

Benefits and Harms of Intensive Blood Pressure Treatment in Adults Aged 60 Years or Older

A Systematic Review and Meta-analysis

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Background: Recent guidelines recommend a systolic blood pressure (SBP) goal of less than 150 mm Hg for adults aged 60 years or older, but the balance of benefits and harms is unclear in light of newer evidence.

Purpose: To systematically review the effects of more versus less intensive BP control in older adults.

Data Sources: Multiple databases through January 2015 and MEDLINE to September 2016.

Study Selection: 21 randomized, controlled trials comparing BP targets or treatment intensity, and 3 observational studies that assessed harms.

Data Extraction: Two investigators extracted data, assessed study quality, and graded the evidence using published criteria.

Data Synthesis: Nine trials provided high-strength evidence that BP control to less than 150/90 mm Hg reduces mortality (relative risk [RR], 0.90 [95% CI, 0.83 to 0.98]), cardiac events (RR, 0.77 [CI, 0.68 to 0.89]), and stroke (RR, 0.74 [CI, 0.65 to 0.84]). Six trials yielded low- to moderate-strength evidence that lower targets ($\leq 140/85$ mm Hg) are associated with marginally significant decreases in cardiac events (RR, 0.82 [CI, 0.64 to 1.00]) and

stroke (RR, 0.79 [CI, 0.59 to 0.99]) and nonsignificantly fewer deaths (RR, 0.86 [CI, 0.69 to 1.06]). Low- to moderate-strength evidence showed that lower BP targets do not increase falls or cognitive impairment.

Limitation: Data relevant to frail elderly adults and the effect of multimorbidity are limited.

Conclusion: Treatment to at least current guideline standards for BP ($< 150/90$ mm Hg) substantially improves health outcomes in older adults. There is less consistent evidence, largely from 1 trial targeting SBP less than 120 mm Hg, that lower BP targets are beneficial for high-risk patients. Lower BP targets did not increase falls or cognitive decline but are associated with hypotension, syncope, and greater medication burden.

Primary Funding Source: U.S. Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. (PROSPERO 2015: CRD42015017677)

Ann Intern Med. doi:10.7326/M16-1754

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This article was published at www.annals.org on 17 January 2017.

Hypertension is a very common modifiable risk factor for cardiovascular morbidity and mortality, affecting up to two thirds of adults older than 60 years (1). Older adults might also be more susceptible to adverse effects from blood pressure (BP) lowering, including falls, fractures, and cognitive impairment. In 2014, new guidelines increased the treatment goal for adults aged 60 years or older to a systolic BP (SBP) less than 150 mm Hg (2), but the change was controversial and a newer trial has further fueled debate (3). We conducted a systematic review to examine the balance of benefits and harms of more versus less intensive BP lowering in adults aged 60 years or older.

METHODS

This article was developed to inform guideline development and is part of a larger report commissioned by the Veterans Health Administration (4). A protocol describing the review plan was posted to a publicly accessible Web site before the study was initiated (5).

Data Sources and Searches

We searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov from database inception (Appendix A of the Supplement, available at www.annals.org). The end search date for the larger report for the Veterans Health Ad-

ministration was January 2015; we updated the MEDLINE search in September 2016. We also examined the full text of all studies included in the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2) and the Blood Pressure Lowering Treatment Trialists' Collaboration (6).

Study Selection

We reviewed titles and abstracts, and 2 independent reviewers reviewed the full articles for inclusion; disagreements were resolved through consensus. We included randomized trials of adults with a diagnosis of hypertension and mean age of at least 60 years that directly compared either 2 or more BP targets or more versus less intensive antihypertensive therapy and that included 1 or more outcomes of interest (detailed criteria in Appendix B of the Supplement). We excluded

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trials directly comparing antihypertensive drugs with one another and studies in populations with specific diagnoses in which medications were used primarily for effects other than BP lowering (for example, studies of β -blockade in patients with systolic heart failure or studies of acute myocardial infarction). We included cohort studies that reported adverse effects associated with reductions in BP among patients receiving antihypertensive therapy.

Data Extraction and Quality Assessment

One investigator abstracted data elements from each study, and a second investigator reviewed entries for accuracy. Two reviewers independently assessed the quality of each trial using a tool developed by the Cochrane Collaboration (7). Disagreements were resolved through discussion. Each trial was given an overall summary assessment of low, high, or unclear risk of bias (Appendix C of the Supplement).

