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Benefits and Harms of Treating Blood Pressure in Older Adults: A Systematic Review and Meta-analysis

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Prepared by:
Evidence-based Synthesis Program (ESP)
Portland VA Health Care System
Portland, OR
Devan Kansagara, MD, MCR, Director

Investigators:

Principal Investigators:
Jessica Weiss, MD
Devan Kansagara, MD, MCR

Co-Investigators:
Amy Kerfoot, MD
Michele Freeman, MPH
Makalapua Motu'apuaka, BS
Rochelle Fu, PhD
Allison Low, BA
Robin Paynter, MLIS
Karli Kondo, PhD

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

INTRODUCTION

Hypertension is a very common chronic illness in the United States and among Veterans. Use of antihypertensive medications can lower the risk of cardiovascular disease, cerebrovascular disease, renal disease, and death. The most beneficial blood pressure targets for patients of specific age groups, however, has been a topic of some debate and controversy, stemming from concerns that the ratio of benefit to harm of a given blood pressure level may vary with age. In 2014, the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (previously JNC-FG8, referred to in this report as JNC-BP) published new guidelines for the treatment of hypertension, as well as a new treatment goal for older individuals (over age 60) for systolic blood pressure (SBP) of < 150 mm Hg rather than < 140 mm Hg. The new goal for those over 60 years of age has been very controversial; the issue of the appropriate (safest and most beneficial) goal for older people has been debated among experts with viewpoints supporting both higher and lower treatment goals. The objectives of this review are to examine the benefits and harms of differing blood pressure targets among adults over age 60.

METHODS

Data Sources and Searches

We searched MEDLINE®, Embase®, and Ovid EBM Reviews from database inception through January 2015, and updated the MEDLINE® search in September 2016. We additionally examined all trials included in the JNC-BP review as well as the Blood Pressure Lowering Treatment Trialists Collaborative (BPLTTC) at the full-text level. We also searched ClinicalTrials.gov to identify in-progress or unpublished studies, and included related publications if in-progress trials were completed by December 2015. Using pre-specified inclusion/exclusion criteria, we reviewed titles and abstracts and retrieved full-text articles with potential relevance to the Key Questions. Two independent reviewers reviewed the full-text articles to determine a final inclusion/exclusion decision.

Study Selection

We only included studies in which the study population had mean age of ≥ 60 years and all participants carried a diagnosis of hypertension at the time of enrollment. We included controlled trials which examined the health outcome effects of lower versus higher blood pressure targets, or which compared more intensive to less intensive treatment strategies in the absence of a specific blood pressure goal. We excluded comparative effectiveness trials which directly compared the effects of different antihypertensive drugs to one another. We excluded observational studies in considering our primary health outcomes (mortality, stroke, cardiac events), given the risk of confounding and the existence of many controlled trials. We included observational studies to assess potential harms of antihypertensive therapy.

Data Abstraction and Quality Assessment

Data from published reports were abstracted into a customized database by one reviewer and reviewed for accuracy and completeness by a second reviewer. Outcomes of interest for Key Questions 1 to 3 of this review included potential benefits of lower versus higher blood pressure

targets: all-cause mortality, cardiovascular mortality, stroke (fatal or non-fatal), and cardiovascular morbidity (myocardial infarction and sudden cardiac death). Outcomes of interest related to Key Questions 4 and 5 (potential harms of lower versus higher blood pressure targets) included changes in cognition, changes in quality of life, falls and fractures, hypotension, and acute kidney injury (defined as doubling of serum creatinine or requiring renal-replacement therapy).

Two reviewers independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration. Disagreements were resolved through discussion. Each trial was given an overall summary assessment of low, high, or unclear risk of bias.

Data Synthesis and Analysis

We conducted meta-analyses using study-level data to get more precise estimates for several outcomes including death from all causes, cardiovascular death, fatal and nonfatal stroke, major cardiac events, and withdrawal due to adverse events. We used the profile-likelihood random-effects model to combine risk ratios, while incorporating variation among studies. We assessed the presence of statistical heterogeneity among the studies by using the standard Cochran's chi-square test, and assessed the magnitude of heterogeneity by using the I^2 statistic. We qualitatively synthesized results for all other outcomes.

We classified the overall quality of evidence as high, moderate, low, or insufficient using a method which considers the consistency, coherence, and applicability of a body of evidence, as well as the internal validity of individual studies.

RESULTS

Results of Literature Search

We reviewed 11,268 titles and abstracts from the combined searches. We selected 330 articles for full-text review. We identified 21 randomized controlled trials (RCTs) and 3 cohort studies that contained primary data relevant to the Key Questions.

Results for Key Questions

The following section briefly describes the findings for each Key Question. The strength of evidence and pooled estimates are provided in the Summary of Evidence table below.

Key Question 1. In adults aged over age 60, what are the health outcome effects of differing blood pressure targets?

We found 8 trials comparing blood pressure treatment targets, and 13 trials comparing more versus less intensive treatment. Overall, there was clear and consistent evidence that treating blood pressure in older adults reduced mortality, cardiac events, and stroke. We found the most consistent and largest effects among trials in which participants had higher baseline blood pressures (SBP ³ 160 mm Hg) and achieved moderate blood pressure control (< 150/90 mm Hg).

Six trials compared more aggressive blood pressure treatment targets (SBP < 140 mm Hg or diastolic blood pressure [DBP] < 85 mm Hg) to higher targets and found that lower targets were associated with a nonsignificant reduction in all-cause mortality (RR 0.86, 95% CI 0.69-1.06;

ARR 0.80; I^2=13.3%), a reduction in stroke (RR 0.79, 95% CI 0.59-0.99; ARR 0.49; I^2=16.2%), and a marginally significant reduction in cardiac events (RR 0.82, 95% CI 0.64-1.00; ARR 0.94; I^2=15.5%). Most of the evidence supporting the benefit of lower treatment targets came from one large trial of non-diabetic patients at high cardiovascular risk which compared an SBP target of 120 mmHg to an SBP target of 140 mmHg.

Key Question 1b. In patients who have suffered a transient ischemic attack (TIA) or stroke, does treatment of blood pressure to specific targets affect outcomes?

Pooled analyses of 2 trials of participants with mean baseline SBP of 140 to 150 mm Hg and known cerebrovascular disease found that treating to SBP < 140 mm Hg compared to slightly higher targets reduced recurrent stroke (RR 0.76, 95% CI 0.66 to 0.92, I^2 = 0%), but not cardiac events (RR 0.78, 95% CI 0.61 to 1.08) or mortality (RR 0.98, 95% CI 0.85 to 1.19). One of the trials targeted SBP < 130 mm Hg and found a non-significant trend towards reduced stroke. The other trial found that a more intensive treatment strategy achieving SBP < 140 mm Hg reduced stroke and cardiac events.

Key Question 2: How does age modify the benefits of differing blood pressure targets?

We found no evidence that age modifies treatment effects: 12 trials found no age-treatment interactions on health outcome effects, and 3 trials found that the rate of harms from more intensive treatment was similar in those age ≥ 75 years and < 75 years.

Key Question 3: How does the patient burden of comorbidities modify the benefits of differing blood pressure targets?

We found no studies examining the impact of comorbidity burden on antihypertensive treatment effects.

We found subgroup analyses from 4 trials which examined whether treatment effects varied according to cardiovascular risk profile. These studies provide low-strength evidence that there may be greater absolute treatment effects amongst patients with high cardiovascular risk, though relative treatment effects are similar across risk groups. Confidence in these conclusions is tempered by the post hoc nature of some of these analyses, the small number of studies, and variation in the outcomes contributing to these findings.

Key Question 4. What are the harms of targeting lower blood pressure in older patients? Do the harms vary with age?

General Adverse Events

Four of 10 trials found that more intensive blood pressure treatment was associated with a statistically significant increase in withdrawals due to adverse events, with relative risk increases ranging from 44 to 100%. Cough and hypotension were among the most frequently reported events. Two of 3 trials found more intensive treatment was associated with a higher risk of syncope.

Renal Outcomes

We found low-strength evidence from 11 trials that more intensive blood pressure treatment was not associated with worsening of renal outcomes.

Cognitive Outcomes

We found moderate-strength evidence from 7 RCTs that use of antihypertensive treatment to achieve moderately strict blood pressure control for up to 5 years does not worsen cognitive outcomes compared to less strict blood pressure control.

Quality of Life and Functional Status

Overall, we found moderate-strength evidence from prospective substudies of 4 large, low risk of bias trials that use of antihypertensive therapy to achieve moderate blood pressure control (SBP 140 to 150 mm Hg) was not associated with a deterioration in quality of life compared to less intensive blood pressure control. We did not find data about quality of life in trials achieving lower blood pressures (SBP < 140 mm Hg).

Falls and Fractures

We found moderate-strength evidence from 3 large, low risk of bias trials that more intensive blood pressure treatment (SBP targets of < 120 mm Hg and < 150 mm Hg, and achieved SBP < 150 mm Hg in the third trial) did not increase risk of fracture. We found low-strength evidence that more aggressive blood pressure control did not consistently increase the risk of falls. Two of the trials found that very aggressive blood pressure lowering (SBP < 120 mm Hg) did not increase the risk of falls, while a third trial found that moderate blood pressure control (SBP < 150 mm Hg) was associated with a small increase in the risk of fall.

Effects of Age

We found limited evidence from 3 studies that differences in rates of adverse events such as unsteadiness, dizziness, and renal failure between intervention and control groups were not appreciably different in those greater and less than 75 years of age.

Key Question 5. Do the harms of targeting lower blood pressure vary with patient burden of comorbidities?

We found no trials which examined the impact of participants' burden of comorbidities on risk of adverse events.

SUMMARY OF EVIDENCE AND DISCUSSION

Key Findings and Strength of Evidence

In this systematic review, we examined the benefits and harms of treating hypertension to lower compared more moderate blood pressure targets in patients over age 60. The table that follows provides a summary of the evidence. Overall, we found high strength evidence that treating blood pressure in patients over age 60 to current treatment targets (< 150/90 mmHg) substantially reduces mortality, stroke, and cardiac events. Much of this data comes from trials in which the mean baseline SBP was > 160 mmHg. We also found evidence, driven mainly by one

large trial, that lower targets (SBP < 140 mmHg or DBP < 85 mmHg) compared to higher targets reduced stroke (moderate strength evidence) and cardiac events (low strength evidence); mortality was also reduced though not significantly (low strength evidence). There is little data that directly helps distinguish benefits between SBP 140 and 150 mmHg. Most of the trials achieving SBP < 140 mmHg were the treat-to-target trials. Only one trial included patients with baseline SBP 140-150 mmHg and found an improvement in mortality, but not other outcome. We found moderate strength evidence that more aggressive blood pressure control (SBP < 140 mmHg) in patients with prior stroke substantially reduced rates of recurrent stroke.

The treat-to-target trials overall support a lower blood pressure treatment target in some patients with high cardiovascular risk. Most of the evidence in support of lower treatment targets comes from one large trial examining an SBP target of < 120 mmHg in which a substantial proportion of intervention patients achieved SBP 120-130 mmHg. Lower targets may prevent (on average, across a population) roughly 10-20 events for every 1000 high-risk patients treated over 5 years (Table 2), but more aggressive treatment is likely associated with a higher medication burden and higher risk of adverse effects such as hypotension and syncope. On the other hand, we found that lower targets are unlikely to increase the risk of dementia, fractures, and falls, or reduce quality of life.

Applicability

The generalizability of our findings to the oldest age groups and the frail elderly is limited. Very few patients over age 80 were included in the trials, though one trial exclusively enrolled patients over age 80 and found a reduced risk of stroke with moderate blood pressure control (< 150/90 mm Hg). Patients with serious life-limiting illness, frailty, or dementia were excluded from most studies.

Conclusions

Lowering blood pressure in adults over age 60 reduces mortality, stroke, and cardiac events. The most consistent and largest effects are seen in studies of patients with higher baseline blood pressures (SBP ≥ 160 mmHg) achieving moderate blood pressure control (< 150/90 mmHg). Lower treatment targets (< 140/85 mmHg) are likely to be beneficial for some patients at high cardiovascular risk, but the results across trials are less consistent. Lower treatment targets are largely supported by findings from one trial which targeted SBP <120 mmHg and in which most intervention patients achieved SBP < 130 mmHg. In patients with cerebrovascular disease, more aggressive blood pressure lowering (SBP <140 mmHg) likely reduces recurrent stroke. Lower treatment targets are associated with higher medication burden and an increased risk of short-term harms such as hypotension. On the other hand, evidence that there is not an increased risk in cognitive impairment, falls, and reduced quality of life may provide some flexibility for providers in crafting an individualized antihypertensive treatment plan. There is little data to assess the risks and benefits of antihypertensive treatment among institutionalized elder patients or those with multiple comorbidities.

Summary of the Evidence on More vs Less Intensive Treatment for Hypertension in the Elderly

Outcome	N studies (N = total patients combined)	Combined estimates: RR (95% CI) ARR N: events (95% CI) prevented per 1000 high-risk patients over 5 years[a]	Strength of Evidence[b]	Summary of findings
Mortality	9 RCTs[c] (N = 46,450)	RR 0.90 (0.83-0.98) ARR 1.64 N: 34 (7-58)	High[d]	Consistent benefit of treating blood pressure to levels < 150/90 mmHg.
	6 RCTs[e] (N = 41,491)	RR 0.86 (0.69-1.06) ARR 0.80 N: 18 (n/a[f]-40)	Low	Lower treatment targets (SBP ≤ 140 mmHg or DBP ≤ 85 mmHg, or lower) associated with non-significant mortality reduction compared to higher targets. Findings were inconsistent across studies and estimate was imprecise.
Stroke	9 RCTs[c] (N = 46,450)	RR 0.74 (0.65-0.84) ARR 1.13 N: 26 (16-35)	High[d]	Clear, consistent benefit of treating blood pressure to levels < 150/90 mmHg.
	6 RCTs[e] (N = 41,491)	RR 0.79 (0.59-0.99) ARR 0.49 N: 9 (0-17)	Moderate	Lower treatment targets (SBP ≤ 140 mmHg or ≤ DBP 85 mmHg, or lower) reduced the risk of stroke compared to higher targets; some inconsistency but relatively stable effect across analyses[f]
Cardiac events	9 RCTs[c] (N = 46,450)	RR 0.77 (0.68-0.89) ARR 1.25 N: 65 (31-90)	High[d]	Clear, consistent benefit of treating blood pressure to levels < 150/90 mmHg.
	6 RCTs[e] (N = 41,491)	RR 0.82 (0.64-1.00) ARR 0.94 N: 18 (n/a[f]-36)	Low	Lower treatment targets (SBP ≤ 140 mmHg or DBP ≤ 85 mmHg, or lower) may reduce the risk of cardiac events compared to higher targets. Findings were inconsistent across studies and estimate was imprecise.
Short-term adverse events	19 RCTs (N = 98,964)	---	---	Mixed findings: withdrawal due to adverse events was increased in the intervention group by 44-100% in 4 of 10 trials reporting this outcome. Cough and hypotension were the most frequently reported events. The risk of syncope was increased in 2 of 3 trials reporting this outcome. Excessive heterogeneity among trials precluded pooling of results.
Renal outcomes	13 RCTs (N = 66,607)	---	Low	More intensive blood pressure treatment did not worsen renal outcomes. Outcome definitions varied, and event rates for clinically significant outcomes such as end stage renal disease were low.
Cognitive outcomes	7 RCTs (N = 25,901)	Incident dementia in 4 RCTs of patients without prior stroke: OR 0.89 (0.74-1.07)	Moderate	No effect on degree of cognitive decline or incidence of dementia. Loss to follow-up ranged across studies; patients lost to follow-up may differ in risk for dementia.
Falls/ fracture	Fracture: 3 RCTs (N = 11,680)	---	Moderate (fracture)	Mixed findings: 3 trials found no effect of lower blood pressure targets on risk of fracture. Two trials with SBP target of 120 mmHg found no effect on risk of falls, while a 3rd (with achieved SBP < 150 mmHg) found a small increase in risk of fall.
	Falls: 3 RCTs (N = 17,196)	---	Low (falls)	

Outcome	N studies (N = total patients combined)	Combined estimates: RR (95% CI) ARR N: events (95% CI) prevented per 1000 high-risk patients over 5 years[a]	Strength of Evidence[b]	Summary of findings
Quality of life (QOL)	4 RCTs (N = 7,154)	---	Moderate (QOL) Low (functional status)	Moderate BP control (SBP 140-150 mmHg) did not affect QOL. One study found no effect on functional status.
Effects of age	12 RCTs (N = 76,137)	---	Low	Similar effects across different age groups in age-treatment interaction analyses, but based on study-level subgroup analyses and dichotomized at a younger age in many studies.
Effects of comorbidity burden	---	---	No evidence	No studies reported outcomes based on comorbidity burden; most trials excluded patients with dementia, serious comorbidities, and life-limiting illness.
Effects in the frail elderly	2 RCTs (N = 5,166)	---	Insufficient	Treatment effects did not vary with frailty score in post-hoc analyses from 2 trials, one of which had large amount of missing data. Most trials did not assess frailty, and many trials excluded patients who were frail, had dementia, or were institutionalized.
Effects in stroke patients	2 RCTs (N = 9,125)	Stroke recurrence: RR 0.76 (0.66-0.92) ARR 3.02 Cardiac events: RR 0.78 (0.61-1.08) Mortality: RR 0.98 (0.85-1.19)	Moderate	Targeting SBP < 140 mmHg reduced recurrent stroke.

Abbreviations: ARR = absolute risk reduction; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; N = population size (N total / n subgroup); OR = odds ratio; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk; SBP = systolic blood pressure.

[a] We used observed control group event rates standardized to 5 years. As poorly controlled blood pressure itself contributes to cardiovascular risk, we used data from the 2 most contemporary trials for each set of analyses. We used the HYVET study (22) to estimate event rates in the higher baseline blood pressure analyses, and data from SPRINT (the older age subgroup since the mean age was comparable to that in HYVET) for the treat to target analyses (50).

[b] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient = Any estimate of effect is very uncertain.

[c] The analyses presented here are of trials with baseline SBP ³ 160 mmHg. The achieved SBP in 3 of the trials was < 140 mmHg, but these studies contributed relatively few events. Achieved SBP in all the other studies was ³ 140 mmHg.

[d] Most of the evidence comes from trials in which baseline SBP ≥160 mmHg and achieved SBP was 140-150 mmHg. These are large trials providing consistent evidence, and a precise summary estimate.

[e] All trials that tested strict versus less strict blood pressure targets in which the target blood pressure in the intervention group was SBP < 140 mmHg or DBP < 85 mmHg, or even lower.

[f] The number of prevented events is not applicable because the upper bound of the confidence interval for relative risk was ³ 1.00.

ABBREVIATIONS

Abbreviation	Definition
α-B	Alpha-blocker
β-B	Beta-blocker
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin converting enzyme
ADL	Activities of daily living
ADVANCE	Action in Diabetes and Vascular Disease
AE	Adverse effect or event
AHRQ	Agency for Healthcare Research and Quality
ARB	Angiotensin II receptor blockers
ARR	Absolute risk reduction
BENEDICT-B	Bergamo Nephrologic Diabetes Complications Trial-B
BioLINCC	Biologic Specimen and Data Repository Information Coordinating Center
BP	Blood Pressure
BPLTTC	Blood Pressure Lowering Treatment Trialists Collaborative
CAD	Coronary artery disease
Cardio-Sis	Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica
CCB	Calcium channel blocker
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CVA	Cerebrovascular accident
CVD	Cerebrovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DSST	Digit Symbol Substitution Test
ESP	Evidence-based Synthesis Program
EuroQOL	European Quality of Life scale
EWPHE	European Working Party on High Blood Pressure in the Elderly
FEVER	Felodipine Event Reduction Study
HOT	Hypertension Optimal Treatment
HR	Hazard ratio
HYVET	Hypertension in the Very Elderly Trial
JATOS	Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients
JNC-BP	Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
KQ	Key Question(s)
LVH	Left Ventricular Hypertrophy
MI	Myocardial infarction
mm Hg	Millimeters of mercury (unit of pressure)

MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
N	Number randomized (N= total, n = subgroup)
NNT	Number needed to treat
NR	Not reported
ns	Not statistically significant
OR	Odds ratio
PALT	Paired Associate Learning Test
PGWB	Psychological General Well-Being
PICOTS	Population, intervention, comparator, outcome, timing, study design
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
QOL	Quality of life
RCT	Randomized controlled trial
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
RR	Relative risk
SBP	Systolic blood pressure
SCOPE	Study on Cognition and Prognosis in the Elderly
SD	Standard deviation
SHEP	Systolic Hypertension in the Elderly Program
SIP	Sickness Impact Profile
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
SSA-P	Subjective Symptoms Assessment Profile
STONE	Shanghai Trial of Nifedipine in the Elderly
Syst-China	Systolic Hypertension in China
Syst-Eur	Systolic Hypertension in Europe
TIA	Transient ischemic attack
TRANSCEND	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease
VA	Veterans Administration
VALISH	Valsartan in Elderly Isolated Systolic Hypertension
WHO	World Health Organization

EVIDENCE REPORT

INTRODUCTION

Hypertension is a very common chronic illness in the United States, with an estimated prevalence of 27% among adults over age 18 and as much as 67% in adults over age 60, and possibly a higher prevalence among Veterans.[1] Hypertension management is known to modify the risk of cardiovascular disease, renal disease, cerebrovascular disease, and death.[2-5] The issue is of great relevance to Veterans Affairs (VA) given the very high prevalence of hypertension and other vascular risk factors such as diabetes and hyperlipidemia in Veterans generally and the aging Veteran population more specifically. The benefit of some versus no blood pressure control has been shown to be consistent for older adults (aged ≥ 60 years), even the very elderly (aged ≥ 80 years).[6-8] The most beneficial blood pressure targets for patients of specific age groups, however, has been a topic of some debate and controversy, stemming from concerns that the ratio of benefit to harm of a given blood pressure level may vary with age. Further, the disease-disease and disease-treatment interactions which can occur when treating hypertension in older adults with multiple chronic comorbidities remain unclear. This holds particular relevance for Veterans over age 65, who experience an average of 5 comorbidities and for whom the most common comorbidity clusters in both men and women include hypertension.[9]

In 2014, the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (previously JNC-FG8, referred to in this report as JNC-BP) published new guidelines for the treatment of hypertension as well as a new treatment goal for older individuals (age ≥ 60 years) for systolic blood pressure (SBP) of < 150 mm Hg rather than < 140 mm Hg.[10] The new goal for those ages ≥ 60 years has been very controversial. The recent publication of a trial showing a benefit from aggressive blood pressure treatment in older individuals has further fueled debate about the safest and most beneficial blood pressure goal for older people.[11] The objectives of this review are to examine the benefits and harms of differing blood pressure targets among older adults (aged ≥ 60 years).

METHODS

TOPIC DEVELOPMENT

This topic was nominated by Dr. Dawn Bravata with the Stroke Quality Enhancement Research Initiative. Additional key stakeholders for this project include the directors for the offices of Neurology, Clinical Analytics and Reporting, the Evidence-based Practice Program, and Preventive Medicine. The research questions for this systematic review were developed after a topic refinement process that included a preliminary review of published peer-reviewed literature, discussion with internal partners and investigators, and consultation with content experts and key stakeholders. A protocol describing the review plan was posted to a publicly accessible website before the study was initiated.[12]

In this report we address the following Key Questions which all apply to adults over age 60:

Key Question 1. What are the health outcome effects of differing blood pressure targets? b) What are the health outcome effects of differing blood pressure targets in patients who have suffered a transient ischemic attack (TIA) or stroke?

Key Question 2. How does age modify the benefits of differing blood pressure targets?

Key Question 3. How does the patient burden of comorbidities modify the benefits of differing blood pressure targets?

Key Question 4. What are the harms of targeting lower blood pressure in older patients? Do the harms vary with age?

Key Question 5. Do the harms of targeting lower blood pressure vary with patient burden of comorbidities?

SEARCH STRATEGY

We developed a literature search strategy in consultation with a research librarian (Appendix A). We searched MEDLINE®, Embase®, and Ovid EBM Reviews from database inception through January 2015, and updated the MEDLINE® search in September 2016. We also examined all trials included in the recent JNC-BP review[10] and the Blood Pressure Lowering Treatment Trialists Collaborative (BPLTTC)[13] at the full-text level. We conducted an additional search from January 2012 through January 2015 focused specifically on blood pressure treatment trials (because all trials in JNC-BP and BPLTTC were published before 2012). We further evaluated the bibliographies of included primary studies and recent systematic reviews. We also searched ClinicalTrials.gov to identify in-progress or unpublished studies, and identified related publications if in-progress trials were completed through December 2015.

STUDY SELECTION

The criteria for patient population, intervention, comparator, outcome measures, timeframe for outcomes, and study design (PICOTS) vary by Key Question. Table 1 shows how each parameter in the PICOTS corresponds to the Key Questions. We applied specific inclusion/exclusion codes in screening the literature for relevant studies (Appendix B). We reviewed titles and abstracts and retrieved full-text articles with potential relevance to the Key Questions. Two independent reviewers reviewed the full-text articles to determine a final inclusion/exclusion decision.

Studies were considered for inclusion if the study population had mean age of ≥ 60 years, all participants carried a diagnosis of hypertension at the time of enrollment, and the study design either compared higher versus lower blood pressure targets or more versus less intensive antihypertensive therapy (*ie*, compared the addition of an antihypertensive medication to placebo). We excluded studies in populations with specific diagnoses in which medications were used primarily for effects other than blood pressure lowering (*eg*, studies of beta-blockade in patients with systolic heart failure, or studies of acute myocardial infarction). We also excluded studies focused on the management of acute stroke.

We excluded comparative effectiveness trials which directly compared the effects of different antihypertensive drugs to one another. We excluded observational studies in considering our primary health outcomes (mortality, stroke, cardiac events) given the risk of confounding and the existence of many controlled trials. We included observational studies to assess potential harms of antihypertensive therapy. Because harms may be relatively infrequent and are not always immediate, we surmised the larger patient numbers and longer follow-up of cohort studies may be more likely to identify important harms/adverse events of blood pressure management. We only included observational studies in which there was some assessment of blood pressure change over time and in which patients were receiving antihypertensive therapy. We did not include studies examining the relationship between a baseline blood pressure and subsequent outcomes. We included trial extension studies and companion studies which reported subgroup analyses of interest such as treatment effect modifications based on age.

Table 1. Key Questions, Inclusion Criteria, and Scope Parameters

Key Question (KQ) In adults over age 60 with hypertension:	**KQ1.** What are the health outcome effects of differing blood pressure targets? b) What are the health outcome effects of differing blood pressure targets in patients who have suffered a TIA or stroke?	**KQ2**. How does age modify the benefits of differing blood pressure targets?	**KQ3.** How does the patient burden of comorbidities modify the benefits of differing blood pressure targets?	**KQ4.** What are the harms of targeting lower blood pressure in older patients? Do these harms vary with age?	**KQ5.** Do the harms of targeting lower blood pressure vary with patient burden of comorbidities?
Population	Adults aged ≥ 60 years with hypertension		Adults aged ≥ 60 years with hypertension and CVA or other existing comorbidity	Adults aged ≥ 60 years with hypertension	Adults aged ≥ 60 years with hypertension and at least one comorbidity
Intervention	**Include**: Pharmacologic treatment of hypertension to specified targets; or more versus less intensive treatment of hypertension **Exclude:** · Interventions for which hypertension management was not the primary objective *(Example: studies conducted in patients with heart failure for which vasoactive medications are being used for cardiac remodeling effects.)* · Non-pharmacologic interventions for blood pressure control			**Include**: Pharmacologic treatment of hypertension, not necessarily to specified targets **Exclude:** Management of hypertension in patients with acute stroke; non-pharmacologic interventions for blood pressure control	
Comparators	Placebo or a higher blood pressure target				
Outcomes	· All-cause mortality · Mortality related to stroke, coronary heart disease, congestive heart failure, and renal disease · Morbidity including stroke, coronary heart disease, congestive heart failure, and renal disease			· Changes in cognition · Falls · Changes to quality of life · Polypharmacy/medication burden · Hypotension · Acute kidney injury (defined as doubling of serum creatinine or requiring renal replacement therapy)	
Timing	Long term (> 6 months) outcomes			Any	
Study design	**Include:** Controlled study designs (RCT and non-randomized controlled clinical trials)			**Include:** · Controlled study designs (RCT and non-randomized controlled clinical trials used for KQs 1-3) · Cohort extensions of trials that examined specific blood pressure targets · Cohort studies that examined the effects of lower blood pressure in the context of antihypertensive medication · Cohort studies that reported the effects of lower blood pressure despite that hypertension management was not the primary objective of the intervention studied.	
	Exclude: Case reports; case series; controlled before/after studies, RCTs with less than 6 month follow-up.				

Abbreviations: CVA = cerebrovascular accident; KQ = Key Question; RCT = randomized controlled trials; TIA = transient ischemic attack

DATA ABSTRACTION

Data from published reports were abstracted into a customized database by one reviewer and reviewed for accuracy and completeness by a second reviewer. From each study, we abstracted the following characteristics:

- study design
- objectives
- setting
- demographic variables (including sex and age)
- comorbidities (burden of comorbidity, number of medications/burden at baseline, baseline cognitive function)
- subject eligibility and exclusion criteria
- number of subjects
- years of enrollment
- duration of follow-up
- the study and comparator interventions (including screening intervals, antihypertensive agents used, blood pressure targets)
- important co-interventions
- health outcomes (all-cause mortality, mortality/morbidity related to cerebrovascular accident, coronary heart disease, congestive heart failure, renal disease)
- adverse events (including changes in cognitive status, falls, changes in quality of life, polypharmacy, and acute kidney injury)

Additional study result characteristics of interest included achieved blood pressures (systolic and diastolic), documented cognitive changes, and number of antihypertensive medications required.

