nonfatal stroke (HR 0.93, CI=0.70–1.26; *p*=.65). As noted earlier, the doses of diuretics or ACEIs used in ANBP2 were not specified.

The significant benefit for fatal stroke seen in ANBP2 favoring diuretic therapy over ACEI 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 had narrow confidence limits, the results of ALLHAT were given greater weight by the panel.

ES5. Diuretic Evidence Statement 5: 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 ACEI.

***Evidence Quality:* Moderate**

Rationale/Comments: This evidence statement is based on one trial (ALLHAT) in which race was a prespecified subgroup and 35 percent of study subjects were Black.[5] ALLHAT was rated as good, and stroke was a prespecified secondary outcome. In the overall trial results, there was a reduction in stroke in the group initially treated with a diuretic compared to the group initially treated with an ACEI relative risk (RR) for use of an ACEI compared to use of a diuretic was 1.15; CI=1.02–1.30; *p*=.02). This benefit was driven by the reduction in stroke seen in the Black subgroup. Among Blacks, stroke increased by 40 percent in the ACEI group compared to the diuretic group (CI=1.17–1.68; *p*-value not reported).

There were differences in the percentage of subjects achieving the BP goal of less than 140/90 mmHg at each annual visit, with BP significantly higher at 5 years in the lisinopril group compared to the chlorthalidone group (by 2 mmHg for all participants and by 4 mmHg in Black participants). Analysis of the relative risk for stroke adjusted for followup BPs suggests that the SBP difference between the lisinopril and chlorthalidone groups is only partly responsible for the observed differences in stroke.

ES6. **Diuretic Evidence Statement 6: 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 CCB.**

Evidence Quality:* *High

Rationale/Comments: Four trials contributed to this evidence statement (ALLHAT, SHELL, INSIGHT, and MIDAS).[5,6,58,60] ALLHAT and INSIGHT were rated as good with study populations of 33,357 and 6,321, respectively. SHELL and MIDAS were rated as fair with study populations of 1,882 and 883, respectively. In all four trials, cerebrovascular outcomes were prespecified secondary outcomes. The recommended doses of diuretics and CCBs used in all four trials were similar to those used in studies that showed benefit for these classes of antihypertensive medications. In all four trials, initiation of antihypertensive drug therapy with a diuretic yielded similar cerebrovascular outcomes when compared to initiation of antihypertensive therapy with a CCB. The quality of this evidence statement is graded as high because four contributing trials yielded consistent results.

ES7. **Diuretic Evidence Statement 7: 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 BB.**

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

Rationale/Comments: Three trials contributed to this evidence statement (MRC, HAPPHY, and MAPHY).[35,62,63] All three trials were rated as fair. MRC was the largest trial with 17,354 participants aged 35–64 years and an approximately equal number of males and females. The populations in both HAPPHY and MAPHY were exclusively males, aged 40–64 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 stroke favoring the diuretic (0.8 per 1,000 patient-years [n=18] vs. 1.9 per 1,000 patient-years [n=42]; p=.002).

HAPPHY randomized participants to a diuretic (HCTZ 50 mg daily or bendroflumethiazide 5 mg daily) or a BB (atenolol 100 mg daily or metoprolol 200 mg daily). There was no difference in fatal and nonfatal stroke (OR 1.29; CI=0.82–2.04; p>.20). The difference in fatal stroke trended toward significance, but there were few events overall (10 events in the diuretic group compared with 3 events in the BB 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 BB group; however, there were few events overall (nine events in the diuretic group compared with two events in the BB group at 10.8 years of followup; p=.043). Total stroke 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.

ES8. **Diuretic Evidence Statement 8: 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.[5,57] The alpha blocker (doxazosin) arm of ALLHAT, which included 9,067 participants, was terminated early due to a 25 percent (CI=1.17–1.33; $p<.001$) greater incidence of combined cardiovascular outcomes when compared to the diuretic (chlorthalidone) arm, which included 15,268 participants. Combined cardiovascular outcomes were defined as CHD death, nonfatal MI, stroke, coronary revascularization procedures, angina, heart failure, and PAD. Stroke increased by 26 percent (CI=1.10–1.46; $p=.001$), and heart failure (including fatal, hospitalized, and treated heart failure) increased by 80 percent (CI=1.61–2.02; $p<.001$) 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.

ES9. **Diuretic Evidence Statement 9: 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 CCB.**

Evidence Quality: ***High***

Rationale/Comments: Five trials contributed to this evidence statement (ALLHAT, SHELL, VHAS, INSIGHT, and MIDAS).[5,6,58-60,65] 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 CCB group; however, in INSIGHT the heart failure event rate was low, so the absolute reduction was small. In ALLHAT, there were 38 percent more heart failure events in the CCB group compared to the diuretic group (CI=1.25–1.52; $p<.001$). 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 nonfatal heart failure events in the CCB group (OR 2.20, CI=1.07–4.49; $p=.028$); however, there were few heart failure events overall (11 in the diuretic group and 24 in the CCB 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 CCB 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.

ES10. Diuretic Evidence Statement 10: 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 ACEI.

***Evidence Quality:* Moderate**

Rationale/Comments: Two trials contributed to this evidence statement (ALLHAT and ANBP2).[5,61] ALLHAT compared chlorthalidone (dose range 12.5–25 mg) to lisinopril (dose range 10–40 mg) and was rated as good. In ANBP2, HCTZ was the recommended diuretic and enalapril was the recommended ACEI; 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 percent higher (CI=1.07–1.31; $p<.001$) among the participants on the ACEI compared to those on the diuretic. In ANBP2, there was no significant difference in heart failure (HR 0.85, CI=0.62–1.18; $p=.33$), and the direction of the HR favored the ACE inhibitor. The 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).

ES11. Diuretic Evidence Statement 11: 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 CVD outcomes compared to initial antihypertensive drug therapy with an ACEI.

***Evidence Quality:* Low**

Rationale/Comments: Two trials contributed to this evidence statement (ALLHAT and ANBP2).[5,61] ALLHAT was rated as good, and ANBP2 was rated as fair. Non-Blacks comprised 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 CVD 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 CVD was 1.06 (CI=1.00–1.13; *p*-value not reported). Outcomes favored the diuretic, but the CI included 1.00, so it did not quite achieve statistical significance. Among Blacks, the relative risk was 1.19, also favoring the diuretic (CI=1.09–1.30; *p*-value not reported), and in this case the CI does not cross 1.00, so the result was statistically significant. This evidence is addressed further in the next evidence statement. For combined CVD 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 ACEI for this outcome. Combined CVD was a secondary composite end point that included CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and hospitalization or revascularization for PAD.

In ANBP2, the primary composite outcome of all cardiovascular events and death from any cause was lower by 11 percent in the ACEI group compared to the diuretic group; however, the CI included 1.00 (CI=0.79–1.00; $p=.05$), so it did not quite achieve statistical significance. Cardiovascular events in the primary composite outcome were 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 noncardiac 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 ANPB2 favored the ACEI) and the fact that the CIs included 1.00 in both trials. In addition, each trial defined composite outcomes differently and included softer end points 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.

ES12. Diuretic Evidence Statement 12: In the general Black population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic improves combined CVD outcomes compared to initial antihypertensive drug therapy with an ACEI.

***Evidence Quality:* Low**

Rationale/Comments: This evidence statement is based on one trial (ALLHAT) in which race was a prespecified subgroup and 35 percent of study subjects were Black.[5] ALLHAT was rated as good, and combined CVD was a prespecified secondary composite end point. Among Blacks, there was a significant 19 percent lower occurrence of the combined CVD end points in the diuretic group compared to the ACEI group (CI=1.09–1.30; $p<.001$). 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 CVD end point included softer end points such as angina and revascularization.

ES13. Diuretic Evidence Statement 13: In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic results in similar combined CVD outcomes compared to initial antihypertensive drug therapy with a CCB.

***Evidence Quality:* High**

Rationale/Comments: Five studies contributed to this evidence statement (ALLHAT, INSIGHT, MIDAS, SHELL, and VHAS).[5,6,58-60] Two of these trials (ALLHAT and INSIGHT) were rated as good. ALLHAT included 24,303 participants in the diuretic and CCB 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 CVD 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 CVD outcomes between the diuretic and CCB groups in any of the five trials. In the largest trial, ALLHAT, there was a 4 percent lower occurrence of composite cardiovascular events with the diuretic group compared to the CCB group, but the result was not significant (HR 1.04; CI=0.99–1.09; $p=.12$). In INSIGHT, there was an 11 percent higher occurrence of composite cardiovascular events in the CCB group, but it was not significant (CI=0.90–1.36; $p=.34$). In MIDAS, there was a 78 percent lower occurrence of major vascular events, but it was not significant (RR 1.78; CI=0.94–3.38; $p=.07$). In SHELL, the hazard ratio for the composite primary end point was 1.01 (CI=0.75–1.36; $p=.94$). 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 (nine in the diuretic group and eight in the CCB group). The evidence quality was graded as high because none of the five studies found a significant difference in composite CVD outcomes between groups treated initially with a diuretic compared to a CCB.

ES14. Diuretic Evidence Statement 14: 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 ACEI or CCB.

***Evidence Quality:* Moderate**

Rationale/Comments: Two trials contributed to this evidence statement (ALLHAT and INSIGHT).[5,6] Although three additional trials compared a diuretic to an ACEI or CCB (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 ACEI (lisinopril) or CCB (amlodipine), whereas INSIGHT compared a combination diuretic (HCTZ and amiloride) to a CCB (nifedipine). The ALLHAT inclusion criteria allowed enrollment of subjects with serum creatinine <2.0 mg/dL. INSIGHT did not have study inclusion or exclusion criteria based on serum creatinine levels; 170 subjects (2.7 percent) had proteinuria at baseline defined as 0.5 grams of 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–ACEI comparison was 1.11 (CI=0.88–1.38; p=.38) favoring the diuretic. For the diuretic–CCB comparison, the relative risk was 1.12 (CI=0.89–1.40; p=.33) and also favored the diuretic. In INSIGHT, the OR 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; CI=0.26–1.49; p=.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 HCTZ, although both in the diuretic class, are somewhat different compounds. Additionally, INSIGHT used a combination diuretic that included HCTZ and amiloride. These differences in the diuretics used in each study, together with the wide CIs for the kidney end points, led to an overall grading of the evidence quality as moderate.

ES15. Diuretic Evidence Statement 15: In the general population 55 years of age or older with hypertension, initial antihypertensive drug therapy with a diuretic results in a 3–4 mg/dL increase in fasting blood glucose and a 2–4 percent absolute increase in hyperglycemia or incident diabetes compared to initial antihypertensive drug therapy with an ACEI or CCB.

***Evidence Quality:* Moderate**

Rationale/Comments: Three studies contributed to this evidence statement (ALLHAT, INSIGHT, and VHAS).[5,6,59] In these studies, initiation of antihypertensive treatment with a diuretic, compared to initiation of treatment with an ACEI or CCB, 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 CQ3, Diuretic Evidence Statements 1, 3, 4, 5, 6, 9, 10, 11, 12, 13, and 14). It should be noted, however, that this 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, result 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 ACEI or the CCB arms in the three trials that assessed these outcomes. However, the 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 this literature review was not designed to evaluate the comparative effects of different antihypertensive medications on these end points.

iv. Beta Blockers Versus Other Drugs

ES1. **Beta Blocker Evidence Statement 1: In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a BB compared to initial antihypertensive drug therapy with a CCB 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).[7,66] These trials were not specifically designed to test whether a BB compared to a CCB 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 CCB or BB) and a second drug was added (ACEI to the CCB group and diuretic to the BB group) as needed to control BP. The intent was that most study participants would receive at least two antihypertensive drugs, and 78 percent 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 CQ3, Combination Therapy Evidence Statement 1), because, in ASCOT, treatment was initiated with a single drug and then stepped up with a second drug. In ACCOMPLISH, treatment was initiated with two-drug combination therapy in a single-capsule formulation.[4,7]

ASCOT showed a significant reduction in events for CCB-based therapy compared to BB-based therapy, including a 13 percent reduction in nonfatal MI plus fatal CHD (CI=0.76–1.00; p=.0458), 23 percent reduction in fatal and nonfatal stroke (CI=0.66–0.89; p=.0003), and 11 percent reduction in all-cause mortality (CI=0.81–0.99; p=.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 CCB compared to a BB, the study population comprised 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 ACEI in the amlodipine arm. Because of these issues pertaining to ASCOT, and the fact that ELSA did not assess any of the clinical end points prespecified by the panel, it was determined that evidence from these two trials was insufficient to determine whether initial antihypertensive drug therapy with a BB compared to a CCB improves cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.

ES2. **Beta Blocker Evidence Statement 2: In the general population 55–80 years of age with hypertension, initial antihypertensive drug therapy with an ARB compared to initial antihypertensive drug therapy with a BB decreases stroke and a primary composite end point (consisting of cardiovascular 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).[8] LIFE compared initial antihypertensive drug therapy with an ARB to initial therapy with a BB. LIFE was rated as good and included 9,193 participants aged 55–80 years, all of whom had hypertension and LVH as determined by ECG. Atenolol was the BB and losartan was the ARB. The primary end point was a composite of cardiovascular death, MI, and stroke. There was a significant 13 percent reduction in the primary composite endpoint in the ARB group compared to the BB group (CI=0.77–0.98; *p*=.021). 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 percent decrease in stroke (adjusted HR 0.75; CI=0.63–0.89; *p*=.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 as determined by ECG.

ES3. **Beta Blocker Evidence Statement 3: In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive therapy with a BB has an effect on kidney outcomes that is different than the effect of initial antihypertensive therapy with a diuretic, CCB, ACEI, or ARB.**

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 BB to a diuretic, CCB, ACEI, or ARB and reported the kidney outcomes prespecified by the panel (ESRD, doubling of creatinine, halving of eGFR). CQ3, Chronic Kidney Disease Evidence Statement 1 addresses this evidence in those patients 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 percent (CI=0.75–0.97; *p*=.0187) lower rate of renal impairment for CCB-based therapy compared to BB-based therapy.[7] IPPPSH reported a lower rate of renal impairment with BBs compared to placebo alone or added to other non-BB antihypertensives.[67] HAPPHY reported a nonsignificant difference in the change in creatinine between the BB and diuretic groups.[62] However, renal impairment and change in creatinine were not defined with sufficient rigor to be considered eligible kidney outcomes.

ES4. **Beta Blocker Evidence Statement 4: In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a BB compared to initial antihypertensive drug therapy with a CCB 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).[7] ASCOT included 19,257 subjects and was rated as good. Antihypertensive drug therapy in ASCOT was initiated with one drug (a CCB or BB) and was then stepped up to another drug (an ACEI for the CCB group and a diuretic for the BB group) as needed to control BP; 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 percent lower with CCB-based therapy compared to BB-based therapy (CI=0.63–0.78; $p<.0001$).

The panel graded the evidence as insufficient because of the low percentage of study participants who received a BB or a CCB as monotherapy prior to the addition of step 2 agents and the categorization of new-onset diabetes as a tertiary end point. In addition, the evidence was graded as insufficient because this review was not primarily designed to evaluate the association of different antihypertensive medications with new-onset diabetes.

ES5. Beta Blocker Evidence Statement 5: In the general population 55–80 years of age with hypertension, initial antihypertensive drug therapy with a BB compared to initial antihypertensive drug therapy with an ARB results in a 2 percent absolute increase in new-onset diabetes.

***Evidence Quality:* Low**

Rationale/Comments: One trial contributed to this evidence statement (LIFE).[8] LIFE compared atenolol and losartan in participants aged 55–80 years with essential hypertension and LVH as determined by ECG. At baseline, 7,998 patients did not have diabetes mellitus. New-onset diabetes occurred in 241 participants receiving losartan (5.99 percent) and 319 receiving atenolol (8.01 percent) for a relative risk of 0.75 (CI=0.63–0.88; $p<.001$). Diabetes was defined according to 1985 WHO 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 as determined by ECG.

Additional comments relating to dysglycemia and BB use: UKPDS compared two different BP goals in a population 25–65 years of age with hypertension and type 2 diabetes.[10] The group of 758 study participants assigned to tight BP control with a target BP of <150/85 mmHg 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 end points. For followup years 1 through 4, mean hemoglobin A1c (standard deviation) was 7.0 percent (1.4 percent) for captopril versus 7.5 percent (1.4 percent) for atenolol ($p=.0044$). For followup years 1 through 4, 53 percent of participants in the captopril group received additional glucose-lowering treatment compared to 66 percent in the atenolol group ($p=.0015$). For followup years 5 through 9, 71 percent of participants in the captopril group received additional glucose-lowering treatment compared to 81 percent in the atenolol group ($p=.029$). 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.

v. Calcium Channel Blockers Versus Other Drugs

ES1. Calcium Channel Blocker Evidence Statement 1: In the general population 50 years of age or older with hypertension, initial antihypertensive drug therapy with a CCB compared to initial antihypertensive drug therapy with an ARB results in no difference in overall mortality.

***Evidence Quality:* Moderate**

Rationale/Comments: The contributing clinical trials comparing a CCB to an ARB were VALUE, CASE-J, and MOSES, all of which used dihydropyridine CCB.[54-56] IDNT[18] 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 HR for overall mortality was 1.04 (CI=0.94–1.15; *p*=.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*=.725). The panel graded the evidence as moderate. Although findings were consistent across the three trials, and the CI in the largest trial (VALUE) was narrow; overall mortality was a secondary outcome in each trial.

ES2. Calcium Channel Blocker Evidence Statement 2: In the general population with hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a CCB compared to initial antihypertensive drug therapy with an ARB results in a difference in CHD 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 1 (VALUE, CASE-J, and MOSES).[54-56] CHD, cerebrovascular disease, heart failure, and kidney outcomes were all secondary end points. Each trial used a composite end point as the primary outcome. VALUE and CASE-J were rated as good, and MOSES was rated as fair.

CHD outcomes: In VALUE, the hazard ratio for fatal and nonfatal MI was 1.19 (CI=1.02–1.38; *p*=.02) favoring amlodipine over valsartan. In CASE-J, there was no difference in cardiac events (defined as heart failure, angina pectoris, or acute MI) with a HR of 0.92 (CI=0.61–1.39; *p*=.68). In MOSES, the relative risk for fatal and nonfatal cardiovascular events (defined as any cardiovascular event including MI and new cardiac failure) was 0.75 (CI=0.55–1.02; *p*=.061) favoring eprosartan over nitrendipine.

Improved CHD outcomes with the CCB 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 three trials, there is insufficient evidence to suggest a difference in CHD 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 HR for the ARB (valsartan) compared to the CCB (amlodipine) for fatal and nonfatal stroke was 1.15 (CI=0.98–1.35; *p*=.08). In CASE-J, the HR for the ARB (candesartan) compared to the CCB (amlodipine) group for cerebrovascular events (defined as fatal and nonfatal stroke and TIA) was 1.23 (CI=0.85–1.78; *p*=.282). In contrast, MOSES showed a 25 percent reduction (RR 0.75; CI=0.58–0.97; *p*=.026) 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 HR for fatal and nonfatal heart failure was 0.89 (CI=0.77–1.03; *p*=.12) favoring the ARB while in CASE-J, the HR was 1.25 favoring the CCB (CI=0.65–2.42; *p*=.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 end point in the two treatment groups (RR 0.75; CI=0.55–1.02; *p*=.061). With the inconsistency of findings across trials and wide CIs, 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 HR for kidney events (defined as a composite of serum creatinine of 4.0 mg/dL or higher, doubling of serum creatinine, or ESRD) was 0.70 with wide CIs (CI=0.39–1.26; *p*=.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.

ES3. Calcium Channel Blocker Evidence Statement 3: In the general population 50 years of age or older with hypertension, initial antihypertensive therapy with a CCB compared to initial antihypertensive therapy with an ARB results in no difference in composite outcomes.

***Evidence Quality:* Low**

Rationale/Comments: Three trials contributed to this evidence statement (VALUE, CASE-J, and MOSES).[54-56] Each trial used a composite end point 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 HR was 1.04 (CI=0.94–1.15; *p*=.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 HR was 1.01 (CI=0.79–1.28; *p*=.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 (CI=0.66–0.96; *p*=.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.

vi. Combination Therapy

ES1. Combination Therapy Evidence Statement 1: 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 cardiovascular morbidity and mortality, and doubling of serum creatinine, but there is no difference in overall mortality, stroke, heart failure, or ESRD outcomes when compared to initial antihypertensive drug therapy with the combination of benazepril and HCTZ.

***Evidence Quality:* Moderate**

Rationale/Comments: This evidence statement is based on one trial (ACCOMPLISH), which was rated as good.[4,68] 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-HCTZ. The benazepril-amlodipine arm of the

study had a significant 20 percent decrease (CI=0.72–0.90; $p<.001$) in the primary outcome compared to the benazepril-HCTZ arm, despite similar BP lowering in both groups (131.6/73.3 and 132.5/74.4 mmHg, respectively). The trial was terminated early after a mean followup 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 to 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, due to concerns about the dose of the diuretic used in the study, and due to conflicting evidence from multiple studies that compared CCBs and diuretics when used with add-on agents other than ACEIs (see CQ3, 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 followup, and adherence information was reported at 6 months and 1 year but not at the end of followup (although reporting adherence at all is a strength).

vii. Other Drug Classes

ES1. **Other Drug Classes Evidence Statement 1: There are drug classes for which there are no RCTs 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 BBs
- 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 RCTs 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;[19,22,30,36] 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;[19,33,35,69] however, these active treatment arms were compared to placebo or usual care.

C. Statements for the Population With Chronic Kidney Disease

ES1. **Chronic Kidney Disease Evidence Statement 1: In the population 18 to 75 years of age with CKD and hypertension, treatment with an ACEI improves kidney outcomes (ESRD, halving of GFR, or doubling of serum creatinine) compared to treatment with a CCB or a BB.**

Evidence Quality: ***Moderate***

Rationale/Comments: Three studies contributed to this evidence statement (AASK, ESPIRAL, and AVER).[13,16,17] AASK was rated as good and included 1,094 participants followed for 3–6.4 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: 18–70 years for AASK, 18–75 years for ESPIRAL, and 18–80 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 percent (95% CI, 14%, 59%; p=.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 percent or more or ≥25 mL/min/1.73 m² from baseline. AASK used a complex trial design with two BP goals for each of three 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 percent (CI=0.26–0.84; p=.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 SBPs 4–6 mmHg lower than participants receiving a CCB. At 3 years of followup in AVER, 15.4 percent of participants in the ACEI group had a secondary composite end point compared to 21.1 percent in the CCB group (p-value nonsignificant). The secondary composite end point included renal replacement therapy, discontinuation due to deterioration of renal function, 50 percent decrease in GFR, doubling of serum creatinine, and hospitalization for transient renal failure. Limitations of this end point are that it was a secondary composite consisting of many end points, some of which were soft end points such as hospitalization for transient kidney failure. Attrition rates were negligible in AASK but were 33 percent for AVER and 32 percent for ESPIRAL.

ES2. **Chronic Kidney Disease Evidence Statement 2: In the population 30–70 years of age with CKD with proteinuria and hypertension, antihypertensive treatment with an ARB improves kidney outcomes compared to antihypertensive treatment with a CCB.**

Evidence Quality: ***Low***

Rationale/Comments: One trial (IDNT) contributed to this evidence statement.[18] IDNT, which was rated a fair study, included 1,715 participants with diabetic nephropathy, 30–70 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 ≥6.0 mg/dL), and all-cause mortality. There was a 24 percent (CI=0.63–0.92; p=.005) reduction in the primary outcome for the ARB group compared to the CCB group. Doubling of serum creatinine was significant with a 39 percent (CI=0.48–0.79; p<.001) reduction in the ARB group compared to the CCB group, but the 24 percent (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, BBs, 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.[70]

ES3. Chronic Kidney Disease Evidence Statement 3: In the population 18–70 years of age with CKD and hypertension, antihypertensive treatment with an ACEI does not improve combined CVD outcomes compared to antihypertensive treatment with a CCB or BB.

***Evidence Quality:* Moderate**

Rationale/Comments: One study (AASK) contributed to this evidence statement.[13,46] 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 BB (metoprolol). AASK was not powered for cardiovascular outcomes, but they were prespecified secondary outcomes as 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 MI, stroke, heart failure, revascularization procedures, and other hospitalizations for cardiovascular events. Hazard ratios for the composite cardiovascular outcome were 0.77 (CI=0.48–1.24; p=.28) for amlodipine versus metoprolol, 1.27 (CI=0.78–2.06; p=.33) for ramipril versus amlodipine, and 0.98 (CI=0.69–1.39; p=.90) for ramipril versus metoprolol. There were 149 total cardiovascular events.

ES4. Chronic Kidney Disease Evidence Statement 4: In the population 30 years of age or older with CKD and hypertension, antihypertensive treatment with an ARB does not improve combined CVD outcomes compared to antihypertensive treatment with a CCB.

***Evidence Quality:* Moderate**

Rationale/Comments: The two trials contributing to this evidence statement (IDNT and VALUE) showed no differences between groups.[18,70] Both trials were rated as fair. IDNT included 1,715 participants, 30–70 years of age, with diabetic nephropathy, followed for a mean of 2.6 years. VALUE included 15,245 participants aged 50 or older, with 9,566 aged 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 CVD was a secondary outcome in IDNT and included death from cardiovascular causes, nonfatal MI, heart failure 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 (CI=0.81–1.32; *p*=.78). However, the mean followup 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 CQ3, Chronic Kidney Disease 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 coronary artery bypass grafting, death as a result of heart failure, death associated with recent MI according to autopsy, heart failure requiring hospital management, nonfatal MI, or emergency procedures to prevent MI. Among participants with baseline serum creatinine greater than 1.7 mg/dL, 21.9 percent in the amlodipine group experienced the primary composite end point compared to 19.7 percent in the valsartan group (*p*=.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.

ES5. Chronic Kidney Disease Evidence Statement 5: In the population 30–70 years of age with CKD and hypertension, initial antihypertensive treatment with an ARB reduces the incidence of heart failure compared to initial antihypertensive treatment with a CCB.

***Evidence Quality:* Low**

Rationale/Comments: One trial (IDNT) contributed to this evidence statement.[18,71] 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 percent (CI=0.48–0.87; *p*=.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 (HR 0.90; CI=0.74–1.10; *p*>.2). The mean followup time of 2.6 years may have been too short to see sufficient cardiovascular end points.

i. 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.[7] 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.[8] The panel assessed the LIFE substudy of participants with baseline albuminuria but did not include it as a study contributing to the CQ3 Chronic Kidney Disease Evidence Statement because of how CKD was defined in the study.[72] 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.

D. Statements for the Adult Population With Diabetes

i. Diuretic Evidence Statements in Diabetes

ES1. **Diabetes Diuretic Evidence Statement 1: In the population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a thiazide and thiazide-type diuretic improves heart failure outcomes compared to initial antihypertensive drug therapy with an ACEI or CCB, but there is no difference in overall mortality, CHD 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).[5,73,74] Diabetes was a prespecified subgroup in both trials. At baseline, 12,063 (36 percent) participants in ALLHAT and 1,302 (20.6 percent) participants in INSIGHT had diabetes. Both trials compared a CCB with a thiazide-type diuretic. ALLHAT also compared an ACEI with a thiazide-type diuretic. Several trials (CAPPP, CONVINCE, and NORDIL) reported outcomes in diabetes subgroups, but they compared an ACEI or CCB to "conventional therapy," which was an investigator selection of a diuretic or beta blocker.[75-77] These trials were not included because the contributing role of the diuretic or BB could not be evaluated.

Among the diabetes population in ALLHAT, there was a 22 percent (CI=1.05–1.42; *p*-value not reported) higher incidence of heart failure in the ACEI group compared to the diuretic group. There was also an 8 percent (CI=1.00–1.17) increase in the composite outcome of combined CVD, but it was of borderline significance and was driven mainly by the higher incidence of heart failure. There was also a 42 percent (CI=1.23–1.64) higher incidence of heart failure in the CCB group compared to the diuretic group. For both the ACEI/chlorthalidone comparison and the CCB/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 ACEI.

Among the diabetes population in INSIGHT, there was a nonsignificant higher incidence of heart failure in the CCB group compared to the diuretic group (RR 1.51; CI=0.54–4.22), but there were only 15 events overall (6 events in the diuretic group versus 9 in the CCB group). The primary composite outcome of cardiovascular death, MI, heart failure, and stroke was similar between the two groups, with a relative risk of 0.99 (CI=0.69–1.42; *p*=1.00).

ES2. **Diabetes Diuretic Evidence Statement 2: 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 ACEI, CCB, or alpha-1 blocker.**

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

Rationale/Comments: One trial contributed to this evidence statement (ALLHAT).[73] ESRD was reported in a secondary ALLHAT publication rated as fair that 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 (CI=0.97–1.67; *p*=.08) and lisinopril compared to chlorthalidone was 1.09 (CI=0.82–1.46; *p*=.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.

ES3. **Diabetes Diuretic Evidence Statement 3: In the population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a diuretic improves heart failure and combined cardiovascular outcomes, but there is no difference in CHD 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.[78] 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 percent greater incidence of combined CVD compared with the chlorthalidone arm. Combined CVD was defined as combined CHD, stroke, treated angina without hospitalization, heart failure, and peripheral arterial disease (PAD). Combined CHD included the primary outcome (combined fatal CHD or nonfatal MI), coronary revascularization, or angina with hospitalization. In the entire ALLHAT population, the risk for stroke was 26 percent higher (CI=1.10–1.46; *p*<.001), and the risk for fatal or hospitalized heart failure was 66 percent higher (CI=1.46–1.89; *p*<.001) in the doxazosin group compared to the chlorthalidone group.[57] However, in the smaller diabetic cohort, the relative risk was significant for only heart failure with a point estimate of 1.85 (CI=1.56–2.19; *p*<.001) and combined CVD with a point estimate of 1.22 (CI=1.11–1.33; *p*<.001) for doxazosin compared to chlorthalidone. The differences for CHD (RR 1.07; CI=0.91–1.27; *p*=.41) and stroke (RR 1.21; CI=0.97–1.50; *p*=.09) were not statistically significant for the diabetes subgroup.

ES4. **Diabetes Diuretic Evidence Statement 4: In the population <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 ACEI, CCB, 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 RCTs of any quality that compared initial antihypertensive drug therapy with a diuretic to initial antihypertensive drug therapy with an ACEI, CCB, or alpha-1 blocking agent in a population <55 years of age with hypertension and diabetes. ALLHAT compared initial antihypertensive therapy with a diuretic to an ACEI, CCB, and alpha-1 blocking agent; and INSIGHT compared initial antihypertensive therapy with a diuretic to a CCB. However, neither ALLHAT nor INSIGHT included participants <55 years of age.

ii. Beta Blocker Evidence Statements in Diabetes

ES1. **Diabetes Beta Blocker Evidence Statement 1: In the population 55–80 years of age with diabetes and hypertension, initial antihypertensive drug therapy with an ARB improves cardiovascular and total mortality, heart failure, and composite cardiovascular outcomes compared to initial antihypertensive drug therapy with a BB.**

***Evidence Quality:* Low**

Rationale/Comments: One trial contributed to this evidence statement (LIFE).[79] The LIFE trial had 1,195 participants with diabetes (13 percent 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 55–80 years of age with LVH determined by ECG. Diabetes was defined according to the 1985 WHO criteria. The primary end point was a composite of cardiovascular morbidity and mortality, which included cardiovascular death, stroke, and MI.

In participants with diabetes, there was a significant 24 percent (CI=0.58–0.98; *p*=.031) lower occurrence in the primary composite outcome in the losartan group compared to the atenolol group. Cardiovascular mortality was reduced by 37 percent (CI=0.42–0.95; *p*=.028), total mortality was reduced by 39 percent (CI=0.45–0.84; *p*=.002), and heart failure hospitalizations were reduced by 41 percent (CI=0.38–0.92; *p*=.019). SBP reduction favored losartan, with mean achieved BP of 146/79 mmHg compared to 148/79 mmHg in the atenolol arm. This corresponds to attainment of goal BP in 85 percent of participants in the losartan group compared with 82 percent in the atenolol group. The evidence quality was graded as low because it was based on a subgroup analysis of one trial, rated as fair, that was limited by the entry criterion of LVH as determined by ECG.

ES2. **Diabetes Beta Blocker Evidence Statement 2: In the population 25–65 years of age with diabetes and hypertension, initial antihypertensive drug therapy with an ACEI has a similar effect on overall mortality, stroke, heart failure, CHD, and CVD outcomes compared to initial antihypertensive drug therapy with a BB.**

***Evidence Quality:* Low**

Rationale/Comments: One trial contributed to this evidence statement (UKPDS).[10] UKPDS randomized 758 participants with diabetes to tight BP control (defined as a target BP less than 150/85 mmHg) with captopril or atenolol and followed them for 9 years. The trial was rated as fair. Mean achieved BPs were 144/83 mmHg in the captopril arm and 143/81 mmHg in the atenolol arm.

The primary outcome was a first clinical end point 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 (CI=0.86–1.41; *p*=.43).

No differences were seen between groups for overall mortality or any cardiovascular end point. For captopril versus atenolol, the relative risk for all-cause mortality was 1.14 (CI=0.81–1.61; *p*=.44); for strokes it was 1.12 (CI=0.59–2.12; *p*=.74); for MI it was 1.20 (CI=0.82–1.76; *p*=.35); and for heart failure it was 1.21 (CI=0.39–3.78; *p*=.66). The evidence quality was graded as low because it was based on one small study that was rated as fair.

ES3. **Diabetes Beta Blocker Evidence Statement 3: In the population 40–79 years of age with diabetes and hypertension, there is insufficient evidence to determine whether initial antihypertensive drug therapy with a BB (followed by a thiazide diuretic) compared to initial antihypertensive drug therapy with a CCB (followed by an ACEI) 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).[7,80] 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 BP; the intent was that most patients would receive at least two antihypertensive drugs. Participants with diabetes were a prespecified subgroup and accounted for 27 percent of the trial population. The primary outcomes were fatal CHD and nonfatal MI. In participants with diabetes, there was no difference between groups for the primary outcome (HR 0.92; CI=0.74–1.15; p=.46), which was similar to the result for the overall population (HR 0.90; CI=0.79–1.02; p=.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 use of different drugs as add-on therapy for each study arm, different achieved BPs in each study arm, and insufficient power due to early trial termination. In addition, the statement is based on only one trial that was rated as fair due to its many limitations.

iii. Angiotensin-Converting Enzyme Inhibitors Evidence Statements in Diabetes

ES1. **Diabetes ACE Inhibitor Evidence Statement 1: In the population with diabetes and hypertension, there are no trials meeting this review's eligibility criteria comparing initial antihypertensive drug therapy with an ACEI to initial antihypertensive drug therapy with an ARB, alpha-1 adrenergic blocker, or renin inhibitor that assessed cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes, or mortality.**

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

Rationale/Comments: This evidence statement reflects the inclusion criteria used to select the clinical trials that constituted this systematic evidence review. For example, ONTARGET, which demonstrated similar outcomes between ACEIs and ARBs in a large group of participants with CVD or diabetes, was not eligible for inclusion because the study was not designed to assess the effects of BP lowering in hypertension and not all participants in the study were hypertensive. Similarly, this review's inclusion criteria restricted kidney outcomes to those used in trials that represent clinical end points, which included doubling of serum creatinine, halving of eGFR, or progression to ESRD. 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 U.S. Food and Drug Administration 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 this review's eligibility criteria that compared these drugs in head-to-head studies and assessed their effects on these health outcomes.

iv. Calcium Channel Blockers Evidence Statements in Diabetes

ES1. **Diabetes Calcium Channel Blocker Evidence Statement 1: In the population 30 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a CCB has a similar benefit on cardiovascular composite outcomes compared to initial antihypertensive drug therapy with an ARB.**

Evidence Quality: ***Low***

Rationale/Comments: Two trials contributed to this evidence statement (IDNT, VALUE).[18,70,71] Both trials, which were rated as fair, compared the CCB amlodipine with an ARB. IDNT used irbesartan, while VALUE used valsartan. IDNT included 1,715 participants aged 30–70 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. Of these, 4,823 (31.6 percent) participants at baseline had diabetes, which was a prespecified subgroup. In both trials, BP differences between the different drug arms were 2 mmHg 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, MI, congestive heart failure (CHF), stroke, and coronary revascularization) had a HR of 0.90 (CI=0.74–1.10; $p>.2$). In the prespecified diabetes subgroup analysis for VALUE, the primary end point occurred in 14.6 percent of the amlodipine group and 14.7 percent of the valsartan group ($p=.528$). The primary end point in VALUE was time to first cardiac event, which was a composite of sudden cardiac death, fatal or nonfatal MI, death during or after percutaneous coronary intervention or coronary artery bypass grafting, death as a result of heart failure, heart failure requiring hospital management, death associated with recent MI according to 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 CCB to initial antihypertensive drug therapy with an ARB. In IDNT, there was a significant 35 percent (CI=0.48–0.87; $p=.0004$) reduction in heart failure in the ARB group compared to the CCB 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.

ES2. **Diabetes Calcium Channel Blocker Evidence Statement 2: In the hypertensive population with diabetes, initial antihypertensive drug therapy with a CCB has a similar benefit on combined nonfatal MI and fatal CHD compared to initial antihypertensive drug therapy with an ACEI.**

Evidence Quality: ***Low***

Rationale/Comments: Three trials contributed to this evidence statement (ABCD Hypertensive Cohort, FACET, and ALLHAT).[50,81,82] 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 ACEI and CCB 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 CCB nisoldipine with the ACEI enalapril. ABCD showed a significantly higher rate of events for the secondary outcome of fatal and nonfatal MI in the CCB group compared to the ACEI group with

an adjusted risk ratio of 7.0 (CI=2.3–21.4; p=.001). However, there were a small number of events (25 cases in the CCB arm versus 5 cases in the ACEI arm). The level of achieved BPs 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 ACEI fosinopril to the CCB 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, more than 25 percent of participants received both study drugs during the course of the trial to control their BP. SBP was 4 mmHg lower in the CCB arm (p<.01). The secondary composite outcome of major vascular events was reduced by 51 percent (CI=0.26–0.95; p=.030) in the ACEI group compared to the CCB group. The composite included fatal and nonfatal MI, stroke, and hospitalization for angina. However, there were a small number of events (14 cases in the ACEI arm versus 27 cases in the CCB arm). Fatal and nonfatal MI were not significantly different between the two groups (HR 0.77; CI=0.34–0.1.75; p>.1).

ALLHAT assessed the effects of treatment with an ACEI compared to a CCB on a prespecified group of 6,535 participants who had diabetes at baseline. They found no difference between the ACEI and CCB groups for the primary outcome of fatal CHD and nonfatal MI (HR 1.00; 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 ACEI.

v. Combination Therapy in Diabetes

ES1. Diabetes Combination Therapy Evidence Statement 1: In the population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with the combination of an ACEI and a CCB 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 cardiovascular causes) compared to initial antihypertensive drug therapy with the combination of an ACEI 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).[4,83] 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 percent) 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-HCTZ.

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 percent (CI=0.68–0.92; p=.003) lower occurrence of the primary composite outcome in the benazepril-amlodipine group compared to the benazepril-HCTZ group. However, only one component of the primary composite outcome, coronary revascularization, achieved statistical significance. The trial was terminated early after a mean followup 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 HCTZ 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 BPs. 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 CCBs when used with other add-on agents in studies with participants with diabetes and hypertension (see CQ3, Diabetes Diuretic Evidence Statement 1).

vi. Evidence Statements for Blacks With Diabetes

ES1. **Blacks With Diabetes Evidence Statement 1: 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 lowered occurrence of heart failure, cerebrovascular, and combined cardiovascular outcomes compared to initial antihypertensive drug therapy with an ACEI, but there is no difference in overall mortality or CHD outcomes.**

Evidence Quality: ***Low***

Rationale/Comments: One trial contributed to this evidence statement (ALLHAT).[84] 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 percent of Black participants had diabetes, and more than 50 percent 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 ACEI group. Blacks treated with the ACEI had a 30 percent (CI=1.10–1.54; p=.003) higher occurrence of heart failure, a 40 percent (CI=1.17–1.68; p<.001) increase in stroke, and a 19 percent (CI=1.09–1.30; p<.001) increase in combined cardiovascular events. There were no differences for overall mortality or CHD outcomes.

Supporting evidence for this statement is also provided by a post hoc analysis of Black participants in ALLHAT who met the criteria for metabolic syndrome, 68 percent of whom had diabetes and 73 percent of whom had either diabetes or impaired fasting glucose.[85] Among Black participants in ALLHAT with metabolic syndrome treated with an ACEI, there was a 49 percent (CI=1.17–1.90; p-value not reported) increase in the incidence of heart failure, a 37 percent (CI=1.07–1.76; p-value not reported) increase in stroke, and a 24 percent (CI=1.09–1.40; p-value not reported) higher occurrence of combined cardiovascular events compared to those treated with a diuretic. However, this post hoc analysis was not eligible for inclusion in this 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.

ES2. **Blacks With Diabetes Evidence Statement 2: In the Black population 55 years of age or older with diabetes and hypertension, initial antihypertensive drug therapy with a CCB is associated with fewer cerebrovascular and combined cardiovascular outcomes compared to initial antihypertensive drug therapy with an ACEI, but there is no difference in heart failure or CHD outcomes.**

Evidence Quality: ***Low***

Rationale/Comments: One trial contributed to this evidence statement (ALLHAT).[50] The primary comparison in ALLHAT was between thiazide-type diuretics and other antihypertensive drug classes, while the CCB blocker and ACEI comparison was secondary. The paper presenting the CCB and ACEI 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 percent (CI=1.22–1.86; *p*-value not reported) higher occurrence of stroke and a significant 13 percent (CI=1.02–1.24; *p*-value not reported) increase in combined cardiovascular events in Blacks treated with an ACEI compared with Blacks treated with a CCB. There were no differences between the use of these drugs in resulting CHD outcomes or heart failure. Outcomes for the comparison between initial use of a CCB and initial use of an ACEI in Blacks with diabetes were not reported in any of the papers that were eligible for this evidence review. Therefore, this evidence statement is extrapolated from the fact that 46 percent of Black participants in ALLHAT had diabetes, and more than 50 percent of Black participants had either diabetes or impaired fasting glucose.[85]

Appendixes

APPENDIX A.

Methods

Appendix A: Methods

A. Description of How Panel Members Were Selected

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 Web site for several weeks and was also distributed to a Leadership Group that had given advice to NHLBI on its evidence review 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 NHLBI COI disclosures and copies of their curricula 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 (GEC), which worked with NHLBI to select panel members from the list of nominees. Beginning in September 2011, the GEC set up its own approach to manage relationships with industry and other potential COIs (see http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm).

NHLBI received 440 nominations for panel members. Panel members were selected based on 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 includes senior scientists from NHLBI and NIDDK with expertise in hypertension, clinical trials, translational research, nephrology, guideline development, and evidence-based methodology. In assembling the panel, a balance of expertise and perspectives was sought.

B. 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 report: 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; these were sent to all panel members. Panel members discussed these questions on multiple conference calls and then independently ranked the top five questions felt to be of highest priority. The five highest ranked questions were discussed further and prioritized. This report focuses on the three highest ranked questions.

With support from the methodologist and systematic review team, priority questions were formatted using the PICOTSS framework and inclusion/exclusion criteria (I/E criteria) were defined, as shown below. PICOTSS is a framework for a structured research question and includes the following components in the statement of the question or in the question's I/E criteria:

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

I/E criteria define the parameters for the selection of literature for a particular question. I/E 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.

C. Literature Search Infrastructure, Search Strategy Development, and Validation

The literature search was performed by 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 evidence review initiative.

The central repository consisted of 1.9 million citations and 71,000 full-text articles related to CVD risk reduction. Citations were acquired from PubMed, Embase, CINAHL, Cochrane, PsycInfo, Wilson Science, and Biological Abstracts databases. Literature searches were conducted by 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 I/E 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 the following items:

- A natural language processing module for automated extraction of data elements in support of application of I/E criteria. Frequently extracted and utilized data elements were study size and intervention followup 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 cutoff 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.

D. Process for Literature Review and Application of I/E Criteria

Using results of the search strategy, criteria were applied to screen 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.

i. 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 applied clearly 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.

ii. 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."

iii. 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.

iv. Phase 3: Resolution and Consultation Phase

In this phase, reviewers discussed their votes (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.

E. Quality Assessment 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.

i. Design of the Quality Assessment Tools

Appraisal of individual study quality was based on quality assessment tools developed jointly by methodologists from NHLBI and Research Triangle Institute International. The tools were based on quality assessment methods, concepts, and other tools developed by researchers in the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, the Cochrane Collaboration, the USPSTF, the Scottish Intercollegiate Guidelines Network, and the National Health Service Centre for Reviews and Dissemination, as well as consulting epidemiologists and others working in evidence-based medicine, with adaptations by methodologists and NHLBI staff for this project. These tools were designed to assist reviewers in focusing on concepts that are key for critical appraisal of the internal validity of a study. The tools were not designed to provide a list of factors comprising a numeric score. The tools were specific to individual types of included study designs and are described in more detail below. 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 Blood Pressure Panel). This quality assessment tool is provided in table 1.

The tools included items for evaluating potential flaws in study methods or implementation, including sources of bias (e.g., patient selection, performance, attrition, and detection), confounding, study power, and strength of causality in the association between interventions and outcomes, and other factors. Quality reviewers could select "yes," "no," or "cannot determine (CD)/not reported (NR)/not applicable (NA)" in response to each item on the tool. For each item where "no" was selected, 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.