Data Synthesis and Analysis

Our primary effectiveness outcomes of interest were all-cause mortality, stroke (fatal or nonfatal), and cardiac events (myocardial infarction and sudden cardiac death), all after at least 6 months of treatment. We examined the following harms: cognitive impairment, quality of life, falls, fractures, syncope, functional status, hypotension, acute kidney injury (defined as doubling of serum creatinine level or need for renal replacement therapy), medication burden, and withdrawal due to adverse events. We did not specifically search for studies reporting well-known drug-specific adverse effects, such as angiotensin-converting enzyme inhibitor (ACEI)-induced cough or thiazide diuretic-induced hypokalemia, but we described common adverse events of intensive therapy leading to higher rates of withdrawal among trials. The overall strength of evidence for each outcome was classified after group discussion as high, moderate, low, or insufficient based on the consistency, coherence, and applicability of the body of evidence as well as the internal validity of individual studies (8).

We conducted study-level meta-analyses to generate pooled estimates for each outcome after considering clinical and methodological diversity among studies. The profile-likelihood random-effects model (9) was used to combine relative risks (RRs). We assessed the magnitude of statistical heterogeneity among studies using the standard Cochran chi-square test, the I^2 statistic (10). All analyses were performed using Stata/IC 13.1 (StataCorp).

We performed several sensitivity analyses to help address the heterogeneity of study design and patient populations. Because studies with a lower mean age were likely to include patients younger than 60 years, we conducted separate analyses of studies with a mean population age of at least 70 years and studies with inclusion criteria stipulating entry age of at least 60 years to ensure that results were consistent. We analyzed studies according to baseline BP to compare treatment effects among patients with moderate to severe hypertension (SBP \geq 160 mm Hg) versus those with

mild hypertension (SBP <160 mm Hg), and we analyzed studies according to achieved BP (SBP <140 mm Hg). We also conducted analyses with and without trials that achieved minimal between-group differences in SBP (\leq 3 mm Hg).

We examined trials specifically comparing blood pressure targets of SBP less than 140 mm Hg or diastolic BP (DBP) of 85 mm Hg or lower versus higher targets because these trials most directly address the incremental benefit of treatment intensification in mild hypertension. Finally, we examined secondary prevention of stroke by examining BP treatment effects in studies of patients with prior stroke, but we excluded studies of acute management of stroke (<1 week).

Role of the Funding Source

This research was funded by the U.S. Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The funding source had no role in study design, conduct, data collection, data analysis, preparation of the manuscript, or the decision to submit the manuscript for publication.

RESULTS

From 11 268 titles and abstracts, we identified 330 articles for full-text review. We included 46 publications representing 21 randomized, controlled trials and 3 cohort studies that contained primary data relevant to the key questions. A flow diagram of the literature yield and the disposition of included studies is presented in the Appendix Figure (available at www.annals.org).

Eight trials compared BP targets (3, 11-17), and 13 trials randomly assigned patients to more versus less intensive antihypertensive therapy (18-30). Two of the trials included only patients with prior stroke and are considered separately for secondary stroke prevention (15, 23). Three trials had serious methodological flaws placing them at high risk of bias (17, 27, 28), whereas the other 18 trials were judged to have low risk of bias. Because we were focused primarily on comparing the effects of more versus less aggressive BP lowering, we conducted sensitivity analyses without 3 trials (2 achieved minimal between-group differences in SBP [\leq 3 mm Hg], and a third did not report achieved BP) and found similar results (19, 24, 30). In the following sections on health outcome effects, we present results from the remaining 15 trials (Table 1). The characteristics of the 6 trials excluded from meta-analysis and the results of the sensitivity analyses are presented in Tables 1 and 2 of the Supplement.

Treatment of Moderate to Severe Versus Mild Hypertension

A large body of evidence from 9 trials showed that intensive BP treatment substantially improved outcomes in patients with moderate to severe hypertension (SBP \geq 160 mm Hg) (Figure 1). Four trials of patients with mild hypertension (SBP <160 mm Hg) also showed benefit, though the results were less consistent and the summary estimates less precise.

Of the trials of patients with baseline SBP less than 160 mm Hg, 2 were treat-to-target trials of patients with well-controlled hypertension that produced discrepant results (3, 11). Another trial (FEVER [Felodipine Event Reduction]), which tested the effects of felodipine in patients with a baseline SBP of 158 mm Hg, found substantial reductions in all 3 outcomes of interest (21). The fourth trial (ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicon - MR Controlled Evaluation]) tested the effects of a fixed-dose combination of an ACEI and a calcium-channel blocker in diabetic patients and found a reduction in mortality but not in other outcomes (18).