QUALITY ASSESSMENT

Two reviewers independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration.[14] Disagreements were resolved through discussion. Each trial was given an overall summary assessment of low, high, or unclear risk of bias (Appendix C).

DATA SYNTHESIS

Outcomes of interest for Key Questions 1 to 3 of this review included potential benefits of lower versus higher blood pressure targets: all-cause mortality, cardiovascular mortality, stroke (fatal or non-fatal), and cardiovascular morbidity (myocardial infarction and sudden cardiac death). We do not present cardiovascular mortality data in this report because these data were very similar to the all-cause mortality and cardiac events data. Because hypertension therapy is long-term in both nature and benefit, we were interested only in these outcomes when they occurred at ≥ 6 months of treatment. For each outcome, we abstracted the number of events and total participants from each treatment group to obtain a pooled estimate of relative risk (RR).

Outcomes of interest related to Key Questions 4 and 5 (potential harms of lower versus higher blood pressure targets) included changes in cognition and changes in quality of life, falls and fractures, hypotension, and acute kidney injury (defined as doubling of serum creatinine or requiring renal-replacement therapy). From the included trials, we also reported medication burden (number of antihypertensive medications required in each group), and withdrawals due to

adverse events. We did not specifically search for studies reporting well-known drug-specific adverse effects such as angiotensin converting enzyme (ACE) inhibitor-induced cough or thiazide diuretic-induced hypokalemia, but we described the common adverse events leading to withdrawal among the trials.

Study-level Meta-analysis

We conducted meta-analyses using study-level data to get more precise estimates for several outcomes including death from all causes, cardiovascular death, fatal and nonfatal stroke, major cardiac events and withdrawal due to adverse events. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. For each outcome, we abstracted the number of events and total participants from each treatment group. We used the profile-likelihood random-effects model[15] to combine risk ratios, while incorporating variation among studies. We assessed the presence of statistical heterogeneity among the studies using the standard Cochran's chi-square test, and the magnitude of heterogeneity using the I^2 statistic.[16]

We performed a number of sensitivity analyses to help address the heterogeneity of study design and patient populations. We stratified analyses by baseline study characteristics (mean age, enrollment age, SBP) and achieved SBP level. We conducted analyses of studies whose mean population age was ≥ 70 and studies whose inclusion criteria stipulated entry age of ≥ 60 to ensure results were consistent among study populations which most definitively met the age criteria of interest. We conducted analyses grouping studies in which the intervention group did and did not achieve mean SBP < 140 mm Hg to better examine outcomes among patient populations whose achieved blood pressure was genuinely lower than that suggested by current guidelines (SBP < 150 mm Hg). To examine whether blood pressure treatment affected populations with mild to moderate versus more severe hypertension differently, we also conducted analyses of studies with mean baseline SBP > 160 mm Hg and ≤ 160 mm Hg.

We conducted subgroup analyses of trials specifically examining blood pressure targets since these trials are most directly applicable to the clinical questions of interest guiding this report. Analyses included evaluation of those studies which stipulated target SBP ≤ 140 mm Hg or lower for the more intensive treatment arm. We also included one study which compared 3 diastolic blood pressure (DBP) targets.[17] In order to most directly address current guidelines, we dichotomized data from this study to DBP ≤ 90 mm Hg versus a combination of the 2 lower targets (≤ 85 plus ≤ 80 mm Hg). In an additional sensitivity analysis we incorporated only the 2 more disparate DBP groups from this trial (≤ 80 vs ≤ 90 mm Hg) as this provided the optimal difference between achieved SBP and DBP between groups (Appendix D).

Finally, we conducted analyses excluding trials which achieved negligible differences in SBP (≤ 3 mm Hg) between study arms. We also conducted analyses excluding methodologically flawed studies with a high risk of bias.

All analyses were performed using Stata/IC 13.1 (StataCorp, College Station, TX).

Individual Patient Data Meta-analysis

In an effort to better understand treatment effects among different age subgroups, we explored the possibility of gathering data to conduct analysis based on individual patient data from blood

pressure treatment trials. We contacted authors from all included RCTs. We received responses from 13, and we ultimately received either individual patient data or analyses of outcomes according to age subgroups from 4 trials (Valsartan in Elderly Isolated Systolic Hypertension [VALISH], Systolic Hypertension in Europe [Syst-Eur], European Working Party on High Blood Pressure in the Elderly [EWPHE], Action in Diabetes and Vascular Disease [ADVANCE]). We were also able to obtain study data from the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) of the National Heart, Lung, and Blood Institute on 2 studies: the Action to Control Cardiovascular Risk in Diabetes study (ACCORD) and the Systolic Hypertension in the Elderly Program (SHEP) trial. We anticipate using data from these 6 trials to conduct meta-analyses examining blood pressure treatment benefits and harms in those aged 60 to 69 years, 70 to 79 years, over age 80 years. We will also conduct analyses examining the impact of comorbidity burden on outcomes if this data is available. We anticipate these analyses will be completed and published at a later date.

RATING THE BODY OF EVIDENCE

We assessed the overall quality of evidence for each outcome using a method developed by the Agency for Healthcare Research and Quality (AHRQ).[18] We considered the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies, to classify the strength of evidence for each outcome as follows:

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient = Any estimate of effect is very uncertain.

PEER REVIEW

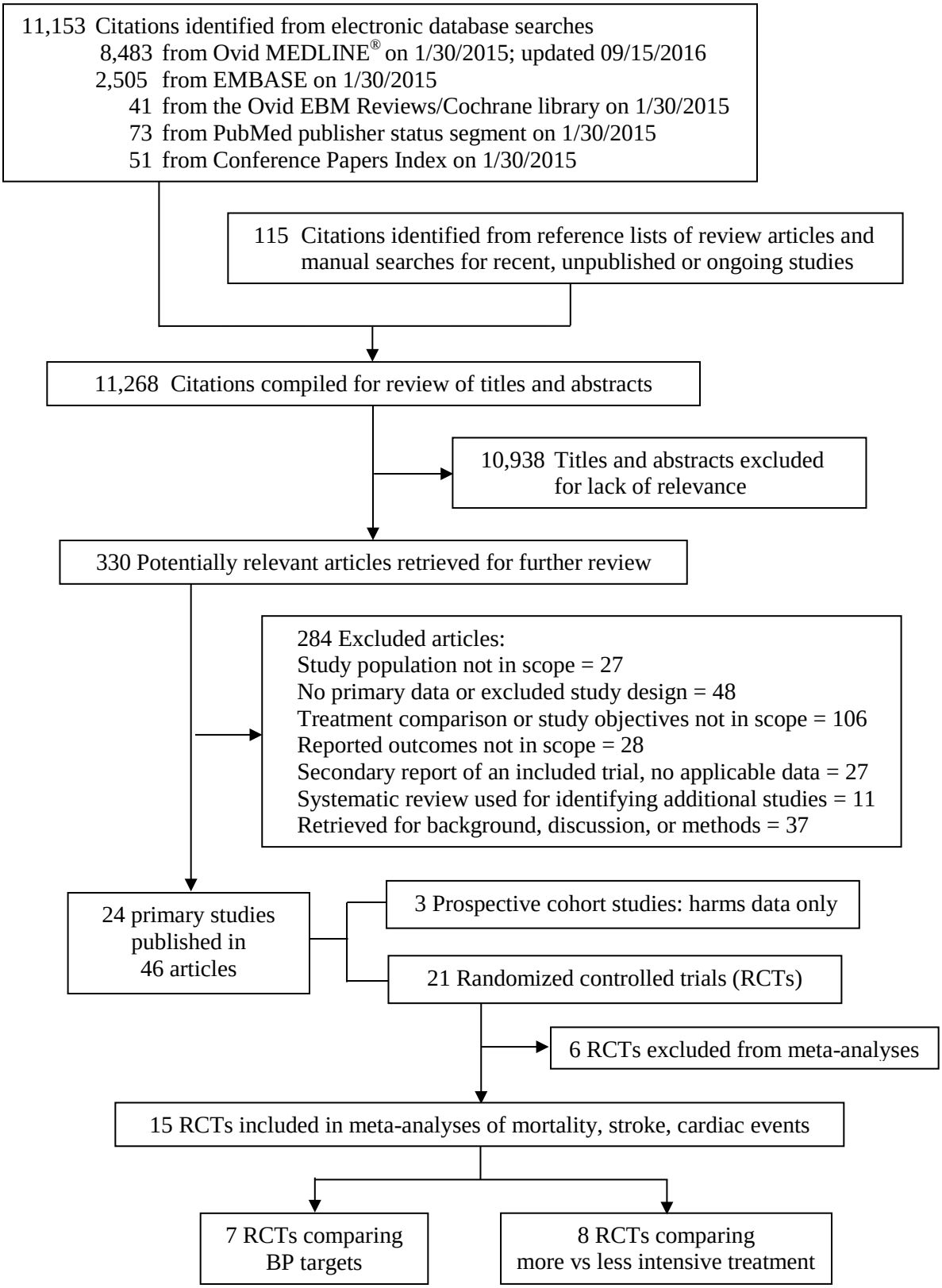
A draft version of this report was reviewed by 12 individuals with technical expertise and clinical leadership. Their comments and our responses are presented in Appendix E.

RESULTS

LITERATURE FLOW

The combined literature searches yielded 11,268 titles and abstracts, including 11,153 from electronic database searches, and 115 from reference lists of systematic reviews and other relevant articles. We applied pre-specified inclusion criteria (Appendix B) in screening the abstracts and selected 330 articles for full-text review. We identified 21 randomized controlled trials (RCTs) and 3 cohort studies that contained primary data relevant to the Key Questions (Figure 1).

Figure 1. Literature Flow Diagram



KEY QUESTION 1: In adults over age 60, what are the health outcome effects of differing blood pressure targets?

Overview of Results

We found 21 trials comparing blood pressure treatment targets, or more versus less intensive treatment. Overall, there was clear and consistent evidence that treating blood pressure in older adults reduced mortality, cardiac events, and stroke. We found the most consistent and greatest absolute benefit among trials in which participants had higher baseline blood pressures (SBP ³ 160 mm Hg) and achieved moderate blood pressure control (< 150/90 mm Hg). Six trials compared more aggressive blood pressure treatment targets (SBP < 140 mm Hg or DBP < 85 mm Hg) to higher targets and found no significant effect on all-cause mortality. More aggressive treatment did reduce the risk of cardiac events and stroke, but the absolute effects were smaller than those seen among trials of patients with higher baseline blood pressures achieving moderate control.

Trial Characteristics

The 21 included clinical trials varied significantly in study design and primary outcomes. All studies were considered low risk of bias with the exception of 3 studies.[19-21] Eight studies randomized patients to different blood pressure targets (Table 2).[11,17,21-26] The remaining 13 trials randomized patients to more versus less intensive hypertensive therapy, which often resulted in different achieved blood pressures across treatment arms (Table 3).[6,8,19,20,27-35]

Target blood pressures varied widely across studies. The SBP treatment target for the more intensive treatment arm ranged from 120 to 150 mm Hg; one study targeted DBP.[17] Achieved blood pressures also varied widely; SBP in the more intensive arm (either lower target or more intensive therapy) ranged from 119 to 149 mm Hg and in half the trials achieved SBP was ≥ 140 mm Hg. Three studies had ≤ 2 mm Hg difference in achieved SBP between treatment arms.[28,32,35] All but 3 trials[25,34,35] reported DBP at trial end, and 14 of these noted a > 1 mm Hg difference between arms in achieved DBP, but only 3 trials[8,11,22] reported DBP < 70 mm Hg in the more intensive arm and none of the trials reported achieved DBP > 90 mm Hg in the less intensive arm.

The examined patient populations varied widely across studies, from differences in race to differences in burden of comorbid illness. Three studies included only patients with type 2 diabetes,[22,27,32] 3 excluded all patients with diabetes,[11,19,23] and 6 excluded patients with type 1 diabetes or insulin-requiring diabetes.[8,17,22,27,29,32] Five studies enrolled patients with history of stroke or with high cardiovascular risk.[11,25,27,31,35]

Examined outcomes also varied across included trials. Nine of the 21 studies had a composite outcome for the primary outcome,[11,17,22,24,26,27,33,35] and 6 had a primary outcome related to stroke.[6,8,20,25,30,31] The remaining studies had primary outcomes related to renal disease or microalbuminuria[28,32] or additional outcomes not specified of interest for this review (left ventricular hypertrophy regression).[23] Use of antihypertensive agents varied widely across studies. Among trials which specified a particular medication as first-line therapy, 7 used ACE inhibitor or angiotensin II receptor blockers, 5 used calcium channel blockers, and 6 used diuretics (Tables 2 and 3).

Not surprisingly, differences between study populations and methodologies yielded differences in event rates. The proportion of patients experiencing an event varied from 0.36% to 35.1% for all-cause mortality, from 0.27% to 13.75% percent for stroke, and from 0.26% to 11.39% for major cardiac events.

Table 2. Characteristics of Trials that Compared Blood Pressure Target Goals

Study BP goals (mm Hg), T vs C Mean or median(*) length of follow-up	Antihypertensive therapy used to reach targets	Sample size, T vs C Mean age (SD) % Male	Comorbidities % DM % CAD % CVD	Baseline SBP/DBP, T vs C	Achieved SBP/DBP, T vs C	Mean number or % distribution of antihypertensive medications used, T vs C
ACCORD, 2010[22] SBP < 120 vs < 140 4.7 years	Step 1: a diuretic combined with an ACEI or β-B. Medications that could be added to reach BP target: dihydropyridine and nondihydropyridine CCB, α-B, ARB, sympatholytics, α-B/β-B, and the following combinations: thiazide diuretic + a potassium-sparing diuretic; β-B + diuretic; ACEI + diuretic, ARB + a diuretic; dihydropyridine CCB + ACEI.	2362 vs 2371 62.2 (6.9) 52.3%	100% DM 33.7% CAD	139.0/75.9 vs 139.4/76.0	119.3/64.4 vs 133.5/70.5	Mean 3.5 vs 2.2
Cardio-Sis, 2009[23] SBP < 130 vs < 140 2.0* years	Diuretics (hydrochlorothiazide + ramipril or telmisartan, furosemide), β-B (bisoprolol), CCB (amlodipine), ACEI (ramipril ± hydrochlorothiazide), ARB (telmisartan ± hydrochlorothiazide), centrally acting sympathetic inhibiting drugs (clonidine), plus drugs previously taken by subjects.	557 vs 553 67 (7.0) 52.3%	12% CAD 8.5% CVD	163.3/89.7 vs 163.3/89.6	131.9/77.4 vs 135.6/78.7	Mean 2.9 vs 2.9 OR (95% CI) at 2-year follow-up, T vs C: Diuretic: 1.36 (1.08 to 1.71) ARB: 1.17 (0.90 to 1.52) β-B, CCB, and ACEI: no difference
HOT, 1998[17] DBP ≤ 80 vs ≤85 vs ≤ 90 3.8 years	Step 1: low-dose felodipine Step 2: + low-dose ACEI or β-B Step 3: + high-dose felodipine Step 4: + high-dose ACEI or β-B Step 5: + other, mainly thiazide	6262 vs 6264 vs 6264 61.5 (7.5) 53%	1.5% MI 1.2% CVD 8% DM	170/105 vs 170/105 vs 170/105	By assigned DBP, ≤ 80 vs ≤ 85 vs ≤ 90: 139.7/81.1 vs 141.4/83.2 vs 143.7/85.2	% using drug per DBP target, ≤ 80 vs ≤ 85 vs ≤ 90: Felodipine: 79 vs 78 vs 77 ACEI: 45 vs 42 vs 35 β-B: 32 vs 28 vs 25 Diuretic: 24 vs 22 vs 19
JATOS, 2008[24] SBP < 140 vs < 160 2.0 years	Efonidipine, 20-40 mg once daily, increasing to 60 mg once or twice daily if needed. Drugs other than CCB were added if needed.	2212 vs 2206 73.6 (5.2) 38.8%	11.8% DM 9.1% CVD 9.9% Renal disease	171.6/89.1 vs 171.5/89.0	139.3/76.1 vs 146.5/ 78.5	N drugs used by % of patients: 1: 47.7 vs 57.8 (P < .001) 2: 31.6 vs 27.3 (P = .002) 3: 15.1 vs 9.3 (P < .001) 4: 2.9 vs 1.9 (P = .05) 5: 0.1 vs 0.14 (P = 1.0)

Study BP goals (mm Hg), T vs C Mean or median(*) length of follow-up	Antihypertensive therapy used to reach targets	Sample size, T vs C Mean age (SD) % Male	Comorbidities % DM % CAD % CVD	Baseline SBP/DBP, T vs C	Achieved SBP/DBP, T vs C	Mean number or % distribution of antihypertensive medications used, T vs C
SPS3, 2013[25] SBP < 130 vs 130-149 3.7 years	At the discretion of the physician; at least one drug from each major class was available.	1501 vs 1519 63 (11.0) 63%	36.5% DM 100% CVD 10.5% CAD	142/78 vs 144/79	SBP 127 vs 138 DBP NR	Mean 2.4 vs 1.8 (P < .001) Drugs used by T vs C (%) at 1 year: Thiazides: 58 vs 43 ACEI/ARB: 80 vs 63 CCB: 43 vs 30 β-B: 31 vs 25 Other: 11 vs 9
SPRINT, 2015[11] SBP < 120 vs < 140 3.26* years	Thiazide-type diuretic, and/or an ACEI or ARB (but not both) and/or a CCB. Titrate or add therapy not already in use as needed.	4678 vs 4683 67.9 (9.5) 64.4%	0% DM 0% CVD 20.1% CAD 28.3% CKD	139.7/78.2 vs 139.7/78.0	121.5/66 vs 134.6/74	Mean 2.7 (1.2) vs 1.8 (1.1) % using N meds: 0: 2.7 vs 11.3 1: 10.5 vs 31.1 2: 30.5 vs 33.3 3: 31.8 vs 17.2 4+: 24.3 vs 6.9
VALISH, 2010[26] SBP < 140 vs < 150 3.0* years	Step 1: Valsartan, 40-80 mg once daily Step 2: Increase valsartan up to 160 mg, and/or other agents (diuretics, CCBs) except other ARBs	1545 vs 1534 76.1 (4.1) 37.6%	13.0% DM 6.5% CVD 5.0% CAD 1.4% Renal insufficiency	169.5/81.7 vs 169.6/81.2	136.6/74 vs 142/76.5	% using drug: Valsartan only: 56.1 vs 57.6 (P = ns) Valsartan dose, mg: 91.2 vs 88.1 (P =.0236) CCB: 37.1 vs 36.4 (P = ns) Diuretic: 13.0 vs 11.9 (P = ns) β-B: 6.0 vs 5.0 (P = ns) ACEI: 2.1 vs 2.5 (P = ns)
Wei, 2013[21] SBP < 140 vs < 150 4.0 years	Step 1: Monotherapy with enalapril 10mg/d; bisoprolol 2.5-5 mg or metoprolol 50-100 mg/d; amlodipine 5-10 mg/d; or indapamide 1.5-2.5 mg/d Step 2: Add 1, 2, or 3 anti-hypertension drugs stepwise Step 3: Increase dosage of anti-hypertension drugs	363 vs 361 76.6 (4.6) 66%	23.3% DM 6.6% CVD	158.8/83.7 vs 160.3/84.8	135.7/76.2 vs 149.7/82.1	% using combination therapy: 53.7 vs 39.1 (P < .01).

Abbreviations: α-B = alpha-blocker; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blockers; β-B = beta-blocker; BP = blood pressure; Cardio-Sis = Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica; C = comparator/control; CAD = coronary artery disease; CCB = calcium channel blocker; CI = confidence interval; CKD = chronic kidney disease; CVD = cerebrovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; HOT = Hypertension Optimal Treatment; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; mg = milligram; MI = myocardial infarction; N/n = population size (total/sub); NR = not reported; ns = not statistically significant; OR = odds ratio; SBP = systolic blood pressure; SD = standard deviation; SPRINT = Systolic Blood Pressure Intervention Trial; SPS3 = Secondary Prevention of Small Subcortical Strokes; T = treatment; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

Table 3. Characteristics of Trials that Compared More vs Less Intensive Antihypertensive Treatment

Study BP goal (mm Hg) Mean or median* length of follow-up	Antihypertensive treatment strategies	Sample size, T vs C Age mean (SD) % Male	Comorbidities % DM % CAD % CVD	Baseline SBP/DBP, T vs C	Achieved SBP/DBP, T vs C	Mean number or % distribution of antihypertensive medications used, T vs C
ADVANCE, 2007[27] Goal NR 4.3 years	T: Perindopril + indapamide ± physician's discretion C: Placebo ± physician's discretion Not permitted: thiazide diuretics, other ACEI	5569 vs 5571 66 (6.5) 57%	100% DM 12% CAD 9% CVD	145/81 vs 145/81	136/73 vs 140/73	% using drug (at end of follow-up): Any BP lowering drug: 74 vs 83 Perindopril: 45 vs 55 Other ACEI: 5 vs 5 ARB: 10 vs 13 β-B: 31 vs 35 CCB: 32 vs 43 Thiazides: 3 vs 5 Other diuretics: 14 vs 16
BENEDICT-B, 2011[28] ≤ 120/80 mm Hg 4.5 years	T: VeraTran (Verapamil + trandolapril) ± physician's discretion C: Trandolapril ± physician's discretion	138 vs 143 62.3 (8.3) 62.4%	100% DM	149.5/86.3 overall	141.0/81.6 vs 141.8/82.3	% using drug (on follow-up): Any antihypertensive agent: 94.9 vs 92.3 Diuretic: 87.7 vs 84.6 β-B: 14.5 vs 16.1 CCB: 44.2 vs 50.3 Sympatholytic agent: 66.7 vs 69.9 P = ns
EWPHE, 1985[29] ≤ 160/90 mm Hg 4.7 years	T: Hydrochlorothiazide + triamterene ± methyldopa C: Placebo	416 vs 424 72 (8.0) 69.8%	3.5% CAD 1.2% CVD	183/101 vs 182/101	148/85 vs 167/90	Used by % of treatment group in addition to active study medication: Methyldopa: 35%
FEVER, 2005[30] < 160/95 mm Hg 3.3 years	T: Felodipine ± physician's discretion C: Placebo ± physician's discretion	4841 vs 4870 61.5 (7.2) 61%	12.8% DM 15.5% CAD 14.9% CVD	158.7/92.4 vs 158.9/92.7	138.1/82.3 vs 141.6/83.9	Add-on medication used by % of group: No add-on: 66.1 vs 57.7 (P < .001) Diuretic: 12.6 vs 19.8 (P < .001) β-B: 7.3 vs 8.8 (P = .008) α-B: 0.2 vs 0.6 (P = .004) ACEI: 16.8 vs 26.0 (P < .001) ARB: 0.9 vs 1.1 (P = .325) CCB: 12.1 vs 12.8 (P = .263) Other antihypertensive medications: 5.5 vs 8.2 (P < .001)

Study **BP goal (mm Hg)** **Mean or median* length of follow-up**	**Antihypertensive treatment strategies**	**Sample size, T vs C** **Age mean (SD)** **% Male**	**Comorbidities** **% DM** **% CAD** **% CVD**	**Baseline SBP/DBP, T vs C**	**Achieved SBP/DBP, T vs C**	**Mean number or % distribution of antihypertensive medications used, T vs C**
HYVET, 2008[6] < 150/80 mm Hg 1.8* years	T: Indapamide ± perindopril C: Placebo Patients withdrawn from double-blind follow-up if used additional antihypertensive agents for > 3 months, or had received the maximum dose of the study drugs yet had SBP ≥ 220 mm Hg or DBP ≥ 110 mm Hg on at least 2 consecutive visits ≥ 2 weeks apart.	1933 vs 1912 83.5 (3.2) 60.5%	6.9% DM 3.2% CAD 6.8% CVD	173/90.8 vs 173/90.8	143.5/77.9 vs 158.5/84.0	% using drug or corresponding placebo (at 2-year follow-up): Indapamide only: 25.8 vs 14.2 (corresponding placebo) Indapamide + perindopril (2 mg): 23.9 vs 13.4 (corresponding placebo) Indapamide + perindopril (4 mg): 49.5 vs 71.8 (corresponding placebo)
PROGRESS, 2001[31] Goal NR 3.9 years	T: Perindopril ± indapamide C: Placebo	3051 vs 3054 64 (10.0) 70%	13% DM 100% CVD	147/86 vs 147/86	138/82 vs 147/86	% of treatment group assigned to use: Perindopril only = 42% Perindopril + Indapamide = 58%
RENAAL, 2001[32] < 140/90 mm Hg 3.4 years	T: Losartan ± physician's discretion C: Placebo ± physician's discretion Not permitted: ACEIs, ARBs	751 vs 762 60 (7.0) 63.2%	100% DM 11% CAD 0.1% CVD	152/82 vs 153/82	140/74 vs 142/74	A mean of 3.5 different antihypertensive medications were used in addition to the randomized drug to achieve BP goal of < 140/90 mm Hg. % using drug: CCB: 77.9 vs 81.1 Diuretic: 83.8 vs 84.0 α-B: 40.2 vs 45.7 β-B: 34.1 vs 36.7 Centrally acting agent: 18.0 vs 21.7
SCOPE, 2003[33] < 160/85 mm Hg 3.7 years	T: Candesartan ± physician's discretion C: Placebo ± physician's discretion Not permitted: ACEIs, ARBs	2477 vs 2460 76.4 (NR) 64.5%	12% DM 4.5% CAD 3.9% CVD	166.0/90.3 vs 166.5/90.4	145.2/79.9 vs 148.5/81.6	% using drug: Study drug only: 25 vs 16 Study drug + hydrochlorothiazide: 26 vs 18 Add-on treatment: 49 vs 66 Diuretic: 33 vs 44 β-B: 17 vs 26 CCB: 18 vs 28 ACEI: 8 vs 11 ARB: 3 vs 4

Study **BP goal (mm Hg)** **Mean or median* length of follow-up**	**Antihypertensive treatment strategies**	**Sample size, T vs C** **Age mean (SD)** **% Male**	**Comorbidities** **% DM** **% CAD** **% CVD**	**Baseline SBP/DBP, T vs C**	**Achieved SBP/DBP, T vs C**	**Mean number or % distribution of antihypertensive medications used, T vs C**
SHEP, 1991[8] SBP < 160 mm Hg or reduction of ≥ 20 mm Hg[a] 4.5 years	T: Chlorthalidone ± atenolol or reserpine C: Placebo Upper BP threshold above which active treatment indicated in placebo arm (escape criteria): SBP > 240 mm Hg or DBP > 115 mm Hg at a single visit, or sustained SBP > 220 mm Hg or DBP > 90 mm Hg.	2365 vs 2371 71.6 (6.7) 64.5%	10.1% DM 4.9% CAD 1.4% CVD	170.5/76.7 vs 170.1/76.4	143/68 vs 155/72	0 (No active drug): 9% vs 53% 1: Chlorthalidone: 46% of treatment group 2: Chlorthalidone + atenolol: 23% of treatment group Other active medication: 21% of treatment group % meeting escape criteria: 3 vs 15 % prescribed active hypertensive therapy in placebo group: 13% at year 1, 33% at year 3, 44% at year 5
STONE, 1996[19] 140-159/< 90 mm Hg 2.5 years	T: Nifedipene ± captopril ± dihydrochlorothiazide C: Placebo Upper BP threshold above which active treatment (captopril ± dihydrochlorothiazide) indicated in placebo arm: SBP ≥ 200 mm Hg or DBP ≥ 110 mm Hg at 2 subsequent follow-ups.	815 vs 817 66.4 (5.3) 46.8%	NR	168/99 vs 168/97	146.9/85.0 vs 156.2/89.3	0: 98.8% of placebo 1: Nifedipene only was used by 99.1% of treatment group
Syst-China, 2000[20] SBP < 150 mm Hg (reduction of ≥ 20 mm Hg) 3.0* years	T: Nitrendipine ± captopril ± hydrochlorothiazide C: Placebo	1253 vs 1141 66.5 (5.5) 65.5%	4.1% DM 11.2% CVD	170.5/86.0 overall, T vs C NR	150.5/81 vs 159.5/84	1: Nitrendipine only: 72.3% vs 57.0% (corresponding placebo) 2+: Combination of nitrendipine ± captopril ± hydrochlorothiazide: 20.0% vs 32.9% (corresponding placebo)

Study BP goal (mm Hg) Mean or median* length of follow-up	**Antihypertensive treatment strategies**	**Sample size, T vs C Age mean (SD) % Male**	**Comorbidities % DM % CAD % CVD**	**Baseline SBP/DBP, T vs C**	**Achieved SBP/DBP, T vs C**	**Mean number or % distribution of antihypertensive medications used, T vs C**
Syst-Eur, 2014[34] SBP < 150 mm Hg (reduction of ≥ 20 mm Hg) 2.0* years	T: Nitrendipine ± enalapril ± hydrochlorothiazide C: Placebo	2297 vs 2398 70.25 (6.7) 33.2%	10.5% DM 29.8% CAD	173.8 vs 85.5 overall, P = ns for T vs C	NR	0: 14.9% of placebo 1: 55.0% of treatment 2: 26.1% of treatment 3: 16.4% of treatment % using drug or corresponding placebo (at 2-year follow-up): Nitrendipine: 84.4 vs 92.4 (corresponding placebo) Enalapril: 32.6 vs 55.1 (corresponding placebo) Hydrochlorothiazide: 16.2 vs 34.2 (corresponding placebo) % of patients started on multiple drug treatment or proceeding to open follow-up increased faster in the placebo group than active treatment group (P < .001)
TRANSCEND, 2008[35] Goal NR 4.7* years	T: Telmisartan ± physician's discretion C: Placebo ± physician's discretion	2954 vs 2972 66.9 (7.4) 57%	35.7% DM 74.5% CAD 22% CVD	140.7/81.8 vs 141.3/82.0	NR	% using drug: Non-study ARB: 5.8 vs 7.6 (P = NR) Diuretic: 33.7 vs 40.0 (P < .0001) CCB: 38.0 vs 45.9 (P < .0001) β-B: 56.6 vs 59.0 (P = .081) α-B: 5.3 vs 7.5 (P = .002)

Abbreviations: α-B = alpha-blocker; β-B = beta-blocker; ACEI = Angiotensin converting enzyme inhibitor; ADVANCE = Action in Diabetes and Vascular Disease; ARB = Angiotensin II receptor blockers; BENEDICT-B = Bergamo Nephrologic Diabetes Complications Trial-B; BP = blood pressure; C = control/comparator; CAD = Coronary artery disease; CCB = calcium channel blocker; CVD = Cerebrovascular disease; DBP = Diastolic blood pressure; DM = diabetes mellitus; EWPHE = European Working Party on High Blood Pressure in the Elderly; FEVER = Felodipine Event Reduction Study; HYVET = Hypertension in the Very Elderly Trial; NR = not reported; ns = not statistically significant; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SBP = Systolic blood pressure; SCOPE = Study on Cognition and Prognosis in the Elderly; SD = standard deviation; SHEP = Systolic Hypertension in the Elderly Program; STONE = Shanghai Trial of Nifedipine in the Elderly; Syst-China = Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe; T = treatment; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease.