Each of the quality assessment tools had a detailed guidance document, which was also developed by the methodology team and NHLBI. The guidance documents were specific to each tool and provided more detailed descriptions and examples of application of the items, as well as justifications for each item's inclusion. For some items, examples were provided to clarify the intent of the question and the appropriate rater response. The four quality assessment tools and guidance documents used in this evidence review are included in tables A–1 through A–4 below.

ii. 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 and draw conclusions. 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 Blood Pressure Panel because there were good and/or fair quality studies that met the I/E criteria for each question.

iii. Training for Application of the Quality Assessment Tools

The methodology team conducted a series of training sessions on the use of four of the quality assessment tools. Initial training consisted of two 2-day, in-person training sessions. Reviewers trained in the quality rating were master's- or doctoral-level staff with a background in public health or health sciences. Training sessions provided instruction on identifying the 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 evaluation of multiple example articles, both with the instructors and during group work. 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 telephone to review the results and resolve any remaining issues. Based on the results of these and other evaluations, a third round of exercises and training sessions was sometimes convened.

iv. 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.

v. Quality Assessment Tool for Controlled Intervention Studies

The quality assessment tool for controlled intervention studies is included in table A–1. The guidance document for the tool is also included in table 1. This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-Based Practice Centers, the USPSTF, and the National Health Service Centre for Reviews and Dissemination. Because the Blood Pressure 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 Blood Pressure Panel.

This tool addresses 14 elements of quality assessment. They include randomization and allocation concealment, similarity of compared groups at baseline, use of ITT analysis (i.e., all patients randomized were analyzed even if some were lost to followup), adequacy of blinding, the overall percentage of study participants lost to followup, the differential rates of loss to followup between the intervention and control groups, and other factors.

Table A–1. Quality Assessment Tool for 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 its end point 20% or less than the number originally allocated to treatment?			
8. Was the differential drop-out rate between groups at the study's end point 15% or less?			
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)?			

Quality Rating (good, fair, poor) (see guidance)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

Note: CD = cannot determine; NA = not applicable; NR = not reported

vi. Guidance for Assessing the Quality of Controlled Intervention Studies

The guidance document below is organized by question number from the tool for quality assessment of controlled intervention studies.

Question 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?

Questions 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. (Few if any GRTs are anticipated 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.

Questions 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." One checks 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 the comments section.

Question 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, one should see it when abstracting baseline characteristics. Baseline characteristics for intervention groups are usually presented in a table within 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 one has any concerns about baseline difference in the groups, write them down in the comments section and consider them in the overall determination of the study quality.

Questions 7–8. Drop-out

By "drop-out," is meant participants for whom there are no end point measurements—the most common reason being that they dropped out of the study (for whatever reason) and were lost to followup.

Generally, an acceptable overall drop-out rate is considered 20 percent 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. When conducting a systematic review on the comparative efficacy of antidepressants, setting the cap at 20 percent for an overall drop-out is appropriate. On the other hand, if 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 the systematic review.

The same flexibility does not apply to the differential drop-out rate, which should be capped at 15 percent. If there is a differential drop-out rate of 15 percent 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.

Question 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 participants 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.

Question 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 a study was 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 it could not be known whether the difference in outcome was due to the dietary intervention or the drugs.

Question 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 one 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 BP

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 in the control group.

Question 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 percent power to detect a clinically relevant difference in an outcome using a two-sided alpha of .05. Often, however, older studies will not report anything about power.

Question 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 researchers 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.

Question 14. Intention-to-treat (ITT) analysis

ITT 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, one is 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 it is thought to be 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.

vii. Some General Guidance for Determining the Overall Quality Rating

The questions on the form are designed to help focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that is simply tallied 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.

F. 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.

APPENDIX B.

Development of Evidence Tables and Summary Tables

Appendix B: Development of Evidence Tables and Summary Tables

A. 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 which 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 Blood Pressure Panel 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: I/E criteria for the study, primary outcome, secondary outcome, composite outcome definitions
- Study design details: treatment groups, description of interventions, duration of treatment, duration of followup, run-in, wash-out, sample size
- Baseline population characteristics: age, sex, race/ethnicity, mean BP, CHD, cerebrovascular disease, heart failure, diabetes, CKD, PAD, 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.

B. 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 summary tables was determined by the question addressed by the table. For Question 1, studies were listed by ascending BP 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 BP treatment goal; separate summary tables were created for systolic, diastolic, and mixed systolic/diastolic treatment goal. 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.

C. Process for the Development of Evidence Statements and Panel Voting

Using summary and evidence tables as needed, panel members wrote evidence statements with input from methodology staff and oversight by NHLBI staff. Evidence statements aimed to summarize key messages from the evidence that could be provided to primary care providers and other stakeholders. In some cases, the evidence was too limited or inconclusive, so no evidence statement was developed, or a statement of insufficient evidence was made.

Methodology staff provided the expert panel with overarching guidance on how to grade the 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 (COIs) 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.

Voting could be open so that differing viewpoints could be identified easily and facilitate further discussion and revisions to address areas of disagreement (e.g., by wordsmithing or dividing an evidence statement into more than one statement). Voting could be by confidential ballot if the group chose.

A record of the vote count (for, against, or recusal) was made without attribution. The ideal was 100 percent consensus, but a two-thirds majority was considered acceptable.

D. Description of Methods for Grading the Body of Evidence

The NHBLI Adult Cardiovascular Disease Systematic Evidence Review Project applied related but distinct processes for grading the bodies of evidence for questions, for different outcomes included within questions. Each of these processes is described in turn below.

i. Grading the Body of Evidence

In developing the system for grading the body of evidence, NHLBI reviewed a number of systems, including GRADE, USPSTF, American College of Cardiology/American Heart Association (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 NHLBI project. NHLBI therefore developed its own hybrid version that incorporated features of those systems. This system was used by all panels and work groups in the NHBLI Adult

Cardiovascular Disease Systematic Evidence Review Project and was strongly supported by expert panel and work group members. In using the system, decisions about evidence rating 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.

Table B–1. Evidence Quality Grading System

Type of Evidence	Strength of Evidence Grade
▪ 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; and ▪ Meta-analyses of such studies. ▪ There is high confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of effect.	**High**
▪ RCTs with minor limitations affecting confidence in, or applicability of, the results, including minor flaws in design or execution; ▪ Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies; and ▪ Meta-analyses of such studies. ▪ 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.	**Moderate**
▪ RCTs with major limitations; ▪ Nonrandomized intervention studies and observational studies with major limitations affecting confidence in, or applicability of, the results; ▪ Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports); ▪ Physiological studies in humans; and ▪ Meta-analyses of such studies. ▪ There is low confidence that the evidence reflects the true effect. Further research is likely to alter confidence in the estimate of effect and is likely to change the estimate.	**Low**

Guidance was provided by methodologists for assessing the strength of the body of evidence supporting each evidence statement 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 NHLBI Evidence Quality Grading System shown above. The four domains are explained in more detail below.

ii. 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 NHLBI 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.

iii. 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, nonoverlapping 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 the NHLBI project, consistent with the Evidence-based Practice Centers 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, multicentered, well-designed, well-executed RCT that performs well in the other domains could in some circumstances be considered high-quality evidence after thoughtful consideration.

iv. 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 I/E 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 Blood Pressure 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.

v. 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, which have 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 because 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 with 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. 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.

APPENDIX C.

Search Strategy Overview and Syntax of Queries

Appendix C: Search Strategy Overview and Syntax of Queries

This section provides a description of how search strategies for the NHLBI initiative were constructed and explains how to interpret search strategies that are documented in the following section.

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 C–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 C–2. Commonly used macro queries are defined in table C–3.

Table C–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 C–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 C–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?))

Macro Name	Query
{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

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 I/E criteria for each question, which were 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-pyrrolidinyl) 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 "Bretylium 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 "Cyclopenthiazide" 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 "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 "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 (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

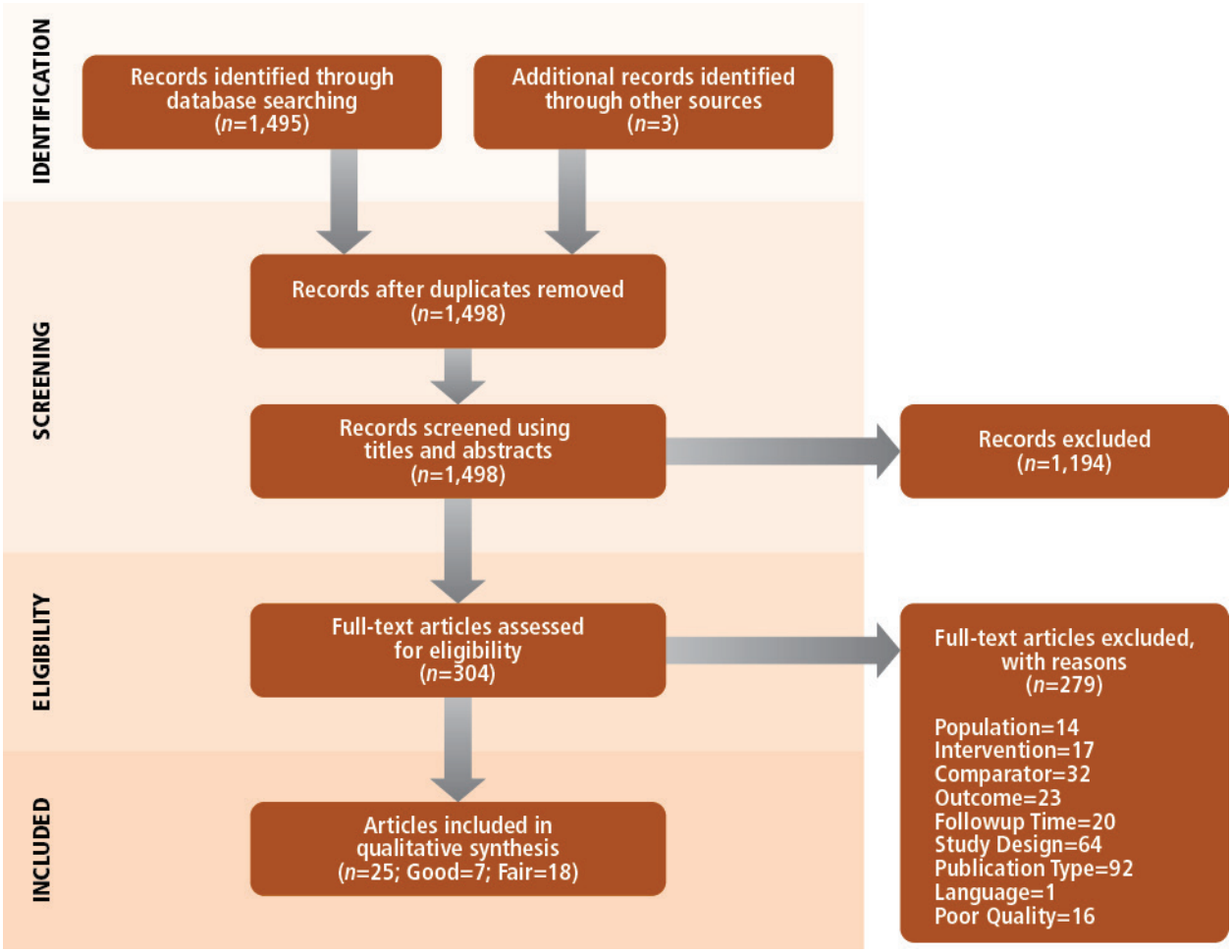
Because we conducted our own systematic review using original publications dating back to 1966, SR/MA of RCTs conducted and published by others were not used as part of the formal evidence review (i.e., they were not abstracted and included in the evidence and summary tables). However, SR/MA identified 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 1,495 citations. Three additional citations were added for review. Two of these citations were for the ACCORD[11] and ROADMAP[86] studies, which were published after December 2009. Per NHLBI policy, these citations could be formally reviewed for inclusion after the search cutoff date because they met the criteria of being a multicenter RCT of greater than 2,000 participants. The third citation was a secondary publication of the HDFP trial[87] which was not identified in the initial search.

The titles and abstracts of these 1,498 publications were screened against the I/E 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 I/E criteria. An additional 16 publications were excluded because they were rated as poor quality using the NHLBI quality assessment tool for controlled intervention studies. Twenty-five RCTs were included in the Question 1 Evidence Base.

Figure C-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 group has a different BP goal than the intervention group, or the comparator group has no stated BP goal whereas 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-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 "Bretylium 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 "Cyclopenthiazide" 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 "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 "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" 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

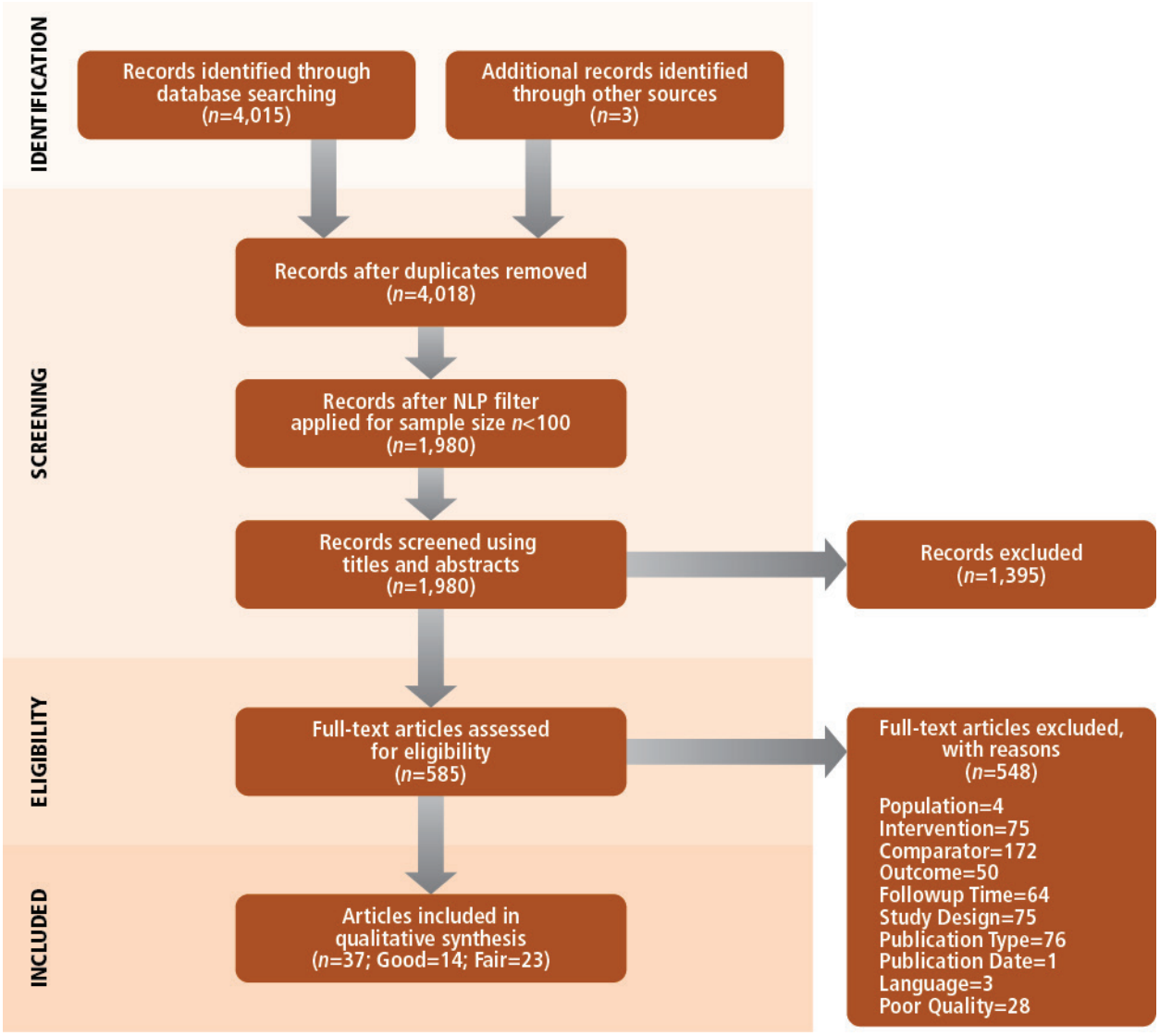
- PsycInfo from January 1998 to July 2008
- EBM (evidence-based medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

As in Question 1, systematic reviews and meta-analyses (SR/MAs) 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 4,015 citations. Three additional citations were added for review. These citations were for the ACCORD,[11] VALISH[41] and ROADMAP[86] studies which were published after December 2009. Per NHLBI policy, these citations could be formally reviewed for inclusion after the search cutoff 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 BP 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 1,980 remaining publications were screened against the I/E 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 I/E criteria. An additional 29 publications were excluded because they were rated as poor quality using the NHLBI quality assessment tool for controlled intervention studies. Thirty-seven RCTs were included in the Question 2 Evidence Base.

Figure C-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-pyrrolidinyl) 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 "Bretylium 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 "Cyclopenthiazide" 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 "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 "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:

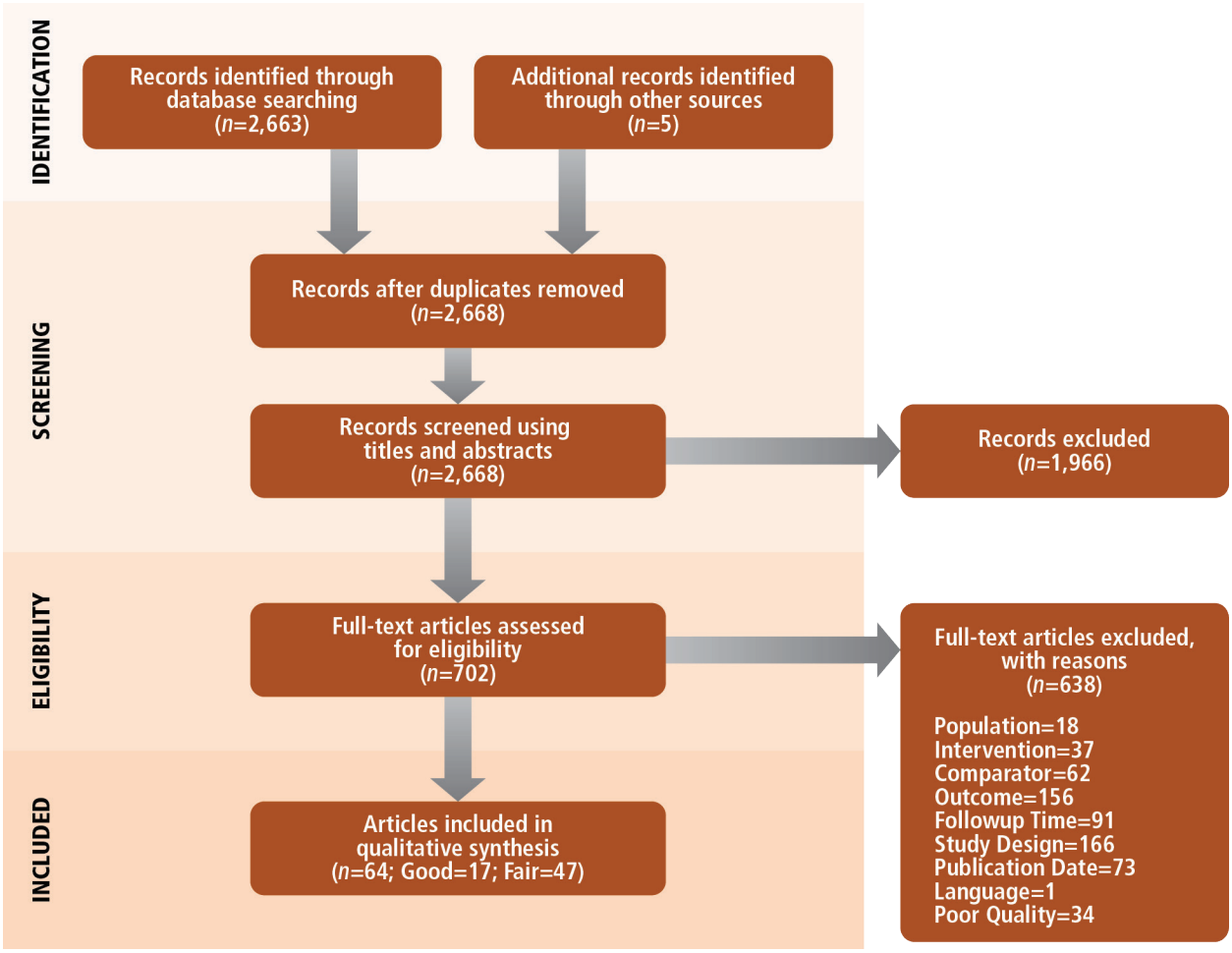
- PubMed from January 1966 to December 2009
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycInfo from January 1998 to July 2008
- EBM (evidence-based medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

As in Question 1 and Question 2, SR/MAs 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 2,663 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 cutoff 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.[68,83]

The titles and abstracts of these 2,668 publications were screened against the I/E 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 I/E criteria. An additional 34 publications were excluded because they were rated as poor quality using the NHLBI quality assessment tool for controlled intervention studies. Sixty-four RCTs were included in the Question 3 Evidence Base.

Figure C-3. PRISMA Diagram for Question 3



APPENDIX D.

Summary Tables

Appendix D: Summary Tables

Question 1 Summary Tables: Evidence from randomized controlled trials on initiating antihypertensive pharmacological therapy at specific blood pressure thresholds

Press the Control key and click the link to navigate to the desired table:

Table D–1a. Evidence From Randomized Controlled Trials on Initiating Antihypertensive Pharmacological Therapy at SBP Thresholds <140 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes
PHARAO Lüders et al., 2008[31]	1,008	3 years	Fair	Drug: Ramipril Control: Unclear if placebo tablet administered	Adults ≥50 years who are not on any anti-HTN medication	SBP: 130–139 or DBP: 85–89	Death, # events (%) Drug: 5 (1.0) Control: 2 (0.4) HR (95% CI): 2.36 (0.46, 12.19) *p*=.304	MI, # events (%) Drug: 4 (0.8) Control: 5 (1.0) HR (95% CI): 0.76 (0.20, 2.83) *p*=.681 New or worsening CAD, # events (%) Drug: 9 (1.8) Control: 9 (1.8) HR (95% CI): 0.97 (0.38, 2.45) *p*=.949	Cerebrovascular endpoints, # events (%) Drug: 6 (1.2) Control: 5 (1.0) HR (95% CI): 1.12 (0.34, 3.68) *p*=.851 Stroke, # events (%) Drug: 2 (0.4) Control: 1 (0.2) HR (95% CI): 1.81 (0.16, 19.97) *p*=.630 TIA, # events (%) Drug: 3 (0.6) Control: 4 (0.8) HR (95% CI): 0.72 (0.16, 3.24) *p*=.672 Hemorrhage, # events (%) Drug: 1 (0.2) Control: 0 HR (95% CI): NR *p*=NR	Heart Failure/AF, # events (%) Drug: 14 (2.8) Control: 19 (3.8) HR (95% CI): 0.71 (0.35, 1.41) *p*=.324	Cardiovascular endpoints, # events (%) Drug: 27 (5.3) Control: 33 (6.6) HR (95% CI): 0.79 (0.47, 1.31) *p*=.354

Table D–1b. Evidence From Randomized Controlled Trials on Initiating Antihypertensive Pharmacological Therapy at SBP Thresholds ≥140 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes
Hypertension-Stroke Cooperative Hypertension-Stroke Cooperative Study Group, 1974[30]	452	Mean 27.4 months	Fair	Drug: Deserpidine and methyclothiazide Placebo: 2 tablets daily	Adults with a stroke or TIA in previous year, <75 years	SBP: 140–220 and DBP: 90–115	Deaths due to medical endpoints, # events Drug: 20 Placebo: 14 HR (95% CI): NR *p*=NR	MI (certain), # events Drug: 4 Placebo: 4 HR (95% CI): NR *p*=.69 Sudden death, # events Drug: 2 Placebo: 2 HR (95% CI): NR *p*=.99 Deaths from MI (certain), # events Drug: 1 Placebo: 2 HR (95% CI): NR *p*=NR	PRIMARY OUTCOME: Total stroke recurrence, n (%) Drug: 37 (15.9) Placebo: 42 (19.2) HR (95% CI): NR *p*=.42	CHF, # events Drug: 0 Placebo: 6 HR (95% CI): NR *p*=.012	CV endpoints, # events Drug: 12 Placebo: 19 HR (95% CI): NR *p*=.20 Other CV endpoints, # events Drug: 2 Placebo: 3 HR (95% CI): NR *p*=.68 Deaths due to CV endpoints, # events Drug: 9 Placebo: 9 HR (95% CI): NR *p*=NR Deaths due to other CV endpoints, # events Drug: 2 Placebo: 0 HR (95% CI): NR *p*=NR

Table D–1c. Evidence From Randomized Controlled Trials on Initiating Antihypertensive Pharmacological Therapy at SBP Thresholds ≥160 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes
EWPHE primary article Amery et al., 1985[19*]	840	Mean 4.6 years	Fair	Drug: HCTZ and triamterene, plus methyldopa Placebo: Placebo tablet	Adults ≥60 years	SBP: 160–239 and DBP: 90–119	All-cause mortality, n (rate per 1000 p-y) Drug: 135 (69) Placebo: 149 (76) % change for active treatment (95% CI): –9 (–28, 15) *p*=.41	Cardiac mortality, n (rate per 1000 p-y) Drug: 29 (15) Placebo: 47 (24) % change for active treatment (95% CI): –38 (–61, –1) *p*=.036	PRIMARY OUTCOME Cerebrovascular mortality, n (rate per 1000 p-y) Drug: 21 (11) Placebo: 31 (16) % change for active treatment (95% CI): –32 (–61, 19) *p*=.1		CV mortality, n (rate per 1000 p-y) Drug: 67 (34) Placebo: 93 (47) % change for active treatment (95% CI): –27 (–46, –1) *p*=.037
EWPHE – subsequent article on CV mortality Amery et al., 1986[88]	840	Mean 4.6 years	Fair	Drug: HCTZ and triamterene, plus methyldopa Placebo: Placebo tablet	Adults ≥60 years	SBP: 160–239 and DBP: 90–119					CV mortality, n (rate per 1000 p-y) Drug: 67 (34) Placebo: 93 (47) % change for active treatment (95% CI): –27 (–47, –1) *p*=.037
EWPHE– subsequent article on adverse effects Fletcher et al., 1991[20†]	840	Mean 4.6 years	Fair	Drug: HCTZ and triamterene, plus methyldopa Placebo: Placebo tablet	Adults ≥60 years	SBP: 160–239 and DBP: 90–119		Fatal cardiac events at 1 year Overall difference between Drug vs. Placebo per 1000 p-y: –11% *p*<.05	PRIMARY OUTCOME Nonfatal cerebrovascular events at 1 year Overall difference between Drug vs. Placebo per 1000 p-y: –11% *p*<.05 PRIMARY OUTCOME Fatal cerebrovascular events at 1 year Overall difference between Drug vs. Placebo per 1000 p-y: –6% *p*=NR	Severe CHF at 1 year Overall difference between Drug vs. Placebo per 1000 p-y: –8% *p*<.05	

[*] A subsequent article on kidney function in the EWPHE trial (de Leeuw et al., 1991) met the eligibility criteria for this question but was not used in the development of evidence statements.

[†] Kidney outcome data from this paper were not used in the development of evidence statements.

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes
HYVET Beckett et al., 2008[21]	3,845	Mean 2.1 years	Good	Drug: Indapamide plus perindopril Placebo: Placebo	Adults ≥80 years	SBP: ≥160 DBP: 90–109 at start of trial but in 2003 relaxed to <110	Death from any cause, rate per 1000 p-y (# events) Drug: 47.2 (196) Placebo: 59.6 (235) HR (95% CI): 0.79 (0.65, 0.95) *p*=.02 Note: study stopped early due to mortality reduction in drug group	Death from cardiac cause, rate per 1000 p-y (# events) Drug: 6.0 (25) Placebo: 8.4 (33) HR (95% CI): 0.71 (0.42, 1.19) *p*=.19 Fatal or nonfatal MI, rate per 1000 p-y (# events) Drug: 2.2 (9) Placebo: 3.1 (12) HR (95% CI): 0.72 (0.30, 1.70) *p*=.45	Death from stroke, rate per 1000 p-y (events) Drug: 6.5 (27) Placebo: 10.7 (42) HR (95% CI): 0.61 (0.38, 0.99) *p*=.046 PRIMARY OUTCOME Fatal or nonfatal stroke, rate per 1000 p-y (events) Drug: 12.4 (51) Placebo: 17.7 (69) HR (95% CI): 0.70 (0.49, 1.01) *p*=.06	Death from HF, rate per 1000 p-y (# events) Drug: 1.5 (6) Placebo: 3.0 (12) HR (95% CI): 0.48 (0.18, 1.28) *p*=.14 Fatal or nonfatal HF, rate per 1000 p-y (# events) Drug: 5.3 (22) Placebo: 14.8 (57) HR (95% CI): 0.36 (0.22, 0.58) *p*<.001	Death from CV cause, rate per 1000 p-y (# events) Drug: 23.9 (99) Placebo: 30.7 (121) HR (95% CI): 0.77 (0.60, 1.01) *p*=.06 Fatal or nonfatal any CV event, rate per 1000 p-y (# events) Drug: 33.7 (138) Placebo: 50.6 (193) HR (95% CI): 0.66 (0.53, 0.82) *p*<.001

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes
SHEP – primary article Systolic Hypertension in the Elderly Program Cooperative Research Group, 1991[22]	4,736	Mean 4.5 years	Good	Drug: Stepped chlorthalidone to atenolol or reserpine Placebo: Placebo QD	Adults ≥60 years with isolated systolic HTN	SBP: 160–219 and DBP: <90	Total deaths, n of events Drug: 213 Placebo: 242 RR (95% CI): 0.87 (0.73, 1.05) *p*=NR	Nonfatal MI, n of events Drug: 50 Placebo: 74 RR (95% CI): 0.67 (0.47, 0.96) *p*=NR CABG, n of events Drug: 30 Placebo: 47 RR (95% CI): 0.63 (0.40, 1.00) *p*=NR Angioplasty, n of events Drug: 19 Placebo: 22 RR (95% CI): 0.86 (0.47, 1.59) *p*=NR Nonfatal MI or CHD deaths, n of events Drug: 104 Placebo: 141 RR (95% C): 0.73 (0.57, 0.94) *p*=NR CHD, n of events Drug: 140 Placebo: 184 RR (95% CI): 0.75 (0.60, 0.94) *p*=NR Total CHD deaths, n of events Drug: 59 Placebo: 73 RR (95% CI): 0.80 (0.57, 1.13) *p*=NR MI death, n of events Drug: 15 Placebo: 26 RR (95% CI): 0.57 (0.30, 1.08) *p*=NR Sudden death (<1 hour), n of events Drug: 23 Placebo: 23 RR (95% CI): 1.00 (0.56, 1.78) *p*=NR Rapid death (1–24 hours), n of events Drug: 21 Placebo: 24 RR (95% CI): 0.87 (0.48, 1.56) *p*=NR	Nonfatal stroke, n of events Drug: 96 Placebo: 149 RR (95% CI): 0.63 (0.49, 0.82) *p*=NR PRIMARY OUTCOME Nonfatal plus fatal stroke at 5 years, per 100 participants (SE) Drug: 5.2 (0.5) Placebo: 8.2 (0.7) RR (95% CI): 0.64 (0.50, 0.82) *p*=.0003 Stroke deaths, n of events Drug: 10 Placebo: 14 RR (95% CI): 0.71 (0.31, 1.59) *p*=NR TIA, n of events Drug: 62 Placebo: 82 RR (95% CI): 0.75 (0.54, 1.04) *p*=NR		CVD, n of events Drug: 289 Placebo: 414 RR (95% CI): 0.68 (0.58, 0.79) *p*=NR Total CVD deaths, n of events Drug: 90 Placebo: 112 RR (95% CI): 0.80 (0.60, 1.05) *p*=NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes
SHEP subsequent article Systolic Hypertension in the Elderly Program Cooperative Research Group, 1993[39]	4,736	Mean 4.5 years	Fair:	Drug: Stepped chlorthalidone to atenolol or reserpine Placebo: Placebo QD	Adults ≥60 years with isolated systolic HTN	SBP: 160–219 and DBP: <90		Reduction in nonfatal MI and CHD death, % Drug vs. Placebo: 27 *p*=NR	PRIMARY OUTCOME Reduction in nonfatal and fatal stroke, % Drug vs. Placebo: 36 *p*=.0003		Reduction in all major CV events, % Drug vs. Placebo: 32 *p*=NR
SHEP subsequent article on the prevention of heart failure Kostis et al., 1997[24]	4,736	Mean 4.5 years	Good	Drug: Stepped chlorthalidone to atenolol or reserpine Placebo: Placebo QD	Adults ≥60 years with isolated systolic HTN	SBP: 160–219 and DBP: <90				Nonfatal HF, n (%) Drug: 48 (2.0) Placebo: 102 (4.3) RR (05% CI): 0.46 (0.33, 0.65) *p*<.001 Nonfatal hospitalized HF, n (%) Drug: 38 (1.6) Placebo: 75 (3.2) RR (95% CI): 0.50 (0.34–0.74 *p*<.001 Fatal and nonfatal HF, n (%) Drug: 55 (2.3) Placebo: 105 (4.4) RR (95% CI): 0.51 (0.37, 0.71) *p*<.001 Fatal and hospitalized nonfatal HF, n (%) Drug: 45 (1.9) Placebo: 79 (3.3) RR (95% CI): 0.57 (0.34, 0.81) *p*=.002	
SHEP subsequent article on subtypes of stroke Perry et al., 2000[25]	4,736	Mean 4.5 years	Fair	Drug: Stepped chlorthalidone to atenolol or reserpine Placebo: Placebo QD	Adults ≥60 years with isolated systolic HTN	SBP: 160-219 and DBP: <90		Symptomatic MI, n Drug: 63 Placebo: 98 RR (95% CI): NR *p*=.005	Deaths due to all stroke, n Drug: 24 Placebo: 38 RR (95% CI): NR *p*=.91		

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes
Syst-Eur – primary article Staessen et al., 1997[23‡]	4, 695	Median 24 months	Good	Drug: Nitrendipine and/or enalapril, HCTZ Placebo: Placebo tablet	Adults ≥60 years	SBP: 160–219 and DBP <95	Death due to all causes, number (rate per 1000 p-y) Drug: 123 (20.5) Placebo: 137 (24.0) Difference (95% CI): –14 (–33, 9) *p*=.22	Coronary mortality (MI and sudden death), number (rate per 1000 p-y) Drug: 32 (5.3) Placebo: 42 (7.4) Difference (95% CI): –27 (–54, 15) *p*=.17 Death due to MI, number (rate per 1000 p-y) Drug: 7 (1.2) Placebo: 15 (2.6) Difference (95% CI): –56 (–82, 9) *p*=.08 Sudden death, number (rate per 1000 p-y) Drug: 25 (4.2) Placebo: 27 (4.7) Difference (95% CI): –12 (–49, 52) *p*=.65 Fatal and nonfatal cardiac endpoints (HF, MI, and sudden death), number (rate per 1000 p-y) Drug: 89 (15.1) Placebo: 114 (20.5) Difference (95% CI): –26 (–44, –3) *p*=.03 Nonfatal cardiac endpoints, number (rate per 1000 p-y) Drug: 50 (8.5) Placebo: 70 (12.6) Difference (95% CI): –33 (–53, –3) *p*=.03 Fatal and nonfatal MI, number (rate per 1000 p-y) Drug: 33 (5.5) Placebo: 45 (8.0) Difference (95% CI): –30 (–56, 9) *p*=.12 Nonfatal MI, number (rate per 1000 p-y) Drug: 26 (4.4) Placebo: 31 (5.5) Difference (95% CI): –20 (–53, 34) *p*=.40	Death due to stroke, number (rate per 1000 p-y) Drug: 16 (2.7) Placebo: 21 (3.7) Difference (95% CI): –27 (–62, 39) *p*=.33 PRIMARY OUTCOME Fatal and nonfatal stroke, number (rate per 1000 p-y) Drug: 47 (7.9) Placebo: 77 (13.7) Difference (95% CI): –42 (–60, –17) *p*=.003 Nonfatal stroke, number (rate per 1000 p-y) Drug: 34 (5.7) Placebo: 57 (10.1) Difference (95% CI): –44 (–63, –14) *p*=.007	Death due to HF, number (rate per 1000 p-y) Drug: 8 (1.3) Placebo: 10 (1.8) Difference (95% CI): –24 (–70, 93) *p*=.57 Fatal and nonfatal HF, number (rate per 1000 p-y) Drug: 37 (6.2) Placebo: 49 (8.7) Difference (95% CI): –29 (–53, 10) *p*=.12 Nonfatal HF, number (rate per 1000 p-y) Drug: 29 (4.9) Placebo: 43 (7.6) Difference (95% CI): –36 (–60, 2) *p*=.06	Death due to all CV causes, number (rate per 1000 p-y) Drug: 59 (9.8) Placebo: 77 (13.5) Difference (95% CI): –27 (–48, 2) *p*=.07 All fatal and nonfatal CV endpoints, number (rate per 1000 p-y) Drug: 137 (23.3) Placebo: 186 (33.9) Difference (95% CI): –31 (–45, –14) *p*<.001

Study	N	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes
Syst-Eur – subsequent article Staessen et al., 1998[26]	4, 695	Median 24 months	Fair	Drug: Nitrendipine and/or enalapril, HCTZ Placebo: Placebo tablet	Adults ≥60 years	SBP: 160–219 and DBP <95	Total mortality, unadjusted relative hazard rate (95% CI): 0.86 (0.67, 1.10) *p*=NR	Fatal and nonfatal cardiac endpoints (HF, MI, and sudden death), adjusted relative hazard rate (95% CI): 0.71 (0.54, 0.94) *p*<.05 Fatal and nonfatal cardiac endpoints (HF, MI, and sudden death), unadjusted relative hazard rate (95% CI): 0.74 (0.56, 0.97) *p*<.05	PRIMARY OUTCOME Fatal and nonfatal stroke, adjusted relative hazard rate (95% CI): 0.59 (0.38, 0.79) *p*<.01 PRIMARY OUTCOME Fatal and nonfatal stroke, unadjusted relative hazard rate (95% CI): 0.58 (0.40, 0.83) *p*<.001		CV mortality, unadjusted relative hazard rate (95% CI): 0.73 (0.52, 1.03) *p*=.07 All fatal and nonfatal CV endpoints, adjusted relative hazard rate (95% CI): 0.67 (0.54, 0.84) *p*<.001 Fatal and nonfatal CV endpoints, unadjusted relative hazard rate (95% CI): 0.69 (0.55, 0.86) *p*<.001

Table D–1d. Evidence From Randomized Controlled Trials on Initiating Antihypertensive Pharmacological Therapy at DBP Thresholds ≥90 mmHg

Study	N	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes/Primary Composite Outcomes
EWPHE primary article Amery et al., 1985[19§]	840	Mean 4.6 years	Fair	Drug: HCTZ and triamterene, plus methyldopa Placebo: Placebo tablet	Adults ≥60 years	SBP: 160–239 and DBP: 90–119	All-cause mortality, n (rate per 1000 p-y) Drug: 135 (69) Placebo: 149 (76) % change for active treatment (95% CI): –9 (–28, 15) *p*=.41	Cardiac mortality, n (rate per 1000 p-y) Drug: 29 (15) Placebo: 47 (24) % change for active treatment (95% CI): –38 (–61, –1) *p*=.036	PRIMARY OUTCOME Cerebrovascular mortality, n (rate per 1000 p-y) Drug: 21 (11) Placebo: 31 (16) % change for active treatment (95% CI): –32 (–61, 19) *p*=.16		CV mortality, n (rate per 1000 p-y) Drug: 67 (34) Placebo: 93 (47) % change for active treatment (95% CI): –27 (–46, –1) *p*=.037

‡ Kidney outcome data from this paper were not used in the development of evidence statements.

§ A subsequent article on kidney function in the EWPHE trial (de Leeuw et al., 1991) met the eligibility criteria for this question but was not used in the development of evidence statements.