Achievement of SBP Less Than 140 mm Hg

Overall, studies of patients achieving SBP of at least 140 mm Hg had effects similar to studies of patients achieving SBP less than 140 mm Hg, though the reduction in stroke risk was more consistent among studies of patients achieving higher SBP (Figure 1 of the Supplement). Baseline SBP was at least 160 mm Hg in all 5 studies of patients achieving the higher SBP. Among the 8 studies of patients achieving lower SBP, 6 were treat-to-target studies that are discussed later (3, 11-14, 16). The other 2 studies were the aforementioned FEVER and ADVANCE studies that produced discrepant results (18, 21).

Trials Comparing Treatment Targets

Six trials evaluated a total of 41 491 patients and found that treatment targets of SBP less than 140 mm Hg or DBP of 85 mm Hg or lower are associated with a nonsignificant reduction in all-cause mortality (RR, 0.86 [95% CI, 0.69 to 1.06]; absolute risk reduction, 0.80; $I^2 = 13.3%$), a reduction in stroke (RR, 0.79 [CI, 0.59 to 0.99]; absolute risk reduction, 0.49; $I^2 = 16.2%$), and a marginally significant reduction in cardiac events (RR, 0.82 [CI, 0.64 to 1.00]; absolute risk reduction, 0.94; $I^2 = 15.5%$) (Figure 2). 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 the results have important inconsistencies and because the CIs are relatively wide, encompassing the possibility of both marked benefit and no effect. The strength of evidence for stroke is considered moderate because the direction and magnitude of effect were more consistent across analyses.

SPRINT (Systolic Blood Pressure Intervention Trial) and the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial contribute the most weight to these analyses because of their size and the event rates (3, 11). Mortality rates were very low in the other 4 trials (12-14, 16), and cardiac event rates were very low in 3 of them (12, 14, 16).

SPRINT contributed substantially to findings of benefit. When we removed SPRINT in additional sensitivity analyses, effects on mortality (RR, 0.96 [CI, 0.80 to 1.15]; $I^2 = 0%$) were reduced and effects on cardiac events (RR, 0.88 [CI, 0.74 to 1.04]; $I^2 = 4.0%$) were no longer significant, but effects on stroke remained

largely unchanged (RR, 0.74 [CI, 0.56 to 0.99]; $I^2 = 25.8%$). Taken together, SPRINT and the ACCORD trial contribute to the uncertainty about the true effect of more intensive BP lowering because of their discrepant results. Both trials compared an SBP target of less than 120 mm Hg versus less than 140 mm Hg in patients with well-controlled hypertension and high cardiovascular risk, but SPRINT found marked reductions in mortality and cardiac events, whereas the ACCORD trial did not. There are several potential reasons that the trials produced different results. The ACCORD trial included only diabetic patients, whereas SPRINT excluded them; the mean age of participants in the ACCORD trial was lower (62 vs. 68 years, though the event rates in both trials were similar); the ACCORD trial was smaller; and SPRINT was stopped early for benefit, which could have exaggerated treatment effects.

Blood Pressure Targets for Secondary Stroke Prevention

One trial included only patients with lacunar stroke and compared SBP targets of less than 130 mm Hg versus 130 to 140 mm Hg (15). The other trial included patients with prior ischemic or hemorrhagic stroke or transient ischemic attack and randomly assigned them to the addition of an ACEI with or without a diuretic or to placebo (23). Achieved SBP in both trials was 130 to 140 mm Hg. Pooled analyses showed that more intensive BP management decreased the risk for recurrent stroke (RR, 0.76 [CI, 0.66 to 0.92]; $I^2 = 0%$) but not cardiac events (RR, 0.78 [CI, 0.61 to 1.08]) or mortality (RR, 0.98 [CI, 0.85 to 1.19]) (Figure 2 of the Supplement).

Harms

General Adverse Effects and Medication Burden

Ten trials reported withdrawals due to adverse events: 4 found a significant increase in the intervention group (most commonly due to cough or hypotension) (18, 23, 26, 30), whereas 6 did not find an increase (14, 16, 19, 20, 24, 25). Meta-analysis was not possible because of excess heterogeneity ($I^2 = 92.1%$). In general, the mean number of medications or the proportion of participants taking multiple medications was higher in the intervention groups, though variation in reporting precludes precise estimates (Table 1; Table 1 of the Supplement).