[a]For individuals with SBP ≥180 mm Hg, the goal was < 160 mm Hg; for those with SBP 160-179 mm Hg, the goal was an SBP reduction of ≥ 20 mm Hg.

Detailed Study Results

All Studies

We found varied results across the 21 included studies, but overall more intensive blood pressure treatment was associated with significant reductions in mortality, major cardiac events, and stroke. However, the marked differences among the studies in their baseline, intended, and achieved blood pressures make it difficult to interpret pooled estimates of all results. Rather, we present analyses according to achieved blood pressure, baseline blood pressure, and then focus on those trials which explicitly compared blood pressure treatment targets. Medication choice varied widely among studies but we found no discernible pattern of antihypertensive choice on treatment effects.

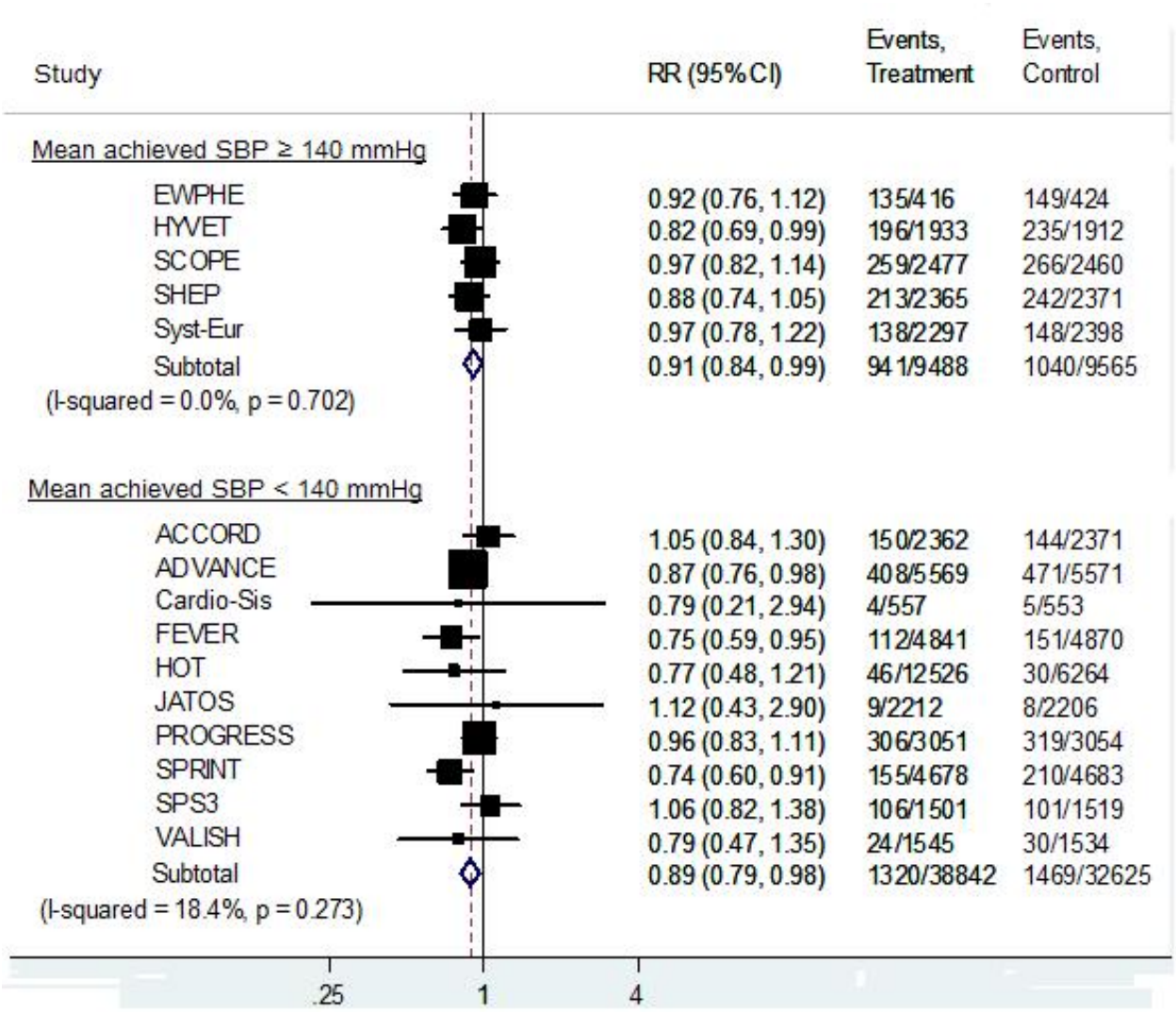
There were 3 trials with almost no difference in achieved blood pressure between intervention and control groups (mean difference SBP < 3 mm Hg).[28,32,35] Another 3 trials rated as high risk of bias had significant methodologic flaws threatening the validity of their results.[19-21] We conducted sensitivity analyses with and without these studies. One of the studies with high risk of bias was a treat-to-target trial.[21] The exclusion of this study lowered absolute effect sizes modestly. Otherwise, these sensitivity analyses did not dramatically alter results, but did reduce heterogeneity. In the following sections we present analyses without these 6 studies. Additional analyses are summarized in Appendix D.

Of the remaining 15 studies presented in the following analyses, relatively few individual studies found statistically significant treatment effects (mortality in 4 studies; stroke in 5 studies; cardiac events in 7 studies).

Studies Grouped by Achieved Blood Pressure

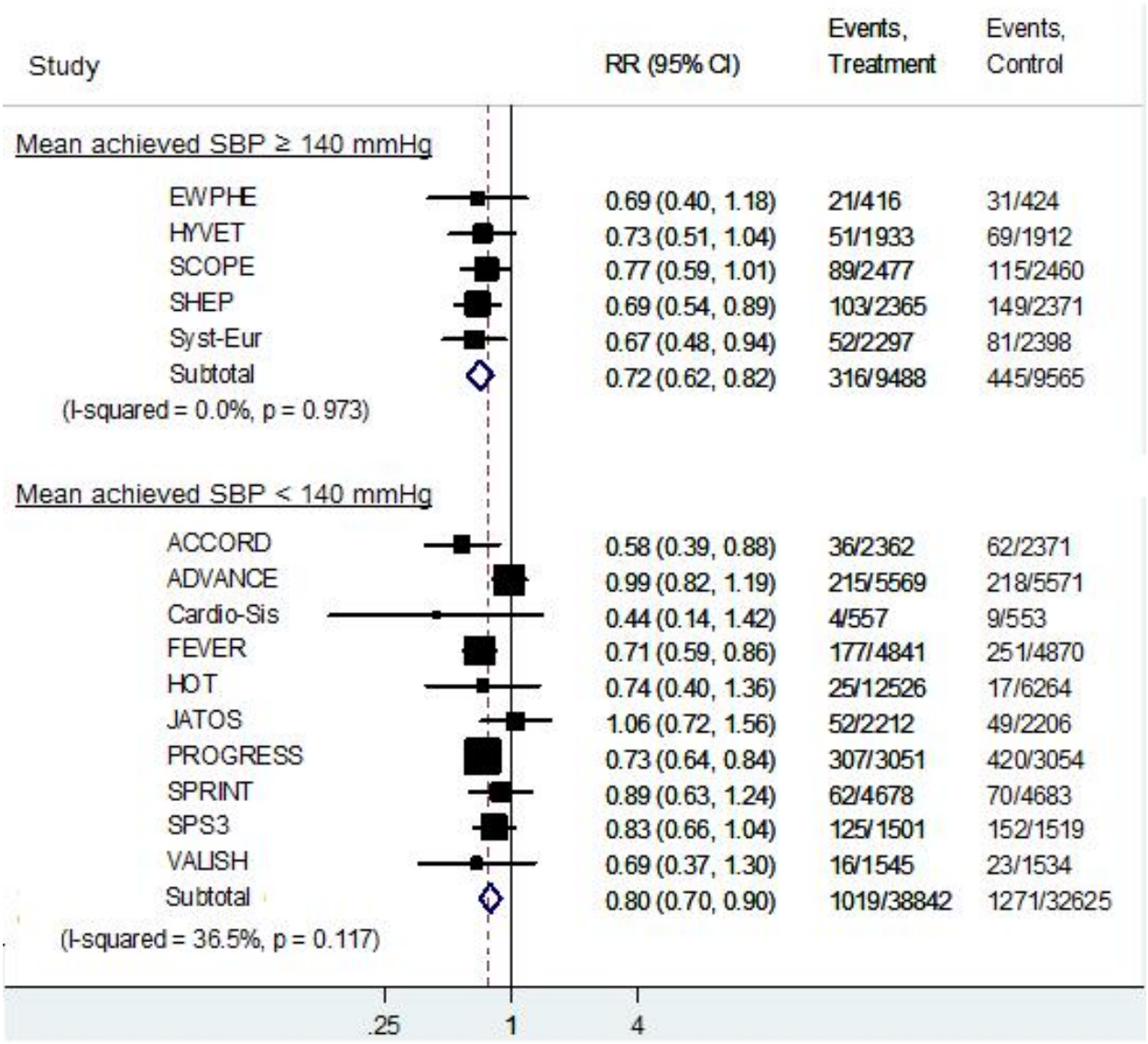
We performed meta-analyses separately grouping studies with achieved SBP ≥ 140 mm Hg and studies with achieved SBP < 140 mm Hg (Figures 2 to 4). We found similar relative treatment effects for mortality (RR 0.91, 95% Confidence Interval [CI] 0.84 to 0.99, number needed to treat [NNT] 105; I^2 = 0% for SBP ≥ 140, and RR 0.88, 95% CI 0.81 to 0.96, NNT 91; I^2 = 18.4% for SBP < 140 mm Hg). We found similar relative treatment effects, but slightly larger absolute effects on major cardiac outcomes among studies achieving higher blood pressure (RR 0.78, 95% CI 0.68 to 0.93, NNT 74; I^2 = 35.9% for SBP ≥ 140) than among those achieving lower blood pressure (RR 0.82, 95% CI 0.72 to 0.91, NNT 108; I^2 = 2.1%). There was a more consistent and slightly larger relative treatment effect on stroke among studies achieving SBP ≥ 140 (RR 0.72, 95% CI 0.62 to 0.82, NNT 76; I^2 = 0%) than among studies achieving SBP < 140 mm Hg (RR 0.80, 95% CI 0.70 to 0.90, NNT 78; I^2 = 36.5%).

Figure 2. Relative risk of mortality stratified by mean achieved SBP, combining trials by achieved mean SBP ≥ 140 or < 140 mm Hg in the intervention group



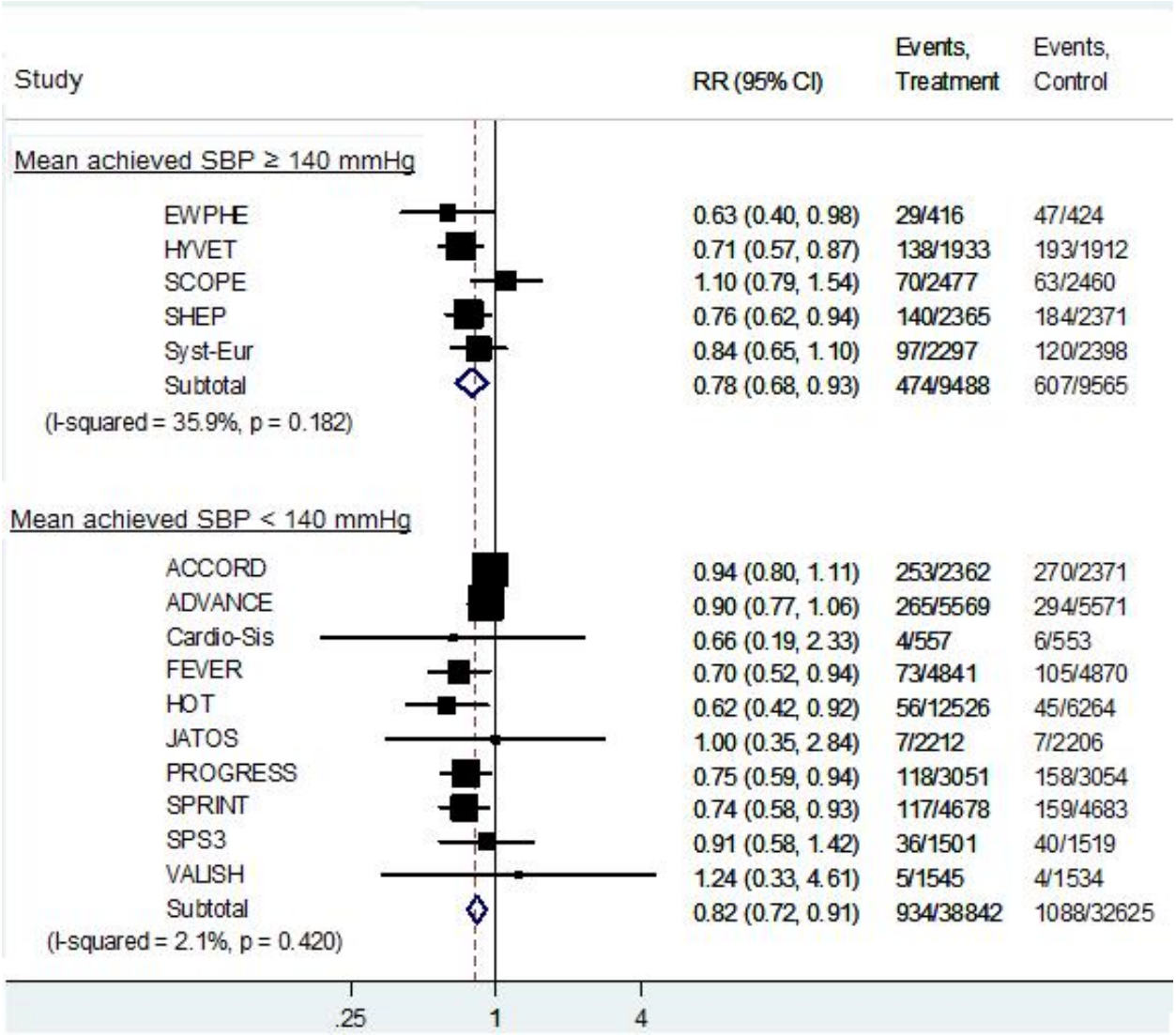
ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; Cardio-Sis = Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica; CI = confidence interval; EWPHE = European Working Party on High Blood Pressure in the Elderly; FEVER = Felodipine Event Reduction Study; HOT = Hypertension Optimal Treatment; HYVET = Hypertension in the Very Elderly Trial; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SBP = systolic blood pressure; SCOPE = Study on Cognition and Prognosis in the Elderly; SHEP = Systolic Hypertension in the Elderly Program; SPRINT = Systolic Blood Pressure Intervention Trial; SPS3 = Secondary Prevention of Small Subcortical Strokes; Syst-Eur = Systolic Hypertension in Europe; VALISH = Valsartan in Elderly Isolated Systolic Hypertension

Figure 3. Relative risk of stroke stratified by mean achieved SBP, combining trials by achieved mean SBP ≥ 140 or < 140 mm Hg in the intervention group



ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; Cardio-Sis = Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica; CI = confidence interval; EWPHE = European Working Party on High Blood Pressure in the Elderly; FEVER = Felodipine Event Reduction Study; HOT = Hypertension Optimal Treatment; HYVET = Hypertension in the Very Elderly Trial; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SBP = systolic blood pressure; SCOPE = Study on Cognition and Prognosis in the Elderly; SHEP = Systolic Hypertension in the Elderly Program; SPRINT = Systolic Blood Pressure Intervention Trial; SPS3 = Secondary Prevention of Small Subcortical Strokes; Syst-Eur = Systolic Hypertension in Europe; VALISH = Valsartan in Elderly Isolated Systolic Hypertension

Figure 4. Relative risk of major cardiac events stratified by mean achieved SBP, combining trials by achieved mean SBP ≥ 140 or < 140 mm Hg in the intervention group



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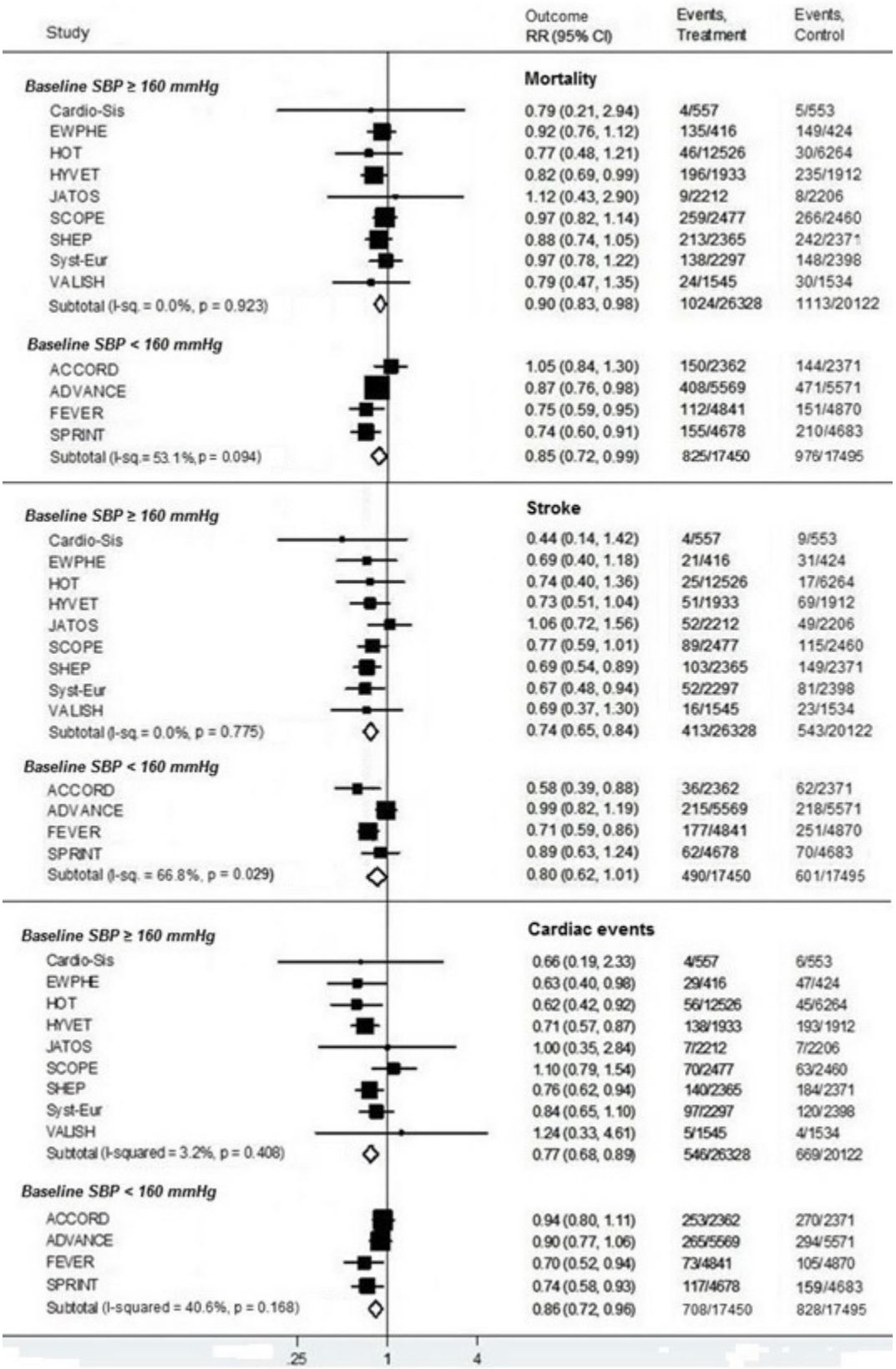
Studies Grouped by Baseline Blood Pressure

To better understand the evidence regarding the thresholds at which to start or intensify blood pressure treatment, we analyzed studies according to baseline blood pressure. Nine studies had higher baseline blood pressures (SBP ≥ 160 mm Hg) including all the studies achieving SBP ≥ 140 mm Hg plus 3 studies which achieved lower blood pressures.[23,24,26] Intensive blood pressure treatment had a more consistent and greater absolute effect on mortality (RR 0.90, 95% CI 0.83 to 0.98, NNT 61, I^2 = 0%), stroke (RR 0.74, 95% CI 0.65 to 0.84, NNT 89, I^2 = 0%), and cardiac events (RR 0.77, 95% CI 0.68 to 0.89, NNT 80, I^2 = 3.2%) in studies of patients with higher baseline blood pressures than in studies of patients with lower baseline blood pressures (mortality RR 0.85, 95% CI 0.72 to 0.99, NNT 118, I^2 = 53.1%), stroke (RR 0.80, 95% CI 0.62 to 1.01, NNT = 159, I^2 =67%), and cardiac events (RR 0.86, 95% CI 0.72 to 0.96, NNT 148, I^2 = 40.6%) (Figure 5). The subgroup with lower baseline blood pressures did not include the 2 trials of patients with prior stroke.[25,31]

Figure 5. Relative risk of death, stroke, and cardiac events, combining trials by mean baseline SBP ≥ 160 or < 160 mm Hg



ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; Cardio-Sis = Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica; CI = confidence interval; EWPHE = European Working Party on High Blood Pressure in the Elderly; FEVER = Felodipine Event Reduction Study; HOT = Hypertension Optimal Treatment; HYVET = Hypertension in the Very Elderly Trial; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; RR = relative risk; SBP = systolic blood pressure; SCOPE = Study on Cognition and Prognosis in the Elderly; SHEP = Systolic Hypertension in the Elderly Program; SPRINT = Systolic Blood Pressure Intervention Trial; Syst-Eur = Systolic Hypertension in Europe; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

Studies Comparing Blood Pressure Treatment Targets

The studies that most directly address the controversy of strict versus more moderate blood pressure control are those that compared treatment targets. We found 8 trials comparing lower and higher blood pressure treatment targets (Table 2). One of these trials, which included only patients with prior stroke, is discussed in the next section and is not included in the analyses in this section.[25] As mentioned previously, another small study with dramatically higher mortality rates had high risk of bias;[21] we present the sensitivity analyses without this study here but additional analysis results are available in Appendix D. The 6 remaining treat-to-target studies evaluated a total of 32,312 patients and were all low risk of bias.

The largest study, the Hypertension Optimal Treatment (HOT) trial (N = 18,790), evaluated DBP targets while the remaining 5 studies examined SBP targets of ≤ 140 mm Hg in the more intensive control arm. Two of these 5 studies targeted SBP < 140 mm Hg in the more intensive treatment arm,[24,26] while the remaining 3 used lower SBP targets (< 120 mm Hg[11,22] and < 130 mm Hg[23]) for the intensive treatment arm. Among the trials specifying initial therapy, 2 used calcium channel blockers,[17,24] one used an angiotensin II receptor blocker,[26] and 2 used a thiazide diuretic in combination with another medication.[11,22] All trials allowed use of the same 4 core antihypertensive drug classes for additional therapy (renin angiotensin system blockade, thiazide diuretics, calcium channel blockers, and beta-blockers). Again, we did not find a consistent pattern of effects according to choice of first-line antihypertensive therapy.

Taken together, these studies show that blood pressure treatment targets of SBP ≤ 140 mm Hg or lower are associated with a non-significant trend toward lower mortality, and have a marginally significant effect on lowering stroke and major cardiac events (Figure 6). These are large trials with low risk of bias, and the meta-analyses suggest acceptable levels of statistical heterogeneity. Nevertheless, the evidence for mortality and cardiac events should be considered low strength because there are important inconsistencies in results, substantial variation in results in different sensitivity analyses, and because the results are imprecise with relatively wide confidence intervals around the summary estimates encompassing both the possibility of marked risk reduction and no effect. For the outcome of stroke, the direction and magnitude of effect was more consistent across analyses and, therefore, the strength of evidence for this outcome should be considered moderate.

We found that the absolute treatment effects varied in our sensitivity analyses. The most pronounced differences involved analyses with the HOT trial.[17] The HOT trial was by far the largest and in some ways the most difficult to assess both because it assessed DBT targets, and because it included 3 arms each with over 6,000 patients. In the analyses in Figure 6, we grouped the 2 HOT arms with DBP targets of ≤ 85 mm Hg or less together because this was the most relevant comparison when considering current guidelines. The numbers needed to treat over 2 to 5 years to prevent one event were 125 (mortality), 204 (stroke), and 106 (major cardiac events). However, the achieved SBP in the group assigned to a DBP target of ≤ 85 mm Hg was > 140 mm Hg (141.4 mm Hg), while the achieved SBP in the group assigned to a target ≤ 80 mm Hg was 139.7 mm Hg. When we excluded this middle group (DBT target of ≤ 85 mm Hg) from our analyses, we found substantially higher NNT (263 for mortality, 286 for stroke, and 238 for major cardiac events).

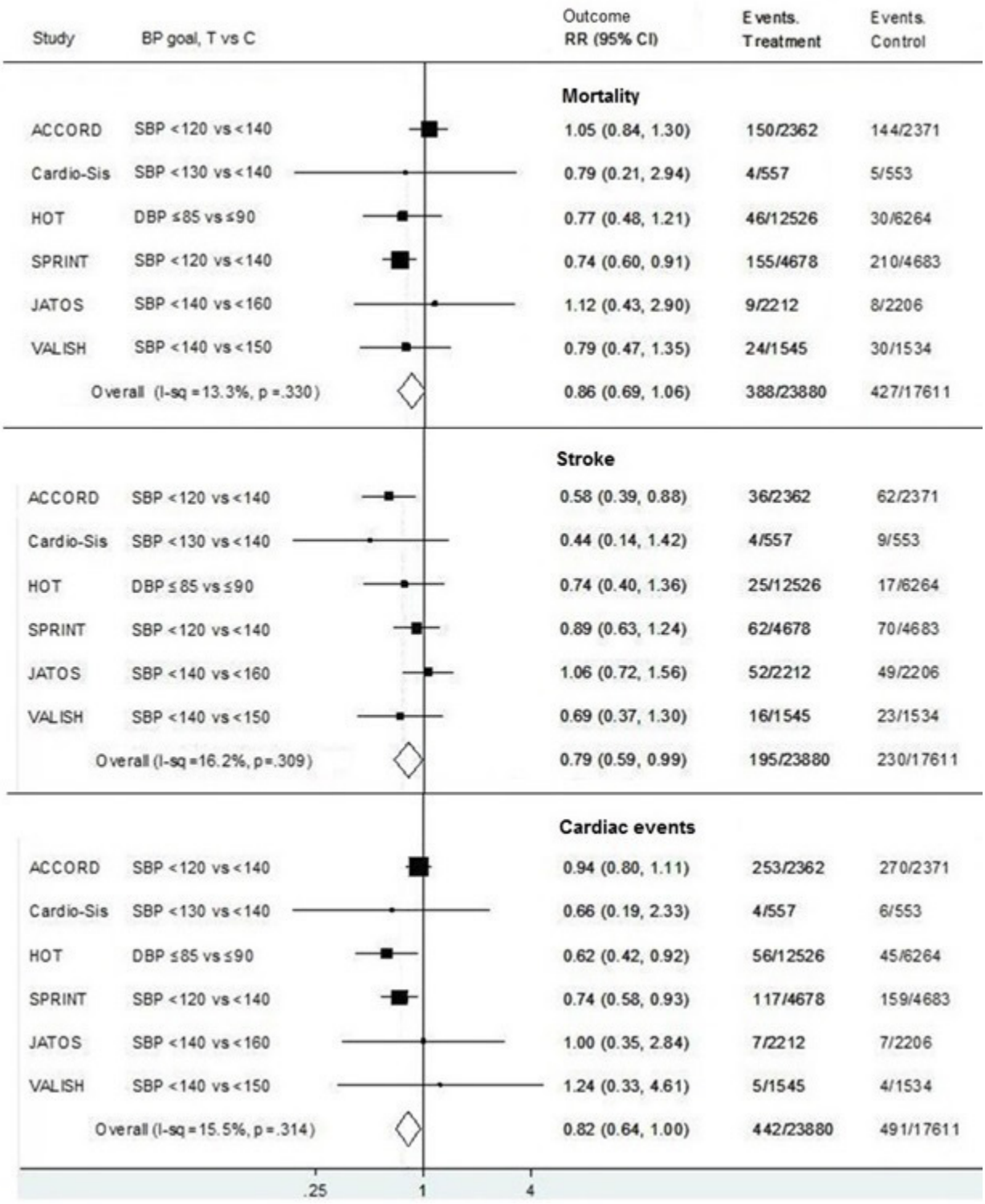
The Systolic Blood Pressure Intervention Trial (SPRINT)[11] and ACCORD[22] trials are different than the other treat-to-target trials both because of the aggressive intervention group SBP target

of < 120 mm Hg, and because the mean baseline SBP was just under 140 mm Hg. Both trials enrolled patients with high cardiovascular risk, but excluded patients on more than 3 antihypertensive medications at baseline. There are several important differences between these 2 studies: 1) ACCORD included only diabetic patients while SPRINT excluded diabetic patients, 2) ACCORD mostly excluded patients ≥ 80 years, and therefore had a population slightly younger than SPRINT (mean age 62 vs 68 years), and 3) the SPRINT trial was stopped early for benefit and consequently had a shorter mean duration of follow-up (3.3 vs 4.7 years). Of note, the proportion of control group participants experiencing each outcome was higher in ACCORD than in SPRINT. As Figure 5 shows, intensive treatment did not reduce mortality or cardiac events in ACCORD, but did reduce the risk of stroke. On the other hand, intensive treatment reduced both mortality and cardiac events in SPRINT, but not stroke risk.