Study	N	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes/Primary Composite Outcomes
EWPHE – subsequent article on CV mortality Amery et al., 1986[88]	840	Mean 4.6 years	Fair	Drug: HCTZ and triamterene, plus methyldopa Placebo: Placebo tablet	Adults ≥60 years	SBP: 160–239 and DBP: 90–119					CV mortality, n (rate per 1000 p-y) Drug: 67 (34) Placebo: 93 (47) % change for active treatment (95% CI): –27 (–47, –1) *p*=.037
EWPHE– subsequent article on adverse effects Fletcher et al., 1991[20**]	840	Mean 4.6 years	Fair	Drug: HCTZ and triamterene, plus methyldopa Placebo: Placebo tablet	Adults ≥60 years	SBP: 160–239 and DBP: 90–119		Fatal cardiac events at 1 year Overall difference between Drug vs. Placebo per 1000 p-y: –11% *p*<.05	PRIMARY OUTCOME Nonfatal cerebrovascular events at 1 year Overall difference between Drug vs. Placebo per 1000 p-y: –11% *p*<.05 PRIMARY OUTCOME Fatal cerebrovascular events at 1 year Overall difference between Drug vs. Placebo per 1000 p-y: –6% *p*=NR	Severe CHF at 1 year Overall difference between Drug vs. Placebo per 1000 p-y: –8% *p*<.05	
HDFP HDFP Cooperative Group, 1979[33]	10,940	5 years	Fair	Stepped: Stepped chlorthalidone and triamterene or spironolactone with addition of reserpine or methyldopa plus hydralazine plus guanethidine sulfate Usual: Referred to usual source of care	Adults 30-69 years	DBP: ≥90	PRIMARY OUTCOME: Mortality from all causes, death rates per 100 (SE) at 5 years Stepped: 6.4 (0.3) Usual: 7.7 (0.4) 95% CI for difference in rates between groups: 0.37, 2.29 *p*<.01	MI deaths, n Stepped: 51 Usual: 69 *p*=NR	Cerebrovascular disease deaths, n Stepped: 29 Usual: 52 *p*=NR		All CV disease deaths, n Stepped: 195 Usual: 240 *p*=NR

** Kidney outcome data from this paper were not used in the development of evidence statements.

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes/Primary Composite Outcomes
HDFP – subsequent article on stroke HDFP Cooperative Group, 1982[34]	10,940	5 years	Fair	Stepped: Stepped chlorthalidone and triamterene or spironolactone with addition of reserpine or methyldopa plus hydralazine plus guanethidine sulfate Usual: Referred to usual source of care	Adults 30–69 years	DBP: ≥90			Incidence of fatal and nonfatal stroke, rate per 100 at 5 years Stepped: 1.9 Usual: 2.9 % Reduction (95% CI): 34.5 (NR) *p*<.01		
Hypertension-Stroke Cooperative Hypertension-Stroke Cooperative Study Group, 1974[30]	452	Mean 27.4 months	Fair	Drug: Deserpidine and methyclothiazide Placebo: 2 tablets daily	Adults with a stroke or TIA in previous year, <75 years	SBP: 140–220 and DBP: 90–115	Deaths due to medical endpoints, # events Drug: 20 Placebo: 14 HR (95% CI): NR *p*=NR	MI (certain), # events Drug: 4 Placebo: 4 HR (95% CI): NR *p*=.69 Sudden death, # events Drug: 2 Placebo: 2 HR (95% CI): NR *p*=.99 Deaths from MI (certain), # events Drug: 1 Placebo: 2 HR (95% CI): NR *p*=NR	PRIMARY OUTCOME: Total stroke recurrence, n (%) Drug: 37 (15.9) Placebo: 42 (19.2) HR (95% CI): NR *p*=.42	CHF, # events Drug: 0 Placebo: 6 HR (95% CI): NR *p*=.012 Death due to CHF, # events Drug: 0 Placebo: 2 HR (95% CI): NR *p*=NR	CV endpoints, # events Drug: 12 Placebo: 19 HR (95% CI): NR *p*=.20 Other CV endpoints, # events Drug: 2 Placebo: 3 HR (95% CI): NR *p*=.68 Deaths due to CV endpoints, # events Drug: 9 Placebo: 9 HR (95% CI): NR *p*=NR Deaths due to other CV endpoints, # events Drug: 2 Placebo: 0 HR (95% CI): NR *p*=NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes/Primary Composite Outcomes
HYVET Beckett et al., 2008[21]	3,845	Mean 2.1 years	Good	Drug: Indapamide plus perindopril Placebo: Placebo tablet	Adults ≥80 years	SBP: ≥160 DBP: 90–109 at start of trial but in 2003 relaxed to <110	Death from any cause, rate per 1000 p-y (# events) Drug: 47.2 (196) Placebo: 59.6 (235) HR (95% CI): 0.79 (0.65, 0.95) *p*=.02 Note: study stopped early due to mortality reduction in drug group	Death from cardiac cause, rate per 1000 p-y (# events) Drug: 6.0 (25) Placebo: 8.4 (33) HR (95% CI): 0.71 (0.42, 1.19) *p*=.19 Fatal or nonfatal MI, rate per 1000 p-y (# events) Drug: 2.2 (9) Placebo: 3.1 (12) HR (95% CI): 0.72 (0.30, 1.70) *p*=.45	Death from stroke, rate per 1000 p-y (events) Drug: 6.5 (27) Placebo: 10.7 (42) HR (95% CI): 0.61 (0.38, 0.99) *p*=.046 PRIMARY OUTCOME Fatal or nonfatal stroke, rate per 1000 p-y (events) Drug: 12.4 (51) Placebo: 17.7 (69) HR (95% CI): 0.70 (0.49, 1.01) *p*=.06	Death from HF, rate per 1000 p-y (# events) Drug: 1.5 (6) Placebo: 3.0 (12) HR (95% CI): 0.48 (0.18, 1.28) *p*=.14 Fatal or nonfatal HF, rate per 1000 p-y (# events) Drug: 5.3 (22) Placebo: 14.8 (57) HR (95% CI): 0.36 (0.22, 0.58) *p*<.001	Death from CV cause, rate per 1000 p-y (# events) Drug: 23.9 (99) Placebo: 30.7 (121) HR (95% CI): 0.77 (0.60, 1.01) *p*=.06 Fatal or nonfatal any CV event, rate per 1000 p-y (# events) Drug: 33.7 (138) Placebo: 50.6 (193) HR (95% CI): 0.66 (0.53, 0.82) *p*<.001
Medical Research Council (MRC) Medical Research Council Working Party, 1985[35]	17,354	Mean 5.5 years	Fair	Diuretic: Bendrofluazide Beta blocker (BB): Propranolol Placebo: Placebo tablet	Adults 35–64 years	SBP: <200 and DBP: 90–109	All deaths, n (rate per 1000 py) Diuretic and BB: 248 (5.8) Placebo: 253 (5.9) % difference (95% CI): 2 (–16, 18) *p*=NR	PRIMARY OUTCOME: Fatal coronary events, n (rate per 1000 py) Diuretic and BB: 106 (2.5) Placebo: 97 (2.3) % difference (95% CI): –9 (NR) *p*=NR PRIMARY OUTCOME: Nonfatal coronary events, n (rate per 1000 py) Diuretic and BB: 116 (2.7) Placebo: 137 (3.2) % difference (95% CI): 16 (NR) *p*=NR PRIMARY OUTCOME: Total coronary events, n (rate per 1000 py) Diuretic and BB: 222 (5.2) Placebo: 234 (5.5) % difference (95% CI): 6 (-31, 21) *p*=NS	PRIMARY OUTCOME: Fatal stroke, n (rate per 1000 py) Diuretic and BB: 18 (0.4) Placebo: 27 (0.6) % difference (95% CI): 34 (NR) *p*=NR PRIMARY OUTCOME: Nonfatal stroke, n (rate per 1000 py) Diuretic and BB: 42 (1.0) Placebo: 82 (1.9) % difference (95% CI): 49 (NR) *p*=NR PRIMARY OUTCOME: Total stroke, n (rate per 1000 py) Diuretic and BB: 60 (1.4) Placebo: 109 (2.6) % difference (95% CI): 45 (25, 60) *p*=.006 once off testing *p*<.01 sequential analysis		All CV death, n (rate per 1000 py) Diuretic and BB: 134 (3.1) Placebo: 139 (3.3) % difference (95% CI): 4 (–22, 24) *p*=NR All CV events, n (rate per 1000 py) Diuretic and BB: 286 (6.7) Placebo: 352 (8.2) % difference (95% CI): 19 (5, 31) *p*=.01 once off testing *p*<.05 sequential analysis

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes/Primary Composite Outcomes
VA Cooperative Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1967[89]	143 with baseline DBP 115–129	Mean 20.7 months for drug group; 15.7 for placebo group	Good	Drug: HCTZ and reserpine plus hydralazine Placebo: Placebo tablet	Adult males ages 30 to 73	DBP: 90–129, this paper reports results for patients with baseline DBP 115–129	Deaths, n Drug: 0 Placebo: 4 *p*=NR				PRIMARY OUTCOME: Total incidence of morbidity and mortality, n Drug: 2 Placebo: 27 *p*<.0001
VA Cooperative Veterans Administration Cooperative Study Group on Antihyperten-sive Agents, 1970[36]	380 with baseline DBP 90–114	Mean 3.2 years for drug group; 3.3 years for placebo group	Good	Drug: HCTZ and reserpine plus hydralazine Placebo: Placebo tablet	Adult males with mean age at baseline of 50 years in drug group and 52 in placebo group	DBP: 90–129, this paper reports results for patients with baseline DBP 90–114	Total related deaths, n Drug: 8 Placebo: 19 *p*=NR	Nonfatal MI, n Drug: 5 Placebo: 2 *p*=NR Total coronary artery disease, n Drug: 11 Placebo: 13 *p*=NR Deaths due to MI, n Drug: 2 Placebo: 3 *p*=NR Sudden deaths, n Drug: 4 Placebo: 8 *p*=NR	Cerebrovascular accident (thrombosis or TIA), n Drug: 4 Placebo: 8 *p*=NR Deaths due to cerebrovascular hemorrhage, n Drug: 0 Placebo: 3 *p*=NR Deaths due to cerebrovascular thrombosis, n Drug: 1 Placebo: 3 *p*=NR Total cerebrovascular accidents, n Drug: 5 Placebo: 20 *p*=NR	Total CHF, n Drug: 0 Placebo: 11 *p*=NR	PRIMARY OUTCOME: Terminating morbid events, n (%) Drug: 9 (4.8) Placebo: 35 (18.0) *p*=NR

Table D–1e. Evidence From Randomized Controlled Trials on Initiating Antihypertensive Pharmacological Therapy at DBP Thresholds ≥95 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes/Primary Composite Outcomes
ANBP ANBP Management Committee, 1980[43]	3,427	Mean 4 years	Fair	Drug: Chlorothiazide and/or methyldopa, propanolol or pindolol plus hydralazine or clonidine Placebo: Placebo tablet	Adults 30–69 years	SBP: <200 *and* DBP: ≥95 but <110	Total fatal endpoints, events (events per 1000 p-y) Drug: 25 (3.6) Placebo: 35 (5.1) *p*=NR	Nonfatal MI, events Drug: 28 Placebo: 22 *p*=NR Fatal ischemic heart disease, events Drug: 5 Placebo: 11 *p*=NR Total ischemic heart disease, events Drug: 98 Placebo: 109 *p*=NR	Nonfatal cerebrovascular event (hemorrhagic or thrombosis), events Drug: 10 Placebo: 16 *p*=NR Nonfatal TIA, events Drug: 4 Placebo: 9 *p*=NR Fatal cerebrovascular events, events Drug: 3 Placebo: 6 *p*=NR Total cerebrovascular events, events Drug: 17 Placebo: 31 *p*=NR	Nonfatal congestive cardiac failure, events Drug: 3 Placebo: 3 *p*=NR	PRIMARY OUTCOME: Incidence of fatal CV endpoints, events (events per 1000 p-y) Drug: 8 (1.1) Placebo: 18 (2.6) *p*<.025 PRIMARY OUTCOME: Incidence of all trial endpoints, events (events per 1000 p-y) Drug: 138 (19.7) Placebo: 168 (24.5) *p*<.05

Table D–1f. Evidence From Randomized Controlled Trials on Initiating Antihypertensive Pharmacological Therapy at Mixed SBP and DBP Thresholds

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Inclusion BP Criteria	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardio-vascular Outcomes/Primary Composite Outcomes
Coope and Warrender Coope J, Warrender TS, 1986[90]	884	Mean 4.4 years	Good	Drug: atenolol plus bendrofluazide plus alpha-methyldopa Control: Observation only; no placebo tablets given	Adults 60–79 years	SBP: ≥170 or DBP: ≥105	All deaths, events per 1000 py (number of events) Drug: 32.5 (60) Control: 33.6 (69) Rate of Treatment/Rate of Control (95% CI): 0.97 (0.70, 1.42) *p*=NS (value NR)	Fatal coronary attacks, events per 1000 py (number of events) Drug: 13.6 (25) Control: 13.6 (28) Rate of Treatment/Rate of Control (95% CI): 1.00 (0.58, 1.71) *p*=NS (value NR) Nonfatal coronary attacks, events per 1000 py (number of events) Drug: 5.4 (10) Control: 4.9 (10) Rate of Treatment/Rate of Control (95% CI): 1.11 (0.46, 2.68) *p*=NS (value NR) PRIMARY OUTCOME: All coronary attacks, events per 1000 py (number of events) Drug: 19.0 (35) Control: 18.5 (38) Rate of Treatment/Rate of Control (95% CI): 1.03 (0.63, 1.63) *p*=NS (value NR)	Fatal stroke, events per 1000 py (number of events) Drug: 2.2 (4) Control: 7.3 (15) Rate of Treatment/Rate of Control (95% CI): 0.30 (0.11, 0.84) *p*<.025 PRIMARY OUTCOME: All stroke, events per 1000 py (number of events) Drug: 12.5 (23) Control: 21.4 (44) Rate of Treatment/Rate of Control (95% CI): 0.58 (0.35, 0.96) p <.03 TIA, events per 1000 py (number of events) Drug: 1.6 (3) Control: 2.4 (5) Rate of Treatment/Rate of Control (95% CI): 0.67 (0.16, 2.77) *p*=NS (value NR)	Fatal ventricular failure, events per 1000 py (number of events) Drug: 2.2 (4) Control: 1.9 (4) Rate of Treatment/Rate of Control (95% CI): 1.11 (0.28, 4.45) *p*=NS (value NR) Nonfatal ventricular failure, events per 1000 py (number of events) Drug: 9.8 (18) Control: 15.6 (32) Rate of Treatment/Rate of Control (95% CI): 0.63 (0.35, 1.11) *p*=NS (value NR)	CV death, events per 1000 py (number of events) Drug: 19.0 (35) Control: 24.3 (50) Rate of Treatment/Rate of Control (95% CI): 0.78 (0.51, 1.20) *p*=NS (value NR)
STOP - Hypertension Dahlöf, 1991[69]	1,627	Mean 25 months	Fair	Drug: Treatment initiated with one of the following 4 drugs and maintained throughout the study: atenolol or metoprolol or pindolol or (HCTZ and amiloride) Placebo: Placebo tablet	Adults 70–84 years	SBP: 180–230 and DBP: ≥90 or DBP 105–120 irrespective of SBP during run-in	Total deaths, number (per 1000 py) Drug: 36 (20.2) Placebo: 63 (35.4) RR (95% CI): 0.57 (0.37, 0.87) *p*=.0079	All MI, number (per 1000 py) Drug: 25 (14.4) Placebo: 28 (16.5) RR (95% CI): 0.87 (0.49, 1.56) *p*=NR Fatal MI, number (per 1000 py) Drug: 6 (3.5) Placebo: 6 (3.5) RR (95% CI): 0.98 (0.26, 3.66) *p*=NR	All stroke, number (per 1000 py) Drug: 29 (16.8) Placebo: 53 (31.3) RR (95% CI): 0.53 (0.33, 0.86) *p*=.0081 Fatal stroke, number (per 1000 py) Drug: 3 (1.7) Placebo: 12 (7.1) RR (95% CI): 0.24 (0.04, 0.91) *p*=NR	CHF, number Drug: 19 Placebo: 39 RR (95% CI): NR *p*=NR	PRIMARY OUTCOME: Composite: stroke, MI and other CV deaths, number (per 1000 py) Drug: 58 (33.5) Placebo: 94 (55.5) RR (95% CI): 0.60 (0.43, 0.85) *p*=.0031

Question 2 Summary Tables: Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to SpecifiedBlood Pressure Goals

Table D–2a. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to a SBP Goal of <130 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
Cardio-Sis Verdecchia et al., 2009[42]	1,111	Median 2 years	Good	Tight goal: SBP goal <130 mmHg Usual goal: SBP goal <140 mmHg	Adults, ages 55 or older, receiving anti-HTN treatment for ≥12 weeks, with at least one additional risk factor but no diabetes or renal dysfunction Mean SBP 163 mmHg Mean DBP 90 mmHg	At 2 years Achieved BP, mmHg Tight: 131.9/77.7 Usual: 135.6/78.7 *p*=NR BP reduction, mmHg (SD) Tight: 27.3/10.4 (11.0/7.5) Usual: 23.5/8.9 (10.6/7.0) *p*=NR BP difference between groups, mmHg (95% CI) 3.8/1.5 (2.4, 5.2/0.6, 2.4) *p*<.0001/ *p*<.041	Death from any cause, n of events (%) Tight: 4 (0.7) Usual: 5 (0.9) HR (95% CI): 0.77 (0.21, 2.88) *p*=.70	MI, n of events (%) Tight: 4 (0.7) Usual: 6 (1.1) HR (95% CI): 0.66 (0.19, 2.34) *p*=.52 Coronary revascularization procedures, n of events (%) Tight: 5 (0.9) Usual: 15 (2.7) HR (95% CI): 0.33 (0.12, 0.91) *p*=.032	Stroke or TIA, n of events (%) Tight: 4 (0.7) Usual: 9 (1.6) HR (95% CI): 0.44 (0.13, 1.42) *p*=.16	Admission for HF, n of events (%) Tight: 3 (0.5) Usual: 7 (1.3) HR (95% CI): 0.42 (0.11, 1.63) *p*=.21	Composite of: death from any cause, MI, stroke, TIA, atrial fibrillation, admission for HF, angina, or coronary revascularization, n of events (%) Tight: 27 (4.8) Usual: 52 (9.4) HR (95% CI): 0.50 (0.31, 0.79) *p*=.003

Table D–2b. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to a SBP Goal of <140 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
JATOS JATOS Study Group, 2008[30††]	4,418	104 weeks	Good	Lower goal: SBP goal <140 mmHg Usual goal: SBP goal 140–160 mmHg	Adults, ages 65–85, with essential HTN (SBP ≥160 and DBP <120) Mean SBP: 172 mmHg Mean DBP: 89 mmHg	At 2 years Achieved BP, mmHg (SD) Lower: 135.9/74.8 (11.7/9.1) Usual: 145.6/78.1 (11.1/8.9) *p*=NR BP difference between groups, mmHg: 9.7/3.3 *p*<.001/ *p*<.001	Death from any cause, n Lower: 54 Usual: 42 HR (95% CI): NR *p*=.22	Cardiac and vascular disease, n (%) Lower: 26 (1.18) Usual: 28 (1.27) HR (95% CI): NR *p*=.78 Cardiac and vascular disease deaths, n (%) Lower: 6 (0.27) Usual: 4 (0.18) HR (95% CI): NR *p*=.53 MI, n Lower: 6 Usual: 6 HR (95% CI): NR *p*=NS Fatal MI, n (%) Lower: 1 Usual: 0 HR (95% CI): NR *p*=NS Sudden death, n (%) Lower: 1 Usual: 1 HR (95% CI): NR *p*=NS	Cerebrovascular disease, n (%) Lower: 52 (2.35) Usual: 49 (2.22) HR (95% CI): NR *p*=.77 Cerebrovascular disease deaths, n (%) Lower: 3 (0.14) Usual: 3 (0.14) HR (95% CI): NR *p*=1.00	CHF, n (%) Lower: 8 Usual: 7 HR (95% CI): NR *p*=NS Fatal CHF, n (%) Lower: 4 Usual: 1 HR (95% CI): NR *p*=NS	PRIMARY OUTCOME: Primary endpoint events and deaths (cerebrovascular disease, cardiac and vascular disease, renal failure), n (%) Lower: 86 (3.89) Usual: 86 (3.90) HR (95% CI): NR *p*=.99 Primary endpoint deaths (cerebrovascular disease, cardiac and vascular disease, renal failure), n (%) Lower: 9 (0.41) Usual: 8 (0.36) HR (95% CI): NR *p*=.81

†† Kidney outcome data from this paper were not used in the development of evidence statements.

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
VALISH Ogihara et al., 2010[41]	3,260	Mean 2.85 years	Good	Strict control: SBP goal <140 mmHg Moderate control: SBP goal ≥140 to <150 mmHg	Adults, ages 70–85, with HTN (SBP ≥160 mmHg and DBP <90 mmHg) Mean SBP: 170 mmHg Mean DBP: 81 mmHg	At mean 2.85 years Achieved BP, mmHg (SD) Strict: 136.6/74.8 (13.3/8.8) Moderate: 142/76.5 (12.5/8.9) *p*<.001 At 36 months BP difference between groups, mmHg 5.6/1.7 *p*<.001/ *p*<.001	All cause death, n (%) Strict: 24 (1.55) Moderate: 30 (1.96) HR (95% CI): 0.78 (0.46, 1.33) *p*=.362	Fatal and nonfatal MI, n (%) Strict: 5 (0.32) Moderate: 4 (0.26) HR (95% CI): 1.23 (0.33, 4.56) *p*=.761 Sudden death, n (%) Strict: 6 (0.39) Moderate: 8 (0.52) HR (95% CI): 0.73 (0.25, 2.11) *p*=.564	Fatal and nonfatal Stroke, n (%) Strict: 16 (1.04) Moderate: 23 (1.50) HR (95% CI): 0.68 (0.36, 1.29) *p*=.237		PRIMARY OUTCOME: Composite of CV events (sudden death, fatal or nonfatal stroke, fatal or nonfatal MI, HF death, other CV death, unplanned hospitalization for CVD, and renal dysfunction (doubling of serum Cr or dialysis)), n (%) Strict: 47 (3.04) Moderate: 52 (3.39) HR (95% CI): 0.89 (0.60, 1.31) *p*=.383 "Hard endpoint" (CV death, nonfatal stroke (excludes TIA), and nonfatal MI), n (%) Strict: 32 (2.07) Moderate: 37 (2.41) HR (95% CI): 0.84 (0.53, 1.36) *p*=.484 CV death, n (%) Strict: 11 (0.71) Moderate: 11 (0.72) HR (95% CI): 0.97 (0.42, 2.25) *p*=.950

Table D–2c. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to a SBP Goal of ≤150 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
HYVET Beckett et al., 2008[21]	3,845	Mean 2.1 years	Good	Drug: Indapamide plus perindopril; BP goal <150/80 mmHg Placebo: Placebo; BP goal <150/80 mmHg	Adults ≥80 years with HTN (SBP ≥160 mmHg and DBP 90–109 mmHg at start of trial but relaxed later to <110 mmHg) Mean SBP: 173 mmHg Mean DBP: 91 mmHg	At 2 years Achieved BP: NR Mean BP decrease from baseline, mmHg (SD) Drug: 29.5/12.9 (15.4/9.5) Placebo: 14.5/6.8 (18.5/10.5) *p*=NR BP difference between groups, mmHg: 15.0/6.1 *p*=NR	Death from any cause, rate per 1000 p-y (# events) Drug: 47.2 (196) Placebo: 59.6 (235) HR (95% CI): 0.79 (0.65, 0.95) *p*=.02 Note: study stopped early due to mortality reduction in drug group	Fatal or nonfatal MI, rate per 1000 p-y (# events) Drug: 2.2 (9) Placebo: 3.1 (12) HR (95% CI): 0.72 (0.30, 1.70) *p*=.45 Death from cardiac cause, rate per 1000 p-y (# events) Drug: 6.0 (25) Placebo: 8.4 (33) HR (95% CI): 0.71 (0.42, 1.19) *p*=.19	PRIMARY OUTCOME Fatal or nonfatal stroke, rate per 1000 p-y (events) Drug: 12.4 (51) Placebo: 17.7 (69) HR (95% CI): 0.70 (0.49, 1.01) *p*=.06 Death from stroke, rate per 1000 p-y (events) Drug: 6.5 (27) Placebo: 10.7 (42) HR (95% CI): 0.61 (0.38, 0.99) *p*=.046	Fatal or nonfatal HF, rate per 1000 p-y (# events) Drug: 5.3 (22) Placebo: 14.8 (57) HR (95% CI): 0.36 (0.22, 0.58) *p*<.001 Death from HF, rate per 1000 p-y (# events) Drug: 1.5 (6) Placebo: 3.0 (12) HR (95% CI): 0.48 (0.18, 1.28) *p*=.14	Death from CV cause, rate per 1000 p-y (# events) Drug: 23.9 (99) Placebo: 30.7 (121) HR (95% CI): 0.77 (0.60, 1.01) *p*=.06 Fatal or nonfatal any CV event, rate per 1000 p-y (# events) Drug: 33.7 (138) Placebo: 50.6 (193) HR (95% CI): 0.66 (0.53, 0.82) *p*<.001

Study	N	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
Syst-Eur – primary article Staessen et al., 1997[23‡‡]	4, 695	Median 24 months	Good	Drug: Nitrendipine and/or enalapril, HCTZ; SBP goal <150 and decrease SBP by ≥20 mmHg Placebo: Placebo tablet; SBP goal <150 and decrease SBP by ≥20 mmHg	Adults, ages ≥60 years, with HTN (SBP 160–219 mmHg and DBP <95 mmHg) Mean SBP: 174 mmHg Mean DBP: 86 mmHg	At 2 years Achieved BP: 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 BP, mmHg (SD) Drug: 23/7 (16/8) Placebo: 13/2 (17/8) *p*=NR At 4 years BP difference between groups, mmHg (95% CI) 10.7/4.7 (8.8, 12.5/3.7, 5.6) *p*=NR	Death due to all causes, number (rate per 1000 p-y) Drug: 123 (20.5) Placebo: 137 (24.0) Difference (95% CI): –14 (–33, 9) *p*=.22	Fatal and nonfatal MI, number (rate per 1000 p-y) Drug: 33 (5.5) Placebo: 45 (8.0) Difference (95% CI): –30 (–56, 9) *p*=.12 Nonfatal MI, number (rate per 1000 p-y) Drug: 26 (4.4) Placebo: 31 (5.5) Difference (95% CI): –20 (–53, 34) *p*=.40 Coronary mortality (MI and sudden death), number (rate per 1000 p-y) Drug: 32 (5.3) Placebo: 42 (7.4) Difference (95% CI): –27 (–54, 15) *p*=.17 Death due to MI, number (rate per 1000 p-y) Drug: 7 (1.2) Placebo: 15 (2.6) Difference (95% CI): –56 (–82, 9) *p*=.08 Sudden death, number (rate per 1000 p-y) Drug: 25 (4.2) Placebo: 27 (4.7) Difference (95% CI): –12 (–49, 52) *p*=.65	PRIMARY OUTCOME Fatal and nonfatal stroke, number (rate per 1000 p-y) Drug: 47 (7.9) Placebo: 77 (13.7) Difference (95% CI): –42 (–60, –17) *p*=.003 Nonfatal stroke, number (rate per 1000 p-y) Drug: 34 (5.7) Placebo: 57 (10.1) Difference (95% CI): –44 (–63, –14) *p*=.007 Death due to stroke, number (rate per 1000 p-y) Drug: 16 (2.7) Placebo: 21 (3.7) Difference (95% CI): –27 (–62, 39) *p*=.33	Fatal and nonfatal HF, number (rate per 1000 p-y) Drug: 37 (6.2) Placebo: 49 (8.7) Difference (95% CI): –29 (–53, 10) *p*=.12 Nonfatal HF, number (rate per 1000 p-y) Drug: 29 (4.9) Placebo: 43 (7.6) Difference (95% CI): –36 (–60, 2) *p*=.06 Death due to HF, number (rate per 1000 p-y) Drug: 8 (1.3) Placebo: 10 (1.8) Difference (95% CI): –24 (–70, 93) *p*=.57	All fatal and nonfatal CV endpoints, number (rate per 1000 p-y) Drug: 137 (23.3) Placebo: 186 (33.9) Difference (95% CI): –31 (–45, –14) *p*<.001 Death due to all CV causes, number (rate per 1000 p-y) Drug: 59 (9.8) Placebo: 77 (13.5) Difference (95% CI): –27 (–48, 2) *p*=.07 Fatal and nonfatal cardiac endpoints (HF, MI, and sudden death), number (rate per 1000 p-y) Drug: 89 (15.1) Placebo: 114 (20.5) Difference (95% CI): –26 (–44, –3) *p*=.03 Nonfatal cardiac endpoints, number (rate per 1000 p-y) Drug: 50 (8.5) Placebo: 70 (12.6) Difference (95% CI): –33 (–53, –3) *p*=.03

‡‡ Kidney outcome data from this paper were not used in the development of evidence statements.

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
Syst-Eur – subsequent article Staessen et al., 1998[26]	4, 695	Median 24 months	Fair	Drug: Nitrendipine and/or enalapril, HCTZ; SBP goal <150 and decrease SBP by ≥20 mmHg Placebo: Placebo tablet; SBP goal <150 and decrease SBP by ≥20 mmHg	Adults, ages ≥ 60 years, with HTN (SBP 160–219 mmHg and DBP <95 mmHg) Mean SBP: NR Mean DBP: 86 NR	At median F/U Achieved BP: NR Mean decrease in sitting BP, mmHg (SD) Drug: 23/7 (16/8) Placebo: 13/2 (17/8) *p*=NR BP difference between groups, mmHg (95% CI) 10.1/4.5 (8.8, 11.4/3.9, 5.1) *p*=NR	Total mortality, unadjusted relative hazard rate (95% CI): 0.86 (0.67, 1.10) *p*=NR		PRIMARY OUTCOME Fatal and nonfatal stroke, adjusted relative hazard rate (95% CI): 0.59 (0.38, 0.79) *p*<.01 PRIMARY OUTCOME Fatal and nonfatal stroke, unadjusted relative hazard rate (95% CI): 0.58 (0.40, 0.83) *p*<.001		CV mortality, unadjusted relative hazard rate (95% CI): 0.73 (0.52, 1.03) *p*=.07 All fatal and nonfatal CV endpoints, adjusted relative hazard rate (95% CI): 0.67 (0.54, 0.84) *p*<.001 Fatal and nonfatal CV endpoints, unadjusted relative hazard rate (95% CI): 0.69 (0.55, 0.86) *p*<.001 Fatal and nonfatal cardiac endpoints (HF, MI, and sudden death), adjusted relative hazard rate (95% CI): 0.71 (0.54, 0.94) *p*<.05 Fatal and nonfatal cardiac endpoints (HF, MI, and sudden death), unadjusted relative hazard rate (95% CI): 0.74 (0.56, 0.97) *p*<.05

Table D–2d. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to a SBP Goal of <160 mmHg (also includes lower goals)

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
SHEP – primary article Systolic Hypertension in the Elderly Program Cooperative Research Group, 1991[22]	4,736	Mean 4.5 years	Good	Drug: Stepped chlorthalidone; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg Placebo: Placebo QD; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg	Adults, ages ≥ 60 years, with isolated systolic HTN (SBP 160–219 and DBP <90 mmHg) Mean SBP: 170 mmHg Mean DBP: 77 mmHg	At 5 years Achieved BP, mmHg (SD) Drug: 144.0/67.7 (19.3/10.2) Placebo: 155.1/71.1 (20.9/12.8) *p*=NR BP decrease from baseline, mmHg Drug: 26.5/9.0 Placebo: 15/5.3 *p*=NR BP difference between groups, mmHg 11.1/3.4 *p*=NR	Total deaths, n of events Drug: 213 Placebo: 242 RR (95% CI): 0.87 (0.73, 1.05) *p*=NR	Nonfatal MI or CHD deaths, n of events Drug: 104 Placebo: 141 RR (95% C): 0.73 (0.57, 0.94) *p*=NR Nonfatal MI, n of events Drug: 50 Placebo: 74 RR (95% CI): 0.67 (0.47, 0.96) *p*=NR CABG, n of events Drug: 30 Placebo: 47 RR (95% CI): 0.63 (0.40, 1.00) *p*=NR Angioplasty, n of events Drug: 19 Placebo: 22 RR (95% CI): 0.86 (0.47, 1.59) *p*=NR CHD, n of events Drug: 140 Placebo: 184 RR (95% CI): 0.75 (0.60, 0.94) *p*=NR Total CHD deaths, n of events Drug: 59 Placebo: 73 RR (95% CI): 0.80 (0.57, 1.13) *p*=NR MI death, n of events Drug: 15 Placebo: 26 RR (95% CI): 0.57 (0.30, 1.08) *p*=NR Sudden death (<1 hour), n of events Drug: 23 Placebo: 23 RR (95% CI): 1.00 (0.56, 1.78) *p*=NR Rapid death (1–24 hours), n of events Drug: 21 Placebo: 24 RR (95% CI): 0.87 (0.48, 1.56) *p*=NR	PRIMARY OUTCOME Nonfatal plus fatal stroke at 5 years, per 100 participants (SE) Drug: 5.2 (0.5) Placebo: 8.2 (0.7) RR (95% CI): 0.64 (0.50, 0.82) *p*=.0003 Nonfatal stroke, n of events Drug: 96 Placebo: 149 RR (95% CI): 0.63 (0.49, 0.82) *p*=NR Stroke deaths, n of events Drug: 10 Placebo: 14 RR (95% CI): 0.71 (0.31, 1.59) *p*=NR TIA, n of events Drug: 62 Placebo: 82 RR (95% CI): 0.75 (0.54, 1.04) *p*=NR		CVD, n of events Drug: 289 Placebo: 414 RR (95% CI): 0.68 (0.58, 0.79) *p*=NR Total CVD deaths, n of events Drug: 90 Placebo: 112 RR (95% CI): 0.80 (0.60, 1.05) *p*=NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
SHEP subsequent article Systolic Hypertension in the Elderly Program Cooperative Research Group, 1993[39]	4,736	Mean 4.5 years	Fair	Drug: Stepped chlorthalidone; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg Placebo: Placebo QD; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg	Adults, ages ≥ 60 years, with isolated systolic HTN (SBP 160–219 and DBP <90 mmHg) Mean SBP: 170 mmHg Mean DBP: 77 mmHg	At 5 years Achieved BP: NR BP decrease from baseline, mmHg Drug: 26/9 Placebo: NR *p*=NR BP difference between groups, mmHg 11–14/3–4 *p*=NR		Reduction in nonfatal MI and CHD death, % Drug vs. Placebo: 27 *p*=NR	PRIMARY OUTCOME Reduction in nonfatal and fatal stroke, % Drug vs. Placebo: 36 *p*=.0003		Reduction in all major CV events, % Drug vs. Placebo: 32 *p*=NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
SHEP subsequent article on the prevention of heart failure Kostis et al., 1997[24]	4,736	Mean 4.5 years	Good	Drug: Stepped chlorthalidone; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg Placebo: Placebo QD; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg	Adults, ages ≥ 60 years, with isolated systolic HTN (SBP 160–219 and DBP <90 mmHg) Mean SBP: 170 mmHg Mean DBP: 77 mmHg	At 5 years Achieved BP: Drug: 143/68 Placebo: 155/72 *p*=NR				Nonfatal HF, n (%) Drug: 48 (2.0) Placebo: 102 (4.3) RR (05% CI): 0.46 (0.33, 0.65) *p*<.001 Nonfatal hospitalized HF, n (%) Drug: 38 (1.6) Placebo: 75 (3.2) RR (95% CI): 0.50 (0.34–0.74 *p*<.001 Fatal and nonfatal HF, n (%) Drug: 55 (2.3) Placebo: 105 (4.4) RR (95% CI): 0.51 (0.37, 0.71) *p*<.001 Fatal and hospitalized nonfatal HF, n (%) Drug: 45 (1.9) Placebo: 79 (3.3) RR (95% CI): 0.57 (0.34, 0.81) *p*=.002	

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes or Composites
SHEP subsequent article on subtypes of stroke Perry et al., 2000[25]	4,736	Mean 4.5 years	Fair	Drug: Stepped chlorthalidone; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg Placebo: Placebo QD; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg	Adults, ages ≥ 60 years, with isolated systolic HTN (SBP 160–219 and DBP <90 mmHg) Mean SBP: 170 mmHg Mean DBP: 77 mmHg	At 5 years Achieved BP: NR BP decrease from baseline, mmHg Drug: 26/9 Placebo: 15/4 *p*=NR		Symptomatic MI, n Drug: 63 Placebo: 98 RR (95% CI): NR *p*=.005	Deaths due to all stroke, n Drug: 24 Placebo: 38 RR (95% CI): NR *p*=.91		

Table D–2e. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to a DBP Goal of <80 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Mortality Outcomes	CHD Outcomes	Cerebrovascular Morbidity and Mortality	Heart Failure Outcomes	Cardiovascular Outcomes or Composites
HOT Hansson et al., 1998[44]	18,790	Mean 3.8 years	Fair	≤80: DBP goal ≤80 mmHg ≤85: DBP goal ≤85 mmHg ≤90: DBP goal ≤90 mmHg	Adults, ages 50–80, with HTN (DBP 100–115) Mean SBP: 170 mmHg Mean DBP: 105 mmHg	Mean of 6 months F/U to study end Achieved BP, mmHg (SD) ≤80: 139.7/81.1 (11.7/5.3) ≤85: 141.4/83.2 (11.7/4.8) ≤90: 143.7/85.2 (11.3/5.1) *p*=NR BP decrease from baseline, mmHg (SD) ≤80: 29.9/24.3 (13.6/5.8) ≤85: 28.0/22.3 (13.2/5.4) ≤90: 26.2/20.3 (13.0/5.6) *p*=NR Mean between group difference in achieved BP, mmHg ≤90 vs. ≤85: 1.8/2.0 ≤85 vs. ≤80: 1.9/2.0 ≤90 vs. ≤80: 3.7/4.0 *p*=NR	Total mortality, n (events per 1000 p-y) ≤80: 207 (8.8) ≤85: 194 (8.2) ≤90: 188 (7.9) *p* for trend: .32 RR (95% CI): ≤90 vs. ≤85: 0.97 (0.79, 1.19) ≤85 vs. ≤80: 0.93 (0.77, 1.14) ≤90 vs. ≤80: 0.91 (0.74, 1.10)	All MI, n (events per 1000 p-y) ≤80: 61 (2.6) ≤85: 64 (2.7) ≤90: 84 (3.6) *p* for trend: .05 RR (95% CI): ≤90 vs. ≤85: 1.32 (0.95, 1.82) ≤85 vs. ≤80: 1.05 (0.74, 1.48) ≤90 vs. ≤80: 1.37 (0.99, 1.91) All MI including silent cases, n (events per 1000 p-y) ≤80: 107 (4.6) ≤85: 107 (4.6) ≤90: 127 (5.4) *p* for trend: .19 RR (95% CI): ≤90 vs. ≤85: 1.19 (0.92, 1.54) ≤85 vs. ≤80: 1.00 (0.76, 1.3) ≤90 vs. ≤80: 1.19 (0.92, 1.53)	All stroke, n (events per 1000 p-y) ≤80: 89 (3.8) ≤85: 111 (4.7) ≤90: 94 (4.0) *p* for trend: .74 RR (95% CI): ≤90 vs. ≤85: 0.85 (0.64, 1.11) ≤85 vs. ≤80: 1.24 (0.94, 1.64) ≤90 vs. ≤80: 1.05 (0.79, 1.41)		PRIMARY OUTCOME: Major CV events (fatal and nonfatal MI, fatal and nonfatal stroke, all other CV death), n (events per 1000 p-y) ≤80: 217 (9.3) ≤85: 234 (10.0) ≤90: 232 (9.9) *p* for trend: .50 RR (95% CI): ≤90 vs. ≤85: 0.99 (0.83, 1.19) ≤85 vs. ≤80: 1.08 (0.89, 1.29) ≤90 vs. ≤80: 1.07 (0.89, 1.28) Major CV events including silent MI, n (events per 1000 p-y) ≤80: 263 (11.3) ≤85: 276 (11.8) ≤90: 274 (11.7) *p* for trend: .66 RR (95% CI): ≤90 vs. ≤85: 0.99 (0.84, 1.17) ≤85 vs. ≤80: 1.05 (0.88, 1.24) ≤90 vs. ≤80: 1.04 (0.88, 1.23) CV mortality, n (events per 1000 p-y) ≤80: 96 (4.1) ≤85: 90 (3.8) ≤90: 87 (3.7) *p* for trend: .49 RR (95% CI): ≤90 vs. ≤85: 0.97 (0.72, 1.30) ≤85 vs. ≤80: 0.93 (0.70, 1.24) ≤90 vs. ≤80: 0.90 (0.68, 1.21)

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Mortality Outcomes	CHD Outcomes	Cerebrovascular Morbidity and Mortality	Heart Failure Outcomes	Cardiovascular Outcomes or Composites
HYVET Beckett et al., 2008[21]	3,845	Mean 2.1 years	Good	Drug: Indapamide plus perindopril; BP goal <150/80 mmHg Placebo: Placebo; BP goal <150/80 mmHg	Adults ≥ 80 years with HTN (SBP ≥160 mmHg and DBP 90–109 mmHg at start of trial but relaxed later to <110 mmHg) Mean SBP: 173 mmHg Mean DBP: 91 mmHg	At 2 years Achieved BP: NR Mean BP decrease from baseline, mmHg (SD) Drug: 29.5/12.9 (15.4/9.5) Placebo: 14.5/6.8 (18.5/10.5) *p*=NR BP difference between groups, mmHg: 15.0/6.1 *p*=NR	Death from any cause, rate per 1000 p-y (# events) Drug: 47.2 (196) Placebo: 59.6 (235) HR (95% CI): 0.79 (0.65, 0.95) *p*=.02 Note: study stopped early due to mortality reduction in drug group	Fatal or nonfatal MI, rate per 1000 p-y (# events) Drug: 2.2 (9) Placebo: 3.1 (12) HR (95% CI): 0.72 (0.30, 1.70) *p*=.45 Death from cardiac cause, rate per 1000 p-y (# events) Drug: 6.0 (25) Placebo: 8.4 (33) HR (95% CI): 0.71 (0.42, 1.19) *p*=.19	PRIMARY OUTCOME Fatal or nonfatal stroke, rate per 1000 p-y (events) Drug: 12.4 (51) Placebo: 17.7 (69) HR (95% CI): 0.70 (0.49, 1.01) *p*=.06 Death from stroke, rate per 1000 p-y (events) Drug: 6.5 (27) Placebo: 10.7 (42) HR (95% CI): 0.61 (0.38, 0.99) *p*=.046	Fatal or nonfatal HF, rate per 1000 p-y (# events) Drug: 5.3 (22) Placebo: 14.8 (57) HR (95% CI): 0.36 (0.22, 0.58) *p*<.001 Death from HF, rate per 1000 p-y (# events) Drug: 1.5 (6) Placebo: 3.0 (12) HR (95% CI): 0.48 (0.18, 1.28) *p*=.14	Death from CV cause, rate per 1000 p-y (# events) Drug: 23.9 (99) Placebo: 30.7 (121) HR (95% CI): 0.77 (0.60, 1.01) *p*=.06 Fatal or nonfatal any CV event, rate per 1000 p-y (# events) Drug: 33.7 (138) Placebo: 50.6 (193) HR (95% CI): 0.66 (0.53, 0.82) *p*<.001

Table D–2f. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to a DBP Goal of <85 mmHg

See HOT (Hansson et al., 1998) in table 2d which compares DBP goals of ≤90 mmHg vs. ≤85 mmHg vs. ≤80 mmHg

Table D–2g. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to a DBP Goal of <90 mmHg

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes
Medical Research Council (MRC) Medical Research Council Working Party, 1985[35]	17,354	5.5 years	Fair	Diuretic: Bendrofluazide; DBP goal <90 mmHg Beta blocker (BB): Propranolol; DBP goal <90 mmHg Placebo: Placebo tablet; DBP goal not stated	Adults, ages 35–64 years, with HTN (SBP <200 and DBP 90–109 mmHg) Mean SBP: Men: 158 mmHg Women: 165 mmHg Mean DBP: Men: 98 mmHg Women: 99 mmHg	At 5 years Achieved BP: NR BP difference between groups, mmHg: Placebo vs. diuretic: Men: 11/6 Women: 15/6 Placebo vs. BB: Men: 9/6 Women: 10/4 *p*=NR	All deaths, n (rate per 1000 py) Diuretic and BB: 248 (5.8) Placebo: 253 (5.9) % difference (95% CI): 2 (–16, 18) *p*=NR	PRIMARY OUTCOME: Total coronary events, n (rate per 1000 py) Diuretic and BB: 222 (5.2) Placebo: 234 (5.5) % difference (95% CI): 6 (–31, 21) *p*=NS PRIMARY OUTCOME: Fatal coronary events, n (rate per 1000 py) Diuretic and BB: 106 (2.5) Placebo: 97 (2.3) % difference (95% CI): –9 (NR) *p*=NR PRIMARY OUTCOME: Nonfatal coronary events, n (rate per 1000 py) Diuretic and BB: 116 (2.7) Placebo: 137 (3.2) % difference (95% CI): 16 (NR) *p*=NR	PRIMARY OUTCOME: Total stroke, n (rate per 1000 py) Diuretic and BB: 60 (1.4) Placebo: 109 (2.6) % difference (95% CI): 45 (25, 60) *p*=.006 once off testing *p*<.01 sequential analysis PRIMARY OUTCOME: Fatal stroke, n (rate per 1000 py) Diuretic and BB: 18 (0.4) Placebo: 27 (0.6) % difference (95% CI): 34 (NR) *p*=NR PRIMARY OUTCOME: Nonfatal stroke, n (rate per 1000 py) Diuretic and BB: 42 (1.0) Placebo: 82 (1.9) % difference (95% CI): 49 (NR) *p*=NR		All CV death, n (rate per 1000 py) Diuretic and BB: 134 (3.1) Placebo: 139 (3.3) % difference (95% CI): 4 (–22, 24) *p*=NR All CV events, n (rate per 1000 py) Diuretic and BB: 286 (6.7) Placebo: 352 (8.2) % difference (95% CI): 19 (5, 31) *p*=.01 once off testing *p*<.05 sequential analysis

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes
VA Cooperative Veterans Administration Cooperative Study Group on Anti-hypertensive Agents, 1967[89]	143 with baseline DBP 115–129	Mean 20.7 months for drug group; 15.7 for placebo group	Good	Drug: HCTZ and reserpine plus hydralazine; DBP goal <90 mmHg implied from titration protocol Placebo: Placebo tablet; DBP goal <90 mmHg implied from titration protocol	Adult males, ages 30 to 73 years, DBP 115–129 mmHg prior to treatment Mean SBP: 186 mmHg Mean DBP: 121 mmHg	At 24 months Achieved BP, mmHg Drug: 91.5 Placebo: 119.7 *p*=NR Mean BP decrease from baseline, mmHg (SD) Drug: 29.7 Placebo: 1.3 *p*=NR BP difference between groups, mmHg 28.4 *p*=NR	Deaths, n Drug: 0 Placebo: 4 *p*=NR				PRIMARY OUTCOME: Total incidence of morbidity and mortality, n Drug: 2 Placebo: 27 *p*<.0001 Note: study stopped early due to morbidity and mortality reduction in drug group
VA Cooperative Veterans Administration Cooperative Study Group on Anti-hypertensive Agents, 1970[36]	380 with baseline DBP 90–114	Mean 3.2 years for drug group; 3.3 years for placebo group	Good	Drug: HCTZ and reserpine plus hydralazine; DBP goal <90 mmHg implied from titration protocol Placebo: Placebo tablet; DBP goal <90 mmHg implied from titration protocol	Adult males, (mean baseline sample age of 50 years in txt, 52 in control), DBP 90–129 mmHg prior to treatment Mean SBP, mmHg: Drug:162.1 Placebo: 165.1 Mean DBP, mmHg Drug: 103.8 Placebo: 101.3	At 4 months Achieved BP: NR Mean BP change from baseline, mmHg Drug: –27.2/ –17.4 Placebo: +4.2/+1.2 *p*=NR	Total related deaths, n Drug: 8 Placebo: 19 *p*=NR	Nonfatal MI, n Drug: 5 Placebo: 2 *p*=NR Total coronary artery disease, n Drug: 11 Placebo: 13 *p*=NR Deaths due to MI, n Drug: 2 Placebo: 3 *p*=NR Sudden deaths, n Drug: 4 Placebo: 8 *p*=NR	Total cerebrovascular accidents, n Drug: 5 Placebo: 20 *p*=NR Cerebrovascular accident (thrombosis or TIA), n Drug: 4 Placebo: 8 *p*=NR Deaths due to cerebrovascular hemorrhage, n Drug: 0 Placebo: 3 *p*=NR Deaths due to cerebrovascular thrombosis, n Drug: 1 Placebo: 3 *p*=NR	Total CHF, n Drug: 0 Placebo: 11 *p*=NR	Terminating morbid events, n (%) Drug: 9 (4.8) Placebo: 35 (18.0) *p*=NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes
ANBP ANBP Management Committee, 1980[43§§]	3,427	Mean 4 years	Fair	Drug: Chlorothiazide and/or methyldopa, propanolol or pindolol plus hydralazine or clonidine; DBP goal ≤90 mmHg; after 2 years goal lowered to 80 mmHg Placebo: Placebo tablet; DBP goal ≤90 mmHg; after 2 years goal lowered to 80 mmHg	Adults, ages 30–69 years, with HTN (DBP ≥95 and <110 with SBP <200 mmHg) Mean SBP: 157 mmHg Mean DBP: 100 mmHg	At 4 years Achieved DBP, mmHg Drug: 88.3 Placebo: 93.9 *p*=NR DBP change from baseline, mmHg Drug: –12.2 Placebo: –6.6 *p*=NR DBP difference between groups, mmHg 5.6 *p*=NR	Total fatal endpoints, events (events per 1000 p-y) Drug: 25 (3.6) Placebo: 35 (5.1) *p*=NR	Total ischemic heart disease, events Drug: 98 Placebo: 109 *p*=NR Nonfatal MI, events Drug: 28 Placebo: 22 *p*=NR Fatal ischemic heart disease, events Drug: 5 Placebo: 11 *p*=NR	Total cerebrovascular events, events Drug: 17 Placebo: 31 *p*=NR Nonfatal cerebrovascular event (hemorrhagic or thrombosis), events Drug: 10 Placebo: 16 *p*=NR Nonfatal TIA, events Drug: 4 Placebo: 9 *p*=NR Fatal cerebrovascular events, events Drug: 3 Placebo: 6 *p*=NR	Nonfatal congestive cardiac failure, events Drug: 3 Placebo: 3 *p*=NR	PRIMARY OUTCOME: Incidence of fatal CV endpoints, events (events per 1000 p-y) Drug: 8 (1.1) Placebo: 18 (2.6) *p*<.025 PRIMARY OUTCOME: Incidence of all trial endpoints, events (events per 1000 p-y) Drug: 138 (19.7) Placebo: 168 (24.5) *p*<.05

§§ Kidney outcome data from this paper were not used in the development of evidence statements.