Renal Outcomes

We found low-strength evidence from 13 trials that more intensive BP treatment was not associated with worse renal outcomes, although outcome definitions varied across trials; results were inconsistent; and the rate of significant outcomes, such as end-stage renal disease, was low (Table 3 of the Supplement). Two trials found an increased risk for acute renal failure with more aggressive BP lowering (3, 31).

Cognitive Outcomes

We found moderate-strength evidence from 7 randomized, controlled trials that use of antihypertensive treatment to achieve moderate BP control for up to 5

Table 1. Characteristics of Trials Included in the Meta-analysis

Study, Year (Reference)	BP Goals (T vs. C), mm Hg	Follow-up, y	Antihypertensive Treatment Strategies	Participants (T vs. C), n
ACCORD, 2010 (11)	SBP: <120 vs. <140	Mean: 4.7	Step 1: Diuretic combined with ACEI or β -blocker. Medications that could be added to reach BP target: dihydropyridine and nondihydropyridine CCB, α -blocker, ARB, sympatholytics, α -/ β -blocker, and the following combinations: thiazide diuretic + potassium-sparing diuretic; β -blocker + diuretic; ACEI + diuretic, ARB + diuretic; and dihydropyridine CCB + ACEI.	2362 vs. 2371
Cardio-Sis, 2009 (12)	SBP: <130 vs. <140	Median: 2.0	Diuretics (hydrochlorothiazide + ramipril or telmisartan, furosemide), β -blocker (bisoprolol), CCB (amlodipine), ACEI (ramipril \pm hydrochlorothiazide), ARB (telmisartan \pm hydrochlorothiazide), centrally acting sympathetic-inhibiting drugs (clonidine), plus drugs previously taken by participants.	557 vs. 553
HOT, 1998 (13)	DBP: \leq 80 vs. \leq 85 vs. \leq 90	Mean: 3.8	Step 1: Low-dose felodipine Step 2: + low-dose ACEI or β -blocker Step 3: + high-dose felodipine Step 4: + high-dose ACEI or β -blocker Step 5: + other, mainly thiazide	6262 vs. 6264 vs. 6264
JATOS, 2008 (14)	SBP: <140 vs. <160	Mean: 2.0	Efonidipine, 20-40 mg once daily, increasing to 60 mg once or twice daily if needed. Drugs other than CCBs were added if needed.	2212 vs. 2206
SPS3, 2013 (15)	SBP: <130 vs. 130-149	Mean: 3.7	At the discretion of the physician; \geq 1 drug from each major class was available.	1501 vs. 1519
SPRINT, 2015 (3)	SBP: <120 vs. <140	Median: 3.26	Thiazide-type diuretic and/or ACEI or ARB (but not both) and/or CCB. Titrate or add therapy not already in use as needed.	4678 vs. 4683
VALISH, 2010 (16)	SBP: <140 vs. <150	Median: 3.0	Step 1: Valsartan, 40-80 mg once daily Step 2: Increase valsartan up to 160 mg and/or other agents (diuretics and CCBs) except other ARBs	1545 vs. 1534
ADVANCE, 2007 (18)	NR	Mean: 4.3	T: Perindopril + indapamide \pm physician's discretion C: Placebo \pm physician's discretion Not permitted: thiazide diuretics, other ACEI	5569 vs. 5571
EWPHE, 1985 (20)	\leq 160/90	Mean: 4.7	T: Hydrochlorothiazide + triamterene \pm methyl dopa C: Placebo	416 vs. 424
FEVER, 2005 (21)	<160/95	Mean: 3.3	T: Felodipine \pm physician's discretion C: Placebo \pm physician's discretion	4841 vs. 4870