When we removed the SPRINT trial in additional sensitivity analyses, effects on mortality (RR 0.96, 95% CI 0.80 to 1.15, I^2 = 0%) and cardiac events (RR 0.88, 95% CI 0.74 to 1.04, I^2 = 4.0%) were no longer significant but effects on stroke remained largely unchanged (RR 0.74, 95% CI 0.56 to 0.99, NNT 182, I^2 = 25.8%).

Of note, there were marked differences in event rates among the studies. The SPRINT and ACCORD trials each enrolled patients with higher cardiovascular risk profiles and, not surprisingly, had higher mortality and cardiac event rates than the other 4 trials. On the other hand, the stroke event rates were more similar among the trials. It is not clear whether differences in event rates entirely explain the nonsignificant mortality reduction since the inconsistency in findings does not clearly follow event rate patterns. For instance, ACCORD and SPRINT have similar event rates but different findings.

Figure 6. Relative risk of death, stroke, and cardiac events in trials in which the intervention arm had an SBP target < 140 mm Hg or DBP ≤ 85 mm Hg, and the control arm had a less strict blood pressure target



ACCORD = Action to Control Cardiovascular Risk in Diabetes; C = control; Cardio-Sis = Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica; CI = confidence interval; DBP = diastolic blood pressure; HOT = Hypertension Optimal Treatment; JATOS = Japanese Trial to Assess Optimal Systolic

Blood Pressure in Elderly Hypertensive Patients; RR = relative risk; SBP = systolic blood pressure; T = treatment; VALISH = Valsartan in Elderly Isolated Systolic Hypertension

Treatment Effects According to DBP

It is difficult to determine whether the treatment effects of blood pressure lowering are mediated through impact on SBP or DBP, or both. The majority of evidence applies most closely to the treatment of SBP. In 15 trials, patients had isolated systolic hypertension (*ie*, SBP > 140 mm Hg with DBP £ 90 mm Hg). There were no trials in which patients had isolated diastolic hypertension with mean DBP > 90 mm Hg and mean SBP < 140 mm Hg.

The HOT trial is most directly relevant as it enrolled patients with high DBP (> 100 mm Hg) and compared, as described above, the effects of 3 DBP targets (≤ 80 vs ≤ 85 vs ≤ 90 mm Hg).[17] Compared to patients assigned to the ≤ 90 mm Hg target, patients assigned to lower DBP targets experienced a reduced risk of cardiac events (RR 0.92, 95% CI 0.42 to 0.92), but not of stroke (RR 0.74, 95% CI 0.4 to 1.36) or mortality (RR 0.77, 95% CI 0.48 to 1.21). Of note, the mean achieved DBP was substantially less than 90 mm Hg in all 3 groups (81.1, 83.2, and 85.2 mm Hg, respectively) and patients also had marked systolic hypertension at baseline (mean baseline SBP 170 mm Hg).

There were 6 trials with baseline DBP > 90 mm Hg.[6,17,19,29,30,33] One of the trials had high risk of bias.[19] In 4 of the other 5 trials, the baseline SBP was ≥ 160 mm Hg and in the other trial the mean baseline SBP was 158.8 mm Hg.[30] The achieved DBP was < 90 mm Hg in all trials. In 4 of the 5 trials, there was a significant reduction in at least one of our outcomes of interest (in the other, there was a nearly significant reduction in stroke risk).[33]

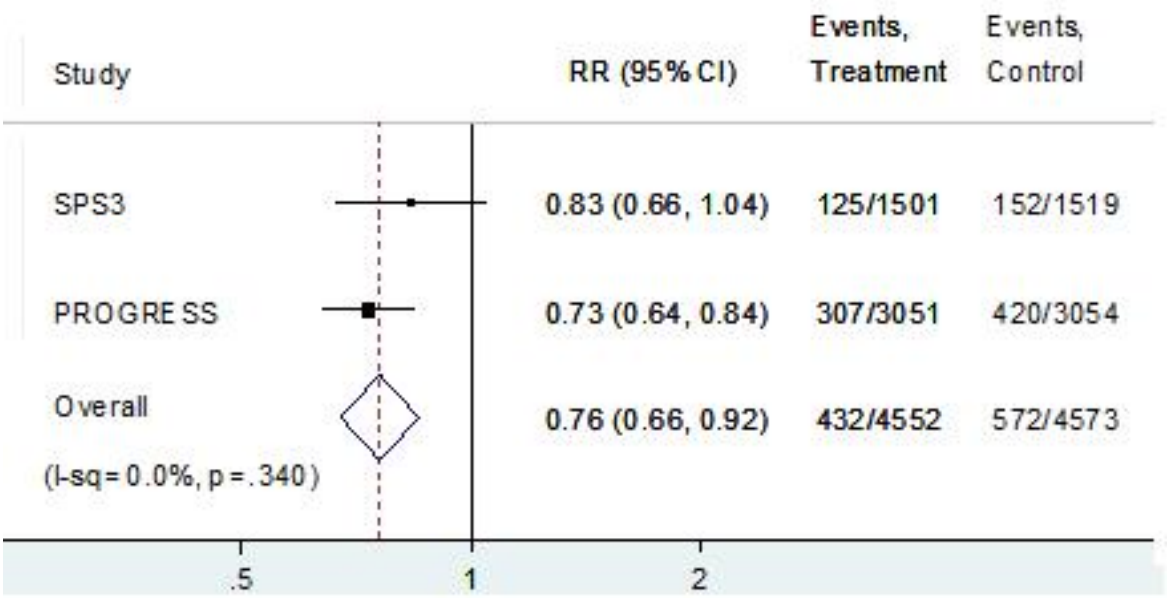
Overall, patients with DBP > 90 mm Hg appear to benefit from blood pressure-lowering treatment, but these patient populations also had marked moderate to severe systolic hypertension at baseline. There was no evidence to assess whether treatment of diastolic hypertension in the absence of systolic hypertension is beneficial.

KEY QUESTION 1B: In patients who have suffered a TIA or stroke, does treatment of blood pressure to specific targets affect outcomes?

Two trials included in this review limited their patient populations to adults with prior history of cerebrovascular accident (stroke or TIA).[25,31] The Secondary Prevention of Small Subcortical Strokes (SPS3) trial evaluated potential benefit of SBP < 130 mm Hg versus 130 to 149 mm Hg as secondary stroke prevention for 3,020 adults over age 30 (mean age 63 years). This study included patients with magnetic resonance imaging (MRI)-confirmed lacunar stroke, but excluded those with prior intracranial hemorrhage, severely disabling strokes, and cortical ischemic stroke.[25] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) included 6,105 adults over age 26 (mean age 64 years) with history of ischemic or hemorrhagic stroke, or TIA.[31] Participants were randomized to placebo or active treatment including an ACE inhibitor to which a diuretic could be added at the discretion of the treating physician. The achieved SBP in the treatment group ranged from 135 to 138 mm Hg (depending on receipt of single or dual therapy).

Pooled analysis of data from these 2 trials showed more intensive versus less intensive blood pressure management decreased the risk of recurrent stroke (RR 0.76, 95% CI 0.66 to 0.92, NNT 33, I^2 = 0%), but not cardiac events (RR 0.78, 95% CI 0.61-1.08) or mortality (RR 0.96, 95% CI 0.86 to 1.12) (Figure 7 and Appendix D). Of note, the results from these trials do not apply to the management of acute stroke.

Figure 7. Relative risk of stroke in trials of patients with history of stroke



CI = confidence interval; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SPS3 = Secondary Prevention of Small Subcortical Strokes

KEY QUESTION 2: How does age modify the benefits of differing blood pressure targets?

Overview of Results

Twelve of the 21 included trials conducted age-stratified analyses (Table 4). We found no evidence that age modifies treatment effects: 12 trials found no age-treatment interactions on health outcome effects, and 3 trials found that the rate of harms from more intensive treatment was similar in those age ≥ 75 years and < 75 years.

Detailed Results

We conducted meta-analyses according to mean age and found similar results in studies with mean age ³ 70 and < 70 for mortality (mean age ≥ 70: RR 0.91, 95% CI 0.84 to 0.99, NNT 133, I^2 = 0%; mean age < 70: RR 0.86, 95% CI 0.75 to 0.95, NNT 76, I^2 = 39.4%); stroke (mean age ≥ 70: RR 0.75, 95% CI 0.66 to 0.86, NNT 101, I^2 = 0%; mean age < 70: RR 0.76, 95% CI 0.66 to 0.86, NNT 68, I^2 = 42.6%); and cardiac events (mean age ≥ 70: RR 0.79, 95% CI 0.69 to 0.94, NNT 101, I^2 = 0%; mean age < 70: RR 0.82, 95% CI 0.71 to 0.90, NNT 68, I^2 = 42.6%). However, we mainly did these analyses to ensure that our findings were not disproportionately driven by studies with lower mean age populations which may have included substantial proportions of patients over age 60. Because of concerns for ecologic fallacy, these analyses cannot reliably estimate age-treatment effects. Rather, we summarize analyses from studies which specifically examined age-treatment interactions.

Of the 12 trials that provided analyses by age subgroups, 5 randomized patients to different blood pressure targets,[17,22,24-26] and 6 randomized patients to more versus less antihypertensive therapy.[6,8,20,27,34,35] All of these studies were considered low risk of bias with the exception of one study that used insufficient methods for randomization and allocation concealment.[20] Seven studies provided age analyses which differentiated adults over age 70 from their younger peers; these analyses were generally for adults ages greater or less than 75 years,[24,26] or by age bands which included age ≥ 70 as compared to younger patients.[8,35,36] The remaining 5 studies provided analyses by age greater or less than 65 years.[20,26,27,37-39] Given that we limited our review to studies with mean population over age 60, these analyses could not meaningfully address our question about the role that advancing age may play in mitigating or modifying the benefits of differing blood pressure targets.

Results were mixed among the 7 studies which performed age-specific analyses for adults ages ≥ 70. The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) described an *increased* risk of cardiovascular disease, cerebrovascular disease, and renal failure when SBP was targeted to be < 140 mm Hg for adults age ≥ 75 but this increase in risk was not demonstrated among their younger peers.[24] Conversely, in the SHEP trial in which the patient population had a mean SBP of 170 mm Hg, the *decreased* risk of stroke associated with achieving SBP was < 150 mm Hg was seen in adults over age 70 but not in their younger counterparts.[8]

In the SPRINT trial, participants assigned to an SBP target of < 120 mm Hg experienced a reduction in cardiac events and there was no significant interaction between age and treatment.[11] This reduction was marginally significant in those under age 75, but statistically significant in the subgroup over age 75, likely because of the substantially higher event rates in this group. The

Hypertension in the Very Elderly Trial (HYVET) examined the benefit of blood pressure control among adults aged 80 to 84 years versus aged ≥ 85 years, and demonstrated decreased risk of cardiovascular mortality and stroke for both age groups, but unclear benefit among those aged ≥ 85 on risk of cardiac events and all-cause mortality.[36] Similarly, in the VALISH study, there was no significant difference in a composite cardiac event outcome for adults older and younger than 75 years.[26] Age-specific results for the Syst-Eur trial are difficult to interpret because they are presented as unadjusted hazard ratios without 95% confidence intervals,[40] and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial reported only a non-significant *P*-value of 0.8 for interaction by age.[35]

Table 4. Effects of Age on Outcomes in Trials that Conducted Age-Stratified Analyses

Direction of association	Study Comparison, T vs C Age stratification	Findings
Beneficial effects decrease with age	JATOS[24] SBP < 140 vs < 160 mm Hg Age: < 75, ≥ 75	Significant age-treatment interaction: benefit of treatment on stroke, cardiac events, and renal failure was limited to those < 75 years old.
	SPS3[39] SBP < 130 vs 130-149 mm Hg Age: < 75, ≥ 75	Benefit of treatment on recurrent stroke was limited to those < 75 years old.
	Syst-China[20] (Nitrendipine ± captopril ± hydrochlorothiazide) vs placebo Age: < 65, 65-69, ≥ 70	Benefit of treatment on cardiac events and cardiovascular death was limited to those < 65 years old.
	Syst-Eur[40] (Nitrendipine ± enalapril ± hydrochlorothiazide) vs placebo Age: 60-69, 70-79, ≥ 80	Significant age-treatment interaction: benefit of treatment on mortality (all-cause and cardiovascular) and stroke was limited to those < 80 years old.
Beneficial effects increase with age	SHEP[8] (Chlorthalidone ± atenolol or reserpine) vs placebo Age: 60-69, 70-79, ≥ 80	Benefit of treatment on stroke was limited to those aged ≥ 70 years old.
	SPS3[39] SBP < 130 vs 130-149 mm Hg Age: < 75, ≥ 75	Benefit of treatment on vascular death was limited to those aged ≥ 75 years old.
No change in effect with age	ACCORD[37] SBP < 120 vs < 140 mm Hg Age: < 65, ≥ 65	Effects of treatment were similar across age groups on composite endpoint (nonfatal MI, nonfatal stroke, or cardiovascular death).
	ADVANCE[27] (Perindopril + indapamide) vs placebo Age: < 65, ≥ 65	Effects of treatment were similar across age groups on combined macrovascular and microvascular events: total death, coronary events, cerebrovascular events, renal events, and eye events (retinopathy and visual deterioration)
	HOT[38] DBP ≤ 80 vs ≤ 85 vs ≤ 90 mm Hg Age: < 65, ≥ 65	Effects of treatment on total death, cardiovascular death, MI/cardiac events, and stroke were similar across age groups
	HYVET[36] (Indapamide ± perindopril) vs placebo Age: 80-84, ≥ 85	Effects of treatment on total death, cardiovascular death, MI/cardiac events, and stroke were similar across age groups.

Direction of association	Study Comparison, T vs C Age stratification	Findings
	SPRINT[11] SBP < 120 vs 140 mm Hg Age < 75, ≥ 75	Benefit of treatment on composite outcome (MI, other acute coronary syndromes, stroke, heart failure, or cardiovascular death) increased from marginally to statistically significant in aged ≥ 75 years old, but age-treatment interaction was not significant.
	SPS3[39] SBP < 130 vs 130-149 mm Hg Age: < 75, ≥ 75	Effects of treatment on MI and total mortality were similar across age groups.
	TRANSCEND[35] Telmisartan vs placebo Age: < 65, 65-74, ≥ 75	Effects of treatment were similar across age groups on composite endpoint (cardiovascular death, MI, or stroke).
	VALISH[26] SBP < 140 vs < 150 mm Hg Age: < 75, ≥ 75	Effects of treatment were similar across age groups on composite endpoint: sudden death, fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, heart failure death, other cardiovascular death, unplanned hospitalization because of cardiovascular diseases, renal dysfunction (doubling of serum creatinine and creatinine, or introduction of dialysis).

Abbreviations: ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; C = comparator/control; DBP = diastolic blood pressure; HOT = Hypertension Optimal Treatment; HYVET = Hypertension in the Very Elderly Trial; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; MI = myocardial infarction; SBP = systolic blood pressure; SHEP = Systolic Hypertension in the Elderly Program; SPRINT = Systolic Blood Pressure Intervention Trial; SPS3 = Secondary Prevention of Small Subcortical Strokes; Syst-China = Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe; T = treatment; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

KEY QUESTION 3: How does the patient burden of comorbidities modify the benefits of differing blood pressure targets?

Comorbidity Burden

No studies examined how comorbidity burden modifies blood pressure treatment effects.

Of note, it is likely that patients with a high burden of comorbidity were not included in the overall group of studies. Table 5 details the types of comorbidity that were excluded from each trial. Fourteen trials excluded patients with heart failure, 11 excluded patients with recent cardiac events, 17 excluded patients based on abnormal renal function criteria, 12 trials excluded patients with malignancy or other life-limiting illness, and 15 studies used criteria that would implicitly or explicitly exclude patients with dementia and/or diminished functional status.

Cardiovascular Risk

We found subgroup analyses from 4 trials which examined whether treatment effects varied according to cardiovascular risk profile.[41-43] These studies provide low-strength evidence that there may be greater absolute treatment effects amongst patients with high cardiovascular risk though relative treatment effects are similar across risk groups. Confidence in these conclusions is tempered by the post hoc nature of some of these analyses, the small number of studies, and variation in the outcomes contributing to these findings.

One substudy of SHEP reported outcomes according to quartiles of cardiovascular risk based on the Multiple Risk Factor Assessment Equation.[43] The number needed to treat for one year to prevent a major cardiac event (myocardial infarction, stroke, or heart failure) ranged from 160 in the lowest risk group to 37 in the highest risk group. A reduction in heart failure incidence appeared to be the major contributor to these findings, while findings for stroke and myocardial infarction were not significant for most of the subgroups.

A substudy grouped participants in the ADVANCE trial into moderate-high and very high 5-year cardiovascular risk according to the Framingham Anderson equation.[41] Similar to the SHEP substudy, these authors found that relative risks remained similar across subgroups (and were often non- or marginally significant), but absolute risk reductions were higher in the very high cardiovascular risk group. For example, the absolute risk reduction for total coronary events was 0.5% in the moderate-high risk group but 2.0% in the very high risk group.

An analysis of the HOT trial similarly grouped participants into medium-high and very high cardiovascular risk according to a World Health Organization (WHO) risk tool.[42] This study did not report absolute event rates and found no significant relative risk reduction in either risk group for any outcome, except for myocardial infarction in which there was a significant reduction in the higher risk group (RR 0.77, 95% CI 0.62 to 0.96) but not in the moderate risk group (RR 0.99, 95% CI 0.76 to 1.29).

In the SPRINT trial, the cardiac event risk reduction was actually greater in those without a history of cardiovascular disease (RR 0.71, 95% CI 0.57 to 0.88 vs RR 0.83, 95% CI 0.62 to 1.09) or chronic kidney disease (RR 0.70, 95% CI 0.56 to 0.87 vs RR 0.82, 95% CI 0.63 to 1.07), though the comorbidity-treatment interactions were not significant.[11]

Table 5. Patient characteristics used to determine eligibility or exclusion from trial enrollment

Trial; Age mean (SD)	Diabetes status	Chronic Kidney Disease	Heart failure (HF)	Criteria likely to exclude those with dementia or diminished functional status*	Comorbidity
ACCORD[22] 62.2 (6.9) years	T2 DM required for inclusion; T1 DM excluded	Excluded (Creatinine > 1.5 mg/dL) -Men eGFR no < 45 -Women eGFR no < 33	Excluded symptomatic HF (NYHA III or IV)	-Excluded for any factors likely to limit adherence to intervention -Excluded those living in SNF	Excluded for: BMI > 45, LFTs > 2 times the upper limit normal limit, cardiac event/procedure within 3 months, or "any condition likely to limit survival to < 3 years or malignancy" (exclude non-melanoma skin cancer)
ADVANCE[27] 66 (6) years	T2-DM diagnosis age ≥ 30 required for inclusion. Excluded if "definite indication for long-term insulin therapy at study entry."	---	---	---	Excluded if definite indication for ACEI not met by perindopril 2 mg or 4 mg.
BENEDICT-B[28] 62.3 (8.3) years	---	Excluded for creatinine > 1.5; non-DM renal disease; or history of kidney transplant -Men no eGFR < 46 -Women no eGFR < 34	Excluded for HF (NYHA III or IV)	Excluded for "any major clinical condition that may jeopardize study participation."	Excluded for: history of CVA, AMI, TIA, unstable angina, cancer, "systemic disease," severe hematologic or liver disorder, malabsorption, valvular disease or heart block.
CARDIO-SIS[23] 67 (7) years	DM excluded	Excluded (Creatinine > 2 mg/dL) -Men eGFR no < 33 -Women eGFR no < 24	Unclear -LVH and valvular heart disease excluded	---	Excluded for: diabetes, atrial fibrillation/flutter, "clinically significant hepatic or hematologic disorder, alcoholism or drug addiction, valvular heart disease, LVH (or other confounders to EKG interpretation), or any disease causing reduced life expectancy"
EWPHE[29] 72 (8) years	Excluded DM requiring insulin therapy	Creatinine ≥ 2.5 mg/dL -Men eGFR no < 25 -Women no eGFR < 19	Excluded for HF	Inability to achieve a sitting position	Excluded for: hypertensive retinopathy, history of cerebral or subarachnoid hemorrhage, or concurrent disease including hepatitis/cirrhosis, gout, and malignancy.
FEVER[30] 61.5 (7.2) years	---	Excluded (Creatinine > 2) -Men eGFR no < 32 -Women no eGFR < 24	Excluded for cardiomyopathy	-Excluded for "unwillingness to cooperate"	Excluded for: CVA or MI within 6 months, unstable angina, gout, uncontrolled DM, "Serious pulmonary or hepatic disease."

Trial; Age mean (SD)	Diabetes status	Chronic Kidney Disease	Heart failure (HF)	Criteria likely to exclude those with dementia or diminished functional status*	Comorbidity
HOT[17] 61.5 (7.5) years	Excluded DM requiring insulin therapy	---	Excluded for HF	---	Excluded for CVA or MI within 12 months, serious concomitant disease which could affect 2-3 years survival, or requirement for β-B, ACEI or diuretic for reasons other than hypertension.
HYVET[6] 83.5 (3.2) years	---	Excluded for creatinine > 1.7 -Men eGFR no < 39 -Women no eGFR < 29	Excluded for "overt" clinical CHF requiring ACEI or diuretics	-Excluded for dementia -Excluded those living in SNF -Excluded for inability to stand up or walk	Excluded for: any condition expected to severely limit survival (terminal illness), cerebral or subarachnoid hemorrhage in past 6 months, gout, hypertensive retinopathy.
JATOS[24] 73.6 (5.2) years	Excluded for DM if HgA1c > 8	Excluded for creatinine > 1.5 -Men eGFR no < 44 -Women no eGFR < 33	Excluded for HF (NYHA II or higher)	-Excluded if "considered unsuitable as subjects."	Excluded for: history of MI/angioplasty in 6 months prior, atrial fibrillation, hypertensive retinopathy, AST or ALT more than double upper limit of normal, malignant disease or collagen disease.
PROGRESS[31] 64 (10) years	---	Unclear. Excluded if had "a definite indication for ACEI" which would include proteinuria.	Unclear. Excluded if had "a definite indication for ACEI" and HF given as example.	-Excluded for "disability that is likely to prevent regular attendance at study clinics."	---
RENAAL[32] 60 (7) years	T2 DM required for inclusion; T1 DM excluded	Excluded relatively severe disease (eGFR < 16 for women and < 21 for men).	Excluded for HF	---	Excluded for: non-diabetic renal disease, history of MI/CABG within 1 month, CVA within 6 months, TIA within 12 months
SCOPE[33] 76.4 years (NR)	---	Excluded for creatinine > 2 in men and > 1.6 in women. -Men eGFR no < 32 -Women no eGFR< 30	Excluded for decompensated HF	-Excluded for dementia -Excluded those with conditions which preclude MMSE (poor vision, aphasia, paralysis, other speech disorders, poor literacy)	Excluded for: CVA or MI within 6 months, LFTs > 3 times the upper limit of normal limit, "serious concomitant disease affecting survival," alcohol/drug abuse, orthostasis, or disorders likely to affect cognition (including vitamin B12 deficiency, new hypothyroidism, neurosyphilis, AIDS, or severe depression).
SHEP[8] 71.6 (6.7) years	Excluded DM requiring insulin therapy	Excluded for "history of renal insufficiency" (no additional definition provided)	---	-Excluded for dementia -Excluded if "presence of medical management problems."	Excluded for: atrial fibrillation or flutter, AV block, bradycardia. Recent MI or CVA, CABG within prior 6 months, and history of alcohol abuse
SPRINT[11] 67.9 (9.5)	DM excluded	Excluded for eGFR < 20	Excluded -for symptomatic HF within 6 months or ejection fraction < 35%	-Excluded for dementia -Excluded those living in SNF -Excluded for factors judged likely to limit adherence to interventions.	Excluded for history of CVA, or "a medical condition likely to limit survival to less than 3 years or a cancer diagnosed/treated in prior 2 years likely to limit trial completion.

Trial; Age mean (SD)	Diabetes status	Chronic Kidney Disease	Heart failure (HF)	Criteria likely to exclude those with dementia or diminished functional status*	Comorbidity
SPS3[25] 63 (11)	---	---	---	---	Excluded if ICH from non-trauma, cortical ischemic stroke, or severely disabling stroke.
STONE[19] 66.4 (5.3)	DM excluded	Excluded for azotemia (BUN > 40)	Excluded for HF	---	Excluded for: angina, MI, severe arrhythmia, atrial fibrillation, COPD, cirrhosis, cancer, and diabetes.
Syst-China[20] 66.5 (5.5)	---	Excluded for creatinine > 2 -Men eGFR no < 33 -Women no eGFR < 24	Excluded for HF	-Excluded for dementia -Excluded for "lack of cooperation."	Excluded for: heart disease, renal or eye manifestations of hypertension, peripheral vascular disease, intracranial hemorrhage or sub arachnoid hemorrhage, MI within 1 year, valvular heart disease, hematologic malignancy or cancer, hyperthyroidism, gout, estrogen hormonal therapy or clotting disorders.
Syst-Eur[34] 70.25 (6.7)	Excluded DM if blood sugar not "adequately controlled."	Excluded for creatinine > 2. -Men eGFR no < 33 -Women eGFR no < 24	Excluded for other diseases that require continuous use of BP lowering drugs including diuretics, ACEI, CCBs, or β-B.	-Excluded for dementia -Excluded for any condition which precludes a sitting or standing condition.	Excluded for: severe sequelae of hypertension (retinopathy, dissection), SAH or cerebral hypertension, nosebleeds, if MI in the year prior, malignancy or hepatic dysfunction, or poorly controlled DM.
TRANS-CEND[35] 66.9 (7.4)	---	Excluded for proteinuria	Excluded for symptomatic CHF	Excluded for significant disability precluding regular follow-up visits.	Excluded for other major non-cardiac illness expected to reduce life expectancy.
VALISH[26] 76.1 (4.1)	---	Excluded for creatinine > 2 -Men eGFR no < 32 -Women no eGFR < 24	Excluded for HF (NYHA III or higher)	-Excluded if "judged to be inappropriate" for the study by the investigator.	Excluded for: history of CVA or MI within 6 months, angioplasty within 6 months or planned, atrial fibrillation /flutter, severe aortic stenosis or valvular disease, or "serious" liver dysfunction.
Wei, 2013[21] 76.6 (4.6)	---	Excluded for creatinine > 3 -Men eGFR no < 20 -Women no eGFR < 15	Excluded for HF (NYHA III or higher) or ejection fraction < 40%	-Excluded for diagnosis of Alzheimer's disease	Excluded for: valvular heart disease, MI or CVA in 6 months prior, hepatic dysfunction, autoimmune disorders, malignant tumor, and "other non-cardiovascular diseases potentially causing death before the end of the study."

Abbreviations: ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACEI = Angiotensin converting enzyme inhibitor; ADVANCE = Action in Diabetes and Vascular Disease; AIDS = acquired immune deficiency syndrome; ALT = alanine aminotransferase; AMI = acute myocardial infarction; AST = aspartate aminotransferase; AV = atrioventricular; β-B = Beta-blocker; BENEDICT-B = Bergamo Nephrologic Diabetes Complications Trial-B; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; CCB = calcium channel blocker; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DM = diabetes mellitus (T2 = type 2, T1= type 1); EKG = electrocardiogram; EWPHE = European Working Party on High Blood Pressure in the Elderly; FEVER = Felodipine Event Reduction Study; HF = heart failure; HOT = Hypertension Optimal Treatment; HYVET = Hypertension in the Very Elderly Trial; ICH = intracerebral hemorrhage; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; LFT = liver function tests; LVH = left ventricular

hypertrophy; MI = myocardial infarction; MMSE = mini-mental state examination; NR = not reported; NYHA = New York Heart Association; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SCOPE = Study on Cognition and Prognosis in the Elderly; SD = standard deviation; SAH = subarachnoid hemorrhage; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; SHEP = Systolic Hypertension in the Elderly Program; SNF = skilled nursing facility; SPRINT = Systolic Blood Pressure Intervention Trial; SPS3 = Secondary Prevention of Small Subcortical Strokes; STONE = Shanghai Trial of Nifedipine in the Elderly; Syst-China = Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe; TIA = transient ischemic attack; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

Notes: Specific exclusion criteria related to type of hypertension (ex: excluded based on secondary hypertension) is not noted here. If mean age was provided by treatment group, mean age by active treatment is listed in column 1. Estimated glomerular filtration rate (eGFR) is calculated using approximated upper end of age range for a given study via the 4-variable MDRD equation.