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes
HDFP HDFP Cooperative Group, 1979[33]	10,940	5 years	Fair	Stepped: Stepped chlorthalidone and triamterene or spironolactone with addition of reserpine or methyldopa plus hydralazine plus guanethidine sulfate; DBP goal 90 mmHg for those entering with DBP ≥100 mmHg or already receiving anti-HTN medication and 10 mmHg decrease for those entering with DBP 90–99 mmHg Usual: Referred to usual source of care; DBP goal not stated	Adults, ages 30–69 years, with HTN (DBP ≥ 90 mmHg) Mean SBP: 159 mmHg Mean DBP: 101 mmHg	At 5 years Achieved DBP, mmHg Txt: 84.1 Placebo: 89.1 *p*=NR DBP change from baseline, mmHg Txt: –17.0 Placebo: –12.1 *p*=NR DBP difference between groups, mmHg 4.9 *p*=NR	PRIMARY OUTCOME: Mortality from all causes, death rates per 100 (SE) at 5 years Stepped: 6.4 (0.3) Usual: 7.7 (0.4) 95% CI for difference in rates between groups: 0.37, 2.29 *p*<.01	MI deaths, n Stepped: 51 Usual: 69 *p*=NR	Cerebrovascular disease deaths, n Stepped: 29 Usual: 52 *p*=NR		All CV disease deaths, n Stepped: 195 Usual: 240 *p*=NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes
HDFP – subsequent article on stroke HDFP Cooperative Group, 1982[34]	10,940	5 years	Fair	Stepped: Stepped chlorthalidone and triamterene or spironolactone with addition of reserpine or methyldopa plus hydralazine plus guanethidine sulfate; DBP goal 90 mmHg for those entering with DBP ≥100 mmHg or already receiving anti-HTN medication and 10 mmHg decrease for those entering with DBP 90–99 mmHg Usual: Referred to usual source of care; DBP goal not stated	Adults, ages 30–69 years, with HTN (DBP ≥ 90 mmHg) Mean SBP: 159 mmHg Mean DBP: 101 mmHg	At 5 years Achieved DBP: NR DBP change from baseline: NR DBP difference between groups: NR			Incidence of fatal and nonfatal stroke, rate per 100 at 5 years Stepped: 1.9 Usual: 2.9 % Reduction (95% CI): 34.5 (NR) *p*<.01		

Table D–2h. Evidence From Randomized Controlled Trials on Treatment with Antihypertensive Pharmacological Therapy to Mixed SBP and DBP Goals

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/ Primary Composite Outcomes
SCOPE Lithell et al., 2003[91]	4,964	Mean 3.7 years	Fair	Drug: Candesartan with other anti-HTN drugs (not ARB or ACE) to achieve control; BP goal not explicitly stated, drug titration began at SBP >160 or DBP >85 or 90 depending upon step Control: Placebo with other anti-HTN drugs (not ARB or ACE) to achieve control; BP goal not explicitly stated, drug titration began at SBP >160 or DBP >85 or 90 depending upon step	Adults, ages 70–89, previously treated or untreated HTN (SBPs 160–179 mmHg and/or DBPs 90–99 mmHg) and MMSE scores of ≥24 Mean SBP: 166 mmHg Mean DBP: 90 mmHg	At last visit Achieved BP, mmHg (SD): Drug: 145.2/79.9 (16.1/8.7) Control: 148.5/81.6 (6.8/8.8) *p*=NR Reduction in BP, mmHg Drug: 21.7/10.8 Control: 18.5/9.2 *p*=NR BP difference between groups, mmHg (95% CI): 3.2/1.6 (–4.4, –1.9/–2.1, –0.9) *p*<.001	Total mortality, n (rate per 1000 p-y) Drug: 259 (27.9) Control: 266 (29.0) RR (95% CI): NR *p*=NS	All MI, n (rate per 1000 p-y) Drug: 70 (7.6) Control: 63 (6.9) RR (95% CI): NR *p*=NS Nonfatal MI, n (rate per 1000 p-y) Drug: 54 (5.9) Control: 47 (5.2) RR (95% CI): NR *p*=NS Fatal MI, n (rate per 1000 p-y) Drug: 18 (1.9) Control: 18 (2.0) RR (95% CI): NR *p*=NS	All stroke, n (rate per 1000 p-y) Drug: 89 (9.7) Control: 115 (12.8) RR (95% CI): 23.6 (–0.7, 42.1) *p*=.056 Nonfatal stroke, n (rate per 1000 p-y) Drug: 68 (7.4) Control: 93 (10.3) RR (95% CI): 27.8 (1.3, 47.2) *p*=.04 Fatal stroke, n (rate per 1000 p-y) Drug: 24 (2.6) Control: 26 (2.8) RR (95% CI) *p*=NS		PRIMARY OUTCOME: Major CV events, n (rate per 1000 p-y) Drug: 242 (26.7) Control: 268 (30.0) RR (95% CI): 10.9 (–6.0, 25.1) *p*=.19 CV deaths, n (rate per 1000 p-y) Drug: 145 (15.6) Control: 152 (16.6) RR (95% CI): NR *p*=NS
STOP – Hyper-tension Dahlöf et al., 1991[69]	1,627	Mean 25 months	Fair	Drug: Treatment initiated with one of the following 4 drugs and maintained throughout the study: atenolol or metoprolol or pindolol or (HCTZ and amiloride); BP goal <160/95 mmHg Placebo: Placebo tablet; BP goal <160/95 mmHg	Adults 70–84 years with untreated or treated essential HTN (SBP 180–230 mmHg and DBP ≥90 mmHg, or DBP 105–120 mmHg irrespective of SBP during run-in) Mean SBP: 195 mmHg Mean DBP: 102 mmHg	At 4 years Achieved BP, mmHg (SD): Drug: 166/85 (21/10) Placebo: 193/95 (20/11) *p*=NR Reduction in BP, mmHg Drug: 29/17 Placebo: 2/7 *p*=NR BP difference between groups, mmHg 27/10 *p*=NR	Total deaths, number (per 1000 py) Drug: 36 (20.2) Placebo: 63 (35.4) RR (95% CI): 0.57 (0.37, 0.87) *p*=.0079	All MI, number (per 1000 py) Drug: 25 (14.4) Placebo: 28 (16.5) RR (95% CI): 0.87 (0.49, 1.56) *p*=NR Fatal MI, number (per 1000 py) Drug: 6 (3.5) Placebo: 6 (3.5) RR (95% CI): 0.98 (0.26, 3.66) *p*=NR	All stroke, number (per 1000 py) Drug: 29 (16.8) Placebo: 53 (31.3) RR (95% CI): 0.53 (0.33, 0.86) *p*=.0081 Fatal stroke, number (per 1000 py) Drug: 3 (1.7) Placebo: 12 (7.1) RR (95% CI): 0.24 (0.04, 0.91) *p*=NR	CHF, number Drug: 19 Placebo: 39 RR (95% CI): NR *p*=NR	PRIMARY OUTCOME: Composite: stroke, MI and other CV deaths, number (per 1000 py) Drug: 58 (33.5) Placebo: 94 (55.5) RR (95% CI): 0.60 (0.43, 0.85) *p*=.0031

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/ Primary Composite Outcomes
Coope and Warrender Coope J, Warrender TS, 1986[90]	884	Mean 4.4 years	Good	Drug: atenolol plus bendrofluazide plus alpha-methyldopa; BP goal not explicitly stated, however additional therapy added if at the end of 3 months SBP >170 mmHg, or DBP >105 mmHg Control: Observation only; no placebo tablets given; BP goal not explicitly stated	Adults, 60–79 years, with HTN (SBP ≥170 or DBP ≥105) Mean SBP, mmHg: Drug: 196.2 Control: 196.1 Mean DBP, mmHg: Drug: 99.7 Control: 98.0	Mean 4.4 years Achieved BP: NR Reduction in BP, mmHg Drug: NR Control: 16/10 *p*=NR BP difference between groups, mmHg 18/11 *p*=NR	All deaths, events per 1000 py (number of events) Drug: 32.5 (60) Control: 33.6 (69) Rate of Treatment/Rate of Control (95% CI): 0.97 (0.70, 1.42) *p*=NS (value NR)	PRIMARY OUTCOME: All coronary attacks, events per 1000 py (number of events) Drug: 19.0 (35) Control: 18.5 (38) Rate of Treatment/Rate of Control (95% CI): 1.03 (0.63, 1.63) *p*=NS (value NR) Fatal coronary attacks, events per 1000 py (number of events) Drug: 13.6 (25) Control: 13.6 (28) Rate of Treatment/Rate of Control (95% CI): 1.00 (0.58, 1.71) *p*=NS (value NR) Nonfatal coronary attacks, events per 1000 py (number of events) Drug: 5.4 (10) Control: 4.9 (10) Rate of Treatment/Rate of Control (95% CI): 1.11 (0.46, 2.68) *p*=NS (value NR)	PRIMARY OUTCOME: All stroke, events per 1000 py (number of events) Drug: 12.5 (23) Control: 21.4 (44) Rate of Treatment/Rate of Control (95% CI): 0.58 (0.35, 0.96) *p*<.03 Fatal stroke, events per 1000 py (number of events) Drug: 2.2 (4) Control: 7.3 (15) Rate of Treatment/Rate of Control (95% CI): 0.30 (0.11, 0.84) *p*<.025 TIA, events per 1000 py (number of events) Drug: 1.6 (3) Control: 2.4 (5) Rate of Treatment/Rate of Control (95% CI): 0.67 (0.16, 2.77) *p*=NS (value NR)	Nonfatal ventricular failure, events per 1000 py (number of events) Drug: 9.8 (18) Control: 15.6 (32) Rate of Treatment/Rate of Control (95% CI): 0.63 (0.35, 1.11) *p*=NS (value NR) Fatal ventricular failure, events per 1000 py (number of events) Drug: 2.2 (4) Control: 1.9 (4) Rate of Treatment/ Rate of Control (95% CI): 1.11 (0.28, 4.45) *p*=NS (value NR)	CV death, events per 1000 py (number of events) Drug: 19.0 (35) Control: 24.3 (50) Rate of Treatment/Rate of Control (95% CI): 0.78 (0.51, 1.20) *p*=NS (value NR)

Table D–2i. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to SBP Goals in Patients With Diabetes

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes	Kidney Outcomes
ACCORD ACCORD Study Group, 2010[11]	4,733	Mean 4.7 years	Good	Intensive: SBP goal <120 mmHg Standard: SBP goal <140 mmHg	Adults with type 2 diabetes and glycated hemoglobin ≥7.5% and SBP 130–180 mmHg taking ≤3 anti-HTN meds and 24hr protein excretion rate <1.0 g; age ≥40 years with CVD or ≥55 years with anatomical evidence of atherosclerosis, albuminuria, LVH, or ≥2 additional risk factors for CVD (dyslipidemia, HTN, smoking, or obesity) Mean SBP: 139 mmHg Mean DBP: 76 mmHg	At 1 year to end of study Average BP, mmHg (95% CI) Intensive: 119.3/64.4 (118.9,119.7/64.1, 64.7) Standard: 133.5/70.5 (133.1,133.8/70.2, 70.8) *p*=NR Average between group BP difference, mmHg (95% CI) 14.2/6.1 (13.7, 14.7/5.7, 6.5) *p*=NR	Death from any cause, n events (% per year) Intensive: 150 (1.28) Standard: 144 (1.19) HR (95% CI): 1.07 (0.85, 1.35) *p*=.55	Nonfatal MI, n events (% per year) Intensive: 126 (1.13) Standard: 146 (1.28) HR (95% CI): 0.87 (0.68, 1.10) *p*=.25 Major coronary disease event, n events (% per year) Intensive: 253 (2.31) Standard: 270 (2.41) HR (95% CI): 0.94 (0.79, 1.12) *p*=.50	Any stroke, n events (% per year) Intensive: 36 (0.32) Standard: 62 (0.53) HR (95% CI): 0.59 (0.39, 0.89) *p*=.01 Nonfatal stroke, n of events (% per year) Intensive: 34 (0.30) Standard: 55 (0.47) HR (95% CI): 0.63 (0.41, 0.96) *p*=.03	Fatal or nonfatal HF, n of events (% per year) Intensive: 83 (0.73) Standard: 90 (0.78) HR (95% CI): 0.94 (0.70, 1.26) *p*=.67	PRIMARY OUTCOME: First occurrence of a major CV event (composite of nonfatal MI, nonfatal stroke, or CV death), n of events (% per year) Intensive: 208 (1.87) Standard: 237 (2.09) HR (95% CI): 0.88 (0.73, 1.06) *p*=.20 Primary outcome plus revascularization or nonfatal HF, n of events (% per year) Intensive: 521 (5.10) Standard: 551 (5.31) HR (95% CI): 0.95 (0.84, 1.07) *p*=.40 Death from CV cause, n of events (% per year) Intensive: 60 (0.52) Standard: 58 (0.49) HR (95% CI): 1.06 (0.74, 1.52) *p*=.74	Renal failure, n (%) Intensive: 5 (0.2) Standard: 1 (0.04) *p*=.12 ESRD or need dialysis, n (%) Intensive: 59 (2.5) Standard: 58 (2.4) *p*=.93 Note: both outcomes reported as AE

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes	Kidney Outcomes
SHEP, 1996 Curb et al., 1996[48]	583 with diabetes at baseline	Mean 4.5 years	Fair (primary SHEP paper rated as Good)	Drug: Stepped chlorthalidone; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg Placebo: Placebo tablet; SBP goal for individuals with SBP of >180 mmHg was <160; SBP goal for those with SBP 160–179 was reduction of at least 20 mmHg	Adults, ages ≥60 years, with isolated systolic HTN (SBP 160–219 and DBP <90 mmHg) For diabetes subpopulation, mean SBP, mmHg: Drug: 170.2 Placebo: 170.2 For diabetes subpopulation, mean DBP, mmHg in diabetes subpopulation: Drug: 76.9 Placebo:74.8	During follow-up For diabetes subpopulation, achieved BP: NR For diabetes subpopulation, BP difference between groups, mmHg: 9.8/2.2 *p*=NR	All-cause mortality, n of events (5-year rate per 100) Drug: 39 (17.5) Placebo: 48 (17.8) RR (95% CI): 0.74 (0.46, 1.18) *p*=NR	Nonfatal MI and fatal CHD, n of events (5-year rate per 100) Drug: 18 (7.7) Placebo: 34 (13.1) RR (95% CI): 0.46 (0.24, 0.88) *p*=NR Major CHD events, n of events (5-year rate per 100) Drug: 23 (9.2) Placebo: 44 (16.1) RR (95% CI): 0.44 (0.25, 0.77) *p*=NR	PRIMARY OUTCOME: Nonfatal and fatal strokes, n of events (5-year rate per 100) Drug: 25 (9.7) Placebo: 36 (14.4) RR (95% CI): 0.78 (0.45, 1.34) *p*=NR		Major CVD events, n of events (5-year rate per 100) Drug: 57 (21.4) Placebo: 83 (31.5) RR (95% CI): 0.66 (0.46, 0.94) *p*=NR	

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes	Kidney Outcomes
Syst-Eur, 1999 Tuomilehto et al., 1999[49]	492 with diabetes at baseline	Median 2 years	Fair (primary SHEP paper rated as Good)	Drug: Nitrendipine and/or enalapril, HCTZ; SBP goal <150 and decrease SBP by ≥20 mmHg Placebo: Placebo tablet; SBP goal <150 and decrease SBP by ≥20 mmHg	Adults, ages ≥ 60 years, with HTN (SBP 160–219 mmHg and DBP <95 mmHg) For diabetes subpopulation, mean SBP: 175.3 mmHg For diabetes subpopulation, mean DBP: 84.5 mmHg	At 2 years Achieved BP: NR For diabetes subpopulation, mean fall in BP, mmHg (SD): Drug: 22.1/6.8 (14.5/8.2) Placebo: 13.5/2.9 (16.5/7.8) *p*=NR For diabetes subpopulation, BP difference between groups, mmHg: 8.6/3.9 *p*=NR	Overall mortality, n of events (endpoints per 1000 p-y) Drug: 26.4 (16) Placebo: 45.1 (26) Benefit of treatment (95% CI): 41 (–9, 69) *p*=.09 *p* for interaction between treatment and diabetes: 0.04	Fatal and nonfatal cardiac events, n of events (endpoints per 1000 p-y) Drug: 11.7 (7) Placebo: 27.1 (15) Benefit of treatment (95% CI): 57 (–6, 82) *p*=.06 *p* for interaction between treatment and diabetes: 0.12	PRIMARY OUTCOME: Fatal and nonfatal stroke, n of events (endpoints per 1000 p-y) Drug: 8.3 (5) Placebo: 26.6 (15) Benefit of treatment (95% CI): 69 (14, 89) *p*=.02 *p* for interaction between treatment and diabetes: 0.13		All CV endpoints, fatal and nonfatal, n of events (endpoints per 1000 p-y) Drug: 22.0 (13) Placebo: 57.6 (31) Benefit of treatment (95% CI): 62 (19, 80) *p*=.002 *p* for interaction between treatment and diabetes: 0.01 CV mortality, n of events (endpoints per 1000 p-y) Drug: 8.3 (5) Placebo: 27.8 (16) Benefit of treatment (95% CI): 70 (19, 89) *p*=.01 *p* for interaction between treatment and diabetes: 0.02	

Table D–2j. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to DBP Goals in Patients With Diabetes

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes	Kidney Outcomes
ABCD – HTN Cohort Estacio et al., 2000[12]	470	Mean 5.3 years	Fair	Intensive: Goal DBP 75 mmHg Moderate: Goal DBP 80–89 mmHg	Adults, ages 40–74 with HTN (DBP ≥90 mmHg) and Type 2 diabetes Mean SBP, mmHg (SD): Intensive: 156 (16.1) Moderate: 154 (16.9) Mean DBP, mmHg: Intensive: 98 (6.4) Moderate: 98 (6.4)	Average for last 4 years of follow-up Average BP, mmHg: Intensive: 132/78 Moderate: 138/86 Average BP change, mmHg: Intensive: –24/–20 Moderate: –16/–12 BP difference between groups, mmHg: 8/8 *p*<.001	All-cause mortality, % Intensive: 5.5 Moderate: 10.7 *p*=.037					
ABCD – Normotensive Cohort Schrier et al., 2002[92]	480	Mean 5.3 years	Good	Intensive: Goal DBP 10 mmHg below baseline Moderate: Goal DBP 80-89 mmHg	Adults, ages 40–74, normotensive (DBP 80–89 mmHg), with Type 2 Diabetes Mean SBP, mmHg (SE): Intensive: 135.6 (0.8) Moderate: 137.2 (0.9) Mean DBP, mmHg (SE): Intensive: 84.4 (0.2) Moderate: 84.4 (0.2)	Average for last 4 years of follow-up Mean BP, mmHg (SE) Intensive: 128/75 (0.8/0.3) Moderate: 137/81 (0.7/0.3) *p*<.0001 BP change, mmHg Intensive: –7.6/–9.4 Moderate: –0.2/–3.4 BP difference between groups, mmHg: 7.4/6 *p*=NR	Death, n (%) Intensive: 18 (7.6) Moderate: 20 (8.2) OR (95% CI): 1.1 (0.56, 2.12) *p*=.80	MI, n (%) Intensive: 19 (8.0) Moderate: 15 (6.2) OR (95% CI): 0.75 (0.37, 1.52) *p*=.43	CVA, n (%) Intensive: 4 (1.7) Moderate: 13 (5.4) OR (95% CI): 3.29 (1.06, 10.25) *p*=.03	CHF, n (%) Intensive: 12 (5.1) Moderate: 11 (4.5) OR (95% CI): 0.89 (0.38, 2.06) *p*=.78		CV death, n (%) Intensive: 13 (5.4) Moderate: 9 (3.7) OR (95% CI): 0.66 (0.28, 1.58) *p*=.35

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes	Kidney Outcomes
HOT Hansson et al., 1998[44]	1501 with diabetes at baseline	Mean 3.8 years for overall population	Fair	≤80: DBP goal ≤80 mmHg ≤85: DBP goal ≤85 mmHg ≤90: DBP goal ≤90 mmHg	Adults, ages 50–80, with HTN (DBP 100–115) For diabetes subpopulation, mean BP at baseline NR For overall population, mean SBP: 170 mmHg For overall population, mean DBP: 105 mmHg	For diabetes subpopulation, achieved BP, mmHg: NR For diabetes subpopulation, BP decrease from baseline, mmHg: NR For diabetes subpopulation, mean between group difference in achieved BP, mmHg: NR	Total mortality, n (events per 1000 p-y) ≤80: 17 (9.0) ≤85: 29 (15.5) ≤90: 30 (15.9) *p* for trend: .068 RR (95% CI): ≤90 vs. ≤85: 1.03 (0.62, 1.71) ≤85 vs. ≤80: 1.72 (0.95, 3.14) ≤90 vs. ≤80: 1.77 (0.98, 3.21)	All MI, n (events per 1000 p-y) ≤80: 7 (3.7) ≤85: 8 (4.3) ≤90: 14 (7.5) *p* for trend: .11 RR (95% CI): ≤90 vs. ≤85: 1.75 (0.73, 4.17) ≤85 vs. ≤80: 1.14 (0.41, 3.15) ≤90 vs. ≤80: 2.01 (0.81, 4.97) All MI including silent cases, n (events per 1000 p-y) ≤80: 15 (8.1) ≤85: 16 (8.7) ≤90: 18 (9.7) *p* for trend: .61 RR (95% CI): ≤90 vs. ≤85: 1.12 (0.57, 2.19) ≤85 vs. ≤80: 1.07 (0.53, 2.16) ≤90 vs. ≤80: 1.20 (0.60, 2.38)	All stroke, n (events per 1000 p-y) ≤80: 12 (6.4) ≤85: 13 (7.0) ≤90: 17 (9.1) *p* for trend: .34 RR (95% CI): ≤90 vs. ≤85: 1.30 (0.63, 2.67) ≤85 vs. ≤80: 1.10 (0.50, 2.40) ≤90 vs. ≤80: 1.43 (0.68, 2.99)		PRIMARY OUTCOME: Major CV events (fatal and nonfatal MI, fatal and nonfatal stroke, all other CV death), n (events per 1000 p-y) ≤80: 22 (11.9) ≤85: 34 (18.6) ≤90: 45 (24.4) *p* for trend: .005 RR (95% CI): ≤90 vs. ≤85: 1.32 (0.84, 2.06) ≤85 vs. ≤80: 1.56 (0.91, 2.67) ≤90 vs. ≤80: 2.06 (1.24, 3.44) Major CV events including silent MI, n (events per 1000 p-y) ≤80: 30 (16.4) ≤85: 42 (23.3) ≤90: 48 (26.2) *p* for trend: .045 RR (95% CI): ≤90 vs. ≤85: 1.13 (0.75, 1.71) ≤85 vs. ≤80: 1.42 (0.89, 2.26) ≤90 vs. ≤80: 1.60 (1.02, 2.35) CV mortality, n (events per 1000 p-y) ≤80: 7 (3.7) ≤85: 21 (11.2) ≤90: 21 (11.1) *p* for trend: .016 RR (95% CI): ≤90 vs. ≤85: 0.99 (0.54, 1.82) ≤85 vs. ≤80: 3.0 (1.29, 7.13) ≤90 vs. ≤80: 3.0 (1.28, 7.08)	

Table D–2k. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to Mixed BP Goals in Patients With Diabetes

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composite Outcomes	Kidney Outcomes
Hypertension in Diabetes Study (UKPDS) UK Prospective Diabetes Study Group, 1998[9]	1148	Mean 8.4 years	Fair	Tight: Goal BP <150/85 mmHg Less tight: Goal BP <180/105 mmHg	Adults, ages 25–65, with newly diagnosed diabetes, HTN (BP ≥150/85 if already taking anti-hypertensives; ≥160/90 if not), and fasting plasma glucose >6 mmol/l Mean SPB: 160 mmHg Mean DBP: 94 mmHg	At 9 years Mean BP, mmHg (SD) Tight: 144/82 (14/7) Less tight: 154/87 (16/7) *p*<.0001 Change in BP, mmHg Tight: –15/–12 Less tight: –6/–7 BP difference between groups (95% CI), mmHg: 10 (9, 12)/5 (4, 6) *p*=NR	PRIMARY OUTCOME: All-cause mortality, n of events (rate per 1000 p-y) Tight: 134 (22.4) Less tight: 83 (27.2) RR (95% CI): 0.82 (0.62, 1.08) *p*=.17	MI, n of events (rate per 1000 p-y) Tight: 107 (18.6) Less tight: 69 (23.5) RR (95% CI): 0.79 (0.59, 1.07) *p*=.13 Sudden death*, n of events (rate per 1000 p-y) Tight: 11 (1.8) Less tight: 4 (1.3) RR (95% CI): 1.39 (0.31, 6.26) *p*=.57 *Subjects attaining individual endpoints during F/U	Stroke, n of events (rate per 1000 py) Tight: 38 (6.5) Less tight: 34 (11.6) RR (95% CI): 0.56 (0.35, 0.89) *p*=.013	Heart Failure*, n of events (rate per 1000 py) Tight: 21 (3.6) Less tight: 24 (8.1) RR (95% CI): 0.44 (0.20, 0.94) *p*=.0043 *Subjects attaining individual endpoints during F/U	PRIMARY OUTCOME: Any diabetes related endpoint, n of events (rate per 1000 p-y) Tight: 259 (50.9) Less tight: 170 (67.4) RR (95% CI): 0.76 (0.62, 0.92) *p*=.0046 PRIMARY OUTCOME: Deaths related to diabetes, n of events (rate per 1000 p-y) Tight: 82 (13.7) Less tight: 62 (20.3) RR (95% CI): 0.68 (0.49, 0.94) *p*=.019	Renal failure*, n of events (rate per 1000 p-y) Tight: 8 (1.4) Less tight: 7 (2.3) RR (95% CI): 0.58 (0.15, 2.21) *p*=.29 Death from renal failure*, n of events (rate per 1000 p-y) Tight: 2 (0.3) Less tight: 3 (1.0) RR (95% CI): 0.35 (0.03, 3.66) *p*=.23 *Subjects attaining individual endpoints during F/U

Table D–2l. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to Mixed BP Goals in Patients With Chronic Kidney Disease

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
REIN-2 Ruggenenti et al., 2005[14]	335	Median 19 months	Fair	Intensive: BP goal <130/80 mmHg Conventional: DBP goal <90 mmHg, irrespective of SBP	Adults, age 18–70, with nondiabetic nephropathy, persistent proteinuria (urinary protein excretion > 1 g/24 h for ≥3 months) and not on ACEI in previous 6 weeks Patients with proteinuria 1–3 g/24 h included if CrCl <70 mL/min/1 73 meters^2 Mean SBP, mmHg (SD): Intensive: 137.0 (16.7) Conventional: 136.4 (17.0) Mean DBP, mmHg (SD): Intensive: 84.3 (9.0) Conventional: 83.9 (10.4)	Achieved BP, mmHg (SD) Intensive: 129.6/79.5 (10.9/5.3) Conventional: 133.7/82.3 (12.6/7.1) *p*=.0019/<0.0001 Change in BP, mmHg Intensive: –7.4/–4.8 Conventional: –2.7/–1.6 *p*=NR BP difference between groups, mmHg 4.1/2.8 *p*=NR						PRIMARY OUTCOME: ESRD, n (%) Intensive: 38 (23) Conventional: 34 (20) HR (95% CI): 1.00 (0.61, 1.64) *p*=.99 Median rate of GFR decline, ml/min/1.73 meters^2/month (IQR): Intensive: 0.22 (0.06, 0.55) Conventional: 0.24 (0.0001, 0.56) *p*=.62

Table D–2m. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy MAP Goals in Patients With Chronic Kidney Disease

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
AASK Wright et al., 2002[13]	1,094	3 to 6.4 years	Good	Low: MAP goal ≤92 mmHg Usual: MAP goal 102–107 mmHg	Adult African-Americans, ages 18–70, with HTN (DBP ≥95) and GFR of 20–65 ml/min/1.73 meters^2, no diabetes Mean MAP, mmHg: Low: 115 (27) Usual: 113 (15) Mean SBP, mmHg (SD): Low:152 (25) Usual: 149 (23) Mean DBP, mmHg: Low: 96 (15) Usual: 95 (14)	Mean from 3 months to study end MAP, mmHg (SD) Low: 95.8 (8) Usual: 104 (7) SBP/DBP, mmHg (SD) Low: 128/78 (12/8) Usual: 141/85 (12/7) MAP change, mmHg Low: –20 Usual: –9 SBP/DBP change, mmHg Low: –24/–8 Usual: –18/–10 Achieved mean BP difference between groups, mmHg MAP: 11 SBP: 16 DBP: 8							GFR event, ESRD, or death, % Risk Reduction (95% CI): 2 (–22, 21) *p*=.85 GFR event or ESRD, % Risk Reduction (95% CI): –2 (–31, 20) *p*=.87 ESRD or death, % Risk Reduction (95% CI): 12 (–13, 32) *p*=.31 ESRD alone, % Risk Reduction (95% CI): 6 (–29, 31) *p*=.72 PRIMARY OUTCOME: Difference in mean slopes, acute GFR slope, ml/min/1.73 meters^2/3 months (SE): –1.82 (0.54) *p*<.001 PRIMARY OUTCOME: Difference in mean slopes, chronic GFR slope, ml/min/1.73 meters^2/year (SE): 0.21 (0.22) *p*=.33 Difference in mean slopes, total GFR slope, ml/min/1.73 meters^2/year (SE): –0.25 (0.22) *p*=.24

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
AASK - subsequent article (analysis by first line drug) Contreras et al., 2005[45]	1,094	3 to 6.4 years	Fair	Low, Amlodipine: MAP goal ≤92 mmHg, Amlodipine (5–10 mg/day) Usual, Amlodipine: MAP goal 102–107 mmHg, Amlodipine (5–10 mg/day) Low, Metoprolol: MAP goal ≤92 mmHg, Metoprolol (50–200 mg/day) Usual, Metoprolol: MAP goal 102–107 mmHg, Metoprolol (50–200 mg/day) Low, Ramipril: MAP goal ≤92 mmHg, Ramipril (2.5–10 mg/day) Usual, Ramipril: MAP goal 102–107 mmHg, Ramipril (2.5–10 mg/day) Note: Amlodipine arms terminated one year early	Adult African-Americans, ages 18–70, with HTN (DBP ≥95) and GFR of 20–65 ml/min/1.73 meters^2, no diabetes Mean MAP, mmHg: Low, Amlodipine: 115.3 (18.3) Usual, Amlodipine: 112.7 (14.7) Low, Metoprolol: 114.5 (17.5) Usual, Metoprolol: 112.4 (14.1) Low, Ramipril: 115.2 (15.2) Usual, Ramipril: 114.0 (16.7) Mean SBP, mmHg: Low, Amlodipine: 152.2 (28.2) Usual, Amlodipine: 147.7 (21.9) Low, Metoprolol: 152.0 (25.7) Usual, Metoprolol: 147.7 (21.4) Low, Ramipril: 151.0 (22.5) Usual, Ramipril: 150.9 (24.1) Mean DBP, mmHg: Low, Amlodipine:96.55 (15.1) Usual, Amlodipine: 94.87 (12.9) Low, Metoprolol: 95.45 (15.4) Usual, Metoprolol: 94.47 (12.5) Low, Ramipril: 96.90 (13.6) Usual, Ramipril: 95.12 (15.3)	Achieved MAP difference between groups, mmHg Amlodipine, Low vs. Usual:12.89 Metoprolol, Low vs. Usual: 11.11 Ramipril, Low vs. Usual: 10.12 *p*=NR Achieved SBP difference between groups, mmHg Amlodipine, Low vs. Usual: 18.4 Metoprolol, Low vs. Usual: 15.4 Ramipril, Low vs. Usual: 12.6 *p*=NR Achieved DBP difference between groups, mmHg Amlodipine, Low vs. Usual: 10.14 Metoprolol, Low vs. Usual: 8.86 Ramipril, Low vs. Usual: 8.96 *p*=NR	Death alone (prior to dialysis), Amlodipine, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 48% (–59, 83) *p*=.25 Metoprolol, Low vs. Usual Goal: Relative Risk Reduction (95% CI): –1 (–110, 5) *p*=.97 Ramipril, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 21% (–92, 67) *p*=.61 *p* for interaction = 0.61						GFR event, ESRD, or death prior to dialysis, Amlodipine, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 32% (–14, 60) *p*=.14 Metoprolol, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 4% (–39, 33) *p*=.84 Ramipril, Low vs. Usual Goal: Relative Risk Reduction (95% CI): –28% (–93, 15) *p*=.24 *p* for interaction = .17 GFR event or ESRD, Amlodipine, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 26% (–33, 58) *p*=.32 Metoprolol, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 7% (–42, 39) *p*=.74 Ramipril, Low vs. Usual Goal: Relative Risk Reduction (95% CI): –42% (–126, 11) *p*=.14 *p* for interaction = .20 ESRD or death prior to dialysis, Amlodipine, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 51% (13, 73) *p*=.016 Metoprolol, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 11% (–40, 44) *p*=.61 Ramipril, Low vs. Usual Goal: Relative Risk Reduction (95% CI): –32% (–114, 18) *p*=.26 *p* for interaction = .035 ESRD alone, Amlodipine, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 54% (8, 77) *p*=.028 Metoprolol, Low vs. Usual Goal: Relative Risk Reduction (95% CI): 11% (–60, 50) *p*=.70 Ramipril, Low vs. Usual Goal: Relative Risk Reduction (95% CI): –65% (–195, 8) *p*=.09 *p* for interaction =.021

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
AASK – subsequent article (Analysis of CV outcomes) Norris et al., 2006[46]	1,094	Mean 4.1 years	Fair	Low: MAP goal ≤92 mmHg Usual: MAP goal 102–107 mmHg	Adult African-Americans, ages 18–70, with HTN (DBP ≥95) and GFR of 20–65 ml/min/1.73 meters^2, no diabetes Mean MAP, mmHg: 114 (16) Mean SBP, mmHg: 150 (24) Mean DBP mmHg: 96 (14)	SBP/DBP, mmHg (SD) Low: 128/78 Usual: 141/85 *p*=NR SBP/DBP change, mmHg Low: –23/–19 Usual: –8/–9 *p*=NR Achieved mean BP difference between groups, mmHge SBP: 15 DBP: 10 *p*=NR	Number of deaths before ESRD, n of events Low: 38 Usual: 47 *p*=NR	Major CAD events, n of events (rate per py) Low: 19 (0.008) Usual: 23 (0.010) *p*=NS	Stroke events, n of events (rate per py) Low: 26 (0.011) Usual: 29 (0.013) *p*=NS	HF events, n of events (rate per py) Low: 27 (0.012) Usual: 23 (0.010) *p*=NS	CV composite outcome, n of events (rate per py) Low: 71 (0.032) Usual: 78 (0.035) *p*=NS Composite outcome or ESRD, n of events (rate per py) Low: 143 (0.064) Usual: 159 (0.072) *p*=NS Overall rate of CV events, n of events (rate per py) Low: 108 (0.048) Usual: 94 (0.042) *p*=NS CV death, n of events (rate per py) Low: 16 (0.007) Usual: 15 (0.006) *p*=NS	

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
MDRD Klahr et al., 1994[15]	840	Mean 2.2 years	Fair	Low: MAP goal ≤92 mmHg for those 18–60 years of age; ≤98 for those ≥61 years of age Usual: MAP goal ≤107 mmHg for those 18–60; MAP ≤113 for subjects ≥61 Two studies: Study 1: above BP goals plus usual or low protein diet (1.3 or 0.58 g protein per kg of body weight per day) Study 2: above BP goals plus low or very low protein diet (0.58 or 0.28 g per kg per day)	Adults, ages18–70, with renal insufficiency (serum Cr 1.2–7.0 mg/dL in women and 1.4–7.0 mg/dL in men or CrCl <70 ml/min per 1.73 m²) and MAP <=125 mmHg (normotensives included) Study 1 included subjects with GFR 25–55 ml/min 1.73 m² (n=585); Study 2 included subjects with GFR 13–24 ml/min 1.73 m² (n=255) Mean MAP, mmHg (SD): Study 1: 98 (11) Study 2: 98 (11) Mean SBP, mmHg (SD): Study 1: 131 (18) Study 2: 133 (18) Mean DBP, mmHg (SD): Study 1: 81 (10) Study 2: 81 (10)	Between group difference in MAP, mmHg 4.7 *p*<.001						Study 2 ESRD or death, Relative Risk (95% CI) for Low vs. Usual: 0.85 (0.60, 1.22) *p*=NR PRIMARY OUTCOME: Study 1 Rate of decline in GFR, ml/min (95% CI) From baseline to 4 months, Low: 3.4 (2.6, 4.1) Usual: 1.9 (1.1, 2.7) *p*=.010 4 months to study end, Low: 2.8 (2.2, 3.3) Usual: 3.9 (3.3, 4.5) *p*=.006 Baseline to 3 years, Low: 10.7 (9.1, 12.4) Usual: 12.3 (10.6, 14.0) *p*=.18 PRIMARY OUTCOME: Study 2 Rate of decline in GFR, ml/min (95% CI) From baseline to end of study, Low: 3.7 (3.1, 4.3) Usual: 4.2 (3.6, 4.9) *p*=.28

Table D–2n. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to Mixed BP Goals in Patients With Chronic Kidney Disease, Analyzed by Baseline Proteinuria Subgroups

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerebrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
REIN-2 Ruggenenti et al., 2005[14]	335	Median 19 months	Fair	Intensive: BP goal <130/80 mmHg Conventional: DBP goal <90 mmHg, irrespective of SBP	Adults, age 18–70, with nondiabetic nephropathy, persistent proteinuria (urinary protein excretion > 1 g/24 h for ≥3 months) and not on ACEI in previous 6 weeks Patients with proteinuria 1–3 g/24 h included if CrCl <70 mL/min/1 73 meters^2 For baseline proteinuria subgroups, mean BP at baseline NR For overall population, mean SBP, mmHg (SD): Intensive: 137.0 (16.7) Conventional: 136.4 (17.0) For overall population, mean DBP, mmHg (SD): Intensive: 84.3 (9.0) Conventional: 83.9 (10.4)	For baseline proteinuria subgroups, result BP values NR For the overall population, achieved BP, mmHg (SD) Intensive: 129.6/79.5 (10.9/5.3) Conventional: 133.7/82.3 (12.6/7.1) *p*=.0019/<.0001 For the overall population, change in BP, mmHg Intensive: –7.4/–4.8 Conventional: –2.7/–1.6 *p*=NR For the overall population, BP difference between groups, mmHg 4.1/2.8 *p*=NR						PRIMARY OUTCOME: ESRD in patients with baseline proteinuria 1–3 g/24 h HR (95% CI): 1.06 (0.51, 2.20) *p*=.89 ESRD in patients with baseline proteinuria >3 g/24 h HR (95% CI): 1.09 (0.55, 2.19) *p*=.81 Median rate of GFR decline, ml/min/1.73 meters^2/month (IQR) in patients with baseline proteinuria <3 g/24: Intensive: 0.18 (0.03, 0.49) Conventional: 0.21 (–0.03, 0.40) *p*=.89 Median rate of GFR decline, ml/min/1.73 meters^2/month (IQR) in patients with baseline proteinuria ≥3 g/24: Intensive: 0.51 (0.16, 1.05) Conventional: 0.39 (0.03, 0.98) *p*=.39

Table D–2o. Evidence From Randomized Controlled Trials on Treatment With Antihypertensive Pharmacological Therapy to MAP Goals in Patients With Chronic Kidney Disease, Analyzed by Baseline Proteinuria Subgroups

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerbrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
AASK Wright et al., 2002[13]	1,094	3 to 6.4 years	Good	Low: MAP goal ≤92 mmHg Usual: MAP goal 102–107 mmHg	Adult African-Americans, ages 18–70, with HTN (DBP ≥95) and GFR of 20–65 ml/min/1.73 meters^2, no diabetes For baseline proteinuria subgroups, mean BP at baseline NR For overall population, mean MAP, mmHg: Low: 115 (27) Usual: 113 (15) For overall population, mean SBP, mmHg (SD): Low:152 (25) Usual: 149 (23) For overall population, mean DBP, mmHg: Low: 96 (15) Usual: 95 (14)	For baseline proteinuria subgroups, result BP values NR Mean from 3 months to study end For overall population, MAP, mmHg (SD) Low: 95.8 (8) Usual: 104 (7) For overall population, SBP/DBP, mmHg (SD) Low: 128/78 (12/8) Usual: 141/85 (12/7) For overall population, MAP change, mmHg Low: –20 Usual: –9 For overall population, SBP/DBP change, mmHg Low: –24/–8 Usual: –18/–10 For overall population, achieved mean BP difference between groups, mmHg MAP: 11 SBP: 16 DBP: 8						PRIMARY OUTCOME: Acute and chronic rate of change in GFR (slope): NS for chronic and total slope in subgroup analyses by baseline proteinuria strata[***] Acute slope: *p*=.08 for interaction Total slope: *p*=.04 for interaction Chronic slope: *p*=.16 for interaction Clinical composite outcome: includes reduction in GFR by 50% or by 25 ml/min/meters², ESRD, death, NS in subgroup analyses by baseline proteinuria strata *p*=.007 for interaction 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

[***] 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 ≤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.”