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Table 1—Continued

Mean Age (SD), y	Male, %	Comorbidities, %	BP (T vs. C), mm Hg		Mean Number or Percentage Distribution of Antihypertensive Medications Used (T vs. C)
			Baseline	Achieved	
62.2 (6.9)	52.3	DM: 100 CAD: 33.7	139.0/75.9 vs. 139.4/76.0	119.3/64.4 vs. 133.5/70.5	Mean: 3.5 vs. 2.2
67 (7.0)	52.3	CAD: 12 CVD: 8.5	163.3/89.7 vs. 163.3/89.6	131.9/77.4 vs. 135.6/78.7	Mean: 2.9 vs. 2.9 Odds ratio (95% CI) at 2-y follow-up (T vs. C): Diuretic: 1.36 (1.08-1.71) ARB: 1.17 (0.90-1.52) β -Blocker, CCB, and ACEI: No difference
61.5 (7.5)	53	MI: 1.5 CVD: 1.2 DM: 8	170/105 vs. 170/105 vs. 170/105	By assigned DBP (≤ 80 vs. ≤ 85 vs. ≤ 90 mm Hg): 139.7/81.1 vs. 141.4/83.2 vs. 143.7/85.2	Proportion using drug per DBP target (≤ 80 vs. ≤ 85 vs. ≤ 90 mm Hg): Felodipine: 79% vs. 78% vs. 77% ACEI: 45% vs. 42% vs. 35% β -Blocker: 32% vs. 28% vs. 25% Diuretic: 24% vs. 22% vs. 19%
73.6 (5.2)	38.8	DM: 11.8 CVD: 9.1 Renal disease: 9.9	171.6/89.1 vs. 171.5/89.0	139.3/76.1 vs. 146.5/78.5	Proportion using: 1 drug: 47.7% vs. 57.8% ($P < 0.001$) 2 drugs: 31.6% vs. 27.3% ($P = 0.002$) 3 drugs: 15.1% vs. 9.3% ($P < 0.001$) 4 drugs: 2.9% vs. 1.9% ($P = 0.05$) 5 drugs: 0.1% vs. 0.14% ($P = 1.0$)
63 (11.0)	63	DM: 36.5 CVD: 100 CAD: 10.5	142/78 vs. 144/79	SBP: 127 vs. 138 DBP: NR	Mean: 2.4 vs. 1.8 ($P < 0.001$) Drugs used by T vs. C at 1 y: Thiazides: 58% vs. 43% ACEI/ARB: 80% vs. 63% CCB: 43% vs. 30% β -Blocker: 31% vs. 25% Other: 11% vs. 9%
67.9 (9.5)	64.4	DM: 0 CVD: 0 CAD: 20.1 CKD: 28.3	139.7/78.2 vs. 139.7/78.0	121.5/66.0 vs. 134.6/74.0	Mean (SD): 2.7 (1.2) vs. 1.8 (1.1) Proportion using: 0 drugs: 2.7% vs. 11.3% 1 drug: 10.5% vs. 31.1% 2 drugs: 30.5% vs. 33.3% 3 drugs: 31.8% vs. 17.2% ≥ 4 drugs: 24.3% vs. 6.9%
76.1 (4.1)	37.6	DM: 13.0 CVD: 6.5 CAD: 5.0 Renal insufficiency: 1.4	169.5/81.7 vs. 169.6/81.2	136.6/74.0 vs. 142.0/76.5	Proportion using: Valsartan only: 56.1% vs. 57.6% ($P = \text{NS}$) (mean dose: 91.2 vs. 88.1 mg [$P = 0.0236$]) CCB: 37.1% vs. 36.4% ($P = \text{NS}$) Diuretic: 13.0% vs. 11.9% ($P = \text{NS}$) β -Blocker: 6.0% vs. 5.0% ($P = \text{NS}$) ACEI: 2.1% vs. 2.5% ($P = \text{NS}$)
66 (6.5)	57	DM: 100 CAD: 12 CVD: 9	145/81 vs. 145/81	136/73 vs. 140/73	Proportion 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 -Blocker: 31% vs. 35% CCB: 32% vs. 43% Thiazides: 3% vs. 5% Other diuretics: 14% vs. 16%
72 (8.0)	69.8	CAD: 3.5 CVD: 1.2	183/101 vs. 182/101	148/85 vs. 167/90	Proportion of treatment group using methyl dopa in addition to active study medication: 35%
61.5 (7.2)	61	DM: 12.8 CAD: 15.5 CVD: 14.9	158.7/92.4 vs. 158.9/92.7	138.1/82.3 vs. 141.6/83.9	Proportion using add-on medication: None: 66.1% vs. 57.7% ($P < 0.001$) Diuretic: 12.6% vs. 19.8% ($P < 0.001$) β -Blocker: 7.3% vs. 8.8% ($P = 0.008$) α -Blocker: 0.2% vs. 0.6% ($P = 0.004$) ACEI: 16.8% vs. 26.0% ($P < 0.001$) ARB: 0.9% vs. 1.1% ($P = 0.325$) CCB: 12.1% vs. 12.8% ($P = 0.263$) Other antihypertensive medications: 5.5% vs. 8.2% ($P < 0.001$)