KEY QUESTION 4: What are the harms of targeting lower blood pressure in older patients? Do the harms vary with age?

General Adverse Effects

Ten trials compared rates of withdrawal due to adverse events (Table 6). We attempted meta-analysis of these results, but the heterogeneity of treatment effects was excessive (I^2 = 92.1%, chi-square $P < 0.001$), precluding the valid estimation of a summary effect. Four trials found more intensive blood pressure treatment was associated with a statistically significant increase in withdrawals due to adverse events, with relative risk increases ranging from 44 to 100%.[8,27,31,35]

Two trials found a trend towards increased adverse events in the intervention group,[26,28] while 4 trials found the intervention group had the same or lower risk of adverse events.[24,29,32,33] One trial found a nearly two-fold increase risk of serious adverse events possibly or definitely related to the intervention.[11] The specific types of adverse events reported varied among trials, though cough or hypotension were among the more frequently reported events (Table 5). There was a higher rate of syncope among those assigned to more aggressive treatment in 2 trials,[8,11] but not in a third.[25]

Medication Burden

Tables 2 and 3 list the mean number of antihypertensive medications used in each group when available, or the proportion of each group taking different antihypertensive medications. It is difficult to define the increase in medication burden associated with different treatment targets given variation in reporting. In general, the mean number of medications or the proportion of participants taking multiple medications was higher in the intervention groups.

Renal Outcomes

We found low-strength evidence from 12 trials that more intensive blood pressure treatment was not associated with worsening of renal outcomes (Table 6). Outcome definitions varied among trials, and event rates of clinically significant outcomes such as end stage renal disease were generally low. Four trials found similar rates of end stage renal disease, need for dialysis, or renal failure in intervention and control groups,[22,24,29,30] while one trial found that use of an angiotensin II receptor blocker was associated with a lower risk of end stage renal disease.[32] One trial found an increased risk for acute renal failure with more aggressive blood pressure lowering.[11]

Table 6. Renal Outcomes and Other Adverse Effects

Study Comparison, T vs C	Adverse effects that occurred frequently, or differed significantly in frequency, % of T vs C	Renal outcomes, % of T vs C
Trials that compared BP target goals		
ACCORD[22] SBP < 120 vs < 140	Hypotension: 0.7 vs 0.04 (P < .001) Hyperkalemia: 0.4 vs 0.04 (P = .01)	ESRD or need for dialysis: 2.5 vs 2.4 (P = .93) Elevation in serum creatinine: > 1.5 mg/dl in men: 12.9 vs 8.4 (P < .001) > 1.3 mg/dl in women: 10.9 vs 7.1 (P < .001) Estimated GFR < 30 ml/min/1.73 m^2: 4.2 vs 2.2 (P < .001)
Cardio-Sis[23] SBP < 130 vs < 140	Peripheral edema: 3.2 vs 4.9 (P = .16) Asthenia: 2.3 vs 0.9 (P = .06) Cough: 2.5 vs 1.3 (P = .13) Skin reactions: 2.7 vs 1.4 (P = .21)	NR
HOT[17] DBP ≤ 80 vs ≤ 85 vs ≤ 90	AEs that exceeded 2%: Dizziness, headache, leg edema, flushing, and coughing. T vs C not reported.	NR
JATOS[24] SBP < 140 vs < 160	Withdrawal due to AE: 1.6 vs 1.6 (P = ns) AEs resulting in discontinuation of treatment: Malignant disease: 0.3 vs 0.5 (P = .31) Psychoneurological symptom: 0.18 vs 0.23 (P = .74) Poor blood pressure control: 0.18 vs 0.23 (P = .74) Cardiac symptom or arrhythmias: 0.32 vs 0.18 (P = .37) Respiratory symptom or disease: 0.18 vs 0.09 (P = .42)	Renal failure: 0.36 vs 0.41 (P = ns)
SPS3[25] SBP < 130 vs 130-149	Syncope: 0.7 vs 0.3 (P = .14)	NR
SPRINT[11] SBP < 120 vs < 140	Serious AE possibly or definitely related to intervention: 4.7 vs 2.5%; HR 1.88 (P < .001) Hypotension: 2.4 vs 1.4; HR 1.67 (P < .001) Syncope: 2.3 vs 1.7; HR 1.33 (P = .05) Electrolyte abnormality: 3.1 vs 2.3; HR 1.35 (P = .02) Fall resulting in ER visit/hospitalization: 2.2 vs 2.3; HR 0.95 (P = .71)	Acute kidney injury or acute renal failure: 4.1 vs 2.5; HR 1.66 (P < .001)
VALISH[26] SBP < 140 vs < 150	Withdrawal due to AE: 1.9 vs 1.2 (P = ns) AEs not otherwise specified.	Renal insufficiency: 0.32 vs 0.13 (P = .267) HR 2.45 (95% CI 0.48 to 12.64), adjusted for sex, age, BMI, smoking, dyslipidemia, diabetes, and anti-hypertension agents used before enrollment.
Wei, 2013[21] SBP < 140 vs < 150	Femoral fracture: 0.8 vs 1.3 (P = .716) Vascular dementia: 0.6 vs 0.8 (P = .995)	NR
Trials that compared more vs less intensive antihypertensive treatment		
ADVANCE[27]	Withdrawal due to AE: 5.7 vs 2.9 (P < .01)	New or worsening nephropathy: 3.3 vs 3.9

Study Comparison, T vs C	Adverse effects that occurred frequently, or differed significantly in frequency, % of T vs C	Renal outcomes, % of T vs C
(Perindopril + indapamide) vs placebo	Cough: 3.3 vs 1.3 (P < .01) Hypotension or dizziness: 1.2 vs 0.4 (P < .01)	(P = ns) RR reduction: 18% (95% CI, -1 to 32)
BENEDICT-B[28] VeraTran (verapamil + trandolapril) vs Trandolapril	Withdrawal due to cough: 14.5 vs 9.1 (P = ns)	NR
EWPHE[29] (Hydrochlorothiazide + Triamterene) vs placebo	Withdrawal due to AE: 6.0 vs 13.2 (P < .01) Withdrawal due to severe increase in BP: 0.5 vs 4.5 (P = .0001)	Death from renal causes: 1.0 vs 0.2 (P = ns) Withdrawn due to 100% increase in serum creatinine: 1.0 vs 0.2 (P = ns) Renal disease: 3.1 vs 0.5 (P < .001) Pyelonephritis: 1.2 vs 0.5 (P = ns) Nephrotic syndrome: 0.2 vs 0 (P = ns) Chronic nephritis: 0.2 vs 0 (P = ns) Renal disease of undetermined origin: 1.4 vs 0 (P = ns)
FEVER[30] Felodipine vs placebo	AEs reported during treatment: Flushness: 1.4 vs 0.2 (P < .001) Fatigue: 0.64 vs 1.05 (P = .037) Ankle edema: 1.0 vs 0.37 (P < .001)	Renal failure: 0.20 vs 0.16 (P = .5) HR 1.38 (95% CI, 0.54 to 3.52)
HYVET[6] Indapamide vs placebo	Serious AEs occurred in 18.5 vs 23.4 (P =.001) Types of AEs not specified.	No significant differences between T vs C in changes from baseline in serum creatinine: 3.4 vs 2.3 µmol/L *(*P =.30) (0.04 vs 0.03 mg/dL)
PROGRESS[31] (Perindopril ± Indapamide) vs placebo	Withdrawal due to AE: 5.2 vs 3.6 (P < .01) Reasons for discontinuation; Cough: 2.2 vs 0.4 (P < .05) Hypotension: 2.1 vs 0.9 (P < .01)	NR
RENAAL[32] Losartan vs placebo	Withdrawal due to AE: 17.2 vs 21.7 (P < .05) AEs leading to discontinuation: Increased serum creatinine: 1.5 vs 1.2 (P = ns) Increased serum potassium: 1.1 vs 0.5 (P = ns)	End-stage renal disease: 19.6 vs 25.5 (P = .002); RR 0.77 (95% CI, 0.63 to 0.93) Doubling of serum creatinine: 21.6 vs 26.0 (P = .006) RR 0.83 (95% CI, 0.63 to 0.99)
SCOPE[33] Candesartan vs placebo	Dizziness/vertigo: 20.9 vs 20.0 (P = ns) Accident/injury: 18.4 vs 18.4 (P = ns) Back pain: 9.2 vs 17.1 (P = ns) Bronchitis: 15.9 vs 16.0 (P = ns) Significant cognitive decline: 13.5 vs 15.2 (P = ns) Dementia: 6.8 vs 6.3 (P = ns) Withdrawal due to AE: 15.0 vs 17.0 (P = .07)	NR
SHEP[8] Chlorthalidone vs placebo	Chest pain or heaviness: 28.0 vs 21.3 (P < .01) Trouble with memory/concentration: 26.4 vs 20.4 (P < .01) Cold or numb hands: 13.6 vs 9.8 (P < .01) Change in bowel habits: 15.4 vs 11.4 (P < .01) Unusual joint pain: 36.4 vs 31.4 (P < .01) Heart beating unusually slowly: 3.8 vs 2.1 (P < .01)	Renal dysfunction or death from renal disease: 0.38 vs 0.55 (P = .40) RR 0.65 (95% CI, 0.30 to 1.62)

Study Comparison, T vs C	Adverse effects that occurred frequently, or differed significantly in frequency, % of T vs C	Renal outcomes, % of T vs C
	Ankle swelling: 19.5 vs 15.6 (P < .01) Falls: 12.8 vs 10.4 (P < .05) Problems in sexual function: 4.8 vs 3.2 (P < .05) Syncope: 2.2 vs 1.3 (P < .05) Withdrawal due to AE: 13.0 vs 7.0 (P < .05)	
STONE[19] Nifedipene vs placebo	NR	NR
Syst-China[20] (Nitrendipine ± Captopril ± Hydrochlorothiazide) vs placebo	NR	NR
Syst-Eur[44] Nitrendipine vs placebo	NR	Mild renal dysfunction: 0.22 vs 0.61 (P = .05) Active treatment reduced the rate of dysfunction by 64% (95% CI, 0 to 87%; *P* = .04) from 2.6 to 0.9 events per 1000 patient-years. In Cox regression with adjustments for sex, age, SBP at entry, previous cardiovascular complications and antihypertensive treatment, body mass index and smoking and alcohol intake at entry, the reduction was 64% (95% CI, 0 to 84%; P < .05). No patient died of renal failure.
TRANSCEND[35] Telmisartan vs placebo	Withdrawal due to AE: 2.6 vs 1.7 (P < .05) Hypotensive symptoms resulting in withdrawal: 0.98 vs 0.54 (P = .049)	Renal abnormalities that led to study withdrawal: 0.81 vs 0.44 (P = .067)

Abbreviations: ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; AE = adverse event; BENEDICT-B = Bergamo Nephrologic Diabetes Complications Trial-B; BMI = body mass index; BP = blood pressure; C = comparator/control; Cardio-Sis = Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica; CI = confidence interval; DBP = diastolic blood pressure; ER = emergency room; ESRD = end-stage renal disease; EWPHE = European Working Party on High Blood Pressure in the Elderly; FEVER = Felodipine Event Reduction Study; GFR = glomerular filtration rate; HOT = Hypertension Optimal Treatment; HR = hazard ratio; HYVET = Hypertension in the Very Elderly Trial; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; NR = not reported; ns = not statistically significant; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; RR = relative risk; SBP = systolic blood pressure; SCOPE = Study on Cognition and Prognosis in the Elderly; SHEP = Systolic Hypertension in the Elderly Program; SPRINT = Systolic Blood Pressure Intervention Trial; SPS3 = Secondary Prevention of Small Subcortical Strokes; STONE = Shanghai Trial of Nifedipine in the Elderly; Syst-China = Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe; T = treatment; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

Cognitive Outcomes

We found moderate-strength evidence from 7 RCTs that use of antihypertensive treatment to achieve moderately strict blood pressure control for up to 5 years does not worsen cognitive outcomes compared to less strict blood pressure control (Table 7). The mean age of trial participants ranged from 62 to 83 years, and baseline cognitive function was generally normal. In most trials, the intervention group achieved SBP in the 140 to 150 mm Hg range, though in one study the intervention group achieved an SBP of 119 mm Hg. Three large-scale trials reported cognitive outcomes for the entire cohort,[45-47] while 3 other trials prospectively collected cognitive outcomes data for a subpopulation of patients.[8,48,49] In patients without a prior history of cerebrovascular disease, 3 trials found no difference in rates of incident dementia,[45,47,48] while one trial found that more intensive blood pressure control was associated with a lower rate of dementia.[46] A prior meta-analysis of these 4 trials found no significant difference in development of dementia (odds ratio [OR] 0.89, 95% CI 0.74 to 1.07, $I^2 = 17\%$).[50] Another trial of patients with a prior history of stroke similarly found no difference in rates of incident dementia (RR 0.88, 95% CI 0.72 to 1.08).[48] Six of the trials with serial cognitive assessments found the groups did not differ in change in cognitive function over time (Table 6).

Six of the trials had low risk of bias, while an older trial had an unclear risk of bias because of poor methods reporting.[51] The 4 trials reporting incident dementia used robust diagnostic criteria centrally adjudicated by blinded outcomes assessors. Rates of missing data or loss to follow-up ranged from 0.5 to 13.8%, but results were consistent across all studies.

We found 2 observational studies that suggested an SBP range of approximately 135 to 150 mm Hg was associated with the lowest risk of cognitive decline.[52,53] However, in both studies there were missing data from a large proportion of patients (13.5 to 37%) who were generally less well-educated than those with full data available. A third observational study in patients ≥ 80 years of age similarly found the lowest rate of cognitive decline among those whose 4 year mean SBP was between 140 to 160 mm Hg, while those with lower or higher blood pressures experienced steeper rates of cognitive decline.[54]

Table 7. Cognitive Outcomes Reported in Trials and Prospective Cohort Studies of Hypertension Management in the Elderly

Study Setting	Study overview	Sample size	Age at base-line	Mean or *median follow-up (years)	Baseline cognitive function	Mean achieved BP (mm Hg) T vs C	Results, T vs C	Comments
Randomized controlled trials (RCTs)								
ACCORD-MIND[47] substudy of ACCORD RCT	SBP target < 120 vs SBP target < 140 mm Hg	1439	62	3.3	DSST: 52.28 MMSE: 27.25	SBP: 119 vs 133.2 DBP: 64 vs 70.2	Change from baseline: DSST: -1.86 vs -1.61 (P = .55) MMSE: -0.25 vs -0.30 (P = .70)	199 (13.8%) of enrollees had one or more missing data points, and those with missing follow-up data were slightly older and had slightly lower cognitive function at baseline
Bird, 1990[51] Medical Research Council multisite outpatient trial, Great Britain RCT	Treat to SBP target < 150 mm Hg if baseline SBP 160-179, or < 160 mm Hg if baseline SBP 180-209; primary intervention medications were hydrochlorothiazide/ amiloride or atenolol	2446	70.3	0.75	PALT: 85% scored 16-18 (normal). 14.8% scored 8-15. 25% scored < 8. Trail making test: 63.6% normal (≤ 60 seconds)	SBP: 149 vs 167 DBP: 79 vs 86	Mean achieved BP atenolol vs hydrochlorothiazide/amiloride vs placebo: 156/79 vs 149/79 vs 167/86 % with abnormal PALT atenolol vs hydrochlorothiazide/amiloride vs placebo: 19.9 vs 21.2 vs 18.5 (P = ns) % with abnormal trail making test (≥ 90 seconds) atenolol vs hydrochlorothiazide/amiloride vs placebo: 5.9 vs 5.7 vs 6.7 (P = ns)	Unclear risk of bias:randomization and allocation concealment procedures not well described; loss to follow-up appears low but poorly reported; little data comparing group baseline characteristics
HYVET-COG[45] substudy of HYVET RCT	BP target 150/80 vs placebo	3336	83.5	2.2	MMSE: 26	Mean decrease in SBP: 29.6 vs 14.6 Mean decrease in DBP: 13.1 vs 7.2	Incident dementia: 126/1687 (7.5%) vs 137/1649 (8.3%) HR 0.86 (95% CI 0.67-1.09) Cognitive decline (fall in MMSE to < 24 or decline of > 3 points in one year): 485/1687 (28.7%) vs 486/1649 (29.5%) HR 0.93 (95% CI 0.82-1.05)	509 (13.2%) of potentially eligible patients did not meet criteria for inclusion in cognitive substudy because of missing data. However, these patients had similar baseline demographic, education, and cognitive characteristics as included patients.

Study Setting	Study overview	Sample size	Age at base-line	Mean or *median follow-up (years)	Baseline cognitive function	Mean achieved BP (mm Hg) T vs C	Results, T vs C	Comments
PROGRESS[48] Multisite RCT in patients with stroke	Perindopril ± indapamide vs placebo	6105	64	3.9	MMSE: 29	Reduction in SBP/DBP: 9.0 vs 4.0	Incident dementia: 193/3051 (6.3%) vs 217/3054 (7.1%) RR 0.88 (95% CI 0.72-1.08) Change in MMSE: -0.05 vs -0.24 (P = .01) Patients with cognitive decline (MMSE decline of 3 or more points): 276/3051 (9.0%) vs 334/3054 (10.9%) RR 0.81 (95% CI 0.68-0.96)	Serial cognitive assessments were available for most patients (96.4%). Dementia assessment done by interviewers blinded to treatment group.
SCOPE[49] Multisite RCT, cognitive outcomes secondary outcome of parent study	Candesartan vs placebo to achieve BP < 160/90 mm Hg	4937	76.4	3.7	MMSE: 28.5	SBP: 145.2 vs 148.5 DBP: 79.9 vs 81.6	Incident dementia: 62/2477 (6.8%) vs 57/2460 (6.3%) (P = ns) Change in MMSE: -0.49 vs -0.64 (P = ns)	Very low loss to follow-up. 99.5% of patients originally randomized were included in analyses. Most (84%) of the control participants also received antihypertensive treatment.
SHEP[8] Multisite RCT	Thiazide ± atenolol to achieve ≥ 20 mm Hg drop in SBP vs placebo	4736	71.6	4.5	Cognitive impairment score[55] ≥ 4 (as cited in SHEP[8]), T vs C: 0.3% vs 0.5%	SBP: 144.0 vs 155.1 DBP: 67.7 vs 71.1	Incident dementia: 37/2365 (1.6%) vs 44/2371 (1.9%) RR 0.84 (95% CI 0.54-1.31)	About 4% in each group referred for dementia evaluation, and about 10% of those referred declined further evaluation. Characteristics of these patients were not described.
Syst-Eur[46] Dementia substudy of larger multisite European RCT	SBP < 150 mm Hg vs placebo	2902	68	3.9*	MMSE: 29	SBP: 149.1 vs 156.1 DBP: 79.4 vs 82.5	Incident dementia: 21/1485 (1.4%) vs 43/1417 (3.0%) Rate per 1000 patient-years: 3.3 vs 7.4 (P < .001) Change in MMSE at 3 years: -0.17 vs -0.14 (P = .73)	326 (10.1%) of eligible cohort did not contribute data to this analysis, but their baseline characteristics are not available.
Prospective cohort studies								

Study Setting	Study overview	Sample size	Age at base-line	Mean or *median follow-up (years)	Baseline cognitive function	Mean achieved BP (mm Hg) T vs C	Results, T vs C	Comments
Liu, 2013[52] Indianapolis cohort of the Indianapolis-Ibadan Dementia Project Prospective cohort study	African Americans aged ≥ 65 years with assessment every 2-3 years from 1992-2009	2721	76	NR	Median Community Screening Interview for Dementia score (possible score 0-80): 68 (interquartile range 62-72)	NR	Nonlinear association between BP and cognitive function. Optimal cognitive function associated with SBP of about 135 mm Hg and DBP of about 80 mm Hg.	424 (13.5%) of original cohort had missing data and were excluded. These patients were older and less educated. Used a semiparametric mixed effects model approach in which each patient could contribute several longitudinal observations
Peng, 2014[54] China Prospective cohort study	Community-dwelling hypertensive participants ≥ 80 years old; no standard treatment protocol	294	84.4	85% with complete 4-year follow-up	MMSE: 26	Baseline: SBP: 176 DBP: 78 4-year mean: SBP: 153 DBP: 75	% change in MMSE: SBP < 140 mm Hg: -7.78 (SD 8.1) SBP 140-160 mm Hg: -3.51 (SD 7.75) SBP >160 mm Hg: -8.8 (SD 9.27) P-value for differences between groups < .001 % change in MMSE by SBP decline: < 15 mm Hg: -8.94 (SD 9.1) 15-35 mm Hg: -3.77 (SD 7.33) Ø 35 mm Hg: -7.03 (SD 8.75) P-value for differences between groups < .001	44 participants excluded from final analysis due to death/stroke/withdrawal. 250/294 (85%) included in analysis.
Sacktor, 1999[53] Baltimore Longitudinal Study of Aging Prospective cohort study	Patients ≥ 60 treated for hypertension with serial BP measures and neuropsychologic testing; tested association between maintenance of low (SBP < 135), intermediate (SBP 135-150), and high (SBP > 150) BP and cognitive outcomes	158	74.5	5.1	MMSE: 28.4	% with Low: 18 Intermediate: 30 High: 51	Change in Low vs Intermediate vs High BP groups: MMSE: 0.2 vs 0.3 vs 0.2 (P = .77) Trail making test part B: -0.1 vs 5.4 vs 5.2 (P = .19) Total free recall: -0.3 vs 0.0 vs 0.6 (P = .02) Delayed recall: 0.4 vs 0.0 vs 0.1 (P = .04)	132 (37%) of the original cohort of 354 patients did not receive longitudinal neuropsychologic testing; these excluded patients were younger and less educated.

Abbreviations: ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACCORD-MIND = Action to Control Cardiovascular Risk in Diabetes - Memory in Diabetes; BP = blood pressure; C = comparator/control; CI = confidence interval; DBP = Diastolic blood pressure; DSST = Digit Symbol Substitution Test; HR = hazard ratio; HYVET = Hypertension in the Very Elderly Trial; HYVET-COG = Hypertension in the Very Elderly Trial - Cognitive Function Assessment; MMSE = mini-mental state examination; NR = not reported; ns = not statistically significant; PALT = Paired Associate Learning Test; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; RCT = randomized

controlled trial; RR = relative risk; SBP = systolic blood pressure; SCOPE = Study on Cognition and Prognosis in the Elderly; SD = standard deviation; SHEP = Systolic Hypertension in the Elderly Program; Syst-Eur = Systolic Hypertension in Europe; T = treatment.

Quality of Life and Functional Status

Overall, we found moderate-strength evidence from prospective substudies of 4 large low risk of bias trials that use of antihypertensive therapy to achieve moderate blood pressure control (SBP 140 to 150 mm Hg) was not associated with a deterioration in quality of life compared to less intensive blood pressure control. We found low-strength evidence from one large low risk of bias trial that moderate blood pressure control was not associated with deterioration in functional status compared to less intensive control.

In the SHEP trial, all participants were included in a longitudinal assessment of functional status.[56] Most participants (intervention group 95.6%, control group 92.8%) completed baseline and follow-up questionnaires about deterioration in Activities of Daily Living (ADLs). At a mean of 5 years of follow-up, a similar proportion of intervention and control group participants reported a deterioration in basic ADLs (18.6 vs 20.1%, $P = .20$), moderate ADLs (22.1 vs 23.4, $P = .30$), and advanced ADLs (46.6 vs 49.1, $P = .72$).

A smaller pre-specified subpopulation (N = 2,034) of SHEP trial participants was included in a longitudinal behavioral assessment that included 3 questions globally assessing quality of life.[56] Baseline and follow-up questionnaires were completed by 1758/2034 (86.4%) of participants. On all 3 measures, quality of life was similar in intervention and control groups at last follow-up. For example, a similar proportion rated their health as good or excellent at follow-up (T vs C, 78.0 vs 76.4%, $P = .70$).

A subpopulation of 1,348 of the 4,695 patients in the Syst-Eur trial was recruited for a quality of life assessment.[57] Six hundred and ten of these patients completed a baseline and at least one follow-up questionnaire which included the Sickness Impact Profile (SIP), a quality of life measure examining the effects of poor health on ambulation, social interaction, home work, and sleep and rest. There were no differences in SIP score changes over time between intervention and control groups, although an age-adjusted model showed slightly more intervention patients reported difficulty on the social interaction scale (OR 1.32, 95% CI 1.02 to 1.69).

In the HOT trial (total N = 19,193), of 922 patients recruited into a quality of life substudy, 610 (66%) completed questionnaires consisting of the Psychological General Well-Being index (PGWB) and the Subjective Symptoms Assessment Profile (SSA-P) at baseline and at the 6 month follow-up visit.[58] There was slightly more improvement in global PGWB scores (potential range 22 to 132) in the group randomized to target DBP of ≤ 80 mm Hg than the 2 less intensive blood pressure target groups (mean change in scores 2.8 vs 0.6 vs 1.3, $P < .001$). These small improvements are of uncertain clinical significance and were driven by very small changes in the anxiety, general well-being, and vitality subscales.

The SSA-P used 7-point Likert-scale questions to assess various subjective symptoms potentially associated with antihypertensive therapy. Headache, dizziness, and cardiac symptoms such as palpitations improved slightly in all groups (approximately -0.5, -0.2, and -0.2, respectively, $P < .01$), while sex-life scores deteriorated slightly in males assigned to the 2 more intensive treatment groups (0.2 vs 0.0, $P < .01$).

The SCOPE trial enrolled 2,850 of its 4,937 in a quality of life substudy.[59] The PGWB, SSA-P, and European Quality of Life scale (EuroQOL, a 100-point visual analog scale assessing self-rated current health) were completed at baseline and last follow-up by 92.9 and 93.7% of the

intervention and control groups, respectively. Quality of life deteriorated slightly less in the intervention than in the control group, though this difference is likely of little clinical significance (-3.1 vs -5.3, mean difference in change -2.19, 95% CI -3.8 vs -0.56). Changes in PGWB and SSA-P scores were similar in the 2 groups.

Falls and Fractures

We found moderate-strength evidence from 3 large low risk of bias trials that more intensive blood pressure treatment (SBP targets < 120 mm Hg and < 150 mm Hg, and achieved SBP < 150 mm Hg in the third trial) did not increase risk of fracture.[60,61] We found low-strength evidence that more aggressive blood pressure control did not consistently increase the risk of falls. Two of the trials found that very aggressive blood pressure lowering (SBP < 120 mm Hg) did not increase the risk of falls,[11,60] while a third trial found that moderate blood pressure control (SBP < 150 mm Hg) was associated with a small increase in the risk of falls.[8]

In meta-analyses of these studies statistical heterogeneity was too high to permit meaningful summary estimates of treatment effects.

In the ACCORD study, 3,099 of the 4,733 participants were enrolled in the ACCORD-BONE substudy.[60] Participants (mean age 62 years), were asked annually to report falls or non-spine fractures over the prior 12 months. Fracture events were centrally adjudicated using radiology reports by blinded outcome assessors. Over a mean of 3.5 years of follow-up, the rate of falls was similar in the intervention and control groups (62.2/100 person-years vs 74.1/100 person-years, RR 0.84, 95% CI 0.54 to 1.29). A similar proportion of participants in each group had one or more falls (20 vs 21%, OR 0.94, 95% CI 0.84 to 1.05). The risk of non-spine fractures was non-significantly lower in the intervention group (hazard ratio [HR] 0.79, 95% CI 0.62 to 1.01). Interaction terms including age and comorbidities were all $P > .05$.

In the SHEP study (N = 4,736) more patients in the intervention group reported one or more falls over the 4.5 year follow-up (12.8 vs 10.4%, $P < .05$), though a similar number in both groups experienced a fracture (2.4 vs 2.0%, $P > .05$).[8]

All participants (N = 3,845, mean age 83.5) in the HYVET study were included in an analysis of hypertension treatment (with a thiazide diuretic ± ACE inhibitor) on risk of fracture.[61] Fractures were identified if included in routine serious adverse event reporting. Additionally, at each trial follow-up investigators were asked to report whether participants had experienced an interim fracture. Fracture events were centrally adjudicated by blinded outcome assessors who examined relevant radiological and medical reports. Over a mean of 2.1 years of follow-up, one or more definite or probable fractures occurred in 38/1933 (2.0%) intervention participants compared to 52/1912 (2.7%) control participants (HR 0.69, 95% CI 0.46 to 1.05).

In the SPRINT trial (N = 9,361, mean age 67.9) a similar proportion of participants in the intervention and control groups had a fall leading to an emergency room visit or hospitalization (2.2 vs 2.3%, HR 0.95, $P = .71$). However, there was a higher risk of syncope among intervention participants (2.3 vs 1.7%; HR 1.33, $P = .05$).