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerbrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
AASK - subsequent article (analysis by first line drug) Contreras et al., 2005[45]	1,094	3 to 6.4 years	Fair	Low, Amlodipine: MAP goal ≤92 mmHg, Amlodipine (5–10 mg/day) Usual, Amlodipine: MAP goal 102–107 mmHg, Amlodipine (5–10 mg/day) Low, Metoprolol: MAP goal ≤92 mmHg, Metoprolol (50–200 mg/day) Usual, Metoprolol: MAP goal 102–107 mmHg, Metoprolol (50–200 mg/day) Low, Ramipril: MAP goal ≤92 mmHg, Ramipril (2.5–10 mg/day) Usual, Ramipril: MAP goal 102–107 mmHg, Ramipril (2.5–10 mg/day) Note: Amlodipine arms terminated one year early	Adult African-Americans, ages 18–70, with HTN (DBP ≥95) and GFR of 20–65 ml/min/1.73 meters^2, no diabetes For baseline proteinuria subgroups, mean BP at baseline NR. Below data are for overall population. Mean MAP, mmHg: Low, Amlodipine: 115.3 (18.3) Usual, Amlodipine: 112.7 (14.7) Low, Metoprolol: 114.5 (17.5) Usual, Metoprolol: 112.4 (14.1) Low, Ramipril: 115.2 (15.2) Usual, Ramipril: 114.0 (16.7) Mean SBP, mmHg: Low, Amlodipine: 152.2 (28.2) Usual, Amlodipine: 147.7 (21.9) Low, Metoprolol: 152.0 (25.7) Usual, Metoprolol: 147.7 (21.4) Low, Ramipril: 151.0 (22.5) Usual, Ramipril: 150.9 (24.1) Mean DBP, mmHg: Low, Amlodipine:96.55 (15.1) Usual, Amlodipine: 94.87 (12.9) Low, Metoprolol: 95.45 (15.4) Usual, Metoprolol: 94.47 (12.5) Low, Ramipril: 96.90 (13.6) Usual, Ramipril: 95.12 (15.3)	For baseline proteinuria subgroups, achieved BP data NR. Below data are for overall population. Achieved MAP difference between groups, mmHg Amlodipine, Low vs. Usual:12.89 Metoprolol, Low vs. Usual: 11.11 Ramipril, Low vs. Usual: 10.12 *p*=NR Achieved SBP difference between groups, mmHg Amlodipine, Low vs. Usual: 18.4 Metoprolol, Low vs. Usual: 15.4 Ramipril, Low vs. Usual: 12.6 *p*=NR Achieved DBP difference between groups, mmHg Amlodipine, Low vs. Usual: 10.14 Metoprolol, Low vs. Usual: 8.86 Ramipril, Low vs. Usual: 8.96 *p*=NR						Within each drug group, risk reductions for any secondary clinical outcome of the low versus usual BP goal were not significantly different between patients with baseline UP/Cr ≤0.22 and >0.22 (*p*=NS)

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Achieved Blood Pressure	Overall Mortality	CHD Outcomes	Cerbrovascular Morbidity and Mortality	HF Outcomes	Cardiovascular Outcomes/Primary Composites	Kidney Outcomes
MDRD Klahr et al., 1994[15]	840	Mean 2.2 years	Fair	Low: MAP goal ≤92 mmHg for those 18–60 years of age; ≤98 for those ≥61 years of age Usual: MAP goal ≤107 mmHg for those 18–60; MAP ≤113 for subjects ≥61 Two studies: Study 1: above BP goals plus usual or low protein diet (1.3 or 0.58 g protein per kg of body weight per day) Study 2: above BP goals plus low or very low protein diet (0.58 or 0.28 g per kg per day)	Adults, ages18–70, with renal insufficiency (serum Cr 1.2–7.0 mg/dL in women and 1.4–7.0 mg/dL in men or CrCl <70 ml/min per 1.73 m²) and MAP <=125 mmHg (normotensives included) Study 1 included subjects with GFR 25–55 ml/min 1.73 m² (n=585); Study 2 included subjects with GFR 13–24 ml/min 1.73 m² (n=255) For baseline proteinuria subgroups, mean BP at baseline NR. Below data are for overall population. Mean MAP, mmHg (SD): Study 1: 98 (11) Study 2: 98 (11) Mean SBP, mmHg (SD): Study 1: 131 (18) Study 2: 133 (18) Mean DBP, mmHg (SD): Study 1: 81 (10) Study 2: 81 (10)	For baseline proteinuria subgroups, achieved BP data NR. Below data are for overall population. Between group difference in MAP, mmHg 4.7 *p*<.001						PRIMARY OUTCOME: Rate of decline in GFR, ml/min (95% CI) Study 1 *p* for interaction of BP goal and degree of baseline proteinuria: First 4 months: *p*=.006 Baseline to 3 years: *p*=.02 Benefit of low BP intervention greatest in 54 subjects with urinary protein excretion >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 <1 g/day (NS) Study 2 *p*=.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 >3 g/day; NS for other baseline proteinuria subgroups

Question 3 Summary Tables: Evidence from randomized controlled trials on antihypertensive pharmacological therapy with various antihypertensive drugs or drug classes

Note: Within each table, trials are organized in ascending dose order by drug name in alphabetical order.
Press the Control key and click the link to navigate to the desired table:

Table D–3a. Initial Treatment With Diuretics Versus Other Drugs

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
MRC Medical Research Council Working Party, 1985[35] Fair	17,354	5.5 years	Fair	BEN: Bendrofluazide: 10 mg QD PRO: Propranolol: 240 mg QD If BP not at satisfactory response, could supplement with methyldopa (note: originally only used to supplement bendrofluazide and guanethidine used to supplement propranolol, but later only methyldopa used for any primary drug)	Adults, ages 35–64 years, with mild to moderate HTN. SBP <200 mmHg and DBP 90–109 mmHg.	PRIMARY OUTCOME: All deaths, n (rate per 1000 py) BEN: 128 (6.0) PRO: 120 (5.5) % difference: BEN: –2; *p*=.71 vs. PRO PRO: 6; *p*=.71 vs. BEN	PRIMARY OUTCOME: Coronary events, n (rate per 1000 py) BEN: 119 (5.6) PRO: 103 (4.8) % difference: BEN: –2 PRO: 13 BEN vs. PRO: *p*=.24	PRIMARY OUTCOME: Strokes, n (rate per 1000 py) BEN: 18 (0.8) PRO: 42 (1.9) % difference: BEN: 67 PRO: 24; *p*=NR BEN vs. PRO: *p*=.002		PRIMARY OUTCOME: All CV events, n (rate per 1000 py) BEN: 140 (6.6) PRO: 146 (6.7) % difference: BEN: 20 PRO: 18 BEN vs. PRO: *p*=.76		Withdrawals due to AE, % BEN : 10 PRO: 6 % calculated by reviewer

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ALLHAT ALLHAT Collaborative Research Group, 2002;[5] Davis et al., 2006[65]	33,357	Mean 4.9 years	Good	CHL: Chlorthalidone: 12.5, 25 mg QD LIS: Lisinopril: 10, 20, and 40 mg QD AML: Amlodipine: 2.5, 5, and 10 mg QD Goal BP to be achieved by titration of assigned study drug (step 1) and when necessary addition of open-label agents at clinicians discretion (step 2: atenolol, reserpine, and clonidine or step 3: hydralazine) Note: randomization ratio was 1.7:1:1 (chlorthalidone: amlodipine: lisinopril) resulting in larger sample size in chlorthalidone group	Adults, ≥55 years of age with at least one additional risk factor for CHD. SBP ≥140 and/or DBP ≥90 mmHg or on medications for HTN.	All-cause mortality, n events (rate per 100 persons) CHL: 2,203 (17.3) LIS: 1,314 (17.2) AML: 1,256 (16.8) LIS vs. CHL: RR (95% CI): 1.00 (0.94, 1.08) *p*=.90 AML vs. CHL: RR (95% CI): 0.96 (0.89, 1.02) *p*=.20	PRIMARY OUTCOME: CHD (fatal CHD and nonfatal MI), n of events (rate per 100 persons) CHL: 1,362 (11.5) LIS: 796 (11.4) AML: 798 (11.3) LIS vs. CHL: RR (95% CI): 0.99 (0.91, 1.08) *p*=.81 AML vs. CHL: RR (95% CI): 0.98 (0.90, 1.07) *p*=.65 Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina) (rate per 100 events) CHL: 2,451 (19.9) LIS: 1,505 (20.8) AML: 1,466 (19.9) LIS vs. CHL: RR (95% CI): 1.05 (0.98, 1.11) *p*=.18 AML vs. CHL: RR (95% CI): 1.00 (0.94, 1.07) *p*=.97 Coronary revascularization, n of events (rate per 100 persons) CHL: 1,113 (9.2) LIS: 718 (10.2) AML: 725 (10.0) LIS vs. CHL: RR (95% CI): 1.10 (1.00, 1.21) *p*=.05 AML vs. CHL: RR (95% CI): 1.09 (1.00, 1.20) *p*=.06 Hospitalized or treated PAD, n of events (rate per 100 persons) CHL: 510 (4.1) LIS: 311 (4.7) AML: 265 (3.7) LIS vs. CHL: RR (95% CI): 1.04 (0.90, 1.19) *p*=.63 AML vs. CHL: RR (95% CI): 0.87 (0.75, 1.01) *p*=.06 MI death, n of events (rate per 100 persons) CHL: 296 (2.4) LIS: 157 (2.2) AML: 169 (2.3) RR (95% CI): NR LIS vs. CHL: *p*=.25 AML vs. CHL: *p*=.66 Definite CHD death, n of events (rate per 100 persons) CHL: 118 (1.1) LIS: 77 (1.0) AML: 72 (1.2) LIS vs. CHL: *p*=.52 AML vs. CHL: *p*=.88 Possible CHD death, n of events (rate per 100 persons) CHL: 128 (1.1) LIS: 95 (1.4) AML: 71 (1.1) RR (95% CI): NR LIS vs. CHL: *p*=.10 AML vs. CHL: *p*=.62	Stroke, n events (rate per 100 persons) CHL: 675 (5.6) LIS: 457 (6.3) AML: 377 (5.4) LIS vs. CHL: RR (95% CI): 1.15 (1.02, 1.30) *p*=.02 AML vs. CHL: RR (95% CI): 0.93 (0.82, 1.06) *p*=.28 Death from stroke, n events (rate per 100 persons) CHL: 162 (1.4) LIS: 121 (1.7) AML: 92 (1.4) RR (95% CI): NR LIS vs. CHL: *p*=.06 AML vs. CHL: *p*=.71	HF, n events (rate per 100 persons) CHL: 870 (7.7) LIS: 612 (8.7) AML: 706 (10.2) LIS vs. CHL: RR (95% CI): 1.19 (1.07, 1.31) *p*<.001 AML vs. CHL: RR (95% CI): 1.38 (1.25, 1.52) *p*<.001 Hospitalized/Fatal HF, n events (rate per 100 persons) CHL: 724 (6.5) LIS: 471 (6.9) AML: 578 (8.4) LIS vs. CHL: RR (95% CI): 1.10 (0.98, 1.23) *p*=.11 AML vs. CHL: RR (95% CI): 1.35 (1.21, 1.50) *p*<.001 HF death, n of events (rate per 100 persons) CHL: 114 (1.0) LIS: 68 (1.1) AML: 83 (1.4) RR (95% CI): NR LIS vs. CHL: *p*=.98 AML vs. CHL: *p*=.17	Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization), n events (rate per 100 events) CHL: 3,941 (30.9) LIS: 2,514 (33.3) AML: 2,432 (32.0) LIS vs. CHL: RR (95% CI): 1.10 (1.05, 1.16) *p*<.001 AML vs. CHL: RR (95% CI): 1.04 (0.99, 1.09) *p*=.12 Cardiovascular death, n events (rate per 100 persons) CHL: 992 (8.0) LIS: 618 (8.5) AML: 603 (8.5) RR (95% CI): NR LIS vs. CHL: *p*=.39 AML vs. CHL: *p*=.76 Other CVD death, n events (rate per 100 persons) CHL: 178 (1.4) LIS: 100 (1.5) AML: 116 (1.7) RR (95% CI): NR LIS vs. CHL: *p*=.66 AML vs. CHL *p*=.46	Kidney disease death, n of events (event rate per 100 persons) CHL: 36 (0.4) LIS: 27 (0.5) AML: 24 (0.5) RR (95% CI): NR LIS vs. CHL: *p*=.37 AML vs. CHL: *p*=.68 ESRD, n of events (event rate per 100 persons) CHL: 193 (1.8) LIS: 126 (2.0) AML: 129 (2.1) LIS vs. CHL: RR (95% CI): 1.11 (0.88, 1.38) *p*=.38 AML vs. CHL: RR (95% CI): 1.12 (0.89, 1.40) *p*=.33	Withdrawals due to AE, % CHL: 1.8 LIS: 2.9 AML: 2.0 % calculated by reviewer Angioedema, n events (%) CHL: 8 (0.1) LIS: 38 (0.4) AML: 3 (<0.1) LIS vs. CHL: *p*<.001 AML vs. CHL: *p*=NR At 4 years Fasting glucose progressing to ≥126 mg/dL among non-DM with baseline fasting glucose <126 mg/dL, n (%): CHL: 302 (11.6) LIS: 119 (8.1) AML: 154 (9.8) LIS vs. CHL: *p*<.001 AML vs. CHL: *p*=.04

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ALLHAT ALLHAT Collaborative Research Group, 2003[57]	24,316	Mean 3.2 years	Good	CHL: Chlorthalidone: 12.5, 25 mg QD DOX: Doxazosin: 2, 4, or 8 mg QD If goal not met with maximum tolerated dose, then open-label Step 2 agent (atenolol, 25–100 mg/d, reserpine, 0.05–0.2 mg/d, or clonidine, 0.1–0.3 mg BID), or an open-label Step 3 agent (hydralazine, 25–100 mg BID) added; use of open-label medications from 1 of the masked classes of drugs was to be avoided unless SBP >160 mmHg and/or DBP >100 mmHg after maximum tolerated titration of drugs from each of the 3 steps or a compelling indication, such as HF, arose. Note: randomization ratio was 1.7:1:1 (chlorthalidone: amlodipine: lisinopril) resulting in larger sample size in chlorthalidone group. Doxazosin arm terminated early because of a 25% greater incidence of combined CVD events compared with chlorthalidone.	Adults, age ≥55 years, with at least one additional risk factor for CHD. SBP ≥140 and/or DBP ≥90 mmHg or on medications for HTN.	All-cause mortality, n of events (event rate per 100) CHL: 1258 (10.51) DOX: 769 (11.04) RR (95% CI): 1.03 (0.94, 1.13) *p*=.50	PRIMARY OUTCOME: Nonfatal MI and fatal CHD, n of events (event rate per 100) CHL: 818 (7.76) DOX: 499 (7.91) RR (95% CI): 1.03 (0.92, 1.15) *p*=.62 Death from MI, n of events (event rate per 100) CHL: 184 (1.65) DOX: 105 (1.76) RR (95% CI): 0.96 (0.76, 1.22) *p*=.75 Death from definite CHD, n of events (event rate per 100) CHL: 57 (0.54) DOX: 39 (0.54) RR (95% CI): 1.16 (0.77, 1.74) *p*=.49 Coronary revascularization, n of events (event rate per 100) CHL: 770 (7.08) DOX: 508 (8.02) RR (95% CI): 1.12 (1.00, 1.25) *p*=.05 Lower extremity PAD, n of events (event rate per 100) CHL: 376 (3.68) DOX: 217 (3.49) RR (95% CI): 0.97 (0.82, 1.15) *p*=.76	Stroke, n of events (event rate per 100) CHL: 434 (4.08) DOX: 325 (5.49) RR (95% CI): 1.26 (1.10, 1.46) *p*=.001 Death from stroke, n of events (event rate per 100) CHL: 92 (0.79) DOX: 76 (1.25) RR (95% CI): 1.39 (1.03, 1.89) *p*=.03	Fatal, hospitalized, treated CHF, n of events (event rate per 100) CHL: 546 (5.35) DOX: 584 (8.89) RR (95% CI): 1.80 (1.61, 2.02) *p*<.001 Fatal, hospitalized CHF, n of events (event rate per 100) CHL: 440 (4.41) DOX: 434 (6.63) RR (95% CI): 1.66 (1.46, 1.89) *p*<.001 Death from CHF, n of events (event rate per 100) CHL: 59 (0.60) DOX: 42 (0.65) RR (95% CI): 1.20 (0.81,1.78) *p*=.36	Combined CHD, n of events (event rate per 100) CHL: 1,642 (14.87) DOX: 1,040 (16.00) RR (95% CI): 1.07 (0.99, 1.66) *p*=.07 Combined CVD, n of events (event rate per 100) CHL: 2,829 (25.09) DOX: 1,947 (28.56) RR (95% CI): 1.20 (1.13, 1.27) *p*<.001 CV mortality, n of events (event rate per 100) CHL: 551 (4.74) DOX: 377 (5.60) RR (95% CI): 1.15 (1.01, 1.32) *p*=.03 Other CV death, n of events (event rate per 100) CHL: 97 (0.88) DOX: 72 (1.12) RR (95% CI): 1.25 (0.92, 1.70) *p*=.15	Kidney disease death, n of events (event rate per 100) CHL: 12 (0.11) DOX: 12 (0.24) RR (95% CI): 1.69 (0.76, 3.77) *p*=.20 ESRD, n of events (event rate per 100) CHL: 104 (1.10) DOX: 64 (1.08) RR (95% CI):1.04 (0.76,1.42) *p*=.80 Doubling of serum Cr from baseline: CHL: 0.8% DOX: 0.5% *p*=.02	Withdrawals due to AE, % NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
SHELL Malacco et al., 2003[58]	1,882	Median 32 months (95% CI, 30-33 months)	Fair	CHL: Chlorthalidone: 12.5, 25 mg QD LAC: Lacidipine: 4, 6 mg QD If SBP response not satisfactory after 4 weeks, treatment titrated upward first by increasing dose of initial monotherapy (CHL to 25 mg QD and LAC to 6 mg QD) and by bringing back monotherapy dose to initial step and adding fosinopril 10 mg QD or any other ACE inhibitor at equivalent dose after another 4 weeks treatment.	Adults ≥60 years with isolated systolic HTN. SBP ≥160 and DBP ≤95 mmHg.	All-cause mortality, n of events CHL: 122 LAC: 145 HR (95% CI): 1.23 (0.97,1.57) *p*=.09	Fatal and nonfatal MI, n of events CHL: 14 LAC: 12 HR (95% CI): 0.85 (0.39, 1.83) *p*=.67 Sudden death, n of events CHL: 13 LAC: 16 HR (95% CI): 1.22 (0.58, 2.53) *p*=.60 Revascularization, n of events CHL: 4 LAC: 2 HR (95% CI): 0.50 (0.09, 2.70) *p*=.41	Fatal and nonfatal stroke, n of events CHL: 38 LAC: 37 HR (95% CI): 0.96 (0.61, 1.51) *p*=.87 TIA, n of events CHL: 13 LAC: 15 HR (95% CI): 1.14 (0.54, 2.40) *p*=.72	Fatal and nonfatal HF, n of events CHL: 19 LAC: 23 HR (95% CI): 1.20 (0.65, 2.20) *p*=.56	PRIMARY OUTCOME: Composite primary endpoint (fatal and nonfatal stroke, sudden death, fatal and nonfatal MI, fatal and nonfatal CHF, myocardial revascularization and carotid endarterectomy), n of events CHL: 88 LAC: 90 HR (95% CI): 1.01 (0.75, 1.36) *p*=.94		Withdrawals due to AE, % NR Orthostatic hypotension, % CHL: 2.5 LAC: 1.9 *p*=NR Edema, % CHL: 4.9 LAC: 14.3 *p*=NR Cough, % CHL: 4.0 LAC: 3.5 *p*=NR Dizziness, % CHL: 12.4 LAC: 12.7 *p*=NR Fatigue, % CHL: 20.5 LAC: 13.7 *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
VHAS Rosei et al., 1997[59]	1,414	2 years	Fair	CHL: Chlorthalidone: 25 mg QD VER: Verapamil: slow release 240 mg QD After 1 month, 25 mg captopril QD added when BP not at goal; after 2nd month, captopril dose increased to 25 mg BID if not yet responding to combined treatment; subsequently, if not responding switched to any open therapy chosen by their treating doctors (free therapy).	Adults, ages 40–65 years, with HTN. SBP ≥160 and DBP ≥95 mmHg	Death by any cause, n of events CHL: 4 VER: 5 *p*=NR	MI, n of events CHL: 5 VER: 5 *p*=NR Revascularization procedures, n of events CHL: 3 VER: 4 *p*=NR Cardiac deaths, n of events CHL: 4 VER: 3 *p*=NR	Strokes, n of events CHL: 4 VER: 3 *p*=NR TIA, n of events CHL: 7 VER: 7 *p*=NR Cerebrovascular deaths, n of events CHL: 0 VER: 2 *p*=NR	CHF, n of events CHL: 0 VER: 2 *p*=NR	PRIMARY OUTCOME: Nonfatal CV events, n of events CHL: 39 VER: 37 *p*=NR PRIMARY OUTCOME: Major CV events, n of events CHL: 9 VER: 8 *p*=NR PRIMARY OUTCOME: Minor CV events, n of events CHL: 30 VER: 29 *p*=NR PRIMARY OUTCOME: CV deaths, n of events CHL: 4 VER: 5 *p*=NR		Withdrawals due to AE, % CHL: 2.5 VER: 2.5 % calculated by reviewer PRIMARY OUTCOME: Glucose, mg/dl (SD) CHL: 99.8 (19.2) VER: 95.7 (16.4) *p*=.01 Change CHL: +1.8 VER: - 1.2 PRIMARY OUTCOME: Constipation, % CHL: 3.1 VER: 13.7 *p*=NR PRIMARY OUTCOME: Hyperuricemia, % CHL: 10.8 VER: 3.9 *p*<.01 PRIMARY OUTCOME: Hypokalemia, % CHL: 24.6 VER: 4.4 *p*<.01 PRIMARY OUTCOME: Severe hypokalemia, n CHL: 8 VER: 4 *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
INSIGHT Brown et al., 2000;[6] Mancia et al., 2003[74]	6,321	Maximum of 51 months F/U; BP outcomes reported at 48 months	Good	Co-am: Co-amilozide: HCTZ 25 mg and amiloride 2.5 mg QD or doubling the dose of both drugs to HCTZ 50 mg QD and amiloride 5 mg QD NIFE: Nifedipine: 30, 60 mg QD 4 optional titration steps for patients whose BP fell by <20/10 mmHg or >140/90 mmHg: Dose doubling of randomized drugs Addition of atenolol 25 mg daily (enalapril 5 mg daily if atenolol contraindicated) Dose doubling of additional drug Addition of any other anti-HTN drug (other than CCB or diuretics) Titration steps could be done in that order at any visit from weeks 2, 4, 8, and 12 after randomization	Men and women age 55–80 years, high risk patients with HTN; one additional CV risk factor. ≥150/95 mmHg or SBP ≥160 mmHg regardless of DBP.	All deaths - first event, n (%) Co-am: 152 (4.8) NIFE: 153 (4.8) OR (95% CI): 1.01 (0.80, 1.27) *p*=.95	Nonfatal MI, n (%) Co-am: 56 (1.8) NIFE: 61 (1.9) OR (95% CI): 1.09 (0.76, 1.58) *p*=.52 Fatal MI, n (%) Co-am: 5 (0.2) NIFE: 16 (0.5) OR (95% CI): 3.22 (1.18, 8.80) *p*=.017	Nonfatal stroke, n (%) Co-am: 63 (2.0) NIFE: 55 (1.7) OR (95% CI): 0.87 (0.61, 1.26) *p*=.52 Fatal stroke, n (%) Co-am: 11 (0.3) NIFE: 12 (0.3) OR (95% CI): 1.09 (0.48, 2.48) *p*=.84 TIA, n (%) Co-am: 25 (0.8) NIFE: 25 (0.8) OR (95% CI): 1.00 (0.57, 1.75) *p*=1.0	Nonfatal HF, n (%) Co-am: 11 (0.3) NIFE: 24 (0.8) OR (95% CI): 2.20 (1.07, 4.49) *p*=.028 Fatal HF, n (%) Co-am: 1 (<0.1) NIFE: 2 (0.1) OR (95% CI): 2.01 (0.18, 22.13) *p*=.63	PRIMARY OUTCOME: Composite of death from any CV or cerebrovascular cause, together with nonfatal stroke, MI and HF, n (%) Co-am: 182 (5.8) NIFE: 200 (6.3) OR (95% CI): 1.11 (0.90, 1.36) *p*=.34 Composite secondary outcomes: primary outcomes plus non-CV deaths, renal failure, angina and TIA, n (%) Co-am: 397 (12.5) NIFE: 383 (12.1) OR (95% CI): 0.96 (0.83, 1.12) *p*=.62 Other CV death, n (%) Co-am: 12 (0.4) NIFE: 13 (0.4) OR (95% CI): 1.09 (0.50, 2.38) *p*=.85 CV Deaths, n (%) Co-am: 52 (1.6) NIFE: 60 (1.9) OR (95% CI): 1.16 (0.80, 1.69) *p*=.45 Nonfatal primary CV events, n (%) Co-am: 130 (4.1) NIFE: 140 (4.4) OR (95% CI): 1.08 (0.85, 1.38) *p*=.53 Nonfatal CV events, n (%) Co-am : 245 (7.7) NIFE: 230 (7.3) OR (95% CI): 0.94 (0.78, 1.13) *p*=.50	Renal Failure (defined as creatinine >2.94 mg/dl), n (%) Co-am: 13 (0.4) NIFE: 8 (0.3) OR (95% CI): 0.62 (0.26, 1.49) *p*=.38 GFR, mL/min Co-am vs. NIFE (95% CI): –2.3 (–3.8, 1.9) Co-amilozide lower than nifedipine	Withdrawals due to AE, % Co-am:16.4 NIFE: 23.0 % calculated by reviewer Impaired renal function as an AE, n (%) Co-am: 144 (4.6) NIFE: 58 (1.8) *p*<.0001 All AEs, n (%) Co-am: 1,327 (42) NIFE: 1,546 (49) *p*<.0001 Serious AE, n (%) Co-am: 880 (28) NIFE: 796 (25) *p*<.02 DM reported as an AE, n (%) Co-am: 137 (4.3) NIFE: 96 (3.0) *p*=.01 New onset DM reported as an outcome, n (%) Co-am: 176 (5.6) NIFE: 136 (4.3) *p*=.02 Hyperglycemia, n (%) Co-am: 244 (7.7) NIFE: 178 (5.6) *p*=.001 Peripheral edema, n (%) Co-am: 137 (4.3) NIFE: 896 (28) *p*<.0001 Hypokalemia, n (%) Co-am: 195 (6.2) NIFE: 61 (1.9) *p*<.0001 Hyponatremia, n (%) Co-am : 61 (1.9) NIFE: 8 (NR) *p*<.0001 Headache, n (%) Co-am: 292 (9.2) NIFE: 384 (12) *p*<.0002 Dizziness, n (%) Co-am: 318 (10) NIFE: 254 (8) *p*<.006

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
MIDAS Borhani et al., 1996[60]	883	3 years	Fair	HCTZ: Hydrochlorothiazide: 12.5 to 25 mg BID ISR: Isradipine: 2.5 to 5.0 mg BID Titrated to achieve DBP goal during the first 4 months; if DBP goal not reached with highest dose allowed by protocol, open-label enalapril added at dosages of 2.5, 5.0, 7.5, or 10.0 mg BID to achieve DBP goal.	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. DBP 90-115 mmHg	All-cause mortality, n (n/100) HCTZ: 9 (2.1) ISR: 8 (1.8) RR (95% CI): 0.89 (0.35, 2.28) *p*=.81	MI, n (n/100) HCTZ: 5 (1.13) ISR: 6 (1.35) RR (95% CI): 1.20 (0.37, 3.89) *p*=.77 CABG, n (n/100) HCTZ: 6 (1.35) ISR: 6 (1.35) RR (95% CI): 1.00 (0.32, 3.07) *p*=.97 Coronary angioplasty, n (n/100) HCTZ: 1 (0.22) ISR: 5 (1.13) RR (95% CI): 4.99 (0.59, 42.53) *p*=.10 Sudden death, n (n/100) HCTZ: 2 (0.45) ISR: 2 (0.45) RR (95% CI): 1.00 (0.14, 7.05) *p*>.99	Stroke, n (n/100) HCTZ: 3 (0.68) ISR: 6 (1.35) RR (95% CI): 2.00 (0.50, 7.93) *p*=.32	CHF, n (n/100) HCTZ: 0 (0.0) ISR: 2 (0.45) RR (95% CI): NR *p*=.16	Any major vascular event, n (n/100) HCTZ:14 (3.17) ISR: 25 (5.65) RR (95% CI): 1.78 (0.94, 3.38) *p*=.07 Major vascular events and procedures, n (n/100) HCTZ: 19 (4.31) ISR: 30 (6.78) RR (95% CI): 1.58 (0.90, 2.76) *p*=.10 Other CVD death, n (n/100) HCTZ: 1 (0.22) ISR: 1 (0.22) RR (95% CI): 1.00 (0.06, 15.90) *p*>.99		Withdrawals due to AE, % HCTZ : 8.2 ISR: 9.3 CV-related adverse reactions, n (%) HCTZ: NR (0.9) ISR: NR (3.0) *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
HAPPHY Wilhelmsen et al., 1987[62]	6,569	Mean 45.1 months	Fair	DIUR: Diuretic: 50 mg HCTZ or 5 mg bendroflumethazide BB: Beta Blocker: 100 mg atenolol or 200 mg QD metoprolol If not at goal, additional drugs added until BP goal reached: Step 2 (until 1981) 2x original dose, however due to side effects of high doses and a "relatively flat" dose-response curve, the dose step was terminated in all patients. Additional treatment for both groups included: Step 1: Hydralazine 75 mg Step 2: Hydralazine 150 mg Step 3: Hydralazine 150 mg + Spironolactone 75 mg Step 4: Hydralazine 150 mg + Spironolactone 150 mg Step 5: Hydralazine 150 mg + Spironolactone 150 mg + Optional drug	Adult men, ages 40–64 years, with mild to moderate HTN. DBP 100–130 mmHg	PRIMARY OUTCOME: All deaths, n events (rate/1000 py) DIUR: 101 (8.25) BB: 96 (7.73) OR (95% CI): 1.06 (0.80, 1.41) *p*>.20	PRIMARY OUTCOME: Nonfatal MI, n events (rate/1000 py) DIUR: 75 (6.13) BB: 84 (6.76) OR (95% CI): 0.90 (0.66, 1.23) *p*>.20 PRIMARY OUTCOME: Fatal and/or nonfatal CHD, n events (rate/1000 py) DIUR: 116 (9.48) BB: 132 (10.62) OR (95% CI): 0.88 (0.68, 1.14) *p*>.20 PRIMARY OUTCOME: Fatal CHD, n events (rate/1000 py) DIUR: 50 (4.09) BB: 54 (4.35) OR (95% CI): 0.93 (0.64, 1.37) *p*>.20	Nonfatal stroke, n events (rate/1000 py) DIUR: 32 (2.61) BB: 29 (2.33) OR (95% CI): 1.11 (0.68, 1.83) *p*>.20 Fatal and/or nonfatal stroke, n events (rate/1000 py) DIUR: 41 (3.35) BB: 32 (2.58) OR (95% CI): 1.29 (0.82, 2.04) *p*>.20 Fatal stroke, n events (rate/1000 py) DIUR: 10 (0.82) BB: 3 (0.24) OR (95% CI): 3.37 (0.96, 9.53) *p*=.09	Heart failure, n events (rate/1000 py) DIUR: 22 (1.8) BB: 32 (2.6) *p*=NS	Patients with an endpoint of death, nonfatal MI, or nonfatal stroke, n events (rate/1000 py) BB: 197 (15.85) DIUR: 192 (15.69) OR (95% CI): 0.98 (0.80, 1.20) *p*>.20 Total endpoints of death, nonfatal MI, or nonfatal stroke, n events (rate/1000 py) BB: 225 (NR) DIUR: 224 (NR) OR (95% CI): 1.00 (0.83, 1.21) *p*>.20 Other deaths, n events (rate/1000 py) BB: 39 (3.14) DIUR: 41 (3.35) OR (95% CI): 1.06 (0.69, 1.64) *p*>.20	Change in serum Cr from baseline, (µmol/l) DIUR: +4.2 BB: +4.0 *p*=NS (value NR)	Withdrawals due to AE, % DIUR: 2.4 BB: 2.0 Developed DM, n events (rate/1000 py) DIUR: 75 (6.1) BB: 86 (6.9) *p*=NS Reporting any symptoms related to drug at 12 month visit, % DIUR: 16.8 BB: 19.1 *p*<.001 Cold hands and feet, % DIUR:12.7 BB: 21.4 *p*<.001 Dry mouth, % DIUR: 15.4 BB: 12.5 *p*<.002 Unusual tiredness, % DIUR: 15.4 BB: 18.2 *p*<.005

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
MAPHY Wilkstrand et al., 1988; [63] Olsson et al., 1991[64]	3,234	Median 4.16 years	Fair	DIUR: Diuretic: HCTZ 50 mg/d or benfro-flumethiazide 5 mg/d MET: Metoprolol: 200 mg/d To achieve goal, dosages could be doubled or additional drugs (hydralazine, spironolactone or others but not BB or thiazide diuretics). In 1981, max dose of baseline drugs reduced to 200 mg/d metoprolol, 50 mg/d HCTZ, or 5 mg/d bendroflumethiazide 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 (see row above).	Adult males, ages 40 to 64, either previously treated patients or newly detected and untreated HTN. DBP ≥100 mmHg and <130 mmHg	At median 4.16 years PRIMARY OUTCOME: Total mortality, deaths per 1000 patient years (n) DIUR: 9.3 (54) MET: 4.8 (28) % difference (95% CI): –48 (–68, –17) *p*=NR At end of study (10.8 years) PRIMARY OUTCOME: Total mortality, deaths per 1000 patient years (n) DIUR: 10.3 (83) MET: 8.0 (65) % difference: –22 *p*=.028 Total sudden mortality, n DIUR: 45 MET: 32 *p*=.017	At 10.8 years PRIMARY OUTCOME: Fatal CHD composite of MI or sudden coronary death, n DIUR: 43 MET: 36 *p*=.048	At 10.8 years Fatal stroke, n DIUR: 9 MET: 2 *p*=.043	At 10.8 years Fatal HF, n DIUR: 0 MET: 3 *p*=NR	At median 4.16 years CV mortality, deaths per 1000 patient years (n) DIUR: 6.2 (36) MET: 2.6 (15) *p*=NR % difference: –58 At end of study (10.8 years) CV mortality, Deaths per 1000 patient years (n) DIUR: 7.1 (57) MET: 5.2 (42) % difference: –27 *p*=.012 Sudden CV mortality, deaths per 1000 patient years (n) DIUR: 5.6 (45) MET: 3.9 (32) % difference: –30 *p*=.017 Nonsudden CV mortality, deaths per 1000 patient years (n) DIUR: 3.2 (26) MET: 2.8 (23) % difference: –13 *p*=NS (value NR)		Withdrawals due to AE, % NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ANBP2 Wing et al., 2003[61]	6,083	Median 4.1 years	Fair	DIUR: Diuretic: HCTZ recommended; dose not specified ACE: ACE Inhibitor: Enalapril recommended; dose not specified To achieve BP goal, addition of BB, CCB, and alpha-blockers recommended in both groups	Adults, ages 65–84, with absence of recent CV events. SBP ≥160 mmHg; or DBP ≥90 mmHg if SBP ≥140 mmHg	Death from any cause, rate per 1000 py (n of events) DIUR: 17.1 (210) ACE: 15.7 (195) HR (95% CI): 0.90 (0.75, 1.09) *p*=.27	Nonfatal MI, rate per 1000 py (n of events) DIUR: 5.8 (71) ACE: 4.1 (50) HR (95% CI): 0.68 (0.47, 0.99) *p*= 0.05 MI, rate per 1000 py (n of events) DIUR: 6.7 (82) ACE: 4.7 (58) HR (95% CI): 0.68 (0.47, 0.98) *p*=.04 Coronary event, rate per 1000 py (n of events) DIUR: 16.2 (195) ACE: 14.3 (173) HR (95% CI): 0.86 (0.70, 1.06) *p*= 0.16 Fatal MI events, rate per 1000 py (n of events) DIUR: 0.9 (11) ACE: 0.7 (9) HR (95% CI): 0.79 (0.31, 1.99) *p*=.61 Fatal coronary events, rate per 1000 py (n of events) DIUR: 4.2 (52) ACE: 3.2 (40) HR (95% CI): 0.74 (0.49, 1.11) *p*=.14	Nonfatal Stroke, rate per 1000 py (n or events) DIUR: 7.8 (94) ACE: 7.5 (91) HR (95% CI): 0.93 (0.70, 1.26) *p*=.65 Stroke, rate per 1000 py (n of events) DIUR: 8.8 (107) ACE: 9.2 (112) HR (95% CI): 1.02 (0.78, 1.33) *p*=.91 Cerebrovascular event, rate per 1000 py (n of events) DIUR: 13.6 (163) ACE: 12.5 (152) HR (95% CI): 0.90 (0.73, 1.12) *p*=.35 Fatal stroke events, rate per 1000 py (n of events) DIUR: 1.2 (15) ACE: 2.3 (29) HR (95% CI): 1.91 (1.04, 3.50) *p*=.04	Nonfatal HF, rate per 1000 py (n of events) DIUR: 6.3 (77) ACE: 5.5 (68) HR (95% CI): 0.85 (0.62, 1.17) *p*=.32 HF, rate per 1000 py (n or events) DIUR: 6.4 (78) ACE: 5.6 (69) HR (95% CI): 0.85 (0.62, 1.18) *p*=.33 Fatal HF events, rate per 1000 py (n of events) DIUR: 0.7 (8) ACE: 0.2 (2) HR (95% CI): 0.24 (0.03, 1.94) *p*=.18	Nonfatal CV event rate per 1000 py (n of events) DIUR: 32.8 (380) ACE: 28.9 (338) HR (95% CI): 0.86 (0.74, 0.99) *p*= 0.03 Nonfatal other CV event rate per 1000 py (n of events) DIUR: 11.3 (137) ACE: 9.9 (120) HR (95% CI): 0.84 (0.66, 1.07) *p*=.17 PRIMARY OUTCOME: All CV events or death from any cause, rate per 1000 py (n of events) DIUR: 59.8 (736) ACE: 56.1 (695) HR (95% CI): 0.89 (0.79, 1.00) *p*=.05 First CV event or death from any cause, rate per 1000 py (n of events) DIUR: 45.7 (529) ACE: 41.9 (490) HR (95% CI): 0.89 (0.79, 1.01) *p*=.06 First CV event, rate per 1000 py (n of events) DIUR: 37.1 (429) ACE: 33.7 (394) HR (95% CI): 0.88 (0.77, 1.01) *p*=.07 Other CV event, rate per 1000 py (n of events) DIUR: 11.9 (144) ACE: 11.0 (134) HR (95% CI): 0.90 (0.71, 1.14) *p*=.36 Fatal CV events, rate per 1000 py (n of events) DIUR: 6.7 (82) ACE: 6.8 (84) HR (95% CI): 0.99 (0.72, 1.35) *p*=.94 Other fatal CV events, rate per 1000 py (n of events) DIUR: 1.2 (15) ACE: 1.2 (15) HR (95% CI): 0.95 (0.46, 1.96) *p*=.89		Withdrawals due to AE, % NR

Table D–3a-1. Diuretic Combination Therapy Versus Other Drugs

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ACCOMPLISH Jamerson et al., 2008[4]	11,506	Mean 36 months	Good	BEN-HCTZ: Benazepril-HCTZ single pill formulation: 20/12.5 mg QD (max: 40/25) BEN-AML: Benazepril-Amlodipine singe pill formulation: 20/5 mg QD (max: 40/10) Addition of other anti-HTN agents permitted (excluding any CCBs, any ACE inhibitors, any ARBs, and any thiazide diuretics but including BBs, alpha-blockers, clonidine, and spironolactone); loop diuretics taken QD permitted for volume management.	Adults, ages ≥60 with one risk factor or 55 to 59 with 2 or more risk factors. SBP ≥160 mmHg or currently on anti-HTN therapy.	Death from any cause, # of events (%) BEN-HCTZ: 262 (4.5) BEN-AML: 236 (4.1) HR (95% CI): 0.90 (0.76,1.07) *p*=.24	Fatal and nonfatal MI, # of events (%) BEN-HCTZ: 159 (2.8) BEN-AML: 125 (2.2) HR (95% CI): 0.78 (0.62, 0.99) *p*=.04 Coronary revascularization procedure, # of events (%) BEN-HCTZ: 386 (6.7) BEN-AML: 334 (5.8) HR (95% CI): 0.86 (0.74, 1.00) *p*=.04	Fatal and nonfatal stroke, # of events (%) BEN-HCTZ: 133 (2.3) BEN-AML: 112 (1.9) HR (95% CI): 0.84 (0.65, 1.08) *p*=.17	Hospitalization for CHF, # of events (%) BEN-HCTZ: 96 (1.7) BEN-AML: 100 (1.7) HR (95% CI): 1.04 (0.79, 1.38) *p*=.77	Composite of CV events, # of events (%) BEN-HCTZ: 592 (10.3) BEN-AML: 494 (8.6) HR (95% CI): 0.83 (0.73, 0.93) *p*=.002 Primary end point plus hospitalization for CHF, # of events (%) BEN-HCTZ: 738 (12.8) BEN-AML: 617 (10.7) HR (95% CI): 0.83 (0.74, 0.92) *p*=.0005 PRIMARY OUTCOME: Composite of CV events and death from CV causes, # of events (%) BEN-HCTZ: 679 (11.8) BEN-AML: 552 (9.6) HR (95% CI): 0.80 (0.72, 0.90) *p*<.001 Composite of death from CV events, nonfatal MI, and nonfatal stroke, # of events (%) BEN-HCTZ: 364 (6.3) BEN-AML: 288 (5.0) HR (95% CI): 0.79 (0.67, 0.92) *p*=.002 Death from CV causes, # of events (%) BEN-HCTZ: 134 (2.3) BEN-AML: 107 (1.9) HR (95% CI): 0.80 (0.62, 1.03) *p*=.08		Withdrawals due to AE, %; BEN-HCTZ: 14.3; BEN-AML: 13.4; *p*=NR Any AE of dizziness, # of events (%); BEN-HCTZ: 1461 (25.4); BEN-AML: 1189 (20.7); *p*=NR Any AE of peripheral edema, # of events (%); BEN-HCTZ: 772; (13.4); BEN-AML: 1792 (31.2) *p*=NR; Serious AE of peripheral edema, # of events (%); BEN-HCTZ: 8 (0.1); BEN-AML: 10 (0.2); *p*=NR Drug-related serious AE of peripheral edema, # of events (%); BEN-HCTZ: 2 (<0.1); BEN-AML: 4 (0.1); *p*=NR Any AE of dry cough, # of events (%); BEN-HCTZ: 1,220 (21.2); BEN-AML: 1,177 (20.5); *p*=NR Serious AE of dry cough, # of events (%); BEN-HCTZ: 7 (0.1); BEN-AML: 7 (0.1); *p*=NR Drug-related serious AE of dry cough, # of events (%); BEN-HCTZ: 3 (0.1); BEN-AML: 3 (0.1); *p*=NR Any AE of hyperkalemia, # of events (%); BEN-HCTZ: 33 (0.6); BEN-AML: 34 (0.6); *p*=NR Serious AE of hyperkalemia, # of events (%); BEN-HCTZ: 11 (0.2); BEN-AML: 10 (0.2); *p*=NR Drug-related serious AE of hyperkalemia, # of events (%); BEN-HCTZ: 6 (0.1); BEN-AML: 6 (0.1); *p*=NR Any AE of hypokalemia, # of events (%); BEN-HCTZ: 17 (0.3); BEN-AML : 3 (0.1); *p*=NR Serious AE of hypokalemia, # of events (%); BEN-HCTZ: 12 (0.2); BEN-AML: 2 (<0.1); *p*=NR Drug-related serious AE of hypokalemia, # of events (%); BEN-HCTZ: 0 (0.0); BEN-AML: 1 (<0.1); *p*=NR Any AE of hypotension, # of events (%); BEN-HCTZ: 208 (3.6); BEN-AML: 142 (2.5); *p*=NR Serious AE of hypotension, # of events (%); BEN-HCTZ: 30 (0.5); BEN-AML: 22 (0.4); *p*=NR Drug-related serious AE of hypotension, # of events (%); BEN-HCTZ: 9 (0.2); BEN-AML: 6 (0.1); *p*=NR Drug-related serious AE of angioedema, # of events (%); BEN-HCTZ: 5 (0.1); BEN-AML: 2 (<0.1); *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ACCOMPLISH Prespecified secondary analysis of kidney outcomes Bakris et al., 2010[68]	11,506	Mean F/U 2.9 years	Fair	BEN-HCTZ: Benazepril-HCTZ single pill formulation: 20/12.5 mg QD (max: 40/25) BEN-AML: Benazepril-Amlodipine singe pill formulation: 20/5 mg QD (max: 40/10) Addition of other anti-HTN agents permitted (excluding any CCBs, any ACE inhibitors, any ARBs, and any thiazide diuretics but including BBs, alpha-blockers, clonidine, and spironolactone); loop diuretics taken QD permitted for volume management.	Adults, ages ≥60 with one risk factor or 55 to 59 with 2 or more risk factors. SBP ≥160 mmHg or currently on anti-HTN therapy.					Progression of CKD and CV death, n (%) BEN-HCTZ: 345 (5.99) BEN-AML: 220 (3.83) HR (95% CI): 0.63 (0.53, 0.74) *p*<.0001 Progression of CKD and all-cause mortality, n (%) BEN-HCTZ: 465 (8.07) BEN-AML: 346 (6.02) HR (95% CI): 0.73 (0.64, 0.84) *p*<.0001 *In patients aged ≥65 years* Progression of CKD and CV death, n (%) BEN-HCTZ: 234 (6.13) BEN-AML: 160 (4.18) HR (95% CI): 0.68 (0.55, 0.83) *p*=.0002 Progression of CKD and all-cause mortality, n (%) BEN-HCTZ: 327 (8.57) BEN-AML: 266 (6.96) HR (95% CI): 0.81 (0.68, 0.95) *p*=.010	Progression of CKD, n (%) BEN-HCTZ: 215 (3.73) BEN-AML: 113 (1.97) HR (95% CI): 0.52 (0.41, 0.65) *p*<.0001 Doubling of serum Cr, n (%) BEN-HCTZ: 208 (3.61) BEN-AML: 105 (1.83) HR (95% CI): 0.51 (0.39, 0.63) *p*<.0001 Dialysis, n (%) BEN-HCTZ: 13 (0.23) BEN-AML: 7 (0.12) HR (95% CI): 0.53 (0.21, 1.35) *p*=.180 eGFR <15 mL/min/1.73m², n (%) BEN-HCTZ: 17 (0.30) BEN-AML: 18 (0.31) HR (95% CI): 1.06 (0.54, 2.05) *p*=.868 GFR decline, mL/min/1.73m² (SD) BEN-HCTZ: –4.22 (16.3) BEN-AML: –0.88 (15.6) *p*=.01 *In patients aged ≥65 years* Progression of CKD, n (%) BEN-HCTZ: 138 (3.62) BEN-AML: 70 (1.83) HR (95% CI): 0.50 (0.37, 0.67) *p*<.0001 Doubling of serum Cr, n (%) BEN-HCTZ: 132 (3.46) BEN-AML: 66 (1.73) HR (95% CI): 0.49 (0.37, 0.67) *p*<.0001 Dialysis, n (%) BEN-HCTZ: 10 (0.26) BEN-AML: 3 (0.08) HR (95% CI): 0.30 (0.08, 1.09) *p*=.053 eGFR <15 mL/min/1.73m², n (%) BEN-HCTZ: 11 (0.29) BEN-AML: 11 (0.29) HR (95% CI): 1.00 (0.43, 2.31) *p*=.99 *In patients with CKD at baseline* GFR decline, mL/min/1.73m² (SD) BEN-HCTZ: –2.3 (10.6) BEN-AML: 1.6 (12.7) *p*=.001	Withdrawals due to AE NR *Patients without CKD at baseline* Peripheral edema, n (%) BEN-HCTZ: 686 (13.1) BEN-AML: 1603 (31.0) *p*<.0001 Dizziness, n (%) BEN-HCTZ: 1329 (25.5) BEN-AML: 1048 (20.3) *p*<.0001 Dry cough, n (%) BEN-HCTZ: 1125 (21.6) BEN-AML: 1056 (20.4) *p*=.14 Hypotension, n (%) BEN-HCTZ: 178 (3.4) BEN-AML: 118 (2.3) *p*=.0005 Hyperkalemia, n (%) BEN-HCTZ: 21 (0.4) BEN-AML: 22 (0.4) *p*=.85 Hypokalemia, n (%) BEN-HCTZ: 16 (0.3) BEN-AML: 3 (0.1) *p*=.003 Angioedema, n (%) BEN-HCTZ: 32 (0.6) BEN-AML: 44 (0.9) *p*=.15 *Patients with CKD at baseline* Peripheral edema, n (%) BEN-HCTZ: 85 (16.0) BEN-AML: 189 (33.7) *p*<.0001 Dizziness, n (%) BEN-HCTZ: 129 (24.2) BEN-AML: 141 (25.1) *p*=.73 Dry cough, n (%) BEN-HCTZ: 93 (17.5) BEN-AML: 120 (21.4) *p*=.10 Hypotension, n (%) BEN-HCTZ: 29 (5.5) BEN-AML: 24 (4.3) *p*=.36 Hyperkalemia, n (%) BEN-HCTZ: 12 (2.3) BEN-AML: 12 (2.1) *p*=.89 Hypokalemia, n (%) BEN-HCTZ: 1 (0.2) BEN-AML: 0 (0) *p*=.30 Angioedema, n (%) BEN-HCTZ: 2 (0.4) BEN-AML: 9 (1.6) *p*=.04

