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

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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