Effects of Age

Three studies reported harms associated with more versus less intensive blood pressure treatment according to age. The SPS3 trial compared results in participants ≥ 75 years (N = 494) and < 75

years (N = 2,526).[39] The rates of adverse events related to blood pressure lowering such as unsteadiness, dizziness, and orthostatic syncope were similar among patients assigned to a lower treatment target (achieved SBP 125 mm Hg) and higher treatment target (achieved SBP 137 mm Hg) in both age groups. Fewer participants assigned to the lower treatment target experienced one or more episodes of postural hypotension (53 vs 65% and 57 vs 62% in the older and younger age groups, respectively; $P < .01$ in both groups).

In the JATOS study, rates of renal failure were similar in lower and higher treatment target groups in older (≥ 75 years) and younger (< 75 years) participants, though event rates were low.[24]

The SPRINT trial did not directly compare harms in different age groups, but found that the pattern of harms in the subgroup of patients over age 75 was similar to overall study findings. For example, a similar proportion of older patients in the intervention and control groups experienced a fall resulting in an emergency room visit or hospitalization (5.3 vs 6.0%; HR 0.88, $P = .42$).[11]

Overall, there were very few participants ≥ 80 years included in most of the trials. The major exception was the HYVET trial which only included patients over age 80 and found that use of medication to achieve moderate blood pressure control (150/80 mm Hg) was not associated with an increased risk of adverse events.[6]

Harms according to DBP

Theoretically, low DBP could also contribute to harms. We found very little data to assess the contribution of low DBP to the harms described above. The only 2 studies in which the achieved DBP was < 70 mm Hg were ACCORD and SPRINT (mean achieved DBP 64.4 and 66 mm Hg), which also examined the effects of aggressive SBP targets of < 120 mm Hg. As described above, these studies found that achieved DBP < 70 mm Hg was not associated with an increased risk of falls, fractures, or cognitive impairment. However, there was an increased risk of symptomatic hypotension in both trials,[11,22] and an increased risk of syncope in one trial.[11] Whether these effects were seen primarily in patients with very low DBP, SBP, or both is unclear.

KEY QUESTION 5: Do the harms of targeting lower blood pressure vary with patient burden of comorbidities?

We found no trials which examined the impact of participants' burden of comorbidities on risk of adverse events. As noted in Key Question 3, patients with severe comorbidities or high comorbidity burden were not well-represented among these studies (Table 5). There is an insufficient body of evidence examining the safety of intensive blood pressure treatment in adults with dementia or other serious illness since these patients were excluded from most trials.

SUMMARY AND DISCUSSION

In this systematic review, we examined the benefits and harms of treating hypertension to lower compared more moderate blood pressure targets in patients over age 60. Table 8 provides a summary of the evidence. Overall, we found high-strength evidence that treating blood pressure in patients over age 60 to current treatment targets (< 150/90 mmHg) substantially reduces mortality, stroke, and cardiac events. Much of this data comes from trials in which the mean baseline SBP was > 160 mmHg. We also found evidence, driven mainly by one large trial, that lower targets (SBP < 140 mmHg or DBP < 85 mmHg) compared to higher targets reduced stroke (moderate strength evidence) and cardiac events (low strength evidence); mortality was also reduced though not significantly (low strength evidence). There is little data that directly helps distinguish benefits between SBP 140 and 150 mmHg. Most of the trials achieving SBP < 140 mmHg were the treat-to-target trials. Only one trial included patients with baseline SBP 140-150 mmHg and found an improvement in mortality, but not other outcome. We found moderate strength evidence that more aggressive blood pressure control (SBP < 140 mmHg) in patients with prior stroke substantially reduced rates of recurrent stroke.

The treat-to-target trials overall support a lower blood pressure treatment target in some patients with high cardiovascular risk. Most of the evidence in support of lower treatment targets comes from one large trial examining an SBP target of < 120 mmHg in which a substantial proportion of intervention patients achieved SBP 120-130 mmHg. Lower targets may prevent (on average, across a population) roughly 10-20 events for every 1000 high-risk patients treated over 5 years (Table 8), but more aggressive treatment is likely associated with a higher medication burden and higher risk of adverse effects such as hypotension and syncope. On the other hand, we found that lower targets are unlikely to increase the risk of dementia, fractures, and falls, or reduce quality of life.

Current guidelines suggest aiming for moderate blood pressure control (< 150/90 mm Hg) in most adults over age 60. We found strong evidence supporting benefit of moderate blood pressure control. The main area of controversy, however, is whether or not there is an additional benefit from more aggressive blood pressure control. Taken as a whole, trials examining lower blood pressure targets suggest there may be some benefit in more aggressive control, though the absolute effect is smaller and there is not a consistent effect on mortality. It is possible that the smaller incremental benefit from more aggressive blood pressure control may be related to the relatively small number of cardiovascular and mortality events in some of the trials.[24,26] As discussed above, 3 studies found that patients with higher baseline cardiovascular risk had higher event rates and tended to experience more absolute benefit.[41-43] However, the magnitude of these effects was modest and was not consistent across outcomes.

Part of the answer may depend on consideration of the individual trials. The SPRINT and ACCORD trials are clearly different than the others in that they included patients with reasonable blood pressure control (about 140/90 mm Hg) at baseline and targeted “normal” SBP of 120 mm Hg. However, these 2 trials provide conflicting results: in SPRINT there was a substantial reduction in mortality and cardiac events but not stroke, while in ACCORD there was a reduction in stroke but not the other outcomes. Both trials included patients with substantial cardiovascular risk (and, in fact, the proportion of patients experiencing events was higher in ACCORD), though the mean age was higher in the SPRINT trial. The ACCORD trial included only diabetic patients, while SPRINT excluded diabetic patients. However, it is not immediately

clear why results would differ based on diabetes status alone. Of note, the SPRINT trial was stopped early for benefit but it is unclear whether this necessarily accounted for the different results. Sensitivity analyses suggest that SPRINT was the main contributor to the non-significant trend towards reduced mortality and the significant effects on cardiac events.

There was consistent evidence that more aggressive blood pressure control modestly reduced stroke outcomes with or without the inclusion of SPRINT. The modest stroke risk reduction may provide rationale for more aggressive treatment in some patients. The main trade-off in considering more aggressive treatment would be a higher medication burden, and the increased risk of adverse effects seen in some studies such as cough and hypotension. Two of 3 trials found higher rates of syncope in the intervention group suggesting that hypotension is potentially a serious short-term harm. Theoretically, there is also reason to be concerned about more serious long-term adverse effects of lowering blood pressure in older adults in whom arterial stiffness, subclinical cerebrovascular disease, cognitive impairment, and multiple comorbidities can combine to increase risk of falls, fracture, dementia, and poor quality of life. However, we found moderate-strength evidence that blood pressure treatment to SBPs as low as 120 mm Hg did not increase the risk of dementia, fractures, falls, or reduce quality of life.

Table 8. Summary of the Evidence on More vs Less Intensive Treatment for Hypertension in the Elderly

Outcome	N studies (N = total patients combined)	Combined estimates: RR (95% CI) ARR N: events (95% CI) prevented per 1000 high-risk patients over 5 years[a]	Strength of Evidence[b]	Summary of findings
Mortality	9 RCTs[c] (N = 46,450)	RR 0.90 (0.83-0.98) ARR 1.64 N: 34 (7-58)	High[d]	Consistent benefit of treating blood pressure to levels < 150/90 mmHg.
	6 RCTs[e] (N = 41,491)	RR 0.86 (0.69-1.06) ARR 0.80 N: 18 (n/a[f]-40)	Low	Lower treatment targets (SBP ≤ 140 mmHg or DBP ≤ 85 mmHg, or lower) associated with non-significant mortality reduction compared to higher targets. Findings were inconsistent across studies and estimate was imprecise.
Stroke	9 RCTs[c] (N = 46,450)	RR 0.74 (0.65-0.84) ARR 1.13 N: 26 (16-35)	High[d]	Clear, consistent benefit of treating blood pressure to levels < 150/90 mmHg.
	6 RCTs[e] (N = 41,491)	RR 0.79 (0.59-0.99) ARR 0.49 N: 9 (0-17)	Moderate	Lower treatment targets (SBP ≤ 140 mmHg or ≤ DBP 85 mmHg, or lower) reduced the risk of stroke compared to higher targets; some inconsistency but relatively stable effect across analyses[f]
Cardiac events	9 RCTs[c] (N = 46,450)	RR 0.77 (0.68-0.89) ARR 1.25 N: 65 (31-90)	High[d]	Clear, consistent benefit of treating blood pressure to levels < 150/90 mmHg.
	6 RCTs[e] (N = 41,491)	RR 0.82 (0.64-1.00) ARR 0.94 N: 18 (n/a[f]-36)	Low	Lower treatment targets (SBP ≤ 140 mmHg or DBP ≤ 85 mmHg, or lower) may reduce the risk of cardiac events compared to higher targets. Findings were inconsistent across studies and estimate was imprecise.
Short-term adverse events	19 RCTs (N = 98,964)	---	---	Mixed findings: withdrawal due to adverse events was increased in the intervention group by 44-100% in 4 of 10 trials reporting this outcome. Cough and hypotension were the most frequently reported events. The risk of syncope was increased in 2 of 3 trials reporting this outcome. Excessive heterogeneity among trials precluded pooling of results.
Renal outcomes	13 RCTs (N = 66,607)	---	Low	More intensive blood pressure treatment did not worsen renal outcomes. Outcome definitions varied, and event rates for clinically significant outcomes such as end stage renal disease were low.
Cognitive outcomes	7 RCTs (N = 25,901)	Incident dementia in 4 RCTs of patients without prior stroke: OR 0.89 (0.74-1.07)	Moderate	No effect on degree of cognitive decline or incidence of dementia. Loss to follow-up ranged across studies; patients lost to follow-up may differ in risk for dementia.
Falls/ fracture	Fracture: 3 RCTs (N = 11,680)	---	Moderate (fracture)	Mixed findings: 3 trials found no effect of lower blood pressure targets on risk of fracture. Two trials with SBP target of 120 mmHg found no effect on risk of falls, while a 3rd (with achieved SBP < 150 mmHg) found a small increase in risk of fall.
	Falls: 3 RCTs (N = 17,196)	---	Low (falls)	

Outcome	N studies (N = total patients combined)	Combined estimates: RR (95% CI) ARR N: events (95% CI) prevented per 1000 high-risk patients over 5 years[a]	Strength of Evidence[b]	Summary of findings
Quality of life (QOL)	4 RCTs (N = 7,154)	---	Moderate (QOL) Low (functional status)	Moderate BP control (SBP 140-150 mmHg) did not affect QOL. One study found no effect on functional status.
Effects of age	12 RCTs (N = 76,137)	---	Low	Similar effects across different age groups in age-treatment interaction analyses, but based on study-level subgroup analyses and dichotomized at a younger age in many studies.
Effects of comorbidity burden	---	---	No evidence	No studies reported outcomes based on comorbidity burden; most trials excluded patients with dementia, serious comorbidities, and life-limiting illness.
Effects in the frail elderly	2 RCTs (N = 5,166)	---	Insufficient	Treatment effects did not vary with frailty score in post-hoc analyses from 2 trials, one of which had large amount of missing data. Most trials did not assess frailty, and many trials excluded patients who were frail, had dementia, or were institutionalized.
Effects in stroke patients	2 RCTs (N = 9,125)	Stroke recurrence: RR 0.76 (0.66-0.92) ARR 3.02 Cardiac events: RR 0.78 (0.61-1.08) Mortality: RR 0.98 (0.85-1.19)	Moderate	Targeting SBP < 140 mmHg reduced recurrent stroke.

Abbreviations: ARR = absolute risk reduction; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; N = population size (N total / n subgroup); OR = odds ratio; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk; SBP = systolic blood pressure.

[a] We used observed control group event rates standardized to 5 years. As poorly controlled blood pressure itself contributes to cardiovascular risk, we used data from the 2 most contemporary trials for each set of analyses. We used the HYVET study (22) to estimate event rates in the higher baseline blood pressure analyses, and data from SPRINT (the older age subgroup since the mean age was comparable to that in HYVET) for the treat to target analyses (50).

[b] The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:

- High = Further research is very unlikely to change our confidence on the estimate of effect.
- Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient = Any estimate of effect is very uncertain.

[c] The analyses presented here are of trials with baseline SBP ³ 160 mmHg. The achieved SBP in 3 of the trials was < 140 mmHg, but these studies contributed relatively few events. Achieved SBP in all the other studies was ³ 140 mmHg.

[d] Most of the evidence comes from trials in which baseline SBP ≥160 mmHg and achieved SBP was 140-150 mmHg. These are large trials providing consistent evidence, and a precise summary estimate.

[e] All trials that tested strict versus less strict blood pressure targets in which the target blood pressure in the intervention group was SBP < 140 mmHg or DBP < 85 mmHg, or even lower.

[f] The number of prevented events is not applicable because the upper bound of the confidence interval for relative risk was ³ 1.00.

We found no data about the role of comorbidity burden in the relationship between blood pressure targets and the identified outcomes of interest, or between burden of comorbidity and potential harm of differing blood pressure targets. The importance of multimorbidity and the disease-disease and disease-treatment interaction which occurs when multiple chronic conditions co-exist is of critical importance to older adults. Co-existence of multiple comorbidities may lead to burdensome therapy regimens and adverse therapy interactions based on combinations of clinical practice guidelines built around a single focus of disease.[62-64] Further, particularly among Veterans, hypertension is the most common comorbidity occurring in over 80% of adults over age 80, and the number of comorbidities for adults is known to increase with advancing age.[9,65] The importance of multimorbidity in older adults makes the relationship between hypertension, common comorbidities, and patient-important outcomes an invaluable target for future research. As noted above, exclusion criteria specified by these trials often decreased the relative comorbidity burden in study populations. In particular, patients with renal disease, heart failure, and cancer or comorbid illness likely to limit life expectancy were frequently excluded.

Importantly, the generalizability of our findings to the oldest age groups is limited. Fewer than half of these studies included adults over age 80. The primary exception is HYVET, which included only adults over age 80 and described a decreased risk of stroke with moderate blood pressure reduction (< 150/90 mm Hg).[6] The HYVET trial was like most of the other trials in implicitly or explicitly excluding patients with dementia or in long-term care, thus limiting the population to relatively high functioning older adults. Given the absence of data on comorbidity burden, the applicability of these data to the most elderly patients is questionable, particularly in adults over age 80 with significant frailty or poor functional status. This limitation may have heightened importance when relevance of these data are considered for the aging Veteran population, which experiences a significant burden of comorbidity and frailty.[9]

A number of recent reviews have also attempted to address the question of optimal blood pressure targets in older adults. Dr. Neal and colleagues with BPLTTC recently presented a patient-level meta-analysis of adults with mild hypertension (baseline SBP 140 to 159 mm Hg).[66] This review was not limited to older adults, however, and the majority of included patients in the individual-level analysis also had diabetes. A recent meta-analysis found that a drop in SBP of 10 mm Hg was associated with reduced mortality, cardiac events, and stroke in patients with diabetes.[67] This study also found that most of the benefit was limited to studies in which the baseline blood pressure was ≥ 140 mm Hg. However, the studies included in this meta-analysis were clinically very heterogeneous and included studies of younger patients, trials of normotensive patients with conditions such as heart failure, and comparative effectiveness studies. The most recently published systematic review concluded that more intensive blood pressure treatment was associated with improvements in stroke and cardiovascular outcomes, but not mortality.[68] However, this review did not focus on older patients, did not include SPRINT, and also did not include several other large trials included in our review.

Our review contributes further to the literature on hypertension management in older adults by specifically limiting study inclusion to populations with mean age over 60 and hypertension, and by focusing on studies that used a treat-to-target strategy for blood pressure goals most commensurate with the controversy of strict versus moderate blood pressure control in older patients. By focusing on treat-to-target studies in addition to studies comparing more versus less intensive therapy we hoped to mitigate potential drug-specific effects which could affect outcomes (*eg*, more versus less renin angiotensin system blockade) as well as potentially larger

and more definitive differences in achieved blood pressures between treatment arms. For similar reasons, we did not include comparative effectiveness studies which might speak more to optimal medication choice in a particular population as opposed to the true benefits or harms of a given level of blood pressure. Finally, our review adds to the existing knowledge base by including a broad examination of potential longer-term harms of blood pressure treatment.

LIMITATIONS

This review has several potential limitations. We could not determine if any specific medication, medication class, or combination of medications may have played a role in influencing clinical outcomes. The wide variety of medications used across studies and the absence of any pattern between medication types and relative risk provides some reassurance that medication-specific effects are likely minimal. Moreover, we focused on pharmacologic therapy and, therefore, may have missed important effects of nonpharmacological therapy of hypertension.

The populations and study design varied considerably across included trials. We incorporated a number of sensitivity analyses to better understand how different trial characteristics contributed to results. While the relative treatment effects remained fairly consistent across different analyses, the variation in numbers needed to treat were probably clinically important. We therefore strived to remain transparent about the analyses which contributed to the chosen summary estimates, and present a range of numbers needed to treat for outcomes in which there were significant findings.

We report study-level data here, but recognize there may be individuals within a study population who benefit more or less from treatment. We found fairly consistent results across many subgroup analyses. We also are in the process of conducting analyses from 6 trials to see if the results reported here remain consistent in patient-level analyses. We focused on comorbidity burden rather than specific comorbidities such as diabetes, but it is possible that results might be different among certain condition-specific subgroups.

FUTURE RESEARCH

There is a need for more research examining how the severity of comorbidity and the presence of multiple comorbidities modifies the effects of more intensive blood pressure treatment. Though there have been more recent trials which have included patients over age 80, there is a need for more research in this age group. Moreover, future studies should enroll patients who have not yet been represented in the evidence, including those with cognitive impairment and other causes of frailty. Finally, future reviews using individual patient-level data on medication use could clarify whether or not the findings in this report apply equally across antihypertensive drug class.

CONCLUSIONS

Lowering blood pressure in adults over age 60 reduces mortality, stroke, and cardiac events. The most consistent and largest effects are seen in studies of patients with higher baseline blood pressures (SBP ≥ 160 mmHg) achieving moderate blood pressure control (< 150/90 mmHg). Lower treatment targets (< 140/85 mmHg) are likely to be beneficial for some patients at high cardiovascular risk, but the results across trials are less consistent. Lower treatment targets are largely supported by findings from one trial which targeted SBP <120 mmHg and in which most intervention patients achieved SBP < 130 mmHg. In patients with cerebrovascular disease, more

aggressive blood pressure lowering (SBP <140 mmHg) likely reduces recurrent stroke. Lower treatment targets are associated with higher medication burden and an increased risk of short-term harms such as hypotension. On the other hand, evidence that there is not an increased risk in cognitive impairment, falls, and reduced quality of life may provide some flexibility for providers in crafting an individualized antihypertensive treatment plan. There is little data to assess the risks and benefits of antihypertensive treatment among institutionalized elder patients or those with multiple comorbidities.

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APPENDIX A. SEARCH STRATEGIES

Databases Searched:

- Ovid Medline
- PubMed [Publisher status segment]
- Embase
- Cochrane Library (Ovid EBM Reviews): Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Health Technology Assessment; NHS Economic Evaluation Database

Grey Literature Sources:

- ClinicalTrials.gov
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)
- International Standard Randomised Controlled Trials Number registry (ISRCTN)
- Conference Papers Index

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to January Week 4 2015
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 29, 2015
Date of search: January 30, 2015

1	Hypertension/	193547
2	hypertension, malignant/	2172
3	hypertension, renal/	12991
4	hypertension, renovascular/	6296
5	(hypertensive or hypertension or ((high or elevated or raised) adj2 blood pressure)).ti,ab.	333658
6	blood pressure/	238359
7	systole/	16952
8	diastole/	14899
9	(blood pressure* or arterial pressure* or systole* or (systol* and (pressure* or mm Hg or mm Hg)) or diastole* or (diastol* and (pressure* or mm Hg or mm Hg)) or BP or DBP or (SBP not spontaneous bacterial peritonitis)).ti,ab.	401649
10	or/1-9	757490
11	antihypertensive agents/ or acebutolol/ or alprenolol/ or amlodipine/ or atenolol/ or bendroflumethiazide/ or bepridil/ or betaxolol/ or bethanidine/ or bisoprolol/ or bupranolol/ or captopril/ or carteolol/ or celiprolol/ or chlorisondamine/ or chlorothiazide/ or chlorthalidone/ or cilazapril/ or clonidine/ or cyclopenthiazide/ or diazoxide/ or dihydralazine/ or diltiazem/ or doxazosin/ or enalapril/ or enalaprilat/ or felodipine/ or fosinopril/ or guanabenz/ or guanfacine/ or hydralazine/ or hydrochlorothiazide/ or hydroflumethiazide/ or indapamide/ or indoramin/ or isradipine/ or labetalol/ or lisinopril/ or losartan/ or methyldopa/ or metipranolol/ or metolazone/ or metoprolol/ or mibefradil/ or minoxidil/ or nadolol/ or nicardipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or oxprenolol/ or pempidine/ or penbutolol/ or perindopril/ or pinacidil/ or pindolol/ or polythiazide/ or prazosin/ or propranolol/ or ramipril/ or reserpine/ or timolol/ or todralazine/ or trichlormethiazide/ or xipamide/ or (antihypertensive or anti-hypertensive).ti,ab.	191932

12	adrenergic alpha-antagonists/ or adrenergic alpha-1 receptor antagonists/ or doxazosin/ or indoramin/ or labetalol/ or prazosin/ or adrenergic alpha-2 receptor antagonists/ or adrenergic beta-antagonists/ or alprenolol/ or bunolol/ or bupranolol/ or carteolol/ or dihydroalprenolol/ or iodocyanopindolol/ or levobunolol/ or metipranolol/ or nadolol/ or oxprenolol/ or penbutolol/ or pindolol/ or propranolol/ or sotalol/ or timolol/ or adrenergic beta-1 receptor antagonists/ or acebutolol/ or atenolol/ or betaxolol/ or bisoprolol/ or celiprolol/ or metoprolol/ or practolol/ or adrenergic beta-2 receptor antagonists/ or adrenergic beta-3 receptor antagonists/ or (adrenergic alpha-antagonist* or adrenergic alphaantagonist*).ti,ab.	93013
13	angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ or angiotensin-converting enzyme inhibitor*.ti,ab.	43990
14	angiotensin receptor antagonists/ or angiotensin ii type 1 receptor blockers/ or losartan/ or saralasin/ or angiotensin ii type 2 receptor blockers/ or angiotensin receptor antagonist*.ti,ab.	17586
15	calcium channel blockers/ or amlodipine/ or amrinone/ or bencyclane/ or bepridil/ or cinnarizine/ or diltiazem/ or felodipine/ or fendiline/ or flunarizine/ or gallopamil/ or isradipine/ or lidoflazine/ or mibefradil/ or nicardipine/ or nifedipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or tiapamil hydrochloride/ or verapamil/ or calcium channel blocker*.ti,ab.	70143
16	diuretics/ or acetazolamide/ or amiloride/ or bendroflumethiazide/ or bumetanide/ or chlorothiazide/ or chlorthalidone/ or clopamide/ or cyclopenthiazide/ or ethacrynic acid/ or ethoxzolamide/ or furosemide/ or hydrochlorothiazide/ or hydroflumethiazide/ or indapamide/ or mefruside/ or methazolamide/ or methyclothiazide/ or metolazone/ or muzolimine/ or polythiazide/ or spironolactone/ or ticrynafen/ or triamterene/ or trichlormethiazide/ or xipamide/ or diuretics, osmotic/ or isosorbide/ or diuretics, potassium sparing/ or epithelial sodium channel blockers/ or mineralocorticoid receptor antagonists/ or sodium chloride symporter inhibitors/ or sodium potassium chloride symporter inhibitors/ or diuretic*.ti,ab.	77139
17	vasodilator agents/ or acetylcholine/ or adenosine/ or "adenosine-5'-(n-ethylcarboxamide)"/ or alprostadil/ or amiodarone/ or amrinone/ or amyl nitrite/ or bencyclane/ or bepridil/ or betahistine/ or bradykinin/ or calcitonin gene-related peptide/ or celiprolol/ or chromonar/ or colforsin/ or cromakalim/ or cyclandelate/ or diazoxide/ or dihydroergocristine/ or dihydroergocryptine/ or dilazep/ or diltiazem/ or dipyridamole/ or dyphylline/ or enoximone/ or ergoloid mesylates/ or erythritol/ or erythrityl tetranitrate/ or flunarizine/ or hexobendine/ or iloprost/ or isosorbide dinitrate/ or isoxsuprine/ or isradipine/ or khellin/ or lidoflazine/ or mibefradil/ or milrinone/ or minoxidil/ or molsidomine/ or moxisylyte/ or nafronyl/ or niacin/ or nicardipine/ or nicergoline/ or nicorandil/ or nicotinyl alcohol/ or nifedipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or nitroglycerin/ or nitroprusside/ or nonachlazine/ or nylidrin/ or oxprenolol/ or oxyfedrine/ or papaverine/ or pentaerythritol tetranitrate/ or pentoxifylline/ or perhexiline/ or phenoxybenzamine/ or pinacidil/ or pindolol/ or pituitary adenylate cyclase-activating polypeptide/ or polymethyl methacrylate/ or prenylamine/ or s-nitroso-n-acetylpenicillamine/ or s-nitrosoglutathione/ or s-nitrosothiols/ or sodium azide/ or suloctidil/ or theobromine/ or theophylline/ or thiouracil/ or tolazoline/ or trapidil/ or trimetazidine/ or vasoactive intestinal peptide/ or verapamil/ or xanthinol niacinate/ or endothelium-dependent relaxing factors/ or nitric oxide/ or vasodilator*.ti,ab.	350538
18	Aldosterone/	21964
19	Chlorisondamine/	543
20	Mineralocorticoids/ or Desoxycorticosterone/ or Desoxycorticosterone Acetate/	8175
21	Pempidine/	163
22	Renin-Angiotensin System/	14256
23	or/11-22	632178
24	exp Cardiovascular Diseases/	1901992
25	exp Heart Failure/	88568
26	exp Kidney Diseases/ or exp Kidney Failure, Chronic/	415035
27	hypotension/	17869

28	stroke/ or brain infarction/ or brain stem infarctions/ or lateral medullary syndrome/ or cerebral infarction/ or dementia, multi-infarct/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or stroke, lacunar/	88131
29	polypharmacy/	2517
30	exp cognition disorders/	63655
31	exp dementia/	121166
32	accidental falls/	15941
33	exp fractures, bone/	142161
34	"quality of life"/	121510
35	(death* or mortalit* or morbidit* or comorbidit* or co-morbidit* or multimorbidit* or multi-morbidit* or coexist* or co-exist* or stroke* or infarct* or multiinfarct* or multi-infarct* or transient ischemic attack* or TIA or cerebrovascular or (heart adj (disease* or failure*)) or ((renal or nephro* or kidney) adj2 (disease* or failure* or disorder* or injury or injuries)) or AKI or fracture* or falls or cognit* or dementia* or hypotension or hypotensive or polypharm* or "quality of life").ti,ab.	2265610
36	or/24-35	3913057
37	and/10,23,36	120955
38	limit 37 to "all aged (65 and over)"	30492
39	(elder* or aged or old or older or oldest or senior* or geriatric* or gerontolog* or sexagenarian* or septuagenarian* or octogenarian* or nonagenarian*).ti,ab.	1436775
40	37 and 39	15236
41	38 or 40	38096
42	cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or ((cohort* or trial*) adj3 extension*).ti,ab.	1387757
43	and/41-42	7501
44	limit 43 to (comment or editorial or letter)	77
45	43 not 44	7424
46	limit 45 to english language [OBSERVATIONAL STUDY RESULTS]	6655
47	limit 41 to (meta analysis or systematic reviews)	643
48	47 not 46	541
49	limit 48 to english language [META-ANALYSIS AND SYSTEMATIC REVIEW RESULTS]	474
50	and/10,23	162820
51	(201212* or 2013* or 2014* or 2015*).ed. or (201212* or 2013* or 2014* or 2015*).dc.	2570599
52	and/50-51	10390
53	limit 52 to (clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)	1037
54	limit 53 to english language	988
55	remove duplicates from 54 [RCT/CCT RESULTS]	956