Table D–3b. Initial Treatment With Beta Blockers Versus Other Drugs

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ASCOT-BPLA Dahlöf et al., 2005[7]	19,342	Median 5.5 years	Good	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 + bendroflumethia-zide 2.5 mg + potassium + doxazosin GITS 4 mg Step 6: Atenolol 100 mg + bendroflumethia-zide 2.5 mg + potassium + doxazosin GITS 8 mg 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 m	Adults, age 40–79 years, with HTN and at least 3 CV risk factors. Inclusion criterion for untreated HTN was SBP ≥160 or DBP ≥100 mmHg or both. Inclusion criterion for treated HTN was SBP ≥140 mmHg or DBP≥90 mmHg or both.	All-cause mortality, rate per 1000 pts (n of pts) ATN: 15.5 (820) AML: 13.9 (738) HR (95% CI): 0.89 (0.81, 0.99) *p*=.0247	Total coronary endpoint, rate per 1000 pts (n of pts) ATN: 16.8 (852) AML: 14.6 (753) HR (95% CI): 0.87 (0.79, 0.96) *p*=.0070 Silent MI, rate per 1000 pts (n of pts) ATN: 0.6 (33) AML: 0.8 (42) HR (95% CI): 1.27 (0.80, 2.00) *p*=.3089 PAD, rate per 1000 pts (n of pts) ATN: 3.9 (202) AML: 2.5 (133) HR (95% CI): 0.65 (0.52, 0.81) *p*=.0001	Fatal and nonfatal stroke, rate per 1000 pts (n of pts) ATN: 8.1 (422) AML: 6.2 (327) HR (95% CI): 0.77 (0.66, 0.89) *p*=.0003	Fatal and nonfatal HF, rate per 1000 pts (n of pts) ATN: 3.0 (159) AML: 2.5 (134) HR (95% CI): 0.84 (0.66, 1.05) *p*=.1257	PRIMARY OUTCOME: Nonfatal MI (including silent MI) and fatal CHD, rate per 1000 pts (n of pts) ATN: 9.1 (474) AML: 8.2 (429) HR (95% CI): 0.90 (0.79, 1.02) *p*=.1052 Nonfatal MI (excluding silent MI) and fatal CHD, rate per 1000 pts (n of pts) ATN: 8.5 (444) AML: 7.4 (390) HR (95% CI): 0.87 (0.76, 1.00) *p*=.0458 Total CV events and procedures, rate per 1000 pts (n of pts) ATN: 32.8 (1602) AML: 27.4 (1362) HR (95% CI): 0.84 (0.78, 0.90) *p*<.0001 Composite of primary endpoints of nonfatal MI including silent MI and fatal CHD plus coronary revascularization procedures, rate per 1000 pts (n of pts) ATN: 13.4 (688) AML: 11.5 (596) HR (95% CI): 0.86 (0.77, 0.96) *p*= 0.0058 CV death, MI and stroke, rate per 1000 pts (n of pts) ATN: 18.4 (937) AML: 15.4 (796) HR (95% CI): 0.84 (0.76, 0.92) *p*=.0003 CV mortality, rate per 1000 pts (n of pts) ATN: 6.5 (342) AML: 4.9 (263) HR (95% CI): 0.76 (0.65, 0.90) *p*=.0010		Withdrawals due to AE (# stopping trial early due to serious adverse events), % ATN: 3 AML: 2 *p*<.0001 Development of DM, n of patients (rate per 1000 patients) ATN: 799 (15.9) AML: 567 (11.0) HR (95% CI): 0.70 (0.63, 0.78) *p*<.0001 Cough, n (%) ATN: 782 (8) AML: 1859 (19) *p*<.0001 Peripheral edema, n (%) ATN: 588 (6) AML: 2188 (23) *p*<.0001 Dizziness, n (%) ATN: 1555 (16) AML: 1183 (12) *p*<.0001 Dyspnoea, n (%) ATN: 987 (10) AML: 599 (6) *p*<.0001 Fatigue, n (%) ATN: 1556 (16) AML: 782 (8) *p*<.0001 Joint swelling, n (%) ATN: 308 (3) AML: 1371 (14) *p*<.0001

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ELSA Zanchetti et al., 2002[66]	2,334	Mean 3.75 years	Fair	ATN: Atenolol: 50, 100 mg/day LAC: Lacidipine: 4, 6 mg/day If DBP not <95 mmHg with fall ≥5 mmHg, dose of LAC could be increased to 6 mg, and ATN could be increased to 100 mg (month 1), with open-label HCTZ added (12.5 mg daily month 3 and 25 mg daily month 6).	Adults, age 45–75 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. Sitting SBP 150–210 mmHg and DBP 95–115 mmHg	All death, n (n/1000 py) ATN: 17 (4.68) LAC: 13 (3.59) *p*=NS	Fatal and nonfatal MI, n (n/1000 py) ATN: 17 (4.68) LAC: 18 (4.97) *p*=NS	Fatal and nonfatal stroke, n (n/1000 py) ATN: 14 (3.86) LAC: 9 (2.49) *p*=NS		Major CV events, n (n/1000 py) ATN: 33 (9.09) LAC: 27 (7.46) *p*=NS Minor CV events, n (n/1000 py) ATN: 42 (11.59) LAC: 45 (12.42) *p*=NS All major and minor CV events, n (n/1000 py) ATN: 73 (19.85) LAC: 69 (19.04) *p*=NS CV death, n (n/1000 py) ATN: 8 (2.20) LAC: 4 (1.10) *p*=NS		Withdrawals due to AE, n ATN: 103 LAC: 114 All serious AEs, n (%) ATN: 201 (55.37) LAC: 186 (51.38) *p*=NS

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
LIFE Dahlöf et al., 2002[8]	9,222	Mean 4.8 years	Good	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): Atenolol100 mg + HCTZ 12.5–25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) 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)	Adults, age 55–80 years, with previously treated or untreated HTN, LVH ascertained by ECG. DBP 95–115 mmHg or SBP 160–200 mmHg or both.	Total mortality, rate per 1000 py (n) ATN: 19.6 (431) LOS: 17.3 (383) AdjHR (95% CI): 0.90 (0.78, 1.03) *p*=.128 UnadjHR (95%CI): 0.88 (0.77, 1.01) *p*=.077	MI, rate per 1000 py (n) ATN: 8.7 (188) LOS: 9.2 (198) AdjHR (95% CI): 1.07 (0.88, 1.31) *p*=.491 UnadjHR (95%CI): 1.05 (0.86, 1.28) *p*=.628 Revascularization, rate per 1000 py (n) ATN: 13.3 (284) LOS: 12.2 (261) AdjHR (95% CI): 0.94 (0.79, 1.11) *p*=.441 UnadjHR (95%CI): 0.91 (0.77, 1.08) *p*=.292	Stroke, rate per 1000 py (n) ATN: 14.5 (309) LOS: 10.8 (232) AdjHR (95% CI): 0.75 (0.63, 0.89) *p*=.001 UnadjHR (95%CI): 0.74 (0.63, 0.88) *p*=.0006	Heart Failure, rate per 1000 py (n) ATN: 7.5 (161) LOS: 7.1 (153) AdjHR (95% CI): 0.97 (0.78, 1.21) *p*=.765 UnadjHR (95%CI): 0.95 (0.76, 1.18) *p*=.622	PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py (n) ATN: 27.9 (588) LOS: 23.8 (508) AdjHR (95% CI): 0.87 (0.77, 0.98) *p*=.021 UnadjHR (95% CI): 0.85 (0.76, 0.96) *p*=.009 CV mortality, rate per 1000 py (n) ATN: 10.6 (234) LOS: 9.2 (204) AdjHR (95% CI): 0.89 (0.73, 1.07) *p*=.206 UnadjHR (95%CI): 0.87 (0.72, 1.05) *p*=.136		Withdrawals due to AE (derived from figure) ATN: between 15 and 20% LOS: between 10 and 15% New diabetes, rate per 1000 py (n) ATN: 17.4 (319) LOS: 13.0 (241) AdjHR (95% CI): 0.75 (0.63, 0.88) *p*=.001 UnadjHR (95% CI): 0.75 (0.63, 0.88) *p*=.001 Angioedema, n (%) ATN: 11 (0.2) LOS: 6 (0.1) *p*=.237 Lower extremity edema, n (%) ATN: 637 (14) LOS: 539 (12) *p*=.002 Cough, n (%) ATN: 113 (2) LOS: 133 (3) *p*=.220 Hypotension, n (%) ATN: 75 (2) LOS: 121 (3) *p*=.001 Dizziness, n (%) ATN: 727 (16) LOS: 771 (17) *p*=.247 Albuminuria, n (%) ATN: 293 (6) LOS: 213 (5) *p*=.0002 Hyperglycemia, n (%) ATN: 300 (7) LOS: 239 (5) *p*=.007 Asthenia/Fatigue, n (%) ATN: 802 (17) LOS: 691 (15) *p*=.001 Back pain, n (%) ATN: 477 (10) LOS: 568 (12) *p*=.004 Chest pain, n (%) ATN: 463 (10) LOS: 519 (11) *p*=.068 Dyspnea, n (%) ATN: 648 (14) LOS: 457 (10) *p*<.0001

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
LIFE *Subanalysis of Isolated Systolic Hypertension* Kjeldsen et al., 2002[93]	9,222; 1,326 with isolated systolic HTN	Mean 4.7 years	Fair	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): Atenolol100 mg + HCTZ 12.5–25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) 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)	Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG; included in subanalysis if SBP 160–200 mmHg with DBP <90 mmHg. BP inclusion criteria for LIFE trial: DBP 95–115 mmHg or SBP 160– 200 mmHg or both	*Subanalysis of patients with Isolated Systolic HTN* Total mortality, rate per 1000 py/n (%) ATN: 30.2/93 (14.0) LOS: 21.2/66 (10.0) AdjRR (95% CI): 0.72 (0.53, 1.00) *p*=.046 UnadjRR (95% CI): 0.70 (0.51, 0.96) *p*=.03 *Subanalysis of patients without Isolated Systolic HTN* Total mortality, rate per 1000 py/n (%) ATN: 17.9/338 (8.6) LOS: 16.7/317 (8.0) AdjRR (95% CI): 0.95 (0.82, 1.11) *p*=.51 UnadjRR (95% CI): 0.93 (0.80, 1.09) *p*=.3	*Subanalysis of patients with Isolated Systolic HTN* MI, rate per 1000 py/n (%) ATN: 11.9/36 (5.4) LOS: 10.2 /31 (4.7) AdjRR (95% CI): 0.89 (0.55, 1.44) *p*=.64 UnadjRR (95% CI): 0.86 (0.53, 1.39) *p*=.54 Revascularization, rate per 1000 py/n (%) ATN: 14.4/44 (6.6) LOS: 16.4/49 (7.4) AdjRR (95% CI): 1.17 (0.78, 1.77) *p*=.45 UnadjRR (95% CI): 1.14 (0.76, 1.72) *p*=.53 *Subanalysis of patients without Isolated Systolic HTN* MI, rate per 1000 py/n (%) ATN: 8.2/152 (3.9) LOS: 9.0/167 (4.2) AdjRR (95% CI): 1.12 (0.90, 1.40) *p*=.30 UnadjRR (95% CI): 1.10 (0.88, 1.36) *p*=.41 Revascularization, rate per 1000 py/n (%) ATN: 13.2/241 (6.1) LOS: 11.5/212 (5.4) AdjRR (95% CI): 0.89 (0.74, 1.08) *p*=.23 UnadjRR (95%CI): 0.87 (0.73, 1.05) *p*=.15	*Subanalysis of patients with Isolated Systolic HTN* Stroke, rate per 1000 py/n (%) ATN: 18.9/56 (8.4) LOS: 10.6/32 (4.8) AdjRR (95% CI): 0.60 (0.38, 0.92) *p*=.02 UnadjRR (95%CI): 0.56 (0.36, 0.86) *p*=.008 *Subanalysis of patients without Isolated Systolic HTN* Stroke, rate per 1000 py/n (%) ATN: 13.8/253 (6.5) LOS: 10.8/200 (5.1) AdjRR (95% CI): 0.79 (0.66, 0.95) *p*=.01 UnadjRR (95% CI): 0.78 (0.65, 0.94) *p*=.01	*Subanalysis of patients with Isolated Systolic HTN* Hospitalization for Heart Failure, rate per 1000 py/n (%) ATN:13.3/40 (6.0) LOS: 8.5/26 (3.9) AdjRR (95% CI): 0.66 (0.40, 1.09) *p*=.11 UnadjRR (95% CI): 0.64 (0.39, 1.05) *p*=.08 *Subanalysis of patients without Isolated Systolic HTN* Hospitalization for Heart Failure, rate per 1000 py/n (%) ATN: 6.5/121 (3.1) LOS: 6.8/127 (3.2) AdjRR (95% CI): 1.06 (0.83, 1.36) *p*=.65 UnadjRR (95% CI): 1.05 (0.82, 1.34) *p*=.72	*Subanalysis of patients with Isolated Systolic HTN* PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py /n (%) ATN: 35.4/104 (15.6) LOS: 25.1/75 (11.4) AdjRR (95% CI): 0.75 (0.56, 1.01) *p*=.06 UnadjRR (95% CI): 0.71 (0.53, 0.95) *p*=.02 CV mortality, rate per 1000 py/n (%) ATN: 16.9/52 (7.8) LOS: 8.7/27 (4.1) AdjRR (95% CI): 0.54 (0.34, 0.87) *p*=.01 UnadjRR (95% CI): 0.51 (0.32, 0.81) *p*=.004 *Subanalysis of patients without Isolated Systolic HTN* PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py /n (%) ATN: 26.7/484 (12.3) LOS: 23.6/433 (11.0) AdjRR (95% CI): 0.90 (0.79, 1.02) *p*=.11 UnadjRR (95%CI): 0.88 (0.78, 1.01) *p*=.06 CV mortality, rate per 1000 py/n (%) ATN: 9.6/182 (4.6) LOS: 9.3/177 (4.5) AdjRR (95% CI): 0.99 (0.80, 1.22) *p*=.90 UnadjRR (95% CI): 0.97 (0.79, 1.19) *p*=.77		Withdrawals due to all AE, % ATN: 22.1 LOS: 14.6 *p*<.001 Withdrawals due to drug related events, % ATN: 13.5 LOS: 7.1 *p*<.001 Withdrawals due to a serious AE, % ATN: 6.6 LOS: 4.6 *p*=.12 Withdrawals due to a serious AE and drug related, % ATN: 2.0 LOS: 1.2 *p*=.38 Angioedema, % ATN: 0.3 LOS: 0.3 *p*=.99 Cough, % ATN: 2.9 LOS: 4.1 *p*=.23 Bradycardia, % ATN: 14.6 LOS: 3.0 *p*<.001 Cold extremities, % ATN: 6.6 LOS: 4.1 *p*=.05 *Subanalysis of patients with Isolated Systolic HTN* New diabetes, rate per 1000 py/n (%) ATN: 20.1/48 (9.0) LOS: 12.6/32 (5.8) AdjHR (95% CI): 0.62 (0.40, 0.97) *p*=.04 UnadjHR (95% CI): 0.63 (0.40, 0.99) *p*=.04 *Subanalysis of patients without Isolated Systolic HTN* New diabetes, rate per 1000 py/n (%) ATN:17.0/272 (7.9) LOS: 13.1/210 (6.1) AdjRR (95% CI): 0.77(0.64, 0.92) *p*=.005 UnadjRR (95% CI): 0.77 (0.64, 0.92) *p*=.004

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
LIFE *Subanalysis of subjects with and without clinically evident vascular disease* Devereux et al., 2003[94]	9,222; 6,886 without clinically evident vascular disease at baseline	Mean 4.8 years	Fair	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): Atenolol100 mg + HCTZ 12.5–25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited) 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)	Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG. DBP 95–115 mmHg or SBP 160–200 mmHg or both.	*Subanalysis of subjects without clinically evident vascular disease* Total mortality, rate per 1000 py (n) ATN: 15.9 (268) LOS: 13.5 (223) AdjHR (95% CI): 0.85 (0.71, 1.02) *p*=.080 *Subanalysis of subjects with clinically evident vascular disease* Total mortality, rate per 1000 py (n) ATN: 31.7 (163) LOS: 28.5 (160) AdjHR (95% CI): 0.94 (0.75, 1.16) *p*>.2	*Subanalysis of subjects without clinically evident vascular disease* MI, rate per 1000 py (n) ATN: 6.0 (100) LOS: 6.8 (110) AdjHR (95% CI): 1.14 (0.87, 1.49) *p*>.2 Revascularization, rate per 1000 py (n) ATN: 9.0 (148) LOS: 7.6 (123) AdjHR (95% CI): 0.85 (0.67, 1.08) *p*=.18 *Subanalysis of subjects with clinically evident vascular disease* MI, rate per 1000 py (n) ATN: 17.7 (88) LOS: 16.3 (88) AdjHR (95% CI): 0.97 (0.72, 1.31) *p*>.2 Revascularization, rate per 1000 py (n) ATN: 28.4 (136) LOS: 26.3 (138) AdjHR (95% CI): 0.98 (0.78, 1.25) *p*>.2	*Subanalysis of subjects without clinically evident vascular disease* Stroke, rate per 1000 py (n) ATN: 11.8 (193) LOS: 7.7 (125) AdjHR (95% CI): 0.66 (0.53, 0.82) *p*<.001 *Subanalysis of subjects with clinically evident vascular disease* Stroke, rate per 1000 py (n) ATN: 23.7 (116) LOS: 20.0 (107) AdjHR (95% CI): 0.87 (0.67, 1.13) *p*>.2	*Subanalysis of subjects without clinically evident vascular disease* Hospitalization for Heart Failure, rate per 1000 py (n) ATN: 4.4 (74) LOS: 4.7 (76) AdjHR (95% CI): 1.06 (0.77, 1.46) *p*>.2 *Subanalysis of subjects with clinically evident vascular disease* Hospitalization for Heart Failure, rate per 1000 py (n) ATN: 17.7 (87) LOS: 14.2 (77) AdjHR (95% CI): 0.84 (0.62, 1.14) *p*>.2	*Subanalysis of subjects without clinically evident vascular disease* PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py (n) ATN: 21.8 (355) LOS: 17.5 (282) AdjHR (95% CI): 0.81 (0.69, 0.95) *p*=.008 CV mortality, rate per 1000 py (n) ATN: 7.8 (132) LOS: 6.2 (103) AdjHR (95% CI): 0.80 (0.62, 1.04) *p*=.092 *Subanalysis of subjects with clinically evident vascular disease* PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py (n) ATN: 48.6 (233) LOS: 43.0 (226) AdjHR (95% CI): 0.93 (0.77, 1.11) *p*>.2 CV mortality, rate per 1000 py (n) ATN: 19.8 (102) LOS: 18.0 (101) AdjHR (95% CI): 0.95 (0.72, 1.25) *p*>.2		Withdrawals due to all AE NR Patients with at least one AE of any type, % ATN: 17.3 LOS: 12.7 *p*<.001 Patients with at least one drug related AE, % ATN: 10.2 LOS: 6.0 *p*<.001 Patients with at least one serious AE, % ATN: 4.4 LOS: 3.8 *p*>.2 Patients with at least one serious drug related AE, % ATN: 1.0 LOS: 0.5 *p*=.018 Asthenia or fatigue, % ATN: 16.9 LOS: 14.2 *p*<.002 Lower extremity edema, % ATN: 13.6 LOS: 11.5 *p*<.008 Dyspnea, % ATN: 13.6 LOS: 8.8 *p*<.001 Hyperglycemia, % ATN: 6.7 LOS: 5.4 *p*=.023 Back pain, % ATN: 10.0 LOS: 12.0 *p*=.009 *Subanalysis of subjects without clinically evident vascular disease* New diabetes, rate per 1000 py (n) ATN: 17.7 (254) LOS: 12.2 (173) AdjHR (95% CI): 0.69 (0.57, 0.84) *p*<.001 *Subanalysis of subjects with clinically evident vascular disease* New diabetes, rate per 1000 py (n) ATN:16.4 (66) LOS: 15.5 (69) AdjHR (95% CI): 0.97 (0.69, 1.36) *p*>.2

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
MAPHY Wilkstrand et al., 1988;[63] Olsson et al., 1991;[64] Wilkstrand et al., 1991[95]	3,234	Median 4.16 years	Fair	MET: Metoprolol: 200 mg/d DIUR: Diuretic: HCTZ 50 mg/d or bendro-flumethiazide 5 mg/d To achieve goal, dosages could be doubled or other drugs added (hydralazine, spironolactone or others but not BB or thiazide diuretics) In 1981, max dose of baseline drugs reduced to 200 mg/d metoprolol, 50 mg/d HCTZ, or 5 mg/d bendro-flumethiazide 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.	Adult males, ages 40–64, either previously treated patients or newly detected and untreated HTN. DBP ≥100 mmHg and <130 mmHg.	At median 4.16 years PRIMARY OUTCOME: Total mortality, deaths per 1000 patient years (n) MET: 4.8 (28) DIUR: 9.3 (54) *p*=NR % difference (95% CI): –48 (–68, –17) At end of study (10.8 years) PRIMARY OUTCOME: Total mortality, deaths per 1000 patient years (n) MET: 8.0 (65) DIUR: 10.3 (83) *p*=NR % difference: –22 *p*=.028 Total sudden mortality, n MET: 32 DIUR: 45 *p*=.017	At 10.8 years PRIMARY OUTCOME: Fatal CHD (composite of MI or sudden coronary death), n MET: 36 DIUR: 43 *p*=.048	At 10.8 years Fatal stroke, n MET: 2 DIUR: 9 *p*=.043	At 10.8 years Fatal Heart Failure, n MET: 3 DIUR: 0 *p*=NR	At median 4.16 years First CV event: definite nonfatal acute MI, n (rate per 1000 py/FU) MET: 44 (5.7) DIUR: 53 (7.0) *p*=NR First CV event: definite nonfatal silent MI, n (rate per 1000 py/FU) MET: 37 (4.8) DIUR: 54 (7.1) *p*=NR First CV event: definite nonfatal stroke, n (rate per 1000 py/FU) MET: 21 (2.7) DIUR: 18 (2.4) *p*=NR First CV event, all definite events, n (rate per 1000 py/FU) MET: 134 (17.3) DIUR: 170 (22.3) RR (95% CI): 0.60 (0.44, 0.81) *p*=.0009 First CV event, all definite and possible events, n (rate per 1000 py/FU) MET: 178 (23.3) DIUR: 228 (30.5) *p*=.0011 First CV event: fatal coronary event, n (rate per 1000 py/FU) MET: 29 (3.7) DIUR: 34 (4.5) *p*=NR First CV event: fatal other CV event, n (rate per 1000 py/FU) MET: 1 (0.1) DIUR: 4 (0.5) *p*=NR First CV event: fatal stroke, n (rate per 1000 py/FU) MET: 2 (0.3) DIUR: 7 (0.9) *p*=NR CV mortality, deaths per 1000 patient years (n) MET: 2.6 (15) DIUR: 6.2 (36) *p*=NR % difference: –58 Sudden CV mortality, deaths per 1000 patient years (n) MET: 2.1 (12) DIUR: 4.8 (28) % difference: –56 *p*=NR At end of study (10.8 years) First CV event, all definite events MET vs. DIUR: RR (95% CI): 0.77 (0.61, 0.98) CV mortality, deaths per 1000 patient years (n) MET: 5.2 (42) DIUR: 7.1 (57) % difference: –27 *p*=.012 Sudden CV mortality, deaths per 1000 patient years (n) MET: 3.9 (32) DIUR: 5.6 (45) % difference: –30 *p*=.017		At 10.8 years Withdrawals due to AE: NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
IPPPSH IPPPSH Collaborative Group, 1985[67]	6,708	3 to 5 years (mean NR)	Fair	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	Adults, age 40–64 years with seated DBPs of 100–125 mmHg, either untreated or receiving anti- HTN at study entry.	Total mortality, rate per 1000 years BB: 8.3 Non-BB: 8.8 RR (95% CI): 0.95 (0.73, 1.24) *p*=NR	Nonfatal MI, rate per 1000 years BB: 4.4 Non-BB: 5.2 RR (95% CI): 0.84 (0.59, 1.20) *p*=NR All MI, rate per 1000 years BB: 4.7 Non-BB: 5.7 RR (95% CI): 0.83 (0.59, 1.16) *p*=NR All cardiac events, rate per 1000 years BB: 7.6 Non-BB: 8.4 RR (95% CI): 0.91 (0.69, 1.20) *p*=NR Fatal MI (first event analysis), rate per 1000 years BB: 0.3 Non-BB: 0.5 RR (95% CI): 0.66 (0.19, 2.34) *p*=NR Fatal MI (includes deaths following nonfatal events), rate per 1000 years BB: 0.3 Non-BB: 0.8 RR (95% CI): 0.40 (0.13, 1.29) *p*=NR Sudden death (first event analysis), rate per 1000 years BB: 2.9 Non-BB: 2.7 RR (95% CI): 1.08 (0.68, 1.72) *p*=NR Sudden death (includes deaths following nonfatal events), rate per 1000 years BB: 2.8 Non-BB: 2.8 RR (95% CI): 1.01 (0.63, 1.60) *p*=NR	Nonfatal CVA, rate per 1000 years BB: 3.1 Non-BB: 3.0 RR (95% CI): 1.04 (0.67, 1.63) *p*=NR All stroke (CVA), rate per 1000 years BB: 3.5 Non-BB: 3.6 RR (95% CI): 0.97 (0.64, 1.47) *p*=NR Fatal CVA (first event analysis), rate per 1000 years BB: 0.4 Non-BB: 0.6 RR (95% CI): 0.62 (0.20, 1.90) *p*=NR Fatal CVA (includes deaths following nonfatal events), rate per 1000 years BB: 0.4 Non-BB: 0.8 RR (95% CI): 0.50 (0.17, 1.47) *p*=NR		PRIMARY OUTCOME: Critical events of sudden cardiac death, fatal or nonfatal definite MI and cerebrovascular accidents, rate per 1000 years BB: 11.1 Non-BB: 12.0 RR (95% CI): 0.99 (0.79, 1.24) *p*=NR	Impaired renal function (creatinine >177 µmol/l and urea >10 mmol/l), n BB: 15 Non-BB: 23 *p*=NR	Withdrawals due to AE, NR Serum potassium <3.5 mmol/l on at least 1 occasion during study, % BB: 18 Non-BB: 29 *p*<.001 Serum potassium <3.0 mmol/l on at least 1 occasion during study, % BB: 2.6 Non-BB: 4.7 *p*=NR Cold extremities, n/1000 patients BB: 35.8 Non-BB: 19.2 *p*<.01 Dyspepsia, n/1000 patients BB: 114.9 Non-BB: 101.5 *p*<.05 Impotence and libido decrease, n/1000 patients BB: 79.8 Non-BB: 100.1 *p*<.05 Anxiety, depression, other emotional disorders, n/1000 patients BB: 148.5 Non-BB: 176.5 *p*<.01 Headache, n/1000 patients BB: 260.3 Non-BB: 312.1 *p*<.01 Dizziness, n/1000 patients BB: 142.5 Non-BB: 154.8 *p*<.05 Constipation, n/1000 patients BB: 349.4 Non-BB: 324.3 *p*<.05 Increased sweating, n/1000 patients BB: 494.6 Non-BB: 464.2 *p*<.05 Dry mouth, n/1000 patients BB: 423.2 Non-BB: 478.3 *p*<.01 Frequency and nocturia, n/1000 patients BB: 544.9 Non-BB: 593.3 *p*<.01

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
MRC Medical Research Council Working Party, 1985[35]	17,354	5.5 years	Fair	PRO: Propranolol: 240 mg QD BEN: Bendrofluazide: 10 mg QD If BP not at satisfactory response, could supplement with methyldopa (note: originally only used to supplement bendrofluazide and guanethidine used to supplement propranolol, but later only methyldopa used for any primary drug)	Adults, ages 35–64 years, with mild to moderate HTN. SBP <200 mmHg and DBP 90–109 mmHg.	PRIMARY OUTCOME: All deaths, n (rate per 1000 py) PRO: 120 (5.5) BEN: 128 (6.0) % difference: PRO: 6; BEN: –2; BEN vs. PRO: *p*=.71	PRIMARY OUTCOME: Coronary events, n (rate per 1000 py) PRO: 103 (4.8) BEN: 119 (5.6) % difference: BEN: –2 PRO: 13 BEN vs. PRO: *p*=.24	PRIMARY OUTCOME: Strokes, n (rate per 1000 py) PRO: 42 (1.9) BEN: 18 (0.8) % difference: BEN: 67 PRO: 24; BEN vs. PRO: *p*=.002		PRIMARY OUTCOME: All CV events, n (rate per 1000 py) PRO: 146 (6.7) BEN: 140 (6.6) % difference: PRO: 18 BEN: 20 BEN vs. PRO: *p*=.76		Withdrawals due to AE, % PRO: 6 BEN : 10 % calculated by reviewer

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
HAPPHY Wilhelmsen et al., 1987[62]	6,569	Mean 45.1 months	Fair	BB: Beta Blocker: 100 mg atenolol or 200 mg QD metoprolol DIUR: Diuretic: 50 mg HCTZ or 5 mg bendro-flumethazide If not at goal, additional drugs added until BP goal reached: Step 2 (until 1981) 2x original dose, however due to side effects of high doses and a "relatively flat" dose-response curve, the dose step was terminated in all patients Additional treatment for both groups included: Step 1: Hydralazine 75 mg Step 2: Hydralazine 150 mg Step 3: Hydralazine 150 mg + Spironolactone 75 mg Step 4: Hydralazine 150 mg + Spironolactone 150 mg Step 5: Hydralazine 150 mg + Spironolactone 150 mg + Optional drug	Adult men, ages 40–64 years, with mild to moderate HTN. DBP 100–130 mmHg.	PRIMARY OUTCOME: All deaths, n events (rate/1000 py) BB: 96 (7.73) DIUR: 101 (8.25) OR (95% CI): 1.06 (0.80, 1.41) *p*>.20	PRIMARY OUTCOME: Nonfatal MI, n events (rate/1000 py) BB: 84 (6.76) DIUR: 75 (6.13) OR (95% CI): 0.90 (0.66, 1.23) *p*>.20 PRIMARY OUTCOME: Fatal and/or nonfatal CHD, n events (rate/1000 py) BB: 132 (10.62) DIUR: 116 (9.48) OR (95% CI): 0.88 (0.68, 1.14) *p*>.20 PRIMARY OUTCOME: Fatal CHD, n events (rate/1000 py) BB: 54 (4.35) DIUR: 50 (4.09) OR (95% CI): 0.93 (0.64, 1.37) *p*>.20	Nonfatal stroke, n events (rate/1000 py) BB: 29 (2.33) DIUR: 32 (2.61) OR (95% CI): 1.11 (0.68, 1.83) *p*>.20 Fatal and/or nonfatal stroke, n events (rate/1000 py) BB: 32 (2.58) DIUR: 41 (3.35) OR (95% CI): 1.29 (0.82, 2.04) *p*>.20 Fatal stroke, n events (rate/1000 py) BB: 3 (0.24) DIUR: 10 (0.82) OR (95% CI): 3.37 (0.96, 9.53) *p*=.09	Heart failure, n events (rate/1000 py) BB: 32 (2.6) DIUR: 22 (1.8) *p*=NS	Patients with an endpoint of death, nonfatal MI, or nonfatal stroke, n events (rate/1000 py) BB: 197 (15.85) DIUR: 192 (15.69) OR (95% CI): 0.98 (0.80, 1.20) *p*>.20 Total endpoints of death, nonfatal MI, or nonfatal stroke, n events (rate/1000 py) BB: 225 (NR) DIUR: 224 (NR) OR (95% CI): 1.00 (0.83, 1.21) *p*>.20 Other deaths, n events (rate/1000 py) BB: 39 (3.14) DIUR: 41 (3.35) OR (95% CI): 1.06 (0.69, 1.64) *p*>.20	Serum Cr at last visit, (µmol/l) BB: 97.7 DIUR: 97.7 *p*=NS (value NR) Change in serum Cr from baseline, (µmol/l) BB: +4.0 DIUR: +4.2 *p*=NS (value NR)	Withdrawals due to AE, % BB: 2.0 DIUR: 2.4 *p*=NR Developed DM, n events (rate/1000 py) BB: 86 (6.9) DIUR: 75 (6.1) *p*=NS Reporting any symptoms related to drug at 12 month visit, % BB: 19.1 DIUR: 16.8 *p*<.001 Cold hands and feet, % BB: 21.4 DIUR: 12.7 *p*<.001 Dry mouth, % BB: 12.5 DIUR: 15.4 *p*<.002 Unusual tiredness, % BB: 18.2 DIUR: 15.4 *p*<.005

Table D–3c. Initial Treatment with ACEIs Versus Other Drugs

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
CAPPP Hansson et al., 1999;[96] Niskanen et al., 2001[75]	10,985	Mean 6.1 years	Fair	CAP: Captopril 50 mg QD, 100 mg QD or BID BB or DIUR: atenolol 50–100 mg QD; metoprolol 50–100 mg QD; HCTZ 25 mg QD; bendrofluazide 2.5 mg QD In conventional therapy group, BB and DIUR could be combined or CCB added to reach BP goals; for captopril group, treatment dose could be increased to 100 mg once or twice daily and if necessary a diuretic added; a calcium antagonist could be added.	Adults, ages 25–66 years, with treated or untreated primary HTN. DBP ≥100 mmHg.	All fatal events CAP vs. BB or DIUR: RR (95% CI): 0.93 (0.76, 1.14) *p*=.49	Nonfatal MI, n CAP: 137 BB or DIUR: 128 *p*=NR Ischemic heart disease, n CAP: 258 BB or DIUR: 251 *p*=NR MI, fatal and nonfatal CAP vs. BB or DIUR: RR (95% CI): 0.96 (0.77, 1.19) *p*=.68 Fatal MI, n CAP: 27 BB or DIUR: 35 *p*=NR Sudden death, n CAP: 6 BB or DIUR: 14 *p*=NR	Nonfatal stroke, n CAP: 173 BB or DIUR: 127 *p*=NR Stroke, fatal and nonfatal CAP vs. BB or DIUR: RR (95% CI): 1.25 (1.01, 1.55) *p*=.044 TIA, n CAP: 31 BB or DIUR: 25 *p*=NR Fatal stroke, n CAP: 20 BB or DIUR: 22 *p*=NR	CHF, n CAP: 75 BB or DIUR: 66 *p*=NR	PRIMARY OUTCOME: Combination of fatal and nonfatal MI and stroke, and other CV deaths CAP vs. BB or DIUR: RR (95% CI): 1.05 (0.90, 1.22) *p*=.52 All cardiac events CAP vs. BB or DIUR: RR (95% CI): 0.94 (0.83, 1.06) *p*=.30 Fatal CV events CAP vs. BB or DIUR: RR (95% CI): 0.77 (0.57, 1.04) *p*=.092 Other CV deaths, n CAP: 23 BB or DIUR: 24 *p*=NR		Withdrawals due to AE, % NR New onset DM CAP: 337 BB or DIUR: 380 CAP vs. BB or DIUR: RR (95% CI): 0.86 (0.74, 0.99) *p*=.039 Hansson et al 1999 Reported as: RR (95% CI): 0.79 (NR) *p*=.001 in Niskanen 2001

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ANBP2 Wing et al., 2003[61]	6,083	Median 4.1 years	Fair	ACE: ACE Inhibitor: Enalapril recommended; dose not specified DIUR: Diuretic: HCTZ recommended; dose not specified To achieve BP goal, addition of BB, CCB, and alpha-blockers recommended in both groups	Adults, ages 65–84, without recent CV events. SBP ≥160 mmHg or DBP ≥90 mmHg (if SBP ≥140 mmHg).	Death from any cause, rate per 1000 py (n of events) ACE: 15.7 (195) DIUR: 17.1 (210) HR (95% CI): 0.90 (0.75, 1.09) *p*=.27	Nonfatal MI, rate per 1000 py (n of events) ACE: 4.1 (50) DIUR: 5.8 (71) HR (95% CI): 0.68 (0.47, 0.99) *p*=.05 Nonfatal coronary event, rate per 1000 py (n of events) ACE: 11.6 (141) DIUR: 12.4 (149) HR (95% CI): 0.92 (0.73, 1.16) *p*=.49 MI, rate per 1000 py (n of events) ACE: 4.7 (58) DIUR: 6.7 (82) HR (95% CI): 0.68 (0.47, 0.98) *p*=.04 Coronary event, rate per 1000 py (n of events) ACE: 14.3 (173) DIUR: 16.2 (195) HR (95% CI): 0.86 (0.70, 1.06) *p*=.16 Fatal MI events, rate per 1000 py (n of events) ACE: 0.7 (9) DIUR: 0.9 (11) HR (95% CI): 0.79 (0.31, 1.99) *p*=.61 Fatal coronary events, rate per 1000 py (n of events) ACE: 3.2 (40) DIUR: 4.2 (52) HR (95% CI): 0.74 (0.49, 1.11) *p*= 0.14	Nonfatal stroke, rate per 1000 py (n of events) ACE: 7.5 (91) DIUR: 7.8 (94) HR (95% CI): 0.93 (0.70, 1.26) *p*=.65 Stroke, rate per 1000 py (n of events) ACE: 9.2 (112) DIUR: 8.8 (107) HR (95% CI): 1.02 (0.78, 1.33) *p*=.91 Cerebrovascular event, rate per 1000 py (n of events) ACE: 12.5 (152) DIUR: 13.6 (163) HR (95% CI): 0.90 (0.73, 1.12) *p*=.35 Fatal stroke events, rate per 1000 py (n) ACE: 2.3 (29) DIUR: 1.2 (15) HR (95% CI): 1.91 (1.04, 3.50) *p*=.04	Nonfatal HF, rate per 1000 py (n of events) ACE: 5.5 (68) DIUR: 6.3 (77) HR (95% CI): 0.85 (0.62, 1.17) *p*=.32 HF, rate per 1000 py (n of events) ACE: 5.6 (69) DIUR: 6.4 (78) HR (95% CI): 0.85 (0.62, 1.18) *p*=.33 Fatal HF events, rate per 1000 py (n of events) ACE: 0.2 (2) DIUR: 0.7 (8) HR (95% CI): 0.24 (0.03, 1.94) *p*=.18	Nonfatal CV event, rate per 1000 py (n of events) ACE: 28.9 (338) DIUR: 32.8 (380) HR (95% CI): 0.86 (0.74, 0.99) *p*=.03 Nonfatal other CV event, rate per 1000 py (n of events) ACE: 9.9 (120) DIUR: 11.3 (137) HR (95% CI): 0.84 (0.66, 1.07) *p*=.17 PRIMARY OUTCOME: All CV events or death from any cause, rate per 1000 py (n of events) ACE: 56.1 (695) DIUR: 59.8 (736) HR (95% CI): 0.89 (0.79, 1.00) *p*=.05 First CV event or death from any cause, rate per 1000 py (n of events) ACE: 41.9 (490) DIUR: 45.7 (529) HR (95% CI): 0.89 (0.79, 1.01) *p*=.06 First CV event, rate per 1000 py (n of events) ACE: 33.7 (394) DIUR: 37.1 (429) HR (95% CI): 0.88 (0.77, 1.01) *p*=.07 Other CV event, rate per 1000 py (n of events) ACE: 11.0 (134) DIUR: 11.9 (144) HR (95% CI): 0.90 (0.71, 1.14) *p*=.36 Fatal CV events, rate per 1000 py (n of events) ACE: 6.8 (84) DIUR: 6.7 (82) HR (95% CI): 0.99 (0.72, 1.35) *p*=.94 Fatal other CV events, rate per 1000 py (n of events) ACE: 1.2 (15) DIUR: 1.2 (15) HR (95% CI): 0.95 (0.46, 1.96) *p*=.89		Withdrawals due to AE, % NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ALLHAT ALLHAT Collaborative Research Group, 2002;[5] Davis et al 2006[65]	33,357	Mean 4.9 years	Good	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 Goal BP to be achieved by titration of assigned study drug (step 1) and when necessary addition of open-label agents at clinicians discretion (step 2: atenolol, reserpine, and clonidine or step 3: hydralazine) Note: randomization ratio was 1.7: 1:1 (chlorthalidone: amlodipine: lisinopril) resulting in larger sample size in chlorthalidone group	Adults, ≥55 years of age with at least one additional risk factor for CHD. SBP ≥140 and/or DBP ≥90 mmHg or on medications for HTN.	All-cause mortality, n of events (rate per 100 persons) LIS: 1,314 (17.2) CHL: 2,203 (17.3) AML: 1,256 (16.8) LIS vs. CHL: RR (95% CI): 1.00 (0.94, 1.08) *p*=.90 AML vs. LIS: NR	PRIMARY OUTCOME: CHD (combined fatal CHD and nonfatal MI), n of events (rate per 100 persons) LIS: 796 (11.4) CHL: 1,362 (11.5) AML: 798 (11.3) LIS vs. CHL: RR (95% CI): 0.99 (0.91, 1.08) *p*=.81 AML vs. LIS: NR Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina) (rate per 100 events) LIS: 1,505 (20.8) CHL: 2,451 (19.9) AML: 1,466 (19.9) LIS vs. CHL: RR (95% CI): 1.05 (0.98, 1.11) *p*=.18 AML vs. LIS: NR Coronary revascularization, n of events (rate per 100 persons) LIS: 718 (10.2) CHL: 1,113 (9.2) AML: 725 (10.0) LIS vs. CHL: RR (95% CI): 1.10 (1.00, 1.21) *p*=.05 AML vs. LIS: NR Hospitalized or treated PAD, n of events (rate per 100 persons) LIS: 311 (4.7) CHL: 510 (4.1) AML: 265 (3.7) LIS vs. CHL: RR (95% CI): 1.04 (0.90, 1.19) *p*=.63 AML vs. LIS: NR MI death, n of events (rate per 100 persons) LIS: 157 (2.2) CHL: 296 (2.4) AML: 169 (2.3) LIS vs. CHL: *p*=.25 AML vs. LIS: NR Definite CHD death, n of events (rate per 100 persons) LIS: 77 (1.0) CHL: 118 (1.1) AML: 72 (1.2) LIS vs. CHL: *p*=.52 AML vs. LIS: NR Possible CHD death, n of events (rate per 100 persons) LIS: 95 (1.4) CHL: 128 (1.1) AML: 71 (1.1) LIS vs. CHL: *p*=.10 AML vs. LIS: NR	Stroke, n of events (rate per 100 persons) LIS: 457 (6.3) CHL: 675 (5.6) AML: 377 (5.4) LIS vs. CHL: RR (95% CI): 1.15 (1.02, 1.30) *p*=.02 AML vs. LIS: NR Death from stroke, n of events (rate per 100 persons) LIS: 121 (1.7) CHL: 162 (1.4) AML: 92 (1.4) LIS vs. CHL: *p*=.06 AML vs. LIS: NR	HF, n of events (rate per 100 persons) LIS: 612 (8.7) CHL: 870 (7.7) AML: 706 (10.2) LIS vs. CHL: RR (95% CI): 1.19 (1.07, 1.31) *p*<.001 AML vs. LIS: NR Hospitalized/fatal HF, n of events (rate per 100 persons) LIS: 471 (6.9) CHL: 724 (6.5) AML: 578 (8.4) LIS vs. CHL: RR (95% CI): 1.10 (0.98, 1.23) *p*=.11 AML vs. LIS*: RR (95% CI) for AML: 1.23 (1.09, 1.38) *p*<.001 *reported in Davis HF death, n of events (rate per 100 persons) LIS: 68 (1.1) CHL: 114 (1.0) AML: 83 (1.4) LIS vs. CHL: *p*=.98 AML vs. LIS: NR	Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization), n of events (rate per 100 events) LIS: 2,514 (33.3) CHL: 3,941 (30.9) AML: 2,432 (32.0) LIS vs. CHL: RR (95% CI): 1.10 (1.05, 1.16) *p*<.001 AML vs. LIS: NR Cardiovascular death, n of events (rate per 100 persons) LIS: 618 (8.5) CHL: 992 (8.0) AML: 603 (8.5) LIS vs. CHL: *p*=.39 AML vs. LIS: NR Other CVD death, n of events (rate per 100 persons) LIS:100 (1.5) CHL: 178 (1.4) AML: 116 (1.7) LIS vs. CHL: *p*=.66 AML vs. LIS: NR	ESRD, n of events (rate per 100 persons) LIS: 126 (2.0) CHL: 193 (1.8) AML: 129 (2.1) LIS vs. CHL: RR (95% CI): 1.11 (0.88, 1.38) *p*=.38 AML vs. LIS: NR Kidney disease death, n of events (rate per 100 persons) LIS: 27 (0.5) CHL: 36 (0.4) AML: 24 (0.5) LIS vs. CHL: *p*=.37 AML vs. LIS: NR	Withdrawals due to AE, % LIS: 2.9 CHL: 1.8 AML: 2.0 % calculated by reviewer Angioedema, n events (%) LIS: 38 (0.4) CHL: 8 (0.1) AML: 3 (<0.1) LIS vs. CHL: *p*<.001 LIS vs. AML: NR At 4 years Fasting glucose progressing to ≥126 mg/dL among non-DM with baseline fasting glucose <126 mg/dL, n (%): LIS: 119 (8.1) CHL: 302 (11.6) AML: 154 (9.8) LIS vs. CHL: *p*<.001 LIS vs. AML: NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
ALLHAT Leenen et al., 2006[50]	18,102 for LIS vs. AML comparison	Mean 4.9 years	Fair	LIS: Lisinopril: 10, 20, and 40 mg QD AML: Amlodipine: 2.5, 5, and 10 mg QD Goal BP to be achieved by titration of assigned study drug (step 1) and when necessary addition of open-label agents at clinicians discretion (step 2: atenolol, reserpine, and clonidine or step 3: hydralazine)	Adults, ≥55 years of age with at least one additional risk factor for CHD. SBP ≥140 and/or DBP ≥90 mmHg or on medications for HTN.	All-cause mortality, n of events (rate per 100 persons) LIS: 1,314 (17.2) AML: 1,256 (16.8) LIS vs. AML: RR (95% CI): 1.05 (0.97, 1.13) *p*=.214	PRIMARY OUTCOME: CHD (fatal CHD and nonfatal MI), n of events (rate per 100 persons) LIS: 796 (11.4) AML: 798 (11.3) LIS vs. AML: RR (95% CI): 1.01 (0.91, 1.11) *p*=.854 Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina), n of events (rate per 100 events) LIS: 1,505 (20.8) AML: 1,466 (19.9) LIS vs. AML: RR (95% CI): 1.04 (0.97, 1.12) *p*=.243 Coronary revascularization, n of events (rate per 100 persons) LIS: 718 (10.2) AML: 725 (10.0) LIS vs. AML: RR (95% CI): 1.00 (0.91, 1.11) *p*=.943 Hospitalized or fatal PAD, n of events (rate per 100 persons) LIS: 311 (4.7) AML: 265 (3.7) LIS vs. AML: RR (95% CI): 1.19 (1.01, 1.40) *p*=.036	Stroke, n of events (rate per 100 persons) LIS: 457 (6.3) AML: 377 (5.4) LIS vs. AML: RR (95% CI): 1.23 (1.08, 1.41) *p*=.003	HF, n of events (rate per 100 persons) LIS: 612 (8.7) AML: 706 (10.2) LIS vs. AML: RR (95% CI): 0.87 (0.78, 0.96) *p*=.007 Hospitalized/fatal HF, n of events (rate per 100 persons) LIS: 471 (6.9) AML: 578 (8.4) LIS vs. AML: RR (95% CI): 0.81 (0.72, 0.92) *p*<.001	Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization), n of events (rate per 100 events) LIS: 2,514 (33.3) AML: 2,432 (32.0) LIS vs. AML: RR (95% CI): 1.06 (1.00, 1.12) *p*=.047	ESRD, n of events (event rate per 100 persons) LIS: 126 (2.0) AML: 129 (2.1) LIS vs. AML: RR (95% CI): 0.99 (0.77, 1.26) *p*=.929	Withdrawals due to AE, % NR Angioedema, n events (%) LIS: 38 (0.42) AML: 3 (0.03) *p*<.001 Hospitalization for GI bleeding, n (6-year rate per 100) LIS: 526 (9.6) AML: 449 (8.0) *p*=.04 At 4 years DM (≥7.0 mmol/L) if no DM at baseline, n (%): LIS: 139 (9.4) AML: 163 (10.4) LIS vs. AML: *p*=.30

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
JMIC-B Yui et al., 2004[97]	1,650	Median 35.7 months	Fair	ACE: ACE inhibitor: enalapril 5–10 mg, or imidapril 5–10 mg, or lisinopril 10–20 mg NIF: Nifedipine long acting10–20 mg BID If BP reduction was unsatisfactory, an alpha-blocker was administered concomitantly. If the antianginal effect of the treatment was inadequate, long-acting or short-acting nitrates and/or BB were used concomitantly.	Adults, ages <75 years with HTN and CAD. SBP ≥160 mmHg or DBP ≥95 mmHg.	Total mortality, n of patients with event (%) ACE: 15 (1.8) NIF: 12 (1.4) ACE vs. NIF: RR (95% CI): 0.76 (0.35, 1.63) *p*=.48	MI, n of patients with event (%) ACE: 13 (1.6) NIF: 16 (1.9) ACEI vs. NIF: RR (95% CI): 1.31 (0.63, 2.74) *p*=.47 Coronary intervention of PTCA, CABG, stenting, n of patients with event (%) ACE: 75 (NR) NIF: 81 (NR) ACE vs. NIF: RR (95% CI): 1.04 (0.76,1.43) *p*=.81 Sudden death/cardiac death, n of patients with event (%) ACE: 6 (0.7) NIF: 6 (0.7) ACE vs. NIF: RR (95% CI): 0.96 (0.31, 3.04) *p*=.95	Cerebrovascular accidents, n of patients with event (%) ACE: 16 (NR) NIF: 16 (NR) ACE vs. NIF: RR (95% CI): 1.00 (0.50, 2.02) *p*=.99	HF requiring hospitalization, n of patients with event (%) ACE: 9 (NR) NIF: 12 (NR) ACE vs. NIF: RR (95% CI): 1.25 (0.52, 2.98) *p*=.62	PRIMARY OUTCOME: Cardiac events (composite of cardiac or sudden death, MI, angina pectoris requiring hospitalization, HF requiring hospitalization, serious arrhythmia, coronary interventions), n of patients with event (%) ACE: 106 (12.9) NIF: 116 (14.0) ACE vs. NIF: RR (95% CI): 1.05 (0.81, 1.37) *p*=.75 Noncardiac death, n of patients with event (%) ACE: 9 (NR) NIF: 6 (NR) ACE vs. NIF: RR (95% CI): 0.64 (0.23, 1.81) *p*=.40	Worsening of renal dysfunction with serum Cr > 353.6 µmol/l, n of patients with event (%) ACE: 2 (NR) NIF: 6 (NR) ACE vs. NIF: RR (95% CI): 2.70 (0.54, 13.49) *p*=.23	Withdrawals due to AE, % ACE: 8.8 NIF: 5.0 *p*=.002 *Withdrawals by AE* Hypotension, n (%) ACE: 2 (0.2) NIF: 8 (1.0) *p*<.01 Edema, n (%) ACE: 0 NIF: 7 (0.8) *p*<.01 Facial erythema, hot flushes, n (%) ACE: 0 NIF: 6 (0.7) *p*<.05 Dry cough, n (%) ACE: 60 (7.3) NIF: 0 *p*<.01

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	AE
STOP Hypertension-2 Hansson et al., 1999[52]	6,614	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	Good	ACE: ACE inhibitors: enalapril 10 mg, or 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 BB patients given HCTZ 25 mg plus amiloride 2.5 mg as additional treatment if target BP not met at 2-month visit or later. Patients started on diuretic treatment or calcium antagonist were given any of the BB in the doses listed, and patients on ACE inhibitors were given HCTZ 12.5–25.0 mg.	Adults 70–84 years old with HTN. SBP ≥180 mmHg, DBP ≥105 mmHg or both.	Total mortality, events per 1000 p-y (no. of events) ACE: 34.4 (380) CCB: 32.8 (362) BB or DIUR: 33.1 (369) ACE vs. CCB: RR (95% CI): 1.03 (0.69, 1.19) *p*=.71 ACE vs. BB or DIUR: RR (95% CI): 1.02 (0.69, 1.16) *p*=.76	All MI, events per 1000 p-y (no. of events) ACE: 12.8 (139) CCB: 16.7 (179) BB or DIUR: 14.1 (154) ACE vs. CCB: RR (95% CI): 0.77 (0.61, 0.96) *p*=.016 ACE vs. BB or DIUR: RR (95%CI): 0.90 (0.72, 1.13) *p*=.36 Sudden death, events per 1000 p-y (no. of events) ACE: 5.3 (59) CCB: 4.7 (52) BB or DIUR: 4.8 (53) *p*=NR Fatal MI, events per 1000 p-y (no. of events) ACE: 4.3 (48) CCB: 5.3 (59) BB or DIUR: 4.9 (55) *p*=NR	All stroke, events per 1000 p-y (no. of events) ACE: 20.2 (215) CCB: 19.5 (207) BB or DIUR: 22.2 (237) ACE vs. CCB: RR (95% CI): 1.02 (0.64, 1.24) *p*=.64 ACE vs. BB or DIUR: RR (95% CI): 0.90 (0.74, 1.06) *p*=.24 Fatal stroke, events per 1000 p-y (no. of events) ACE: 4.5 (50) CCB: 4.2 (46) BB or DIUR: 4.6 (51) *p*=NR	Frequency CHF, events per 1000 p-y (no. of events) ACE: 13.9 (149) CCB: 17.5 (186) BB or DIUR: 16.4 (177) ACE vs. CCB: RR (95% CI): 0.76 (0.63, 0.97) *p*=.025 ACE vs. BB or DIUR: RR (95% CI): 0.63 (0.67, 1.03) *p*=.095	All major CV events, events per 1000 p-y (no. of events) ACE: 41.9 (437) CCB: 43.6 (450) BB or DIUR: 44.1 (460) ACE vs. CCB: RR (95% CI): 0.95 (0.63–1.06) *p*=.42 ACE vs. BB or DIUR: RR (95% CI): 0.94 (0.62, 1.07) *p*=.32 PRIMARY OUTCOME: CV mortality, events per 1000 p-y (no. of events) ACE: 20.5 (226) CCB: 19.2 (212) BB or DIUR: 19.8 (221) ACE vs. CCB: RR (95% CI): 1.04 (0.66, 1.26) *p*=.67 ACE vs. BB or DIUR: RR (95% CI): 1.01 (0.64, 1.22) *p*=.69 Other CV mortality, events per 1000 p-y (no. of events) ACE: 6.2 (69) CCB: 5.0 (55) BB or DIUR: 5.6 (62) *p*=NR		Frequency of DM, events per 1000 p-y (no. of events) ACE: 9.6 (93) CCB: 9.9 (95) BB or DIUR: 10.0 (97) ACE vs. CCB: RR (95% CI): 0.96 (0.74, 1.31) *p*=.91 ACE vs. BB or DIUR: RR (95% CI): 0.96 (0.72, 1.27) *p*=.77 Ankle edema, % ACE: 8.7 CCB: 25.5 BB or DIUR: 8.5 *p*=NR Dry cough, % ACE: 30.1 CCB: 5.7 BB or DIUR: 3.7 *p*=NR Dizziness, % ACE: 27.7 CCB: 24.5 BB or DIUR: 27.8 *p*=NR

Table D–3d. Initial Treatment With Calcium Channel Blockers Versus Other Drugs

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
ALLHAT ALLHAT Collaborative Research Group, 2002;[5] Davis et al., 2006[65]	33,357	Mean 4.9 years	Good	AML: Amlodipine: 2.5, 5, and 10 mg QD LIS: Lisinopril: 10, 20, and 40 mg QD CHL: Chlorthalidone: 12.5, 25 mg QD Goal BP to be achieved by titration of assigned study drug (step 1) and when necessary addition of open-label agents at clinicians discretion (step 2: atenolol, reserpine, and clonidine or step 3: hydralazine). Note: randomization ratio was 1.7:1:1 (chlorthalidone: amlodipine: lisinopril) resulting in larger sample size in chlorthalidone group	Adults, ≥55 years of age with at least one additional risk factor for CHD. SBP ≥140 and/or DBP ≥90 mmHg or on medications for HTN.	All-cause mortality, n of events (rate per 100 persons) AML: 1,256 (16.8) LIS: 1,314 (17.2) CHL: 2,203 (17.3) AML vs. CHL: RR (95% CI): 0.96 (0.89, 1.02) *p*=.20	PRIMARY OUTCOME: CHD (fatal CHD and nonfatal MI), n of events (rate per 100 persons) AML: 798 (11.3) LIS: 796 (11.4) CHL: 1,362 (11.5) AML vs. CHL: RR (95% CI): 0.98 (0.90, 1.07) *p*=.65 Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina), n of events (rate per 100 events) AML: 1,466 (19.9) LIS: 1,505 (20.8) CHL: 2,451 (19.9) AML vs. CHL: RR (95% CI): 1.00 (0.94, 1.07) *p*=.97 Coronary revascularization, n of events (rate per 100 persons) AML: 725 (10.0) LIS: 718 (10.2) CHL: 1,113 (9.2) AML vs. CHL: RR (95% CI): 1.09 (1.00, 1.20) *p*=.06 Hospitalized or treated PAD, n of events (rate per 100 persons) AML: 265 (3.7) LIS: 311 (4.7) CHL: 510 (4.1) AML vs. CHL: RR (95% CI): 0.87 (0.75, 1.01) *p*=.06 MI death, n of events (rate per 100 persons) AML: 169 (2.3) LIS: 157 (2.2) CHL: 296 (2.4) AML vs. CHL: RR (95% CI): NR *p*=.66 Definite CHD death, n of events (rate per 100 persons) AML: 72 (1.2) LIS: 77 (1.0) CHL: 118 (1.1) AML vs. CHL: RR (95% CI): NR *p*=.88 Possible CHD death, n of events (rate per 100 persons) AML: 71 (1.1) LIS: 95 (1.4) CHL: 128 (1.1) AML vs. CHL: RR (95% CI): NR *p*=.62	Stroke, n of events (rate per 100 persons) AML: 377 (5.4) LIS: 457 (6.3) CHL: 675 (5.6) AML vs. CHL: RR (95% CI): 0.93 (0.82, 1.06) *p*=.28 Death from stroke, n of events (rate per 100 persons) AML: 92 (1.4) LIS: 121 (1.7) CHL: 162 (1.4) AML vs. CHL: RR (95% CI): NR *p*=.71	HF, n of events (rate per 100 persons) AML: 706 (10.2) LIS: 612 (8.7) CHL: 870 (7.7) AML vs. CHL: RR (95% CI): 1.38 (1.25, 1.52) *p*<.001 Hospitalized/fatal HF, n of events (rate per 100 persons) AML: 578 (8.4) LIS: 471 (6.9) CHL: 724 (6.5) AML vs. CHL: RR (95% CI): 1.35 (1.21, 1.50) *p*<.001 AML vs. LIS*: RR (95% CI): 1.23 (1.09, 1.38) *p*<.001 *reported in Davis 2006 HF death, n of events (rate per 100 persons) AML: 83 (1.4) LIS: 68 (1.1) CHL: 114 (1.0) AML vs. CHL: RR (95% CI): NR *p*=.17	Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization), n of events (rate per 100 events) AML: 2,432 (32.0) LIS: 2,514 (33.3) CHL: 3,941 (30.9) AML vs. CHL: RR (95% CI): 1.04 (0.99, 1.09) *p*=.12 Cardiovascular death, n of events (rate per 100 persons) AML: 603 (8.5) LIS: 618 (8.5) CHL: 992 (8.0) AML vs. CHL: RR (95% CI): NR *p*=.76 Other CVD death, n of events (rate per 100 persons) AML: 116 (1.7) LIS: 100 (1.5) CHL: 178 (1.4) AML vs. CHL : RR (95% CI): NR *p*=.46	ESRD, n of events (event rate per 100 persons) AML: 129 (2.1) LIS: 126 (2.0) CHL: 193 (1.8) AML vs. CHL: RR (95% CI): 1.12 (0.89, 1.40) *p*=.33 Kidney disease death, n of events (event rate per 100 persons) AML: 24 (0.5) LIS: 27 (0.5) CHL: 36 (0.4) AML vs. CHL: RR (95% CI): NR *p*=.68	Withdrawals due to AE, % AML: 2.0 LIS: 2.9 CHL: 1.8 % calculated by reviewer Angioedema, n events (%) AML: 3 (<0.1) LIS: 38 (0.4) CHL: 8 (0.1) *p*=NR At 4 years Fasting glucose progressing to ≥126 mg/dL among non-DM with baseline fasting glucose <126 mg/dL, n (%): AML: 154 (9.8) LIS: 119 (8.1) CHL: 302 (11.6) AML vs. CHL: *p*=.04

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
ALLHAT Leenen et al., 2006[50]	18,102 for LIS vs. AML comparison	Mean 4.9 years	Fair	AML: Amlodipine: 2.5, 5, and 10 mg QD LIS: Lisinopril: 10, 20, and 40 mg QD Goal BP to be achieved by titration of assigned study drug (step 1) and when necessary addition of open-label agents at clinicians discretion (step 2: atenolol, reserpine, and clonidine or step 3: hydralazine)	Adults, ≥55 years of age with at least one additional risk factor for CHD. SBP ≥140 and/or DBP ≥90 mmHg or on medications for HTN.	All-cause mortality, n of events (rate per 100 persons) AML: 1,256 (16.8) LIS: 1,314 (17.2) LIS vs. AML: RR (95% CI): 1.05 (0.97, 1.13) *p*=.214	PRIMARY OUTCOME: CHD (fatal CHD and nonfatal MI), n of events (rate per 100 persons) AML: 798 (11.3) LIS: 796 (11.4) LIS vs. AML: RR (95% CI): 1.01 (0.91, 1.11) *p*=.854 Combined CHD (CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina), n of events (rate per 100 events) AML: 1,466 (19.9) LIS: 1,505 (20.8) LIS vs. AML: RR (95% CI): 1.04 (0.97, 1.12) *p*=.243 Coronary revascularization, n of events (rate per 100 persons) AML: 725 (10.0) LIS: 718 (10.2) LIS vs. AML: RR (95% CI): 1.00 (0.91, 1.11) *p*=.943 Hospitalized or fatal PAD, n of events (rate per 100 persons) AML: 265 (3.7) LIS: 311 (4.7) LIS vs. AML: RR (95% CI): 1.19 (1.01, 1.40) *p*=.036	Stroke, n of events (rate per 100 persons) AML: 377 (5.4) LIS: 457 (6.3) LIS vs. AML: RR (95% CI): 1.23 (1.08, 1.41) *p*=.003	HF, n of events (rate per 100 persons) AML: 706 (10.2) LIS: 612 (8.7) LIS vs. AML: RR (95% CI): 0.87 (0.78, 0.96) *p*=.007 Hospitalized/fatal HF, n of events (rate per 100 persons) AML: 578 (8.4) LIS: 471 (6.9) LIS vs. AML: RR (95% CI): 0.81 (0.72, 0.92) *p*<.001	Combined CVD (CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and PAD, hospitalized or outpatient revascularization), n of events (rate per 100 events) AML: 2,432 (32.0) LIS: 2,514 (33.3) LIS vs. AML: RR (95% CI): 1.06 (1.00, 1.12) *p*=.047	ESRD, n of events (event rate per 100 persons) AML: 129 (2.1) LIS: 126 (2.0) LIS vs. AML: RR (95% CI): 0.99 (0.77, 1.26) *p*=.929	Withdrawals due to AE, % NR Angioedema, n events (%) AML: 3 (0.03) LIS: 38 (0.42) p<.001 Hospitalization for GI bleeding, n (6-year rate per 100) AML: 449 (8.0) LIS: 526 (9.6) *p*=.04 At 4 years DM (≥7.0 mmol/L) if no DM at baseline, n (%): AML: 163 (10.4) LIS: 139 (9.4) LIS vs. AML: *p*=.30

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
CASE-J Ogihara, 2008[55]	4,728	Mean 3.2 years	Good	AML: Amlodipine 2.5–10 mg/day CAN: Candesartan 4–12 mg/day Dose of randomized drug titrated upward to achieve BP goal; diuretics, alpha blockers, BB, or alpha and BB added (and titrated upward) to achieve BP goal.	Adults with high CVD risk. For those <70 years old SBP ≥140 mmHg and <200 mmHg or DBP ≥90 mmHg and <120 mmHg. For those ≥70 years old SBP ≥160 mmHg and <200 mmHg or DBP ≥90 mmHg and <120 mmHg.	All-cause death, n of events (rate per 1000 p-y) AML: 86 (11.1) CAN: 73 (9.4) HR (95% CI): NR *p*=NS	Acute MI, n of events (%) AML: 18 (0.8) CAN: 17 (0.7) CAN vs. AML: HR (95% CI) for CAN: 0.95 (0.49, 1.84) *p*=.870 Sudden death, n of events (%) AML: 15 (0.6) CAN: 11 (0.5) CAN vs. AML: HR (95% CI) for CAN: 0.73 (0.34, 1.60) *p*=.434	Cerebrovascular events, n of events (%) AML: 50 (2.1) CAN: 61 (2.6) CAN vs. AML: HR (95% CI) for CAN: 1.23 (0.85, 1.78) *p*=.282 Stroke, n of events (%) AML: 47 (2.0) CAN: 60 (2.5) CAN vs. AML: HR (95% CI) for CAN: 1.28 (0.88, 1.88) *p*=.198 TIA, n of events (%) AML: 4 (0.2) CAN: 2 (0.1) CAN vs. AML: HR (95% CI) for CAN: 0.50 (0.09, 2.73) *p*=.414	Heart Failure, n of events (%) AML: 16 (0.7) CAN: 20 (0.8) CAN vs. AML: HR (95% CI) for CAN: 1.25 (0.65, 2.42) *p*=.498	PRIMARY OUTCOME: Primary composite endpoint, n of events (%) AML: 134 (5.7) CAN: 134 (5.7) CAN vs. AML: HR (95% CI) for CAN: 1.01 (0.79, 1.28) *p*=.969 Cardiac events, n of events (%) AML: 47 (2.0) CAN: 43 (1.8) CAN vs. AML: HR (95% CI) for CAN: 0.92 (0.61, 1.39) *p*=.680 Peripheral vascular events, n of events (%) AML: 7 (0.3) CAN: 11 (0.5) CAN vs. AML: HR (95% CI) for CAN: 1.57 (0.61, 4.05) *p*=.348	Renal events, n of events (%) AML: 27 (1.1) CAN: 19 (0.8) CAN vs. AML: HR (95% CI) for CAN: 0.70 (0.39, 1.26) *p*=.230 Creatinine abnormality, n of events (%) AML: 26 (1.1) CAN: 19 (0.8) CAN vs. AML: HR (95% CI) for CAN: 0.73 (0.40, 1.31) *p*=.287 ESRD, n of events (%) AML: 10 (0.4) CAN: 4 (0.2) CAN vs. AML: HR (95% CI) for CAN: 0.40 (0.13, 1.29) *p*=.112	Withdrawals due to AE, % AML: 5.8 CAN: 5.4 New onset diabetes, rate per 1000 p-y AML: 13.6 CAN: 8.7 HR (95% CI) for CAN: 0.64 (0.43, 0.97) p=0.011 Hyperkalemia,% AML: 0.3 CAN: 1.0 *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
ASCOT-BPLA Dahlöf et al., 2005[7]	19,342	Median 5.5 years	Good	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	Adults, age 40–79 years, with HTN and at least 3 CV risk factors. BP inclusion criteria for untreated HTN was SBP ≥160 or DBP ≥100 mmHg or both. BP inclusion criteria for treated HTN was SBP ≥140 mmHg or more or DBP ≥90 mmHg or both.	All-cause mortality, rate per 1000 pts (n of pts) AML: 13.9 (738) ATN: 15.5 (820) HR (95% CI): 0.89 (0.81, 0.99) *p*=.0247	Total coronary endpoint, rate per 1000 pts (n of pts) AML: 14.6 (753) ATN: 16.8 (852) HR (95% CI): 0.87 (0.79, 0.96) *p*=.0070 Silent MI, rate per 1000 pts (n of pts) AML: 0.8 (42) ATN: 0.6 (33) HR (95% CI): 1.27 (0.80, 2.00) *p*= 0.3089 PAD, rate per 1000 pts (n of pts) AML: 2.5 (133) ATN: 3.9 (202) HR (95% CI): 0.65 (0.52, 0.81) *p*= 0.0001	Fatal and nonfatal stroke, rate per 1000 pts (n of pts) AML: 6.2 (327) ATN: 8.1 (422) HR (95% CI): 0.77 (0.66, 0.89) *p*=.0003	Fatal and nonfatal HF, rate per 1000 pts (n of pts) AML: 2.5 (134) ATN: 3.0 (159) HR (95% CI): 0.84 (0.66, 1.05) *p*=.1257	PRIMARY OUTCOME: Nonfatal MI (including silent MI) and fatal CHD, rate per 1000 pts (n of pts) AML: 8.2 (429) ATN: 9.1 (474) HR (95% CI): 0.90 (0.79, 1.02) *p*= 0.1052 Nonfatal MI (excluding silent MI) and fatal CHD, rate per 1000 pts (n of pts) AML: 7.4 (390) ATN: 8.5 (444) HR (95% CI): 0.87 (0.76, 1.00) *p*= 0.0458 Total CV events and procedures, rate per 1000 pts (n of pts) AML: 27.4 (1362) ATN: 32.8 (1602) HR (95% CI): 0.84 (0.78, 0.90) *p*<.0001 Composite of primary endpoints of nonfatal MI including silent MI and fatal CHD plus coronary revascularization procedures, rate per 1000 pts (n of pts) AML: 11.5 (596) ATN: 13.4 (688) HR (95% CI): 0.86 (0.77, 0.96) *p*=.0058 CV death, MI and stroke, rate per 1000 pts (n of pts) AML: 15.4 (796) ATN: 18.4 (937) HR (95% CI): 0.84 (0.76, 0.92) *p*=.0003 CV mortality, rate per 1000 pts (n of pts) AML: 4.9 (263) ATN: 6.5 (342) HR (95% CI): 0.76 (0.65, 0.90) *p*=.0010	Note: component of renal impairment do not meet outcome criteria for this question	Withdrawals due to AE (# stopping trial early due to serious adverse events), % AML: 2 ATN: 3 *p*<.0001 Development of DM, n (%) AML: 567 (11.0) ATN: 799 (15.9) HR (95% CI): 0.70 (0.63, 0.78) *p*<.0001 Cough, n (%) AML: 1859 (19) ATN: 782 (8) *p*<.0001 Peripheral edema, n (%) AML: 2188 (23) ATN: 588 (6) *p*<.0001 Dizziness, n (%) AML: 1183 (12) ATN: 1555 (16) *p*<.0001 Dyspnoea, n (%) AML: 599 (6) ATN: 987 (10) *p*<.0001 Fatigue, n (%) AML: 782 (8) ATN: 1,556 (16) *p*<.0001 Joint swelling, n (%) AML: 1371 (14) ATN: 308 (3) *p*<.0001

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
VALUE Julius et al., 2004;[54] Kjeldsen et al., 2006[98]	15,313	Mean exposure to study medication of 3.6 years; mean 4.2 years F/U	Good	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 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	Adults, ≥50 years with treated or untreated HTN and predefined combinations of CV risk factors or CVD. SBP 160–210 mmHg, DBP <115 mmHg.	All-cause death, n (%) AML: 818 (10.8) VAL: 841 (11.0) VAL vs. AML: HR (95% CI): 1.04 (0.94, 1.14) *p*=.45	Fatal and nonfatal MI, n (%) AML: 313 (4.1) VAL: 369 (4.8) VAL vs. AML: HR (95% CI): 1.19 (1.02, 1.38) *p*=.02	Fatal and nonfatal stroke, n (%) AML: 281 (3.7) VAL: 322 (4.2) VAL vs. AML: HR (95% CI): 1.15 (0.98, 1.35) p= 0.08	Fatal and nonfatal HF, n (%) AML: 400 (5.3) VAL: 354 (4.6) VAL vs. AML: HR (95% CI): 0.89 (0.77, 1.03) *p*=.12	PRIMARY OUTCOME: Primary composite of time to first cardiac event, n (%) AML: 789 (10.4) VAL: 810 (10.6) VAL vs. AML: HR (95% CI): 1.04 (0.94, 1.15) *p*=.49 Cardiac morbidity, n (%) AML: 578 (7.6) VAL: 586 (7.7) VAL vs. AML: HR (95% CI): 1.02 (0.91, 1.15) *p*=.71 Cardiac mortality, n (%) AML: 304 (4.0) VAL: 304 (4.0) VAL vs. AML: HR (95% CI): 1.01 (0.86, 1.18) *p*=.90		Withdrawals due to AE, % AML: 12.9 VAL: 11.9 *p*=NR New onset DM, n (%) AML: 845 (16.4) VAL: 690 (13.1) VAL vs. AML: OR (95%CI): 0.77 (0.69, 0.86) *p*<.0001

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
NORDIL Hansson et al., 2000[77]	10,916	Mean 4.5 years	Good	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 All patients could receive additional anti-HTN agents to reach BP goal. In DIL group, patients could receive ACE, then diuretic or alpha blocker added to ACE and then any other anti-HTN compound. In DIUR or BB group, patients could receive ACE or alpha blocker added to the diuretic and BB combination and then any other anti-HTN compound except calcium antagonist.	Adults 50-74 years old with previously treated or untreated primary HTN. BP inclusion criteria for those previously treated was DBP ≥100 mmHg in the absence of pharmacological anti-HTN treatment. BP inclusion criteria for those previously untreated was DBP ≥100 mmHg.	Total mortality, n of patients (rate per 1000 p-y) DIL: 231 (9.2) DIUR or BB: 228 (9.0) RR (95% CI): 1.00 (0.83, 1.20) *p*=.99	All MI, n of patients (rate per 1000 p-y) DIL: 183 (7.4) DIUR or BB: 157 (6.3) RR (95% CI): 1.16 (0.94, 1.44) *p*=.17 Fatal MI, n of patients (rate per 1000 p-y) DIL: 28 (1.1) DIUR or BB: 25 (1.0) RR (95% CI): 1.10 (0.64, 1.88) *p*=.74 All Cardiac Events, n of patients (rate per 1000 p-y) DIL: 487 (20.2) DIUR or BB: 470 (19.2) RR (95% CI): 1.04 (0.91, 1.18) *p*=.57	All Stroke, n of patients (rate per 1000 p-y) DIL: 159 (6.4) DIUR or BB: 196 (7.9) RR (95% CI): 0.80 (0.65, 0.99) *p*=.04 Fatal Stroke, n of patients (rate per 1000 p-y) DIL: 21 (0.8) DIUR or BB: 22 (0.9) RR (95% CI): 0.96 (0.52, 1.74) *p*=.89 All Stroke plus TIA, n of patients (rate per 1000 p-y) DIL: 200 (8.1) DIUR or BB: 236 (9.5) RR (95% CI): 0.84 (0.70, 1.01) *p*=.07	CHF, n of patients (rate per 1000 p-y) DIL: 63 (2.5) DIUR or BB: 53 (2.1) RR (95% CI): 1.16 (0.81, 1.67) *p*=.42	PRIMARY OUTCOME: Primary endpoint (composite of fatal and nonfatal stroke, fatal and nonfatal MI, and other CV death), n of patients (rate per 1000 p-y) DIL: 403 (16.6) DIUR or BB: 400 (16.2) RR (95% CI): 1.00 (0.87, 1.15) *p*=.97 CV Death, n of patients (rate per 1000 p-y) DIL: 131 (5.2) DIUR or BB: 115 (4.5) RR (95% CI): 1.11 (0.87, 1.43) *p*=.41		Withdrawals due to AE, % NR Diabetes, n of patients (rate per 1000 p-y) DIL: 216 (9.4) DIUR or BB: 251 (10.8) RR (95% CI): 0.87 (0.73, 1.04) *p*=.14 Headaches, n (%) DIL: 458 (8.5) DIUR or BB: 311 (5.7) *p*<.001 Fatigue, n (%) DIL: 239 (4.4) DIUR or BB: 353 (6.5) *p*<.001 Dyspnea, n (%) DIL: 157 (2.9) DIUR or BB: 212 (3.9) *p*=.006 Impotence, n (%) DIL: 126 (2.3) DIUR or BB: 202 (3.7) *p*<.001

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
STOP Hypertension-2 Hansson et al., 1999[52]	6,614	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	Good	CCB: Calcium channel blockers: felodipine 2.5 mg QD or isradipine 2.5 mg QD ACE: ACE inhibitors: enalapril 10 mg, or 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 If BP goal not met, patients started on diuretic or CCB were given any of the BB in the doses listed, and patients on ACE were given HCTZ 12.5–25.0 mg. BB patients given HCTZ 25 mg plus amiloride 2.5 mg as additional treatment if target BP not met at 2-month visit or later.	Adults 70-84 years old with HTN. SBP ≥180 mmHg, DBP ≥105 mmHg or both.	Total mortality, events per 1000 p-y (n of events) CCB: 32.8 (362) ACE: 34.4 (380) BB or DIUR: 33.1 (369) ACE vs. CCB: RR (95% CI) for ACE: 1.03 (0.69, 1.19) *p*=.71 CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.99 (0.66, 1.15) *p*=.90	All MI, events per 1000 p-y (n of events) CCB: 16.7 (179) ACE: 12.8 (139) BB or DIUR: 14.1 (154) ACE vs. CCB: RR (95% CI) for ACE: 0.77 (0.61, 0.96) *p*=.016 CCB vs. BB or DIUR: RR (95% CI) for CCB: 1.18 (0.95, 1.47) *p*=.13 Sudden death, events per 1000 p-y (n of events) CCB: 4.7 (52) ACE: 5.3 (59) BB or DIUR: 4.8 (53) *p*=NR Fatal MI, events per 1000 p-y (n of events) CCB: 5.3 (59) ACE: 4.3 (48) BB or DIUR: 4.9 (55) *p*=NR	All stroke, events per 1000 p-y (n of events) CCB: 19.5 (207) ACE: 20.2 (215) BB or DIUR: 22.2 (237) ACE vs. CCB: RR (95% CI) for ACE: 1.02 (0.64, 1.24) *p*=.64 CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.66 (0.73, 1.06) *p*=.16 Fatal stroke, events per 1000 p-y (n of events) CCB: 4.2 (46) ACE: 4.5 (50) BB or DIUR: 4.6 (51) *p*=NR	Frequency CHF, events per 1000 p-y (n of events) CCB: 17.5 (186) ACE: 13.9 (149) BB or DIUR: 16.4 (177) ACE vs. CCB: RR (95% CI) for ACE: 0.76 (0.63, 0.97) *p*=.025 CCB vs. BB or DIUR: RR (95% CI) for CCB: 1.06 (0.67, 1.31) *p*=.56	All major CV events, events per 1000 p-y (n of events) CCB: 43.6 (450) ACE: 41.9 (437) BB or DIUR: 44.1 (460) ACE vs. CCB: RR (95% CI) for ACE: 0.95 (0.63, 1.06) *p*=.42 CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.99 (0.67, 1.12) *p*=.65 PRIMARY OUTCOME: CV mortality, events per 1000 p-y (n of events) CCB: 19.2 (212) ACE: 20.5 (226) BB or DIUR: 19.8 (221) ACE vs. CCB: RR (95% CI) for ACE: 1.04 (0.66, 1.26) *p*=.67 CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.97 (0.60, 1.17) *p*=.72 Other CV mortality, events per 1000 p-y (n of events) CCB: 5.0 (55) ACE: 6.2 (69) BB or DIUR: 5.6 (62) *p*=NR		Withdrawals due to AE, % NR Frequency of DM, events per 1000 p-y (n of events) CCB: 9.9 (95) ACE: 9.6 (93) BB or DIUR: 10.0 (97) ACE vs. CCB: RR (95% CI) for ACE: 0.96 (0.74, 1.31) *p*=.91 CCB vs. BB or DIUR: RR (95% CI) for CCB: 0.97 (0.73, 1.29) *p*=.63 Ankle edema, % CCB: 25.5 ACE: 8.7 BB or DIUR: 8.5 *p*=NR Dry cough, % ACE: 30.1 CCB: 5.7 BB or DIUR: 3.7 *p*=NR Dizziness, % CCB: 24.5 ACE: 27.7 BB or DIUR: 27.8 *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
MIDAS Borhani et al., 1996[60]	883	3 years	Fair	ISR: Isradipine: 2.5 to 5.0 mg BID HCTZ: Hydrochlorothiazide: 12.5 to 25 mg BID Titrated to achieve DBP goal during the first 4 months; if DBP goal not reached with highest dose allowed by protocol, open-label enalapril added at dosages of 2.5, 5.0, 7.5, or 10.0 mg BID to achieve DBP goal.	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. DBP 90–115 mmHg.	All-cause mortality, n (n/100) ISR: 8 (1.8) HCTZ: 9 (2.1) RR (95% CI): 0.89 (0.35, 2.28) *p*=.81	MI, n (n/100) ISR: 6 (1.35) HCTZ: 5 (1.13) RR (95% CI): 1.20 (0.37, 3.89) *p*=.77 CABG, n (n/100) ISR: 6 (1.35) HCTZ: 6 (1.35) RR (95% CI): 1.00 (0.32, 3.07) *p*=.97 Coronary angioplasty, n (n/100) ISR: 5 (1.13) HCTZ: 1 (0.22) RR (95% CI): 4.99 (0.59, 42.53) *p*=.10 Sudden death, n (n/100) ISR: 2 (0.45) HCTZ: 2 (0.45) RR (95% CI): 1.00 (0.14, 7.05) *p*>.99	Stroke, n (n/100) ISR: 6 (1.35) HCTZ: 3 (0.68) RR (95% CI): 2.00 (0.50, 7.93) *p*=.32	CHF, n (n/100) ISR: 2 (0.45) HCTZ: 0 (0.0) RR (95% CI): NR *p*=.16	Any major vascular event, n (n/100) ISR: 25 (5.65) HCTZ: 14 (3.17) RR (95% CI): 1.78 (0.94, 3.38) *p*=.07 Major vascular events and procedures, n (n/100) ISR: 30 (6.78) HCTZ: 19 (4.31) RR (95% CI): 1.58 (0.90, 2.76) *p*=.10 Other CVD death, n (n/100) ISR: 1 (0.22) HCTZ: 1 (0.22) RR (95% CI): 1.00 (0.06, 15.90) *p*>.99		Withdrawals due to AE, % ISR: 9.3 HCTZ: 8.2 CV-related adverse reactions, n (%) ISR: NR (3.0) HCTZ: NR (0.9) *p*=NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
ELSA Zanchetti et al., 2002[66]	2,334	Mean 3.75 years	Fair	LAC: Lacidipine 4-6 mg/day ATN: Atenolol 50–100 mg/day If DBP not <95 mmHg with fall ≥5 mmHg, dose of lacidipine increased to 6 mg, and atenolol increased to 100 mg (month 1), with open-label HCTZ added (12.5 mg daily month 3 and 25 mg daily month 6)	Adults, age 45–75 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. Sitting SBP 150–210 mmHg and DBP 95–115 mmHg.	All death, n of events (n/1000 p-y) LAC: 13 (3.59) ATN: 17 (4.68) *p*=NS	Fatal and nonfatal MI, n of events (n/1000 p-y) LAC: 18 (4.97) ATN: 17 (4.68) *p*=NS	Fatal and nonfatal Stroke, n of events (n/1000 p-y) LAC: 9 (2.49) ATN: 14 (3.86) *p*=NS		Major CV events, n of events (n/1000 p-y) LAC: 27 (7.46) ATN: 33 (9.09) *p*=NS Minor CV events, n of events (n/1000 p-y) LAC: 45 (12.42) ATN: 42 (11.59) *p*=NS All major and minor CV events, n of events (n/1000 p-y) LAC: 69 (19.04) ATN: 73 (19.85) *p*=NS CV death, n of events (n/1000 p-y) LAC: 4 (1.10) ATN: 8 (2.20) *p*=NS		

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
SHELL Malacco et al., 2003[58]	1,882	Median 32 months	Fair	LAC: Lacidipine: 4, 6 mg QD CHL: Chlorthalidone: 12.5, 25 mg QD If SBP response not satisfactory after 4 weeks, treatment titrated upward first by increasing dose of initial monotherapy (CHL to 25 mg QD and LAC to 6 mg QD) and by bringing back monotherapy dose to initial step and adding fosinopril 10 mg QD or any other ACE inhibitor at equivalent dose after another 4 weeks treatment.	Adults ≥60 years with isolated systolic HTN. SBP ≥160 and DBP ≤95 mmHg.	All-cause mortality, n of events LAC: 145 CHL: 122 HR (95% CI): 1.23 (0.97,1.57) *p*=.09	Fatal and nonfatal MI, n of events LAC: 12 CHL: 14 HR (95% CI): 0.85 (0.39, 1.83) *p*=.67 Sudden death, n of events LAC: 16 CHL: 13 HR (95% CI): 1.22 (0.58, 2.53) *p*=.60 Revascularization, n of events LAC: 2 CHL: 4 HR (95% CI): 0.50 (0.09, 2.70) *p*=.41	Fatal and nonfatal stroke, n of events LAC: 37 CHL: 38 HR (95% CI): 0.96 (0.61, 1.51) *p*=.87 TIA, n of events LAC: 15 CHL: 13 HR (95% CI): 1.14 (0.54, 2.40) *p*=.72	Fatal and nonfatal HF, n of events LAC: 23 CHL: 19 HR (95% CI): 1.20 (0.65, 2.20) *p*=.56	PRIMARY OUTCOME: Composite primary endpoint, n of events LAC: 90 CHL: 88 HR (95% CI): 1.01 (0.75, 1.36) *p*=.94		Withdrawals due to AE, % NR Orthostatic hypotension, % LAC: 1.9 CHL: 2.5 *p*=NR Edema, % LAC: 14.3 CHL: 4.9 *p*=NR Cough, % LAC: 3.5 CHL: 4.0 *p*=NR Dizziness, % LAC: 12.7 CHL: 12.4 *p*=NR Fatigue, % LAC: 13.7 CHL: 20.5 *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
JMIC-B Yui et al., 2004[97]	1,650	Median 35.7 months	Fair	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 If BP reduction unsatisfactory, alpha-blocker administered concomitantly; if antianginal effect of treatment was inadequate, long-acting or short-acting nitrates and/or BB used concomitantly.	Adults, ages <75 years with HTN and CAD. SBP ≥160 mmHg or DBP ≥95 mmHg.	Totally mortality, n of events (%) NIF: 12 (1.4) ACE: 15 (1.8) ACE vs. NIF: RR (95% CI): 0.76 (0.35, 1.63) *p*=.48	MI, n of events (%) NIF: 16 (1.9) ACE: 13 (1.6) ACE vs. NIF: RR (95% CI): 1.31 (0.63, 2.74) *p*=.47 Coronary intervention, n of events (%) NIF: 81 (NR) ACE: 75 (NR) ACE vs. NIF: RR (95% CI): 1.04 (0.76, 1.43) *p*=.81 Sudden death/cardiac death, n of events (%) NIF: 6 (0.7) ACE: 6 (0.7) ACE vs. NIF: RR (95% CI): 0.96 (0.31, 3.04) *p*=.95 Noncardiac death, n of events (%) NIF: 6 (NR) ACE: 9 (NR) ACE vs. NIF: RR (95% CI): 0.64 (0.23, 1.81) *p*=.40	Cerebrovascular accidents, n of events (%) NIF: 16 (NR) ACE: 16 (NR) ACE vs. NIF: RR (95% CI): 1.00 (0.50, 2.02) *p*=.99	HF requiring hospitalization, n of events (%) NIF: 12 (NR) ACE: 9 (NR) ACE vs. NIF: RR (95% CI): 1.25 (0.52, 2.98) *p*=.62	PRIMARY OUTCOME: Cardiac events, n of events (%) NIF: 116 (14.0) ACE: 106 (12.9) ACE vs. NIF: RR (95% CI): 1.05 (0.81, 1.37) *p*=.75	Worsening of renal dysfunction (serum Cr >353.6 µmol/l), n of events (%) NIF: 6 (NR) ACE: 2 (NR) ACE vs. NIF: RR (95% CI): 2.70 (0.54, 13.49) *p*=.23	Withdrawals due to AE, n (%) NIF: 41 (5.0) ACE: 72 (8.8) *p*=.002 *Withdrawals by AE* Hypotension, n (%) NIF: 8 (1.0) ACE: 2 (0.2) *p*<.01 Edema, n (%) NIF: 7 (0.8) ACE: 0 *p*<.01 Facial erythema, hot flushes, n (%) NIF: 6 (0.7) ACE: 0 *p*<.05 Dry cough, n (%) NIF: 0 ACE: 60 (7.3) *p*<.01

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
INSIGHT Brown et al., 2000;[6] Mancia et al., 2003[74]	6,321	Maximum of 51 months F/U; BP outcomes reported at 48 months	Good	NIF: Nifedipine: 30, 60 mg QD Co-am: Co-amilozide: HCTZ 25 mg and amiloride 2.5 mg QD or doubling the dose of both drugs to HCTZ 50 mg QD and amiloride 5 mg QD 4 optional titration steps for patients whose BP fell by <20/10 mmHg or >140/90 mmHg: Dose doubling of randomized drugs Addition of atenolol 25 mg daily (enalapril 5 mg daily if atenolol contraindicated) Dose doubling of additional drug Addition of any other anti-HTN drug (other than CCB or diuretics) Titration steps could be done in that order at any visit from weeks 2, 4, 8, and 12 after randomization	Men and women age 55-80 years, high risk patients with HTN; one additional CV risk factor. BP ≥150/95 mmHg or SBP ≥160 mmHg regardless of DBP.	All deaths - first event, n (%) NIF: 153 (4.8) Co-am: 152 (4.8) OR (95% CI): 1.01 (0.80, 1.27) *p*=.95	Nonfatal MI, n (%) NIF: 61 (1.9) Co-am: 56 (1.8) OR (95% CI): 1.09 (0.76, 1.58) *p*=.52 Fatal MI, n (%) NIF: 16 (0.5) Co-am: 5 (0.2) OR (95% CI): 3.22 (1.18, 8.80) *p*=.017 Sudden death, n (%) NIF: 17 (0.5) Co-am: 23 (0.7) OR (95% CI): 0.74 (0.39, 1.39) *p*=.43	Nonfatal stroke, n (%) NIF: 55 (1.7) Co-am: 63 (2.0) OR (95% CI): 0.87 (0.61, 1.26) *p*=.52 Fatal stroke, n (%) NIF: 12 (0.3) Co-am: 11 (0.3) OR (95% CI): 1.09 (0.48, 2.48) *p*=.84 TIA, n (%) NIF: 25 (0.8) Co-am: 25 (0.8) OR (95% CI): 1.00 (0.57, 1.75) *p*=1.0	Nonfatal HF, n (%) NIF: 24 (0.8) Co-am: 11 (0.3) OR (95% CI): 2.20 (1.07, 4.49) *p*=.028 Fatal HF, n (%) NIF: 2 (0.1) Co-am: 1 (<0.1) OR (95% CI): 2.01 (0.18, 22.13) *p*=.63	PRIMARY OUTCOME: Primary outcome composite: death from any CV or cerebrovascular cause, together with nonfatal stroke, MI and HF, n (%) NIF: 200 (6.3) Co-am: 182 (5.8) OR (95% CI): 1.11 (0.90, 1.36) *p*=.34 Composite secondary outcomes: Primary outcomes plus non-CV deaths, renal failure, angina and TIA, n (%) NIF: 383 (12.1) Co-am: 397 (12.5) OR (95% CI): 0.96 (0.83, 1.12) *p*=.62 Other CV death, n (%) NIF: 13 (0.4) Co-am: 12 (0.4) OR (95% CI): 1.09 (0.50, 2.38) *p*=.85 CV Deaths, n (%) NIF: 60 (1.9) Co-am: 52 (1.6) OR (95% CI): 1.16 (0.80, 1.69) *p*=.45 Nonfatal primary CV events, n (%) NIF: 140 (4.4) Co-am: 130 (4.1) OR (95% CI): 1.08 (0.85, 1.38) *p*=.53 Nonfatal CV events, n (%) NIF: 230 (7.3) Co-am : 245 (7.7) OR (95% CI): 0.94 (0.78, 1.13) *p*=.50	Renal Failure, n (%) NIF: 8 (0.3) Co-am: 13 (0.4) OR (95% CI): 0.62 (0.26, 1.49) *p*=.38 GFR, mL/min Co-am vs. NIF (95% CI): –2.3 (–3.8, 1.9) Co-amilozide lower than nifedipine *p*=NR	Withdrawals due to AE, % NIF: 23.0 Co-am: 16.4 % calculated by reviewer Impaired renal function as an AE, n (%) NIF: 58 (1.8) Co-am: 144 (4.6) *p*<.0001 All AEs, n (%) NIF: 1,546 (49) Co-am: 1,327 (42) *p*<.0001 Serious AEs, n (%) NIF: 796 (25) Co-am: 880 (28) *p*<.02 DM reported as an AE, n (%) NIF: 96 (3.0) Co-am: 137 (4.3) *p*=.01 New onset DM reported as an outcome, n (%) NIF: 136 (4.3) Co-am: 176 (5.6) *p*=.02 Hyperglycemia, n (%) NIF: 178 (5.6) Co-am: 244 (7.7) *p*=.001 Peripheral edema, n (%) NIF: 896 (28) Co-am: 137 (4.3) *p*<.0001 Hypokalemia, n (%) NIF: 61 (1.9) Co-am: 195 (6.2) *p*<.0001 Hyponatremia, n (%) NIF: 8 (NR) Co-am : 61 (1.9) *p*<.0001 Headache, n (%) NIF: 384 (12) Co-am: 292 (9.2) *p*<.0002 Dizziness, n (%) NIF: 254 (8) Co-am: 318 (10) *p*<.006