EMBASE (Elsevier)
http://embase.com
Date of search: January 30, 2015

Search Strategy		Results
44	#41 OR #42 OR #43	2,594
43	#39 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [english]/lim NOT [medline]/lim	1,138
42	#39 AND [english]/lim AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) NOT [medline]/lim	186
41	#40 AND [english]/lim NOT ([editorial]/lim OR [letter]//lim OR [medline]/lim)	1,475
40	#39 AND ('cohort analysis'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'longitudinal study'/de OR 'follow-up study':ab,ti OR 'follow-up studies':ab,ti OR ((cohort* OR trial*) NEAR/3 extension*):ab,ti)	6,637
39	#37 OR #38	65,498
38	#7 AND #22 AND #35 AND (elder*:ab,ti OR aged:ab,ti OR old:ab,ti OR older:ab,ti OR oldest:ab,ti OR senior*:ab,ti OR geriatric*:ab,ti OR gerontolog*:ab,ti OR sexagenarian*:ab,ti OR septuagenarian*:ab,ti OR octogenarian*:ab,ti OR nonagenarian*:ab,ti)	37,068
37	#7 AND #22 AND #35 AND ([aged]/lim OR [very elderly]/lim)	42,220
36	#7 AND #22 AND #35	251,536
35	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #33 OR #34	5,706,843
34	death*:ab,ti OR mortalit*:ab,ti OR morbidit*:ab,ti OR comorbidit*:ab,ti OR 'co-morbidity':ab,ti OR 'co-morbidities':ab,ti OR multimorbidit*:ab,ti OR 'multi-morbidity':ab,ti OR 'multi-morbidities':ab,ti OR coexist*:ab,ti OR 'co-existing':ab,ti OR stroke*:ab,ti OR infarct*:ab,ti OR multiinfarct*:ab,ti OR 'multi-infarction':ab,ti OR 'multi-infarctions':ab,ti OR 'transient ischemic attack':ab,ti OR 'transient ischemic attacks':ab,ti OR tia:ab,ti OR cerebrovascular:ab,ti OR (heart NEXT/1 (disease* OR failure*)):ab,ti OR ((renal OR nephro* OR kidney) NEAR/2 (disease* OR failure* OR disorder* OR injury OR injuries)):ab,ti OR aki:ab,ti OR fracture*:ab,ti OR falls:ab,ti OR cognit*:ab,ti OR dementia*:ab,ti OR hypotension:ab,ti OR hypotensive:ab,ti OR polypharm*:ab,ti OR 'quality of life':ab,ti	2,969,107
33	'quality of life'/de	268,408
32	'fracture'/exp	215,542
31	'falling'/de	25,824
30	'dementia'/exp	238,471
29	'disorders of higher cerebral function'/exp	553,733
28	'polypharmacy'/de	7,732
27	'cerebrovascular disease'/exp	480,125
26	'hypotension'/exp	106,487
25	'kidney disease'/exp	707,514
24	'heart failure'/exp	322,750
23	'cardiovascular disease'/exp	3,134,649
22	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1,125,178
21	'renin angiotensin aldosterone system'/de	31,112
20	'pempidine'/de	283
19	'deoxycorticosterone acetate'/de	2,712
18	'deoxycorticosterone'/de	7,177
17	'mineralocorticoid'/exp	71,060
16	'chlorisondamine'/de	1,025
15	'aldosterone'/de	31,797
14	'vasodilator agent'/exp OR vasodilator*:ab,ti	430,197
13	'diuretic agent'/exp OR diuretic*:ab,ti	310,799
12	'calcium channel blocking agent'/exp OR 'calcium channel blocker':ab,ti OR 'calcium channel blockers':ab,ti	187,980
11	'angiotensin 2 receptor antagonist'/exp OR 'angiotensin ii receptor antagonist':ab,ti OR 'angiotensin ii receptor antagonists':ab,ti	8,252
10	'angiotensin receptor antagonist'/exp OR 'angiotensin receptor antagonist':ab,ti OR 'angiotensin receptor antagonists':ab,ti	63,456
9	'adrenergic receptor blocking agent'/exp OR 'adrenergic alpha-antagonist':ab,ti OR 'adrenergic alpha-antagonists':ab,ti OR 'adrenergic alphaantagonist':ab,ti	342,302

8	'antihypertensive agent'/exp OR antihypertensive:ab,ti OR 'anti hypertensive':ab,ti	593,629
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	1,115,118
6	'blood pressure':ab,ti OR 'arterial pressure':ab,ti OR systole*:ab,ti OR (systol*:ab,ti AND (pressure*:ab,ti OR mm Hg:ab,ti OR 'mm hg':ab,ti)) OR diastole*:ab,ti OR (diastol*:ab,ti AND (pressure*:ab,ti OR mm Hg:ab,ti OR 'mm hg':ab,ti)) OR bp:ab,ti OR dbp:ab,ti OR (sbp:ab,ti NOT 'spontaneous bacterial peritonitis':ab,ti)	505,982
5	'diastole'/de	14,230
4	'systole'/de	13,554
3	'blood pressure'/exp	415,778
2	hypertensive:ab,ti OR hypertension:ab,ti OR (((high OR elevated OR raised) NEAR/2 blood):ab,ti AND pressure:ab,ti)	458,732
1	'hypertension'/exp	513,148

Cochrane Library (Ovid EBM Reviews)

- **Cochrane Central Register of Controlled Trials** December 2014
- **Cochrane Database of Systematic Reviews** 2005 to December 2014
- **Database of Abstracts of Reviews of Effects** 4th Quarter 2014
- **Health Technology Assessment** 4th Quarter 2014
- **NHS Economic Evaluation Database** 4th Quarter 2014

Date of search: January 30, 2015

1	(hypertensive or hypertension or ((high or elevated or raised) adj2 blood pressure)).ti,ab.	29303
2	(blood pressure* or arterial pressure* or systole* or (systol* and (pressure* or mm Hg or mm Hg)) or diastole* or (diastol* and (pressure* or mm Hg or mm Hg)) or BP or DBP or (SBP not spontaneous bacterial peritonitis)).ti,ab.	44700
3	and/1-2	16149
4	(antihypertensive or anti-hypertensive).ti,ab.	8074
5	(adrenergic alpha-antagonist* or adrenergic alphaantagonist*).ti,ab.	0
6	angiotensin-converting enzyme inhibitor*.ti,ab.	2444
7	angiotensin receptor antagonist*.ti,ab.	74
8	calcium channel blocker*.ti,ab.	1575
9	diuretic*.ti,ab.	4287
10	vasodilator*.ti,ab.	2596
11	or/4-10	16071
12	(death* or mortalit* or morbidit* or comorbidit* or co-morbidit* or multimorbidit* or multi-morbidit* or coexist* or co-exist* or stroke* or infarct* or multiinfarct* or multi-infarct* or transient ischemic attack* or TIA or cerebrovascular or (heart adj (disease* or failure*)) or ((renal or nephro* or kidney) adj2 (disease* or failure* or disorder* or injury or injuries)) or AKI or fracture* or falls or cognit* or dementia* or hypotension or hypotensive or polypharm* or "quality of life").ti,ab.	155570
13	(elder* or aged or old or older or oldest or senior* or geriatric* or gerontolog* or sexagenarian* or septuagenarian* or octogenarian* or nonagenarian*).ti,ab.	70846
14	and/3,11-13	536
15	limit 14 to medline records [Limit not valid in CDSR,DARE,CLHTA,CLEED; records were retained]	407
16	14 not 15	129
17	limit 16 to english language [Limit not valid in CDSR,DARE; records were retained]	84

APPENDIX B. STUDY SELECTION

Table 9. Inclusion Codes, Code Definitions, and Criteria Corresponding to the Key Questions

Code	Definition	KQ1.What are the health outcome effects of differing blood pressure targets?	KQ2. How does age modify the benefits of differing blood pressure targets?	KQ3a. How does the patient burden of comorbidities modify the benefits of differing blood pressure targets? KQ3b. In patients who have suffered a TIA/stroke, does treatment of blood pressure to specific targets affect outcomes?	KQ4. Do the harms of targeting lower blood pressure vary with age?	KQ5. Do the harms of targeting lower blood pressure vary with patient burden of comorbidities?
I – Trial	Trials with ≥ 6 months of follow-up that address any of KQs 1-5.	Population: Adults aged ≥60 with hypertension Intervention: Pharmacologic treatment of hypertension Comparator: Usual care, or another specified SBP target. Primary outcomes: · All-cause mortality · Mortality related to stroke, CHD, CHF, and renal disease · Morbidity including stroke, CHD, CHF, and renal disease Timing: Published 2012 or later. Incidence of outcomes ≥ 6 months of hypertension treatment. Study design: Controlled trials (randomized or non-randomized) with ≥ 6 months of follow-up.			PICTS as for KQs 1-3, but with harms outcomes: · Changes in cognition · Falls · Changes to quality of life · Hypotension · Acute kidney injury *Code B: large (n>10k) cohort studies that only report* · *All-cause mortality* · *Cardiovascular outcomes*	
I – Cohort	Cohort studies are included for KQs 4-5 only if they report harms. · Large (N>10,000) multi-center cohort studies. · Cohort extensions of major trials.	Data on the primary outcomes listed above will not be abstracted from cohort studies.			· Controlled study designs (RCT and non-randomized controlled clinical trials used for KQs 1-3) · Cohort extensions of trials that examined specific blood pressure targets · Cohort studies that examined the effects of lower blood pressure in the context of antihypertensive medication · Cohort studies that reported the effects of lower blood pressure despite that hypertension management was not the primary objective of the intervention studied.	
I – Stroke	Trials of any duration that address KQ3a.	*Population KQ3b:* Aged ≥60 with hypertension and recent cerebrovascular accident (≤ 6 months). *Intervention KQ3b:* Pharmacologic treatment of hypertension within the first 6 months post-stroke. *Additional outcomes of interest for KQ3b:* Recurrent cerebrovascular accident; Functional status; Disability				
I – SR	Systematic review or meta-analysis on any of the KQs					

Table 10. Exclusion Codes, Code Definitions, and Criteria Corresponding to the Key Questions

Code	Definition	**KQ1.**What are the health outcome effects of differing blood pressure targets?	**KQ2**. How does age modify the benefits of differing blood pressure targets?	**KQ3a**. How does the patient burden of comorbidities modify the benefits of differing blood pressure targets? **KQ3b**. In patients who have suffered a TIA or stroke, does treatment of blood pressure to specific targets affect outcomes?	**KQ4.** Do the harms of targeting lower blood pressure vary with age?	**KQ5.** Do the harms of targeting lower blood pressure vary with patient burden of comorbidities?
X1	Non-English publication	Note: most foreign language studies will be filtered out during initial library cleaning.				
X2	Article does not pertain in any way to hypertension -Rx treatment in older adults					
X3	Study population is not in scope for any of the KQs	Include: Adults with hypertension aged ≥ 60 or mean age ≥60. For KQ3: existing comorbidity or recent cerebrovascular accident (≤ 6 months). Exclude: Studies with mean age < 60.				
X4	No primary data, or study design not in scope	Exclude: · Controlled before/after studies · Case reports/case series · RCTs with less than 6 month follow-up				
X5	Intervention modality or study objectives are not in scope	Exclude: · Trials for which hypertension management was not the primary objective, despite that secondary effects on hypertension may be reported, *eg*, TNT for the j-curve effect. · Non-pharmacologic interventions for blood pressure control · Blood pressure interventions during the acute phase post-stroke (KQ3a).			Note: For KQs 4- 5, cohort studies that report harms of lower blood pressure may be included even if hypertension management was not the primary objective of the intervention studied.	
X6	None of the reported outcomes are in scope	Primary outcomes of interest: · All-cause mortality · Mortality related to stroke, CHD, CHF, and renal disease · Morbidity including stroke, CHD, CHF, and renal disease			Harms of interest: · Changes in cognition · Falls · Changes to quality of life · Polypharmacy	
X7	Other reason, specify					
B	Background	Add ‘B’ any of the above X codes (*eg*, ‘X6–B’) if the article contains information that may be useful for the introduction, discussion, limitations, future research, or other contextual purposes. Add comments or keywords as needed.				

B = background; KQ = key question; CHD = congenital heart disease; CHF = congestive heart failure; RCT = randomized controlled trials; TIA = transient ischemic attack; TNT = treat to new targets

APPENDIX C. QUALITY ASSESSMENT

Table 11. Assessment of Randomized Controlled Trials for Potential Risk of Bias

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
ACCORD[22]	Yes: central, computer-based randomization	Yes	Yes: non-blinded study, but they used dual, blinded outcome adjudicators	Missing data assumed to be random, sensitivity analysis performed and outcome measures not significantly changed	Yes	Yes	Low	National Heart, Lung, Blood Institute; NIH agencies
ADVANCE[27]	Yes: central, computer-based, randomization	Yes	Yes: participants, providers, outcome assessors all blinded	Yes: extremely low loss-to follow-up, 15 patients in a sample of >11,000	Yes	Yes	Low	Servier; National Health and Medical Research Council of Australia
BENEDICT-B[28]	Yes: central, computer-based randomization	Yes	Yes: participants, providers, outcome assessors all blinded	Yes: all censored events included in analysis, power and statistical significance were adequate	Yes	Yes	Low	Mario Negri Institute for Pharmacologic Research/Institute for Rare Diseases
Cardio-Sis[23]	Yes: central, computer-based randomization	Yes	Yes: open-label study, but outcome adjudicators were blinded	Yes: only one patient lost to follow-up	Yes: Primary outcome was left ventricular hypertrophy, but cardiovascular and mortality endpoints were prespecified secondary outcomes	Yes	Low	Heart Care Foundation; Boehringer-Ingelheim, Sanofi-Aventis; Pfizer

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
EWPHE[29]	Probably: patients were randomized and allocated by a central coordinating center, but exact method of randomization was not reported	Yes: central allocation	Yes: providers, patients, and outcome assessors all blinded	Yes: similar loss to follow-up in both groups (14 vs 16%), ITT analysis for mortality outcome	Yes, though ITT analysis was only performed for mortality outcome	Yes	Low	Belgian National Research Foundation; Merck, Sharp and Dohme and Smith; Kline and French
FEVER[30]	Yes: central, computer-based randomization	Yes	Yes	Yes: life-status could not be obtained at study end but number was low (0.3%)	Yes	Yes	Low	National Science and Technology Ministry; Beijing Hypertension League Institute and Shanxi Kangbao Pharmaceutical Company
HOT[17]	Yes: central, computer-based randomization	Yes	Yes: open-label but outcome adjudicators were blinded	Yes: 2.6% of patients lost to follow-up; total of 1.8% of all patient-years analyzed contained in censored group; analysis conducted up to time of loss and BP or prior morbidity not found to be significantly different	Yes	Yes	Low	Astra AB, Sweden; Astra Merck Inc, USA; TEVA, Israel; Hoechst, Argentina

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
HYVET[6]	Yes: central, computer-based randomization	Yes	Yes: providers, patients, outcome assessors blinded	Yes: very low loss to follow-up (0.3% overall); ITT analysis	Yes	Yes: though of note inclusion criteria changed over time	Low	British Heart Foundation; Institut de Recherches Internationales Servier
JATOS[24]	Yes: central, computer-based randomization	Yes	Yes: outcome assessors blinded; providers and patients likely not blinded but not clearly reported	Yes: censored events reported but no sensitivity analysis performed; ITT analysis	Yes	Unclear: there was not enough precision in protocol information describing outcome definitions	Low	Shionogi and Co. LTD
PRO-GRESS[31]	Yes: central computer-based randomization	Yes	Yes: providers, patients, and outcome assessors blinded	Yes: very low loss to follow-up, though it is unclear whether this refers to vital status outcome or patients attending follow-up visits; ITT analysis	Yes	Yes	Low	Servier; Health Research Council of New Zealand; National Health and Medical Research Council of Australia
RENAAL[32]	Yes: central, computer-based randomization	Yes	Yes: providers, patients, outcome assessors blinded	Yes: very low loss to follow-up; ITT analysis	Yes	Unclear - study was stopped early because of new data that ACE inhibitors were beneficial for population similar to that under study (considered unethical to continue)	Low	Merck

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
SCOPE[33]	Yes: central randomization by fax	Yes	Yes: placebo control	Yes: losses to follow-up accounted for, multiple outcomes reported, ITT analysis	Yes	Yes: dual independent qualitative assessment reviews; sufficiently powered; prospective	Low	AstraZeneca
SHEP[8]	Yes: central randomization and allocation	Yes	Yes: providers, patients, outcome assessors blinded	Yes: only 5 patients in each group were unavailable for follow-up; ITT analysis	Yes	Yes	Low	National Heart, Lung, Blood Institute; National Institute on Aging
SPRINT[11]	Yes: central computer-based randomization	Yes	Yes: open-label, but outcomes were centrally adjudicated by blinded assessors	Yes: losses to follow-up accounted for, multiple outcomes reported, ITT analysis	Yes	Unclear: trial was stopped early by DSMB for benefit	Low	National Institutes of Health
SPS3[25]	Yes: central, computer-based randomization	Yes	Yes: open-label, but outcome assessors blinded	Yes: though details on those lost to follow-up not available, overall rate low (3%); ITT analysis	Yes	Yes	Low	NIH-NINDS
STONE[19]	No: patients were allocated alternately by entry order number	No	Yes: placebo control, but patients in placebo whose DBP >110 after the run-in period were switched by their physicians to active treatment	Yes: 2% loss to follow-up; ITT analysis	Yes: outcomes appear to be fully reported, but with methodological flaws earlier in study protocol	Yes: none others detected; randomization issues are serious	High	Ministry of Health of People's Republic of China; Bayer Canada

Study	Allocation sequence adequately generated?	Allocation adequately concealed?	Knowledge of the allocated intervention adequately prevented during the study?	Incomplete outcome data adequately addressed?	Free of suggestion of selective outcome reporting?	Free of other problems that could put it at a high risk of bias?	Summary assessment High/Low/ Unclear Risk of Bias	Funder
Syst-China[20]	No: eligible patients at each center were alternatingly assigned to type A or type B medication	No	Yes: placebo control	Yes: ITT analysis; patients who withdrew remained in open follow-up; patients without any report within the year before the trial ended classified as lost to follow-up, but included in analysis up to the most recent evaluation of health status	Yes	Yes: randomization and allocation flaws have unclear effect on effectiveness estimates; methodological flaws significant	High	State Planning Commission of the People's Republic of China
Syst-Eur[34]	Yes: central randomization and allocation	Yes	Yes: patients, providers, outcome assessors blinded	No: losses to follow-up and adverse events incompletely discussed, no illustrating figures	Yes	Yes	Low	Bayer; National Fund for Scientific Research
TRANS-CEND[35]	Yes: central, computer-based randomization	Yes	Yes: patients, providers, outcome assessors blinded	Yes: 99.7% had vital status ascertained; primary analysis included all patients, used time-to-event approach, counting the first occurrence of any component of the composite outcome	Yes	Yes	Low	Boehringer Ingelheim
VALISH[26]	Yes: Centralized computer randomization	Yes	No: open label	Yes: 181 (5.5%) patients lost to follow-up; censored patients analyzed up to censoring event; ITT analysis	Yes	Yes	Low	Japan Cardiovascular Research Foundation

Study	**Allocation sequence adequately generated?**	**Allocation adequately concealed?**	**Knowledge of the allocated intervention adequately prevented during the study?**	**Incomplete outcome data adequately addressed?**	**Free of suggestion of selective outcome reporting?**	**Free of other problems that could put it at a high risk of bias?**	**Summary assessment** High/Low/ Unclear Risk of Bias	**Funder**
Wei, 2013[21]	Yes: random numbers table computer-generated	Unclear whether allocation itself was concealed	No: open label and not enough detail about outcome adjudication procedure	No: concerning that those lost-to-follow-up are not mentioned in analysis; ITT analysis	Yes	No: small sample size, generalizability; no limitations section; inadequate description of how they obtained outcome information such as mortality or how they assessed cardiac events	High	Not disclosed

APPENDIX D. DATA SUPPLEMENT

Table 12. Detailed Results of Trials that Conducted Age-stratified Analyses

Study Comparison, T vs C	Age groups (N patients)	Results comparing T vs C, by outcome and age group
Studies that compared BP targets (mm Hg)		
ACCORD[37] SBP < 120 vs < 140	< 65 ≥ 65 (Total N = 4733; n per age group not reported)	Unadjusted HR for combined nonfatal MI, nonfatal stroke, and cardiovascular death (95% CIs not reported, but were not statistically significant, interpreted from graph): < 65: 0.90 ≥ 65: 0.91 Age interaction P-value = .98
HOT[38] DBP ≤ 80 vs ≤ 85 vs ≤ 90	< 65 (n = 12803) ≥ 65 (n = 5987)	Events/1000 patient-years by DBP group ≤ 80 vs ≤ 85 vs ≤ 90 mm Hg (P-value for trend; HR calculated from event rates, 95% CI not reported): Total mortality: < 65: 5.7 vs 5.5 vs 4.5 (P = .13) HR ≤ 80 vs ≤ 85: 1.04 HR ≤ 80 vs ≤ 90: 1.27 ≥ 65: 15.4 vs 13.9 vs 15.7 (P =.89) HR ≤ 80 vs ≤ 85: 1.11 HR ≤ 80 vs ≤ 90: 0.98 Cardiovascular death: < 65: 2.2 vs 2.9 vs 1.9 (P = .52) HR ≤ 80 vs ≤ 85: 0.76 HR ≤ 80 vs ≤ 90: 1.16 ≥ 65: 8.0 vs 5.7 vs 7.6 (P = .81) HR ≤ 80 vs ≤ 85: 1.40 HR ≤ 80 vs ≤ 90: 1.05 MI: < 65: 2.3 vs 2.9 vs 3.2 (P = .13) HR ≤ 80 vs ≤ 85: 0.79 HR ≤ 80 vs ≤ 90: 0.72 ≥ 65: 3.2 vs 2.4 vs 4.4 (P = .22) HR ≤ 80 vs ≤ 85: 1.33 HR ≤ 80 vs ≤ 90: 0.73 Stroke: < 65: 2.4 vs 3.8 vs 2.3 (P = .77) HR ≤ 80 vs ≤ 85: 0.63 HR ≤ 80 vs ≤ 90: 1.04 ≥ 65: 6.7 vs 6.6 vs 7.8 (P = .41)

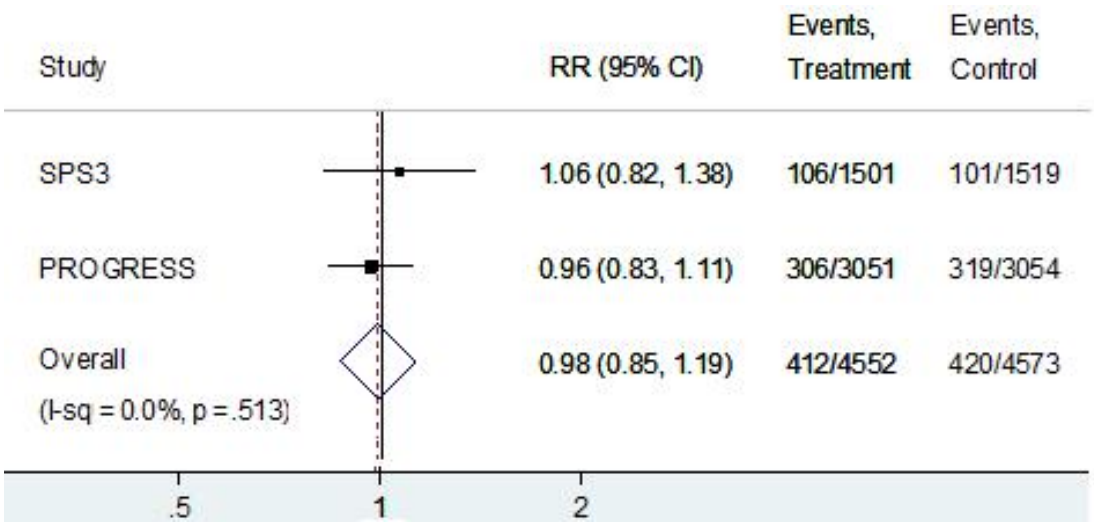
Study Comparison, T vs C	Age groups (N patients)	Results comparing T vs C, by outcome and age group
		HR ≤ 80 vs ≤ 85: 1.02 HR ≤ 80 vs ≤ 90: 0.86
JATOS[24] SBP < 140 vs < 160	< 75 (n = 2549) ≥ 75 (n = 1869)	RR (95% CI) P-value for interaction term in Cox regression with treatment, age, sex, and interaction between treatment and age as covariates: Cerebrovascular disease: < 75: 0.65 (0.29 to 1.45) ≥ 75: 1.52 (0.77 to 3.00) P = .03 Cardiovascular disease: < 75: 0.77 (0.26 to 2.25) ≥ 75: 1.07 (0.43 to 2.67) P = .50 Renal failure: < 75: 0.60 (0.09 to 3.91) ≥ 75: 1.25 (0.22 to 7.00) P = .75
SPS3[39] SBP < 130 vs 130-149	< 75 (n = 2526) ≥ 75 (n = 494)	HR (95% CI) Total mortality < 75: 1.13 (0.80 to 1.59) ≥ 75: 0.83 (0.53 to 1.29) Vascular death < 75: 1.17 (0.68 to 2.01) ≥ 75: 0.42 (0.18 to 0.98) MI: < 75: 0.91 (0.56 to 1.48) ≥ 75: 0.77 (0.23 to 2.52) Recurrent stroke: < 75: 0.77 (0.59 to 1.01) ≥ 75: 1.01 (0.59 to 1.73)
VALISH[26] SBP < 140 vs < 150	< 75 (n = 1233) ≥ 75 (n = 1846)	Combined sudden death; stroke; MI; death due to CHF; other cardiovascular death; unplanned hospitalization for cardiovascular disease; and renal dysfunction, HR (95% CI): < 75: 0.74 (0.35 to 1.56) ≥ 75: 0.95 (0.60 to 1.51)
Studies that compared more vs less intensive treatment for hypertension		
ADVANCE[27]	< 65 (n = 4536)	Major macrovascular or microvascular events combined, unadjusted RR (95% CI):

Study Comparison, T vs C	Age groups (N patients)	Results comparing T vs C, by outcome and age group
(Perindopril + indapamide) vs placebo	≥ 65 (n = 6604)	< 65: 0.95 (0.82 to 1.09) ≥ 65: 0.90 (0.81 to 1.00)
HYVET[36] Indapamide vs placebo	80-84 (n = 2807) ≥ 85 (n = 1038)	HR (95% CI): Total mortality: 80-84: 0.76 (0.60 to 0.97) ≥ 85: 0.88 (0.64 to 1.20) Cardiovascular mortality: 80-84: 0.75 (0.55 to 1.05) ≥ 85: 0.82 (0.53 to 1.32) Cardiac events: 80-84: 0.64 (0.49 to 0.83) ≥ 85: 0.75 (0.50 to 1.12) Stroke: 80-84: 0.70 (0.46 to 1.06) ≥ 85: 0.59 (0.27 to 1.29)
SHEP[8] Chlorthalidone vs placebo	60-69 (n = 1963) 70-79 (n = 2124) ≥ 80 (n = 649)	Stroke RR (95% CI): 60-69: 0.74 (0.48 to 1.14) 70-79: 0.65 (0.46 to 0.92) ≥ 80: 0.53 (0.32 to 0.88)
Syst-China[20] (Nitrendipine ± Captopril ± Hydrochlorothiazide) vs placebo	< 65 (n = 1079) 65-69 (n = 699) ≥ 70 (n = 616)	Unadjusted HR (P-values interpreted from graph): Cardiovascular mortality: < 65: 0.34 (P < .05) 65-69: 0.67 (P = ns) ≥ 70: 0.89 (P = ns) Fatal + nonfatal cardiovascular events: < 65: 0.54 (P < .05) 65-69: 0.80 (P = ns) ≥ 70: 0.62 (P = ns)
Syst-Eur[40,69] Nitrendipine vs placebo	60-69 (n = 2501) 70-79 (n = 1753) ≥ 80 (n = 441)	Unadjusted HR (95% CIs not reported; P-values interpreted from graph):[69] Total mortality: 60-69: 0.59 (P = *ns*) 70-79: 0.58 (P < .05) ≥ 80: 1.11 (P = ns) Cardiovascular death: 60-69: 0.58 (P = ns) 70-79: 0.49 (P < .05) ≥ 80: 0.97 (P = ns) Cardiac events:

Study Comparison, T vs C	Age groups (N patients)	Results comparing T vs C, by outcome and age group
		60-69: 0.64 (P = ns) 70-79: 0.69 (P = ns) ≥ 80: 0.79 (P = ns) Stroke: 60-69: 0.46 (P < .05) 70-79: 0.54 (P < .05) ≥ 80: 0.67 (P = ns) "In Cox regression with adjustment applied for significant covariates, the treatment-by-age interaction term was significant (P = .009) for total mortality and nearly significant (P = .09) for cardiovascular mortality, indicating that the benefit of treatment was lost after the age of about 75 years. In contrast, the treatment-by-age interaction for the combined fatal and nonfatal events was not statistically significant."[40]
TRANSCEND[35] Telmisartan vs placebo	< 65 (n = 2375) 65-74 (n = 2576) ≥ 75 (n = 975)	Composite outcome of cardiovascular death, myocardial infarction, or stroke: No significant age interaction (P = .80)

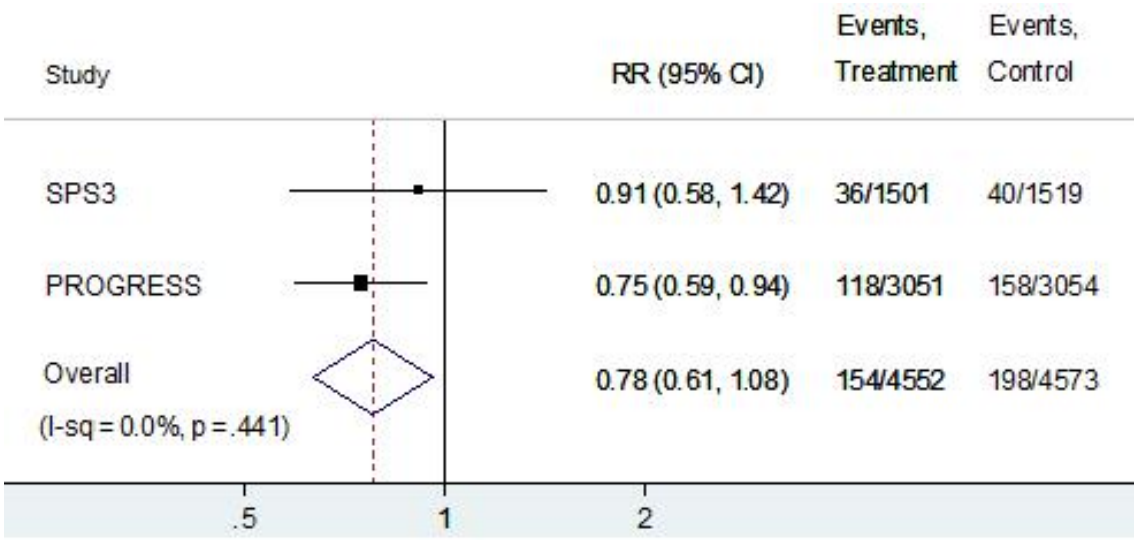
Abbreviations: ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; C = comparator/control; CHF = congestive heart failure; CI = Confidence interval; DBP = Diastolic blood pressure; HOT = Hypertension Optimal Treatment; HR = hazard ratio; HYVET = Hypertension in the Very Elderly Trial; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; MI = myocardial infarction; N = Number randomized; ns = not statistically significant; RR = relative risk; SBP = systolic blood pressure; SHEP = Systolic Hypertension in the Elderly Program; SPS3 = Secondary Prevention of Small Subcortical Strokes; Syst-China = Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe; T = treatment; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

Figure 8. Relative risk of mortality in trials of patients with history of stroke



CI = confidence interval; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SPS3 = Secondary Prevention of Small Subcortical Strokes

Figure 9. Relative risk of major cardiac events in trials of patients with history of stroke



CI = confidence interval; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SPS3 = Secondary Prevention of Small Subcortical Strokes

APPENDIX E. PEER REVIEWER COMMENTS AND AUTHOR RESPONSES

Question Text	Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	2-10, 12, 15, 16	All responded: Yes	
Is there any indication of bias in our synthesis of the evidence?	2-10, 12, 15, 16	All responded: No	
Are there any published or unpublished studies that we may have overlooked?	2, 3, 5, 6, 9, 10, 12, 15, 16	No	
	4	Yes - I'm sure it wasn't overlooked, it just hasn't been published yet. SPRINT. NIH held press conference today. because it has not yet been published it cannot be included in the meta-analysis, but it could and probably should be mentioned in the narrative as being a study to consider when results are published.	SPRINT has been included
	7	Yes - The SHEP study did report a significant increase in falls in the intervention vs control group (which you note in your table but not the text).	We added this information in the text.
		There is a very small observational study (JAMA Int Med, Mosello, 2015) finding that the combination of multiple blood pressure medications and lowest tertile of BP among patients with dementia was associated with greater loss of MMSE points.	This was published after our search. The results are in line with several other observational studies that fell within our search dates. All of the observational studies of cognition, including this one, have some issues with confounding. Given that there were 7 RCTs examining cognitive outcomes and that we've already included several obs studies with similar findings as this one, it is unlikely that the addition of the Mosello study would alter results.
		There is a very recent trial of withdrawal of blood pressure medications in Leiden (the DANTE trial) Annals Internal Medicine 2015 (last week), by Noonen et al, that did not find short term improvements in cognition.	Interesting study – falls out of the scope of our key questions.
	8	Yes - I would not say overlooked, but the SPRINT study is obviously going to be influential.	SPRINT has been included
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	2	See comments in the attached file.	
		A matter not addressed in this review is the important but controversial issue of BP management in the subacute period after stroke. In general, there is fear that dropping BP in the first hours post-stroke (when collaterals may be perfusing at-risk brain) can extend damage in stroke and worsen outcomes, yet a few studies using ACE-I or ARB drugs begun within 24- to 48-hours of stroke decreased recurrence or mortality. I would urge caution in applying the results of long-term trials to the acute post-stroke period.	We have added some language to the methods and results to clarify that we did not examine management of acute stroke.
		While no suggestive signal was seen in this review, the issue remains as to whether some anti-hypertensive individual drugs or classes of drugs might have superior outcomes independent of BP targets or actual reduction in BP achieved. This has been suggested for ACE-Is and ARBs for the outcome of initial or recurrent stroke.	Noted. We were not able to identify a clear pattern, but one would really need to look at comparative effectiveness studies and individual level data to answer this question.