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
MOSES Schrader et al., 2005[56]	1,405	Mean 2.5 years	Fair	NIT: Nitrendipine 10 mg/day EPR: Eprosartan 600 mg/day From week 3 of treatment (earlier if required for medical reasons) dose increased or combination therapy initiated; recommended but not predefined to give diuretics as first combination partner, followed by BB and then alpha-blockers or centrally acting substances.	Adults with HTN and history of a cerebrovascular event.	All cause death, n of events NIT: 52 EPR: 57 EPR vs. NIT: HR (95% CI): 1.07 (0.73, 1.56) *p*=.725		Fatal and nonfatal cerebrovascular events (including recurrent events), n (incidence density ratio per 100 p-y) NIT: 134 (8.78) EPR: 102 (6.56) EPR vs. NIT: IDR (95% CI): 0.75 (0.58, 0.97) *p*=.026 First time occurrence of cerebrovascular event, n of events NIT: 89 EPR: 80 EPR vs. NIT: HR (95% CI): 0.88 (0.65, 1.20) *p*=.425		PRIMARY OUTCOME: Primary combined endpoint: cerebrovascular and CV events and non-CV death (including recurrent events), n (incidence density ratio per 100 p-y) NIT: 255 (16.71) EPR: 206 (13.25) EPR vs. NIT: IDR (95% CI): 0.79 (0.66, 0.96) *p*=.014 Fatal and nonfatal CV events (including recurrent events), n (incidence density ratio per 100 p-y) NIT: 101 (6.62) EPR: 77 (4.95) EPR vs. NIT: IDR (95% CI): 0.75 (0.55, 1.02) *p*=.061 First time occurrence of CV event, n of events NIT: 84 EPR: 60 EPR vs. NIT: HR (95% CI): 0.69 (0.50, 0.97) *p*=.031		Dizziness /hypotension, % NIT: 10.6 EPR: 12.9 *p*=NR Pneumonia, % NIT: 11.4 EPR: 10.8 *p*=NR Metabolic disorder, % NIT: 5.9 EPR: 5.5 *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
CONVINCE Black et al., 2003[76]	16,602	Median F/U 3 years	Fair	VER: Controlled-onset extended-release verapamil 180–360 mg ATN or HCTZ: atenolol 50–100 mg QD or HCTZ 12.5–25 mg QD In VER group, 12.5–25 mg HCTZ could be added to achieve BP control. Thereafter, any additional anti-HTN agent (except nondihydropyridine calcium antagonist, thiazide diuretic, or BB) could be added if needed. In ATN or HCTZ group, 12.5–25 mg HCTZ could be added to the initial dose of atenolol or 50–100 mg of atenolol could be added to the initial dose of HCTZ to achieve BP control. Thereafter, any additional anti-HTN agent (except nondihydropyridine calcium antagonist, thiazide diuretic, or BB) could be added if needed.	Adults age >55 with HTN and 1 or more additional risk factor for CVD. Inclusion BP criteria for those currently using anti-HTN medication(s) for ≥2 months was SBP <175 mmHg and DBP <100 mmHg. Inclusion BP criteria for those not currently using anti-HTN medications within 2 months was 140≤SBP≤190 mmHg or 90≤DBP<110 mmHg.	Death, n (%) VER: 337 (4.1) ATN or HCTZ: 319 (3.8) HR (95% CI): 1.08 (0.93, 1.26) *p*=.32	Fatal or nonfatal MI, n (%) VER: 133 (1.6) ATN or HCTZ: 166 (2.0) HR (95% CI): 0.82 (0.65, 1.03) *p*=.09 Cardiac revascularization/ cardiac transplant, n (%) VER: 163 (2.0) ATN or HCTZ: 166 (2.0) HR (95% CI): 1.01 (0.82, 1.26) *p*=.91	Fatal or nonfatal stroke, n (%) VER: 133 (1.6) ATN or HCTZ: 118 (1.4) HR (95% CI): 1.15 (0.90, 1.48) *p*=.26 TIA or carotid endarterectomy, n (%) VER: 89 (1.1) ATN or HCTZ: 105 (1.3) HR (95% CI): 0.87 (0.66, 1.15) *p*=.33	Heart failure, n (%) VER: 126 (1.5) ATN or HCTZ: 100 (1.2) HR (95% CI): 1.30 (1.00, 1.69) *p*=.05	PRIMARY OUTCOME: Primary composite outcome (first occurrence of stroke, MI, or CVD-related death), n (%) VER: 364 (4.5) ATN or HCTZ: 365 (4.4) HR (95% CI): 1.02 (0.88, 1.18) *p*=.77 Primary event or CV hospitalization, n (%) VER: 793 (9.7) ATN or HCTZ: 775 (9.3) HR (95% CI): 1.05 (0.95, 1.16) *p*=.31 CVD-related death, n (%) VER: 152 (1.9) ATN or HCTZ: 143 (1.7) HR (95% CI): 1.09 (0.87, 1.37) *p*=.47	Renal failure (acute/chronic), n (%) VER: 27 (0.3) ATN or HCTZ: 34 (0.4) HR (95% CI): 0.81 (0.49, 1.35) *p*=.43	Withdrawals due to AE, n (%) VER: 1353 (16.5) ATN or HCTZ: 1278 (15.3) *p*=NR Withdrawals due to poor BP control, n (%) VER: 115 (NR) ATN or HCTZ: 207 (NR) *p*<.001 Withdrawals due to constipation, n (%) VER: 216 (NR) ATN or HCTZ: 28 (NR) *p*=NR Death or hospitalization due to serious AE, n (%) VER: 1381 (16.9) ATN or HCTZ: 1363 (16.4) HR (95% CI): 1.04 (0.97, 1.12) *p*=.29 Hospitalization for serious AE, n (%) VER: 1150 (14.1) ATN or HCTZ: 1143 (13.8) HR (95% CI): 1.03 (0.95, 1.12) *p*=.44

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
VHAS Rosei et al., 1997[59]	1,414	2 years	Fair	VER: Verapamil: slow release 240 mg QD CHL: Chlorthalidone: 25 mg QD After 1 month, 25 mg captopril QD added when BP not at goal; after 2nd month, captopril dose increased to 25 mg BID if not yet responding to combined treatment; subsequently, if not responding switched to any open therapy chosen by their treating doctors (free therapy).	Adults, ages 40–65 years with HTN. SBP ≥160 and DBP ≥95 mmHg.	Death by any cause, n of events VER: 5 CHL: 4 *p*=NR	MI, n of events VER: 5 CHL: 5 *p*=NR Revascularization procedures, n of events VER: 4 CHL: 3 *p*=NR Cardiac deaths, n of events VER: 3 CHL: 4 *p*=NR	Strokes, n of events VER: 3 CHL: 4 *p*=NR TIA, n of events VER: 7 CHL: 7 *p*=NR Cerebrovascular deaths, n of events VER: 2 CHL: 0 *p*=NR	CHF, n of events VER: 2 CHL: 0 *p*=NR	PRIMARY OUTCOME: Nonfatal CV events, n of events VER: 37 CHL: 39 *p*=NR PRIMARY OUTCOME: Major CV events, n of events VER: 8 CHL: 9 *p*=NR PRIMARY OUTCOME: Minor CV events, n of events VER: 29 CHL: 30 *p*=NR PRIMARY OUTCOME: CV deaths, n of events VER: 5 CHL: 4 *p*=NR		Withdrawals due to AE, % VER: 2.5 CHL: 2.5 % calculated by reviewer Glucose, mg/dl (SD) VER: 95.7 (16.4) CHL: 99.8 (19.2) *p*=.01 Change CHL: +1.8 VER: -1.2 PRIMARY OUTCOME: Constipation, % VER: 13.7 CHL: 3.1 *p*=NR PRIMARY OUTCOME: Hyperuricemia, % VER: 3.9 CHL: 10.8 *p*<.01 PRIMARY OUTCOME: Hypokalemia, % VER: 4.4 CHL: 24.6 *p*<.01 PRIMARY OUTCOME: Severe hypokalemia, n VER: 4 CHL: 8 *p*=NR

Table D-3e. Initial Treatment With Angiotensin Receptor Blockers Versus Other Drugs

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
CASE-J Ogihara, 2008[55]	4,728	Mean 3.2 years	Good	CAN: Candesartan 4–12 mg/day AML: Amlodipine 2.5–10 mg/day Dose of randomized drug titrated upward to achieve BP goal; diuretics, alpha blockers, BB, or alpha and BB added (and titrated upward) to achieve BP goal.	Adults with high CVD risk. For those <70 years old SBP ≥140 mmHg and <200 mmHg or DBP ≥90 mmHg and <120 mmHg. For those ≥70 years old SBP ≥160 mmHg and <200 mmHg or DBP ≥90 mmHg and <120 mmHg.	All-cause death, n of events (rate per 1000 py) CAN: 73 (9.4) AML: 86 (11.1) HR (95% CI): NR *p*=NS	Acute MI, n of events (%) CAN: 17 (0.7) AML: 18 (0.8) CAN vs. AML: HR (95% CI): 0.95 (0.49, 1.84) *p*=.870 Sudden death, n of events (%) CAN: 11 (0.5) AML: 15 (0.6) CAN vs. AML: HR (95% CI): 0.73 (0.34, 1.60) *p*=.434	Cerebrovascular events, n of events (%) CAN: 61 (2.6) AML: 50 (2.1) CAN vs. AML: HR (95% CI): 1.23 (0.85, 1.78) *p*=.282 Stroke, n of events (%) CAN: 60 (2.5) AML: 47 (2.0) CAN vs. AML: HR (95% CI): 1.28 (0.88, 1.88) *p*=.198 TIA, n of events (%) CAN: 2 (0.1) AML: 4 (0.2) CAN vs. AML: HR (95% CI): 0.50 (0.09, 2.73) *p*=.414	Heart failure, n of events (%) CAN: 20 (0.8) AML: 16 (0.7) CAN vs. AML: HR (95%CI): 1.25 (0.65, 2.42) *p*=.498	PRIMARY OUTCOME: Primary composite endpoint of sudden death, cerebrovascular events, cardiac events, renal events and vascular events, n of events (%) CAN: 134 (5.7) AML: 134 (5.7) CAN vs. AML: HR (95% CI): 1.01 (0.79, 1.28) *p*=.969 Cardiac events, n of events (%) CAN: 43 (1.8) AML: 47 (2.0) CAN vs. AML: HR (95% CI): 0.92 (0.61, 1.39) *p*=.680 Peripheral vascular events, n of events (%) CAN: 11 (0.5) AML: 7 (0.3) CAN vs. AML: HR (95% CI): 1.57 (0.61, 4.05) *p*=.348	Renal events, n of events (%) CAN: 19 (0.8) AML: 27 (1.1) CAN vs. AML: HR (95% CI): 0.70 (0.39, 1.26) *p*=.230 Creatinine abnormality, n of events (%) CAN: 19 (0.8) AML: 26 (1.1) CAN vs. AML: HR (95% CI): 0.73 (0.40, 1.31) *p*=.287 ESRD, n of events (%) CAN: 4 (0.2) AML: 10 (0.4) CAN vs. AML: HR (95% CI): 0.40 (0.13, 1.29) *p*=.112	Withdrawals due to AE, % CAN: 5.3 AML: 5.7 % calculated by reviewer Hyperkalemia,% CAN: 1.0 AML: 0.3 *p*=NR New onset DM, rate per 1000 p-y CAN: 8.7 AML: 13.6 HR (95% CI): 0.64 (0.43, 0.97) *p*=.033

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
SCOPE Lithell et al., 2003[91]	4,964	Mean 3.7 years	Fair	CAN: Candesartan: Step 1: Candesartan 8 mg QD Step 2: If SBP >160 mmHg or reduction in SBP <10 mmHg or DBP >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 CTL: Control: Step 1: Placebo QD Step 2: If SBP >160 mmHg or reduction in SBP <10 mmHg or DBP >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 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.	Adults, 70-89 years old with treated or untreated HTN and MMSE ≥24. SBP 160–179 mmHg and/or DBP 90–99 mmHg.	Total mortality, n (rate per 1000 p-y) CAN: 259 (27.9) CTL: 266 (29.0) RR (95% CI): NR *p*=NS	Nonfatal MI, n (rate per 1000 p-y) CAN: 54 (5.9) CTL: 47 (5.2) RR (95% CI): NR *p*=NS All MI, n (rate per 1000 p-y) CAN: 70 (7.6) CTL: 63 (6.9) RR (95% CI): NR *p*=NS Fatal MI, n (rate per 1000 p-y) CAN: 18 (1.9) CTL: 18 (2.0) RR (95% CI): NR *p*=NS	Nonfatal stroke, n (rate per 1000 p-y) CAN: 68 (7.4) CTL: 93 (10.3) RR (95% CI): 27.8 (1.3, 47.2) *p*=.04 All stroke, n (rate per 1000 p-y) CAN: 89 (9.7) CTL: 115 (12.8) RR (95% CI): 23.6 (–0.7, 42.1) *p*=.056 Fatal stroke, n (rate per 1000 p-y) CAN: 24 (2.6) CTL: 26 (2.8) RR (95% CI) *p*=NS		PRIMARY OUTCOME: Major CV events (composite of CV death, nonfatal stroke, and nonfatal MI), n (rate per 1000 p-y) CAN: 242 (26.7) CTL: 268 (30.0) RR (95% CI): 10.9 (–6.0, 25.1) *p*=.19 CV deaths, n (rate per 1000 p-y) CAN: 145 (15.6) CTL: 152 (16.6) RR (95% CI): NR *p*=NS	Change in mean serum Cr, µmol/l CAN: +9.6 CTL: +5.3 *p*=NR	Withdrawals due to AEs, % CAN: 15 CTL: 17 *p*=.07 New Onset DM, % CAN: 4.3 CTL: 5.3 *p*=.09 Dizziness/vertigo ,% CAN: 20.9 CTL: 20.0 *p*=NR Accident/injury, % CAN: 18.4 CTL: 18.4 *p*=NR Back pain, % CAN: 19.2 CTL: 17.1 *p*=NR Bronchitis, % CAN: 15.9 CTL: 16.0 *p*=NR AEs indicating possible hypotension, % CAN: 24.6 CTL: 23.4 *p*=NR

Study	*N*	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
MOSES Schrader et al., 2005[56]	1,405	Mean 2.5 years	Fair	EPR: Eprosartan 600 mg/day NIT: Nitrendipine 10 mg/day From week 3 of treatment (earlier if required for medical reasons) dose could be increased or combination therapy could be initiated; recommended but not predefined to give diuretics as the first combination partner, followed by BB and then alpha-blockers or centrally acting agents.	Patients with HTN and history of a cerebrovascular event.	All cause death, n of events EPR: 57 NIT: 52 EPR vs. NIT: HR (95% CI): 1.07 (0.73, 1.56) *p*=.725		Fatal and nonfatal cerebrovascular events, n (Incidence Density per 100 py) EPR: 102 (6.56) NIT: 134 (8.78) EPR vs. NIT: IDR (95% CI): 0.75 (0.58, 0.97) *p*=.026 First time occurrence of cerebrovascular event, n of events EPR: 80 NIT: 89 EPR vs. NIT: HR (95% CI): 0.88 (0.65, 1.20) *p*=.425		PRIMARY OUTCOME: Primary combined endpoint: cerebrovascular and CV events and non-CV death, n (Incidence Density per 100 py) EPR: 206 (13.25) NIT: 255 (16.71) EPR vs. NIT: IDR (95% CI): 0.79 (0.66, 0.96) *p*=.014 Fatal and nonfatal CV events, n (Incidence Density per 100 py) EPR: 77 (4.95) NIT: 101 (6.62) EPR vs. NIT: IDR (95% CI): 0.75 (0.55, 1.02) *p*=.061 First time occurrence of CV event, n of events EPR: 60 NIT: 84 EPR vs. NIT: HR (95% CI): 0.69 (0.50, 0.97) *p*=.031		Withdrawals due to AE NR Metabolic disorder, % EPR: 5.5 NIT: 5.9 *p*=NR Dizziness/ hypotension, % EPR: 12.9 NIT: 10.6 *p*=NR Pneumonia, % EPR: 10.8 NIT: 11.4 *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
LIFE Dahlöf et al., 2002[8]	9,222	Mean 4.8 years	Good	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) 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): Atenolol100 mg + HCTZ 12.5–25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)	Adults, age 55–80 years, with previously treated or untreated HTN, LVH ascertained by ECG. DBP 95–115 mmHg or SBP 160–200 mmHg or both.	Total mortality, rate per 1000 py (n) LOS: 17.3 (383) ATN: 19.6 (431) ATN vs. LOS Adj HR: 0.90 (0.78, 1.03) *p*=.128 Unadj HR: 0.88 (0.77, 1.01) *p*=.077	MI, rate per 1000 py (n) LOS: 9.2 (198) ATN: 8.7 (188) ATN vs. LOS Adj HR: 1.07 (0.88, 1.31) *p*=.491 Unadj HR: 1.05 (0.86, 1.28) *p*=.628 Resuscitated cardiac arrest, rate per 1000 py (n) LOS: 0.4 (9) ATN: 0.2 (5) ATN vs. LOS Adj HR: 1.91 (0.64, 5.72) *p*=.250 Unadj HR: 1.80 (0.60, 5.36) *p*=.294 Revascularization, rate per 1000 py (n) LOS: 12.2 (261) ATN: 13.3 (284) ATN vs. LOS Adj HR: 0.94 (0.79, 1.11) *p*=.441 Unadj HR: 0.91 (0.77, 1.08) *p*=.292	Stroke, rate per 1000 py (n) LOS: 10.8 (232) ATN: 14.5 (309) ATN vs. LOS Adj HR: 0.75 (0.63, 0.89) *p*=.001 Unadj HR: 0.74 (0.63, 0.88) *p*=.0006	Heart failure, rate per 1000 py (n) LOS: 7.1 (153) ATN: 7.5 (161) ATN vs. LOS Adj HR: 0.97 (0.78, 1.21) *p*=.765 Unadj HR: 0.95 (0.76, 1.18) *p*=.622	PRIMARY OUTCOME: Primary composite endpoint of CV death, MI, and stroke, rate per 1000 py (n) LOS: 23.8 (508) ATN: 27.9 (588) ATN vs. LOS Adj HR: 0.87 (0.77, 0.98) *p*=.021 Unadj HR: 0.85 (0.76, 0.96) *p*=.009 CV mortality, rate per 1000 py (n) LOS: 9.2 (204) ATN: 10.6 (234) ATN vs. LOS Adj HR: 0.89 (0.73, 1.07) *p*=.206 Unadj HR: 0.87 (0.72, 1.05) *p*=.136	Change in creatinine, mmol/L (SD) LOS: +11.2 (20.4) ATN: +11.0 (19.7) *p*=NR	Withdrawals due to AE (derived from figure) LOS: between 10 and 15% ATN: between 15 and 20% New DM, rate per 1000 py (n) LOS: 13.0 (241) ATN: 17.4 (319) ATN vs. LOS Adj HR: 0.75 (0.63, 0.88) *p*=.001 Unadj HR: 0.75 (0.63, 0.88) *p*=.001 Lower extremity edema, n (%) LOS: 539 (12%) ATN: 637 (14%) *p*=.002 Angioedema, n (%) LOS: 6 (0.1%) ATN: 11 (0.2%) *p*=.237 Cough, n (%) LOS: 133 (3%) ATN: 113 (2%) *p*=.220 Hypotension, n (%) LOS: 121 (3%) ATN: 75 (2%) *p*=.001 Dizziness, n (%) LOS: 771 (17%) ATN: 727 (16%) *p*=.247 Albuminuria, n (%) LOS: 213 (5) ATN: 293 (6) *p*=.0002 Hyperglycemia, n (%) LOS: 239 (5) ATN: 300 (7) *p*=.007 Dyspnea, n (%) LOS: 457 (10%) ATN: 648 (14%) *p*<.0001 Asthenia/ Fatigue, n (%) LOS: 691 (15%) ATN: 802 (17%) *p*=.001 Back pain, n (%) LOS: 568 (12%) ATN: 477 (10%) *p*=.004 Chest pain, n (%) LOS: 519 (11%) ATN: 463 (10%) *p*=.068

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
LIFE *Subanalyses on those with Isolated Systolic HTN;* Kjeldsen et al., 2002[93] Primary outcome: CV morbidity and death - a composite endpoint of CV death, MI, and stroke	9,222 randomized (1,326 with isolated HTN)	Mean 4.7 years	Fair	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) 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): Atenolol100 mg + HCTZ 12.5–25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)	Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG; included in subanalysis if SBP 160-200 mmHg with DBP <90 mmHg.	*Subanalysis with Isolated Systolic HTN* Total mortality, rate per 1000 py/n (%) LOS: 21.2/66 (10.0) ATN: 30.2/93 (14.0) AdjRR (95% CI): 0.72 (0.53, 1.00) *p*=.046 UnadjRR (95% CI): 0.70 (0.51, 0.96) *p*=.03 *Subanalysis of patients without Isolated Systolic HTN* Total mortality, rate per 1000 py/n (%) LOS: 16.7/317 (8.0) ATN: 17.9/338 (8.6) AdjRR (95% CI): 0.95 (0.82, 1.11) *p*=.51 UnadjRR (95% CI): 0.93 (0.80, 1.09) *p*=.38	*Subanalysis of patients with Isolated Systolic HTN* MI, rate per 1000 py/n (%) LOS: 10.2/31 (4.7) ATN: 11.9/36 (5.4) AdjRR (95% CI): 0.89 (0.55, 1.44) *p*=.64 UnadjRR (95% CI): 0.86 (0.53, 1.39) *p*=.54 Revascularization, rate per 1000 py/n (%) LOS: 16.4/49 (7.4) ATN: 14.4/44 (6.6) AdjRR (95% CI): 1.17 (0.78, 1.77) *p*=.45 UnadjRR (95%CI): 1.14 (0.76, 1.72) *p*=.53 *Subanalysis of patients without Isolated Systolic HTN* MI, rate per 1000 py/n (%) LOS: 9.0/167 (4.2) ATN: 8.2/152 (3.9) AdjRR (95% CI): 1.12 (0.90, 1.40) *p*=.30 UnadjRR (95% CI): 1.10 (0.88, 1.36) *p*=.41 Revascularization, rate per 1000 py/n (%) LOS: 11.5/212 (5.4) ATN: 13.2/241 (6.1) AdjRR (95% CI): 0.89 (0.74, 1.08) *p*=.23 UnadjRR (95% CI): 0.87 (0.73, 1.05) *p*=.15	*Subanalysis of patients with Isolated Systolic HTN* Stroke, rate per 1000 py/n (%) LOS: 10.6/32 (4.8) ATN: 18.9/56 (8.4) AdjRR (95% CI): 0.60 (0.38, 0.92) *p*=.02 UnadjRR (95%CI): 0.56 (0.36, 0.86) *p*=.008 *Subanalysis of patients without Isolated Systolic HTN* Stroke, rate per 1000 py/n (%) LOS: 10.8/200 (5.1) ATN: 13.8/253 (6.5) AdjRR (95% CI): 0.79 (0.66, 0.95) *p*=.01 UnadjRR (95%CI): 0.78 (0.65, 0.94) *p*=.01	*Subanalysis of patients with Isolated Systolic HTN* Hospitalization for Heart Failure, rate per 1000 py/n (%) LOS: 8.5/26 (3.9) ATN:13.3/40 (6.0) AdjRR (95% CI): 0.66 (0.40, 1.09) *p*=.11 UnadjRR (95%CI): 0.64 (0.39, 1.05) *p*=.08 *Subanalysis of patients without Isolated Systolic HTN* Hospitalization for Heart Failure, rate per 1000 py/n (%) LOS: 6.8/127 (3.2) ATN: 6.5/121 (3.1) AdjRR (95% CI): 1.06 (0.83, 1.36) *p*=.65 UnadjRR (95%CI): 1.05 (0.82, 1.34) *p*=.72	*Subanalysis of patients with Isolated Systolic HTN* PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py /n (%) LOS: 25.1/75 (11.4) ATN: 35.4/104 (15.6) AdjRR (95% CI): 0.75 (0.56, 1.01) *p*=.06 UnadjRR (95%CI): 0.71 (0.53, 0.95) *p*=.02 CV mortality, rate per 1000 py/n (%) LOS: 8.7/27 (4.1) ATN: 16.9/52 (7.8) AdjRR (95% CI): 0.54 (0.34, 0.87) *p*=.01 UnadjRR (95%CI): 0.51 (0.32, 0.81) *p*=.004 *Subanalysis of patients without Isolated Systolic HTN* PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py /n (%) LOS: 23.6/433 (11.0) ATN: 26.7/484 (12.3) AdjRR (95% CI): 0.90 (0.79, 1.02) *p*=.11 UnadjRR (95%CI): 0.88 (0.78, 1.01) *p*=.06 CV mortality, rate per 1000 py/n (%) LOS: 9.3/177 (4.5) ATN: 9.6/182 (4.6) AdjRR (95% CI): 0.99 (0.80, 1.22) *p*=.90 UnadjRR (95%CI): 0.97 (0.79, 1.19) *p*=.77		Withdrawals due to all AE, % LOS: 14.6 ATN: 22.1 *p*<.001 Withdrawals due to drug related events, % LOS: 7.1 ATN: 13.5 *p*<.001 Withdrawals due to a serious AE, % LOS: 4.6 ATN: 6.6 *p*=.12 Withdrawals due to a serious AE and drug related, % LOS: 1.2 ATN: 2.0 *p*=.38 Angioedema, % LOS: 0.3 ATN: 0.3 *p*=.99 Cough, % LOS: 4.1 ATN: 2.9 *p*=.23 Bradycardia, % LOS: 3.0 ATN: 14.6 *p*<.001 Cold extremities, % LOS: 4.1 ATN: 6.6 *p*=.05 *Subanalysis of patients with Isolated Systolic HTN* New diabetes, rate per 1000 py/n (%) LOS: 12.6/32 (5.8) ATN: 20.1/48 (9.0) AdjHR (95% CI): 0.62 (0.40, 0.97) *p*=.04 UnadjHR (95%CI): 0.63 (0.40, 0.99) *p*=.04 *Subanalysis of patients without Isolated Systolic HTN* New diabetes, rate per 1000 py/n (%) LOS: 13.1/210 (6.1) ATN: 17.0/272 (7.9) AdjRR (95% CI): 0.77 (0.64, 0.92) *p*=.005 UnadjRR (95% CI): 0.77 (0.64, 0.92) *p*=.004

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
LIFE *Subanalysis of subjects with and without clinically evident vascular disease* Devereux et al., 2003[94]	9,222 (6,886 without clinically evident vascular disease at baseline)	Mean 4.8 years	Fair	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) 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): Atenolol100 mg + HCTZ 12.5–25 mg + other anti-HTN treatment (addition of ACE, angiotensin II type-1 receptor antagonists or BB prohibited)	Adults, age 55 to 80 years, with previously treated or untreated HTN, LVH ascertained by ECG. DBP 95–115 mmHg or SBP 160–200 mmHg or both.	*Subanalysis of subjects without clinically evident vascular disease* Total mortality, rate per 1000 py (n) LOS: 13.5 (223) ATN: 15.9 (268) AdjHR (95% CI): 0.85 (0.71, 1.02) *p*=.080 *Subanalysis of subjects with clinically evident vascular disease* Total mortality, rate per 1000 py (n) LOS: 28.5 (160) ATN: 31.7 (163) AdjHR (95% CI): 0.94 (0.75, 1.16) *p*>.2	*Subanalysis of subjects without clinically evident vascular disease* MI, rate per 1000 py (n) LOS: 6.8 (110) ATN: 6.0 (100) AdjHR (95% CI): 1.14 (0.87, 1.49) *p*>.2 Revascularization, rate per 1000 py (n) LOS: 7.6 (123) ATN: 9.0 (148) AdjHR (95% CI): 0.85 (0.67, 1.08) *p*=.18 *Subanalysis of subjects with clinically evident vascular disease* MI, rate per 1000 py (n) LOS: 16.3 (88) ATN: 17.7 (88) AdjHR (95% CI): 0.97 (0.72, 1.31) *p*>.2 Revascularization, rate per 1000 py (n) LOS: 26.3 (138) ATN: 28.4 (136) AdjHR (95% CI): 0.98 (0.78, 1.25) *p*>.2	*Subanalysis of subjects without clinically evident vascular disease* Stroke, rate per 1000 py (n) LOS: 7.7 (125) ATN: 11.8 (193) AdjHR (95% CI): 0.66 (0.53, 0.82) *p*<.001 *Subanalysis of subjects with clinically evident vascular disease* Stroke, rate per 1000 py (n) LOS: 20.0 (107) ATN: 23.7 (116) AdjHR (95% CI): 0.87 (0.67, 1.13) *p*>.2	*Subanalysis of subjects without clinically evident vascular disease* Hospitalization for Heart Failure, rate per 1000 py (n) LOS: 4.7 (76) ATN: 4.4 (74) AdjHR (95% CI): 1.06 (0.77, 1.46) *p*>.2 *Subanalysis of subjects with clinically evident vascular disease* Hospitalization for Heart Failure, rate per 1000 py (n) LOS: 14.2 (77) ATN: 17.7 (87) AdjHR (95% CI): 0.84 (0.62, 1.14) *p*>.2	*Subanalysis of subjects without clinically evident vascular disease* PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py (n) LOS: 17.5 (282) ATN: 21.8 (355) AdjHR (95% CI): 0.81 (0.69, 0.95) *p*=.008 CV mortality, rate per 1000 py (n) LOS: 6.2 (103) ATN: 7.8 (132) AdjHR (95% CI): 0.80 (0.62, 1.04) *p*=.092 *Subanalysis of subjects with clinically evident vascular disease* PRIMARY OUTCOME: Primary composite endpoint of CV death, MI or stroke, rate per 1000 py (n) LOS: 43.0 (226) ATN: 48.6 (233) AdjHR (95% CI): 0.93 (0.77, 1.11) *p*>.2 CV mortality, rate per 1000 py (n) LOS: 18.0 (101) ATN: 19.8 (102) AdjHR (95% CI): 0.95 (0.72, 1.25) *p*>.2		Withdrawals due to AE NR Patients with at least one AE of any type, % LOS: 12.7 ATN: 17.3 *p*<.001 Patients with at least one drug related AE, % LOS: 6.0 ATN: 10.2 *p*<.001 Patients with at least one serious AE, % LOS: 3.8 ATN: 4.4 *p*>.2 Patients with at least one serious drug related AE, % LOS: 0.5 ATN: 1.0 *p*=.018 Asthenia or fatigue, % LOS: 14.2 ATN: 16.9 *p*<.002 Lower extremity edema, % LOS: 11.5 ATN: 13.6 *p*<.008 Dyspnea, % LOS: 8.8 ATN: 13.6 *p*<.001 Hyperglycemia, % LOS: 5.4 ATN: 6.7 *p*=.023 Back pain, % LOS: 12.0 ATN: 10.0 *p*=.009 *Subanalysis of subjects without clinically evident vascular disease* New diabetes, rate per 1000 py (n) LOS: 12.2 (173) ATN: 17.7 (254) AdjHR (95% CI): 0.69 (0.57, 0.84) *p*<.001 *Subanalysis of subjects with clinically evident vascular disease* New diabetes, rate per 1000 py (n) LOS: 15.5 (69) ATN:16.4 (66) AdjHR (95% CI): 0.97 (0.69, 1.36) *p*>.2

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
Jikei Heart Study Mochizuki et al., 2007[99]	3,081	Median 3.1 years	Good	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 CT: Conventional therapy; given either an increased dose of their existing treatment or an additional conventional treatment to achieve BP goal	Adults, 20–79 years of age with HTN, CHD, HF, or a combination of these CV disorders. BP inclusion criteria unclear.	All-cause mortality, n (%) VAL: 28 (1.8%) CT: 27 (1.8%) CT vs. VAL: HR (95% CI): 1.09 (0.64. 1.85) *p*=.7537	New or recurrent MI, n (%) VAL: 17 (1.1%) CT: 19 (1.2%) CT vs. VAL: HR (95% CI): 0.90 (0.47, 1.74) *p*=.7545 Dissecting aneurysm of the aorta, n (%) VAL: 2 (0.1%) CT: 10 (0.6%) CT vs. VAL: HR (95% CI): 0.19 (0.04, 0.88) *p*=.0340	Stroke or TIA, n (%) VAL: 29 (1.9%) CT: 48 (3.1%) CT vs. VAL: HR (95% CI): 0.60 (0.38, 0.95) *p*=.0280	New occurrence or exacerbation of HF needing hospitalization, n (%) VAL: 19 (1.2%) CT: 36 (2.3%) CT vs. VAL: HR (95% CI): 0.53 (0.31, 0.94) *p*=.0293	PRIMARY OUTCOME: 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), n (%) VAL: 92 (6.0%) CT: 149 (9.7%) CT vs. VAL: HR (95% CI): 0.61 (0.47, 0.79) *p*=.0002 CV mortality, n (%) VAL: 9 (0.6%) CT: 9 (0.6%) CT vs. VAL: HR (95% CI): 1.03 (0.41, 2.60) *p*=.9545	Transition to dialysis, doubling of serum Cr levels, n (%) VAL: 7 (0.5%) CT: 8 (0.5%) CT vs. VAL: HR (95% CI): 0.93 (0.34, 2.61) *p*=.8966	Withdrawals due to AE NR Any adverse event, n (%) VAL: 42 (2.7) CT: 36 (2.3) *p*=NS Dry Cough, n VAL: 1 CT: 1 *p*=NR Elevated serum potassium, n VAL: 2 CT: 0 *p*=NR

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
VALUE Julius et al., 2004;[54] Kjeldsen et al., 2006[98] (see AE column)	15,313	Mean exposure to study medication 3.6 years; mean 4.2 years F/U	Good	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 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	Adults, ≥50 years with treated or untreated HTN and predefined combinations of CV risk factors or CVD. SBP 160–210 mmHg, DBP <115 mmHg.	All-cause death, n (%) VAL: 841 (11.0) AML: 818 (10.8) VAL vs. AML: HR (95%CI): 1.04 (0.94, 1.14) *p*=.45	Fatal and nonfatal MI, n (%) VAL: 369 (4.8) AML: 313 (4.1) VAL vs. AML: HR (95%CI): 1.19 (1.02, 1.38) *p*=.02	Fatal and nonfatal stroke, n (%) VAL: 322 (4.2) AML: 281 (3.7) VAL vs. AML: HR (95%CI): 1.15 (0.98, 1.35) *p*=.08	Fatal and nonfatal HF, n (%) VAL: 354 (4.6) AML: 400 (5.3) VAL vs. AML: HR (95%CI): 0.89 (0.77, 1.03) *p*=.12	PRIMARY OUTCOME: Primary composite of time to first cardiac event, n (%) VAL: 810 (10.6) AML: 789 (10.4) VAL vs. AML: HR (95%CI): 1.04 (0.94, 1.15) *p*=.49 Cardiac morbidity, n (%) VAL: 586 (7.7) AML: 578 (7.6) VAL vs. AML: HR (95%CI): 1.02 (0.91, 1.15) *p*=.71 Cardiac mortality, n (%) VAL: 304 (4.0) AML: 304 (4.0) VAL vs. AML: HR (95%CI): 1.01 (0.86, 1.18) *p*=.90		Withdrawals due to AE, % VAL: 11.9 AML: 12.9 *p*=NR New onset DM, n (%) VAL: 690 (13.1) AML: 845 (16.4) VAL vs. AML: OR (95%CI): 0.77 (0.69, 0.86) *p*<.0001 Hypokalemia, n (%) VAL: 266 (3.5) AML: 469 (6.2) *p*<.0001 Peripheral edema, n (%) VAL: 1135 (14.9) AML: 2492 (32.9) *p*<.0001 Dizziness, n (%) VAL: 1257 (16.5) AML: 1083 (14.3) *p*<.0001 Headaches, n (%) VAL: 1120 (14.7) AML: 947 (12.5) *p*<.0001

Study	N	Duration	Quality Rating	Treatment Groups	Population	Mortality Outcomes	CHD Outcomes	Cerebrovascular Outcomes	HF Outcomes	Composite Outcomes	Kidney Outcomes	Adverse Events
Kyoto Heart Study Sawada et al., 2009[100]	3,031	3.27 years	Fair	VAL: Valsartan 80 mg daily; flexibly adjusted to a dose of 40–80 mg as needed to control BP; dose doubled after 4 weeks if initial dose could not achieve BP goal; after 8 weeks, anti-HTN drugs other than ARBs or ACE allowed if necessary 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.	Adults, ages ≥20 years, with uncontrolled HTN for at least 4 weeks and one or more CV risk factors. SBP ≥140 mmHg and/or mean sitting DBP ≥90 mmHg.	All-cause mortality, n (%) VAL: 22 (1.5) CT: 32 (2.1) CT vs. VAL: HR (95% CI): 0.76 (0.4, 1.3) *p*=.32851	Acute MI, n (%) VAL: 7 (0.5) CT: 11 (0.7) CT vs. VAL: HR (95% CI): 0.65 (0.2, 1.8) *p*=.39466 Dissecting aneurysm of aorta, n (%) VAL: 3 (0.2%) CT: 5 (0.3%) CT vs. VAL: HR (95% CI): 0.60 (0.1, 2.5) *p*=.69987	Stroke, n (%) VAL: 25 (1.5) CT: 46 (3.0) CT vs. VAL: HR (95% CI): 0.55 (0.3, 0.9) *p*=.01488	Heart failure, n (%) VAL: 12 (0.8) CT: 26 (1.7) CT vs. VAL: HR (95% CI): 0.65 (0.3, 1.3) *p*=.20857	PRIMARY OUTCOME: Composite of fatal and nonfatal CV events (stroke, TIA, MI, new occurrence or exacerbation of angina pectoris, new occurrence or exacerbation of HF, dissecting aneurysm of the aorta, lower limb arterial obstruction, emergency thrombosis, transition to dialysis, and doubling of plasma Cr levels), n (%) VAL: 83 (5.5) CT: 155 (10.2) CT vs. VAL: HR (95% CI): 0.55 (0.4, 0.7) *p*=.00001 CV death, n (%) VAL: 8 (0.5%) CT: 13 (0.9%) CT vs. VAL: HR (95% CI): 0.66 (0.3, 1.6) *p*=.37121	Transition to dialysis or doubling serum Cr, n (%) VAL: 6 (0.4) CT: 14 (0.9) CT vs. VAL: HR (95% CI): 0.43 (0.2, 1.1) *p*=.34666	Withdrawals due to AE NR New onset DM, n (%) VAL: 58 (5.2) CT: 86 (7.7) CT vs. VAL: HR (95% CI): 0.67 (0.5, 0.9) *p*=.02817 Dry cough, n (%) VAL: 2 (0.1) CT: 4 (0.3) *p*=NS Elevated serum potassium, n (%) VAL: 4 (0.3) CT: 2 (0.1) *p*=NS

APPENDIX E.

Abbreviations and Acronyms

Appendix E: Abbreviations and Acronyms

ACC	American College of Cardiology
ACEI	angiotensin-converting enzyme inhibitor
AHA	American Heart Association
ARB	angiotensin II receptor blocker
BP	blood pressure
CCB	calcium channel blocker
CD	cannot determine
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
COI	conflict of interest
CPG	Clinical Practice Guidelines
CQ	Critical Question
CVD	cardiovascular disease
DARD	Division for the Application of Research Discoveries
DBP	diastolic blood pressure
ECG	echocardiogram
eGFR	estimated glomerular filtration rate
ES	evidence statement
ESRD	end-stage renal disease
GEC	Guidelines Executive Committee
GFR	glomerular filtration rate
GRTs	group randomized trials
HCTZ	hydrochlorothiazide
HR	hazard ratio
I/E	inclusion/exclusion
IOM	Institute of Medicine
ITT	intention to treat
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MeSH	medical subject headings
MI	myocardial infarction
NA	not applicable
NHLBI	National Heart, Lung, and Blood Institute

NR	not reported
OR	odds ratio
PAD	peripheral artery disease
PICOTSS	population, intervention/exposure, comparison group, outcome, timing, setting, study design
RCT	randomized control trial
RR	relative risk
RWI	relationships with industry
SBP	systolic blood pressure
SR/MA	systematic reviews/meta-analyses
SVD	singular value decomposition
TIA	transient ischemic attack
TIMS	targeted immune modulators
TOS	The Obesity Society
UACR	urine albumin-to-creatinine ratio
USPSTF	U. S. Preventive Services Task Force
VCW	virtual collaborative workspace
WHO	World Health Organization

APPENDIX F.

Names of Studies

Appendix F: Names of Studies

AASK	African American Study of Kidney Disease and Hypertension
ABCD	Appropriate Blood Pressure Control in Diabetes
ACCOMPLISH	Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension
ACCORD	Action to Control Cardiovascular Risk in Diabetes Trial
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ANBP	Australian National Blood Pressure Study
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm
AVER	Amlodipine Versus Enalapril in Renal failure Study Group
CAPPP	The CAPtopril Prevention Project Cardio-Sis Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica
CASE-J	Candesartan Antihypertensive Survival Evaluation in Japan
CONVINCE	Controlled Onset Verapamil Investigation of Cardiovascular End Points
ELSA	European Lacidipine Study on Atherosclerosis
ESPIRAL	Efecto del tratamiento antihipertensivo Sobre la ProgresioÂn de la Insuciencia RenAL en pacientes no diabeaticos
EWPHE	European Working Party on High Blood Pressure in the Elderly
FACET	Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial
HAPPHY	Heart Attack Primary Prevention in Hypertension
HDFP	Hypertension Detection and Follow-Up Program
HOT	Hypertension Optimal Treatment
Hypertension-Stroke Cooperative Study	
HYVET	Hypertension in the Very Elderly Trial
IDNT	Irbesartan in Diabetic Nephropathy Trial
INSIGHT	International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment
IPPPSH	International Prospective Primary Prevention Study in Hypertension
JATOS	Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients
Jikei Heart Study	
JMIC-B	Japan Multicenter Investigation for Cardiovascular Diseases-B

Kyoto Heart Study	
LIFE	Losartan Intervention For Endpoint
MAPHY	Metoprolol Atherosclerosis Prevention in Hypertensives
MDRD	Modification of Diet in Renal Disease Study Group
MIDAS	Myocardial Infarction Data Acquisition System
MOSES	Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention
MRC	Medical Research Council
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial
NORDIL	Nordic Diltiazem study
Oslo Hypertension Study	
PHARAO	Prevention of Hypertension with the Angiotensin-converting enzyme inhibitor Ramipril in patients with high-normal blood pressure
REIN-2	Ramipril Efficacy In Nephropathy 2
SCOPE	Study on Cognition and Prognosis in the Elderly
SHELL	Systolic Hypertension in the Elderly
SHEP	Systolic Hypertension in the Elderly Program
Sprackling	1981 study in Nottingham geriatric facilities
STOP-HTN2	Swedish Trial in Old Patients with Hypertension (second study)
STOP-Hypertension	Swedish Trial in Old Patients with Hypertension
Syst-China	Systolic Hypertension in China Collaborative Group (excluded
Syst-Eur	Systolic Hypertension in Europe trial
TROPHY	Trial of Preventing Hypertension Study Investigators
UKPDS	United Kingdom Prospective Diabetes Study
USPHS	U.S. Public Health Service Hospitals Cooperative Study Group
VA Cooperative	Veterans Administration Cooperative
VALISH	Valsartan in Elderly Isolated Systolic Hypertension
VALUE	Valsartan Antihypertensive Long-term Use Evaluation
VHAS	Verapamil in Hypertension and Atherosclerosis Study

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