Question Text	Reviewer Number	Comment	Response
	3	P31 line 21: I would add that the SPS 3 trial showed a statistically significant reduction in intracerebral hemorrhage, a type of stroke with high mortality.	Noted. We've reported the outcome of all strokes. SPS3 reports 5 different stroke outcomes including a variety of hemorrhagic stroke outcomes. The intracerebral hemorrhage outcome was the only one with $p < 0.05$. Moreover, the rate of disabling or fatal strokes with similar in both groups. It would be misleading for us to report one secondary outcome and not all others.
		P 46, line 52: Discussion: Did any of the studies report sex differences in the benefits of BP lowering?	We did not systematically evaluate this question.
		P 46, line 47: Would add that even though the absolute benefit may be small, the population and health system benefits may be worthwhile	noted
	6	Table on page 5,line 11 comment on mortality says "more moderate targets (SBP<140mm Hg). Shouldn't it say (SBP>140)? Page 6: list of abbreviations under the table (line 33) does not include ROB nor is ROB listed in the abbreviations list on pages 8-9. Page 20, line 15 "monotherapy with benzene"--should that be benazepril instead of benzene? page 32, line 33,"described and increased risk" should be "described an increased risk"	Appreciated – all noted and corrected.
	8	I am including these as attachments.	
	9	The report is well-written.	Thank you
		Page 2, line 39, did cough and hypotension vary with age?	There were no data on this.
		Table 10 provides information about risk of bias, but little text is provided about how these assessments were made.	We followed standard methods for assessment (ref included). We revised table to include more detail, especially for areas in which we noted flaws.
		Page 31, line 9, SPS3 had a "rigorous" definition of stroke as stated, but it was also restrictive to one type of ischemic stroke (namely only lacunar infarcts); therefore, results may not be generalizable to other stroke types (e.g., hemorrhagic stroke or large artery atherosclerotic ischemic stroke). How may the results be applicable to Veterans with a history of transient ischemic attack?	We've revised the language to be more clear about the inclusion criteria in both the SPS3 and PROGRESS trials. The progress trial did include a broader definition of stroke and TIA.
		Page 45, line 18 (typographical error, errant 6).	noted
		General comment: consider hyphenating "treat-to-target" studies throughout (there are occasions without use of hyphens.	done
		Limitations Section: consider including a statement that the included trials used pharmacologic treatment of hypertension and therefore excluded trials that focused on non-pharmacologic approaches to hypertension management.	We have added this.
		A statement about domains where additional research is needed would be of interest.	We have added a brief future research section.
	10	Although a few studies are of questionable quality, they are adequately handled and don't bias the conclusions. Although this was written before SPRINT was announced, if not mentioned, you could add that it may address this question, or you could comment that it is unpublished at this time, but shows benefots for a population average age 68 years.	SPRINT has been included
	15	see attachment for comments	

Question Text	Reviewer Number	Comment	Response
	16	A thorough review of evidence regarding intensity of treatment for hypertension that provides guidance but perhaps more notably identifies the need for additional investigation. 1. Would encourage consistency in the use of abbreviations (i.e. once define use consistently thereafter - risk of bias/ROB). 2. Would also recommend more consistent use of symbols (i.e. < & >) to define blood pressure targets rather than prose ((i.e. 140 mm HG or less). 3. Forest plots are somewhat blurred and would benefit from sharpening. 4. Please include justification for exclusion of comparative effectiveness studies.	Noted and revised accordingly

Additional comments – Reviewer #2	Response
Page 3, Line 6: It would be useful to state whether the difference was significant or not, and by what p value, given the rather high NNTs. (**also insert comma after NNT ##)**	As above, all the #'s have changed. We present CI and NNT throughout
Page 11, Line 54: An interesting and controversial topic is whether some anti-hypertensive individual drugs or classes of drugs have superior outcomes independent of BP target or actual reduction in BP. This has been suggested for ACE-Is and ARBs for the outcome of initial or recurrent stroke. I understand this was outside the scope of your review, but did you find enough in the literature to suggest this as a future topic for exploration?	Agree an interesting topic, but outside scope – as we note in limitations partly this would be answered by comparative effectiveness studies which we did not include.
Page 11, Line 59: We surmised the **(change "the" to "that")**	Noted
Page 15, Line 37: I gather from the below that no studies were excluded if they targeted DBP rather than SBP?	Correct, we have clarified inclusion/exclusion criteria
Page 15 Line 53: In an effort to better understand treatment effects among different age subgroups, we explored the possibility of gathering data to conduct analysis (**change to analyses**) based on individual patient data from blood pressure treatment trials.	Noted
Page 16, Line 6: "We anticipate using data from these six trials to conduct meta-analyses examining blood pressure treatment benefits and harms in those age 60-69, 70-79, 80-89, and over age 90." Will the results be disseminated in a subsequent report?	We anticipate writing up a separate manuscript of these results.
Page 18, Line 11: "Overall, there was little to no consistent evidence of a clinically significant incremental benefit of treating blood pressures to levels substantially below current guideline recommend (**change to recommended**) levels of 150/90 in patients over age 60."	Noted
Page 18, Line 41: "The remaining studies had primary outcomes related to renal disease or microalbuminuria27,31 or additional outcomes not specified **(delete specified)** of interest for this review (LVH regression).20"	Noted
Page 18, Line 43: Among trials which specified a particular medication as first-line therapy, seven used ace (**ACE - term should be defined at first use)** inhibitors or angiotensin-receptor blockers, 5 used calcium channel blockers, and six used diuretics (Tables 2 and 3).	Noted
Page 23, Line 25: You might want to comment on reduced significance (p value) with population subset. However, it's confusing that CI does not include 1 yet $p > 0.05$. Is this a mult. comparisons adjustment?	Again, all #'s have changed. We use CI preferentially throughout.
Just a note that all of the figures appear blurry (out of focus) in my copy.	Noted – we have tried to improve the appearance of the figures.
Page 51, Line 18: Another issue not addressed is the important but controversial issue of BP management in the subacute period after stroke. In general, there is fear that dropping BP in the first hours post-stroke (when collaterals may be perfusing at-risk brain) can extend damage in stroke and worsen outcomes, yet a few studies using ACE-I or ARB drugs begun within 24- to 48-hoours of stroke decreased recurrence or mortality. Perhaps a subject for a future ESP review?	Agree – interesting topic, but out of scope (and we added statement clarifying that we did not include acute stroke).

Additional comments – Reviewer #4	**Response**
Overall, this is an excellent review of the evidence. These are comments that may help make the review more useful to clinicians:	
- It is very helpful that the achieved BPs in the trials has been included.	
- The lack of evidence about effect of comorbidity burden is striking and should be a call to clinical trialists to gather more information in that area.	We added this to future research section
- Possibly more could be done with the available information about ADE rates, for example, in one place there is mention that 4 of 10 trials found increased withdrawals due to ADEs in older individuals (particularly cough and hypotension, with hypotension being potentially serious). Page 7 could use more cautions re the ADE statements.	We have added a statement in discussion about potential seriousness of hypotension given the increased rate of syncope in 2 studies.
- There is mention that HYVET study excluded patients with dementia or nursing home; however, my recollection (should be checked with source data) is that the individuals in HYVET were quite healthy for age (not just "not frail" but healthier than average). Since this group is a major contributor to information about lack of impact on adverse events in those over 75, it is important to provide more detail about how health this group was.	We have created a new table focused on exclusion criteria of each trial to better examine this issues of applicability
- In general, I think it would be good to make more visible the issue of to whom the findings may be generalized. Clinicians are looking for guidance. It is important, for example, not to assume that because HYVET had certain findings that these findings would apply to all patients over age 80.	See above
o It would be helpful to have information in the tables with more detailed descriptions of the study populations at baseline, to make it clearer what where the characteristics of the study populations, so that clinicians managing older Veterans and other older adults can more easily compare the patients in the studies to the patient about whom they are making clinical decisions, to understand how similar (or not) their patient may be to the patients in the clinical trials that form the evidence base.	See above
o Further along those lines, it would be helpful to describe in the narrative some comparisons of the baseline characteristics and the events in the study groups with the typical prevalence among Veterans (who receive their care in VA) in comparable age groups. For example, there is mention of low stroke or other event rates, but the expected rates in the typical Veteran population are not shown so it is hard to make the comparison.	We have included more about study event rates. The rates in Veterans will vary markedly depending on their risk factor profile. We have added more discussion about risk factor profile and study inclusion in the treat to target trial section
o Although there were no studies with evidence about the role of comorbidity, it would be helpful at least to describe to the extent the data are available in the study reports the baseline extent of comorbidity.	See above
o Where ADEs are at low rates, comparison of the rates in general population , or ideally in VA patient population, over time would be helpful for comparison	We have noted comparison of ADEs within trials, but do not have data on these ADEs in general population
- A large study of BP targets is underway in the SPRINT trial. A press briefing by NIH today (9/11/2015) released results. The paper has not yet been peer-reviewed and published, so it cannot be included in the meta-analysis, but some mention of this study should be in this report. Some information from the trial that we would hope to see in the published report:	SPRINT has been included
o subgroup analysis for the older patients (by decades within the older age groups), with outcomes, length of time in trial, achieved BPs, variability in SBPs, pulse pressures, etc, length of time in trial and at target BP and/or on final number of drugs (i.e., how much time for ADEs to become apparent), quality of life reports, intolerance rates for drugs	These analyses would require individual patient level data – we are working on individual patient data meta-analyses with data from 6 trials to get at some of these issues (eg - outcomes by age decile)
o baseline data on comorbidities broken down by age group	Most studies did not report comorbidities in this way.
o analyses of interactions of age and comorbidity and ADEs: - It may be hard for some clinical readers to understand why some studies were included by the criterion of comparing more intensive to less intensive therapy, but other studies were not. There are several studies that compare drug therapy to placebo, so appear to be studies of impact of treating HTN, or studies of impact of a particular drug, rather than specifically more vs less intensive treatment (although drug therapy vs placebo is certainly more intense vs less intense). Without pulling all the studies and looking at the underlying study design, it isn't easily clear to the reader why these studies of drug vs placebo are included while other studies of drug vs placebo are not.	We have tried to clarify this in the methods section under study selection. We did not exclude any studies of drug vs placebo that met other criteria (age and hypertensive population).

Additional comments – Reviewer #4	Response
- the Limitations section acknowledges that there may be specific medication effects that are not part of the analyses in this ESP. this is an important point. There are specific drugs with more effect on outcomes (as in ALLHAT) and there are specific drugs that may, at least theoretically, have lower rates of particular ADEs (for example, thiazide diuretics may block calcium loss and may theoretically decrease risk of osteopenia). I agree that with the already limited number of studies with which to examine the key questions it would seem to be impossible to disentangle the effects of particular drugs.	Noted
- In addition to evidence regarding comorbidities, it would be useful to have evidence about the impact of the total number of medications that patient has apart from antihypertensives. As another descriptive factor about the study populations, information about total number of meds at baseline, as compared with total number of meds for VA patients of same age, would help clinicians with knowing how well the study patients resemble the patients they are seeing every day.	Most studies did not report this information.
- with the NNT of 10,000 given on page 28, seems that any conclusions about stroke should be very cautious.	We have re-run analyses as noted elsewhere and these numbers have changed.

Additional comments – Reviewer #8	Response
I appreciate the concise executive summary. I was surprised that there was no discussion of how to handle HOT, which used DBP targets and the emphasis on achieved BP rather than target BP. In many cases, the studies were described as not having a target BP, but usually there was some information about the approach, though it was not used in this summary, presumably because the details were not precisely defined. I also did not find a justification for combining very disparate intervention and control interventions. Beyond the general idea that one arm achieved at least a tiny bit lower BP than the other in every study, there seems little justification for combining a placebo controlled study where the control arm had only a target SBP of less than 219 mm Hg to a study like HOT, where everyone targeted a DBP below 90, and some lower still. It does not appear the authors considered generating a more qualitative summary or at least some discussion of the implications of combining these very different studies. I did appreciate they looked at a number of more homogeneous subgroups, but the criteria were limited to baseline characteristics or achieved control in the intervention group, it seems. The fact that some of the studies had almost no difference in achieved BP, or had very different BP goals/permitted levels for the less intensive group was not addressed.	Appreciate the insightful comments. We have markedly changed much of the results section and the summary of evidence table both because we re-ran all analyses with SPRINT and in part to respond to these comments. Most of the RR/ARR have changed. We have clarified the rationale for synthesizing the data the way we did – hopefully it will be clear that we examined the data from different directions and that we clarified that the treat to target trials are distinct from the others. We revamped the way we analyzed and discussed the HOT trial. We also, hopefully, more clearly present the rationale and results of the numerous sensitivity analyses which should get at some of the issues noted here. For instance, we ran analyses excluding trials with minimal achieved differences in BP. We also included more detail under the "trial characteristics" section. Finally, we agree that the combination of all studies is relatively meaningless – we've explained this in results and deleted the combined analysis.
The table on page 5 has some useful numbers, though I found some confusing. In the first, mortality, row the point estimates of RR are actually very significant, even though they are not statistically significant. I think that the large N of the studies suggests that they pretty definitively ruled out an important benefit, but actually, the ARR seen in the subset is a pretty important change – the idea of preventing one death for every 100 persons treated is huge. It is a little hard to interpret since you use % when most people would have events per 100 pt – years. Here I can't tell if is 1% a year, or 1% over 20 years of treatment – pretty different things.	See above - these numbers have changed with new analyses
The stroke row is a really confusing one. The apparently statistically significant RR of 0.72 seems like it would be clinically important – a 28% RR reduction is as good as or better than we see with statins and MI in people with CVD!! But then the ARR is 0.01% - that is 1/10000. For me to reconcile these two numbers, I have to have an event rate of 3.6/10,000 compared to an event rate of 2.6/10,000. This seems like the stroke rate per week in some high risk groups and makes the NNT of 10,000 not so unimpressive after all!!! Again, the use of percentages is confusing in an ARR presentation. I think that a statistical explanation of these numbers would help me. I recognize that they likely come from different approaches to synthesizing data, and therefore can't be quite as simplistically interpreted as if they came from a single trial, but the relationship between ARR and RR needs to be transparent.	See above – numbers have changed.

Additional comments – Reviewer #8	Response
Overall, it seems very hard to say that the evidence justifies the conclusion "Overall, we found moderate-strength evidence that using a systolic blood pressure target of 140 mm Hg or less did not appreciably improve outcomes in older patients compared to slightly higher targets." Rather, I would say you "found little evidence that using a target of 140 mm Hg or less appreciably improve outcomes, but (you) cannot exclude as much as a 1/3 reduction in most important cardiovascular outcomes." If you disagree, you need to reconcile your point estimates and 95% CI with the conclusions in some way that I don't see in the current version.	See above – we have revised the conclusions based on newer analyses
I think the conclusion on stroke is not very useful because it does nto discuss a target but a range. And the range is wide enough that people are going to wonder – "so what do you mean? Do you want them below 130 or do you want them below 140?" It is going to take an extra drug to get someone from 139 to 129, in most cases. So you need to describe what the data say iin a little more detail. Are you saying that <130 was better than < 150 and < 140 was better than < 150, but we can't tell if 130 or 140 are any different? Then it seems to me you are saying you can't tell if any further reduction below 140 is worth it. When you discussed the overall numbers, it seems you would not endorse < 140 as better because there was no studies where you took people in the 140-160 range and pushed some lower and left some above 140. So to me, you should say you don't have any studies of people < 140 that showed any additional benefit. So the benefit of <130 is not shown at all.	Agree – we have tried to clarify exactly what each trial showed.
FULL SYNTHESIS	
I won't complain about the summary or the referring to the 'rate' of events without any evidence of a time frame, since I already said I found it confusing. I think that given the persistent references to the relative unimportance of a relative risk reduction of 25% some discussion of why they have that opinion is appropriate. It is greater than the benefit seen in some statin trials for primary and even secondary prevention, and similar to that seen with treatment in younger individuals. I can't account for some of the ARR calculations that suggest a remarkably small ARR in the setting of a significant event rate and a reasonably large summary estimate of RRR. But at least a reasonable approach would be to apply the observed RRR to a typical event rate in the target population and consider whether that would be considered a little more important than they consider the statistically significant drops in mortality and stroke, based solely on the quantitative combined analysis.	As above, we have redone our analyses with SPRINT and with the HOT subgroups combined differently so the RR and ARR have changed substantially as a result.
The comment on less heterogeneity in mortality among the 3 trials comparing <140 to higher targets, while I assume is mathematically true, is counterintuitive, since they include both the study with highest RR and the study with the lower RR among the 6 in Table 2. It really reflects the fact that with these smaller trials the fact that the results are quite disparate is not as statistically unlikely. Maybe you could tone that comment down. And the summary OR is really just the impact of the Wei study, which has 138 of the 164 deaths. I wonder if you should be making some comment on the Wei study, which is quite influential both in this analysis, and in the overall comparison of less intensive to more intensive trgets. The Wei study has a mortality in the less intensive arm that is more than 20% over 4 years. In contrast, the VALISH study has lower than 2% mortality over 3 years. The ages are roughly comparable, the amount of CAD is comparable, and the baseline BP is actually higher in VALISH. There is 10% more DM in the Wei study. But the difference in mortality is ENORMOUS. And the control group ends up with mean SBP around 150 in Wei, but 142 in VALISH even though both are trying to keep the control below 150 mm Hg (to keep a person reliably below 150, one must have a mean quite a bit below 150). The delta in SBP between the groups is 14 compared to less than 5 mm Hg.	We have revised this section substantially and no longer include this statement. Also, there were several peer review comments about the Wei study – we agreed that it seems an unusual study and and was an outlier. We conducted sensitivity analyses with and without this study.
The surprising stroke ARR versus RR numbers are again seen here, again without comment. I can't figure out the math on the ARR. Being a simple person, I see VALISH, a study in Japan, where in 3 years of follow up, in people mean age 76 years old, all with hypertension, the stroke rate is 1/100. Here, the ARR is 7/1000, about 10 times the estimated summary ARR – in the other studies the ARR is even higher, often much higher, except in JATOS, a study of 4000 participants, also from Japan, where there is no benefit for stroke. Yet the summary estimate is < 1/10,000? This makes no sense. The funny treatment of HOT, where you throw the <85 people in the <90 group makes it a little harder to interpret. As I recalled, when I looked up the actual hot numbers, the <85 did the worst of anyone, so it did not obscure a big benefit of BP lowering to put them in the <90 group – just the opposite – but it does not make sense, since it is targeting a number less than current guidelines, which is what you said you wanted to count as the intensive group.	As above, we have revamped our analyses of HOT. Agree that it made more sense to dichotomize 80/85 vs 90. We also conducted additional analyses without the middle group. Because the HOT was such a large trial, these changes had a large impact on results. We added a paragraph to results focused on HOT and the different analyses.

Additional comments – Reviewer #8	Response
The table 3 would benefit from some information about the targets in the intervention group versus controls. Thus, in SHEP the comparison is a target SBP of 140 versus no target SBP, but both groups were treated for a target DBP of <90 – i.e., no matter how high the SBP don't treat the control group unless DBP > 90 mm Hg. In the Sys-Eur study, the control group was treated if they got above 219/99. In other studies in this table, e.g., TRANSCEND, all patients were fairly well controlled and the intervention simply added a drug. Thus, I don't see this analysis as very amenable to combination.	See above. We have examined the data quantitatively from several different angles, and added more description of the differences in studies and how these prompted various sensitivity analyses.
The cardiac event data (Figure 8) is also kind of interesting in that the three Asian studies have zero benefit in reducing an already incredibly low cardiac event rate – again, note how old they are and still very few events. In the American/European studies, lots of benefit. ACCORD is harder to interpret and also had a really low SBP target. Recall that recently we learned that high risk Japanese people don't benefit from aspirin in primary prevention of MI. Although you note the heterogeneity, you don't try to interpret it. I think you have a little freedom, and perhaps obligation to think about why there is heterogeneity, even though you are trying to make this part of the review a quantitative synthesis.	We have added a paragraph to the results and statements to the discussion describing the differences in event rates and speculating whether or not these may have accounted for some of the heterogeneity.
I am not sure why the DBP< 85 group is included with the DBP < 90 group in the HOT study. I would just drop the <85 people if you don't want to consider them separately.	See above
The ARR being greater with greater age is an artifact of higher event rates, not a bigger effect – note the RR are essentially the same.	See above
In the discussion of the results of the trials comparing more and less intensive therapy rather than competing targets, they note that the trials showing the largest ARR are ones with achieved SBP > 140. I would have noted that they are the ones with the largest delta SBP and the ones with the highest even rate in the control groups.	These #'s have changed. We focus now on the baseline BP subgroups (which overlap substantially with achieved BP groups) – the event rates are actually not higher in the higher baseline BP groups (overall).
The analysis of post stroke intensive versus less intensive is interesting in that it is positive and the ARR is considered nontrivial by the authors. I note that the event rate in both trials was over 10% for stroke alone and the delta SBP was 9 mm Hg and 11 mm Hg in the PROGRESS and SPS3 respectively	Noted
I found that the discussion of Key Question 2 was much more forthcoming about the difficulty of quantitatively combining very different studies and (perhaps consequently) very different results.	Noted
The discussion of KQ 3 found that ARR is higher when event rates are higher. This seems consistent with what one sees if one looks at BP Rx in general. Studies like STOP (Swedish Trial in Old People) and EWPHE (included in this review), with high event rates and studies like the MRC I and II trials, with low event rates, have similar RR (and RRR) but STOP and EWPHE had much larger ARR.	Noted
I found the discussions of KQ 4 and 5 similarly well calibrated to the relatively scant evidence.	Noted

Additional comments – Reviewer #15	Response
General comments: This is an excellent and helpful report. Very well written.	Thank you.
Executive summary:	
Next to last line intro---leave out "proposed" since it is done	Done
Last line-----I would be more specific about what older is in this report (eg age> 60)	done
Quality assessment---were observational studies reviewed for quality?	We noted methodologic deficiencies of the few included observational studies in the cognitive study section.
Key findings---line 2----need "with" between compared and more	done
Line7---leave out "more" and state direction (what is the effect?)	done
Introduction:	
~ line 8---I think it should read "age" rather than "ages" groups	done
Table 1---GREAT TABLE	Thank you
Data synthesis:	
I would rewrite 2nd sentence----"We do not present CVD mortality data in this report since ….."	done

Additional comments – Reviewer #15	Response
Study level meta-analysis sxn----last line 2nd p---what currently defines mild htn? Do you want to include a lower boundary? I thought mild was 160-180?	Done
Detailed study results:	
1st p---I think you should say something like "Among 20 studies, X showed benefit from treating more intensely/to target. When data from these studies was combined in meta-analysis, more intensive……"	We revised the results section and have added some more detail to overview section re: # studies showing benefit
I don't understand how you can have a RR of 0.89 with CI 0.83-0.96 and 0 ARR	These #'s have changed with re-analysis
3rd paragraph, last sentence----would be helpful to add the range of bp's (160, range 166-174). Also in 3rd p, how much absolute risk difference do these 4 studies acct for?	We've revamped the entire results section and have included more information about the sensitivity analyses and resultant changes in ARR.
I think adding a figure/forrest plot for CVA and CAD for those younger/older than 70 as you do for total mortality would be very helpful (like figure 2)	We have revised KQ2 and included the age meta-analysis results here. However, because of concerns for ecologic fallacy we did not include the forest plots as we can't really use them to examine age-treatment effects with any degree of confidence
The Wei study stands out both for its results and control event rate. Note that the number of cardiovascular events is similar, the number of strokes 15 less in the I group and 36 total differences in death between the 2 groups. I am worried about the randomization. What are they dying of? Review of the quality ratings doesn't suggest this has low risk of bias to me.	Agree. We have revised accordingly. We also re-ran analyses without 2 other high risk of bias studies (we had overlooked this in first draft)
Page 28----the ARR of 1% for total mortality seems fairly big.	Numbers have all changed with SPRINT and additional analyses
Figure 9----title----add in "comparing x to x"	Done
Note the format of KQ 2 differs from KQ1	We've added subheaders to make more similar
3rd p, line 3 - "an" rather than "and"	Noted
SHEP description in p 3. I might state this: "conversely, the SHEP trial identified a decreased risk of stroke when the treated systolic blood pressures in patients with baseline bp's above 170 was less than 150 (mean X)" to be really clear.	Done
Renal outcomes-----I am uncertain about this but it might be helpful to provide some numbers for changes in creatinine/GFR since this is such a common occurrence in practice.	Specific renal outcomes and numbers are presented in Table 6
Cognitive outcomes-----in general (and this is true throughout) I recommend being more specific about bps rather than stating "moderately tight" as in first P of this section. Similarly, in the last paragraph "large proportion"----what % - this might matter.	The specific BPs are listed in following sentence. Re: large proportion with missing data – these numbers are in table –added the numbers into paragraph as well.
Falls/fractures----thoughts on the non-spine fractures? NSS but interesting. ? thiazides?	Unclear – mainly looking at this as potential harm – the trend towards benefit was seen in 2 studies but not in a third. Not sure we can much of the potential reduction in fracture risk.
The orthostatic hypotension stuff d/n make sense to me. Thoughts?	As we note, a number of trials found increased rates of hypotension. Three trials looked at syncope and 2 found a higher rate. We added sentence to discussion suggesting that the hypotension has potential to be serious given the excess rate of syncope in 2 trials.
Summary/discussion:	
Line 2 "compared *with*…."	Noted
Need to discuss the 1% absolute mortality reduction a little bit more when you note that move aggressive treatment didn't "appreciably" improve outcomes	As above, all numbers have changed
Mid paragraph 1-----can you be more explicit rather than say "modest" effect?	We have put in NNT throughout
Paragraph 3. It would be interesting to find out usual stroke rates in the general age specific population given the low event rates you note.	Added a paragraph to discussion about event rates.
Tables 2 and 3----it might be helpful to add publication dates in column 1. I think there is a wide range	Agree. Done.