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Table 1—Continued

Study, Year (Reference)	BP Goals (T vs. C), mm Hg	Follow-up, y	Antihypertensive Treatment Strategies	Participants (T vs. C), n
HYVET, 2008 (22)	<150/80	Median: 1.8	T: Indapamide ± perindopril C: Placebo Patients were withdrawn from double-blind follow-up if they used additional antihypertensive agents for >3 mo or had received the maximum dose of the study drugs yet had an SBP ≥220 mm Hg or a DBP ≥110 mm Hg on ≥2 consecutive visits ≥2 wk apart.	1933 vs. 1912
PROGRESS, 2001 (23)	NR	Mean: 3.9	T: Perindopril ± indapamide C: Placebo	3051 vs. 3054
SCOPE, 2003 (25)	<160/85	Mean: 3.7	T: Candesartan ± physician's discretion C: Placebo ± physician's discretion Not permitted: ACEIs and ARBs	2477 vs. 2460
SHEP, 1991 (26)	SBP: <160 or reduction of ≥20*	Mean: 4.5	T: Chlorthalidone ± atenolol or reserpine C: Placebo Upper BP threshold above which active treatment was indicated in placebo group (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
Syst-Eur, 2014 (29)	SBP: <150 (reduction of ≥20)	Median: 2.0	T: Nitrendipine ± enalapril ± hydrochlorothiazide C: Placebo	2297 vs. 2398

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ACEI = angiotensin-converting enzyme inhibitor; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicon - MR Controlled Evaluation; ARB = angiotensin II-receptor blocker; BP = blood pressure; C = control/comparator group; CAD = coronary artery disease; Cardio-Sis = Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control; CCB = calcium-channel blocker; CKD = chronic kidney disease; 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; 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; NR = not reported; NS = not statistically significant; 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; T = treatment group; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

* For participants with an SBP ≥180 mm Hg, the goal was <160 mm Hg. For those with an SBP between 160 and 179 mm Hg, the goal was an SBP reduction of ≥20 mm Hg.

years does not worsen cognitive outcomes compared with less strict BP control (Table 4 of the Supplement). The mean age of trial participants ranged from 62 to 83 years, baseline cognitive function was generally normal, and patients in all but 1 trial had achieved SBP of 140 to 150 mm Hg (those in 1 trial had achieved SBP of 119 mm Hg). In 4 trials of patients without a prior history of cerebrovascular disease, there was no effect on rates of incident dementia (odds ratio, 0.89 [CI, 0.74 to 1.07]) (32–35). Another trial of patients with a prior history of stroke also found no difference in rates of incident dementia (RR, 0.88 [CI, 0.72 to 1.08]) (34). Among the observational studies, 2 found that the lowest rates of cognitive decline were associated with achievement of an SBP of 135 to 150 mm Hg (36, 37) and 140 to 160 mm Hg (38).

Quality of Life and Functional Status

Overall, we found moderate-strength evidence from prospective substudies of 4 large trials with low risk of bias that use of antihypertensive therapy to achieve moderate BP control (SBP of 140 to 150 mm Hg) was not associated with a deterioration in quality of life compared with less intensive BP control (39–42). We found low-strength evidence from 1 large trial with low risk of bias that moderate BP control was not associated with deterioration in functional status compared with less intensive control (39).

Falls, Fractures, and Syncope

We found moderate-strength evidence from 3 large trials with low risk of bias that more intensive BP

Table 1—Continued

Mean Age (SD), y	Male, %	Comorbidities, %	BP (T vs. C), mm Hg		Mean Number or Percentage Distribution of Antihypertensive Medications Used (T vs. C)
			Baseline	Achieved	
83.5 (3.2)	60.5	DM: 6.9 CAD: 3.2 CVD: 6.8	173.0/90.8 vs. 173.0/90.8	143.5/77.9 vs. 158.5/84.0	Proportion using drug vs. corresponding placebo at 2-y follow-up: Indapamide only: 25.8% vs. 14.2% Indapamide + perindopril (2 mg): 23.9% vs. 13.4% Indapamide + perindopril (4 mg): 49.5% vs. 71.8%
64 (10.0)	70	DM: 13 CVD: 100	147/86 vs. 147/86	138/82 vs. 147/86	Proportion of treatment group assigned to use: Perindopril only: 42% Perindopril + indapamide: 58%
76.4 (NR)	64.5	DM: 12 CAD: 4.5 CVD: 3.9	166.0/90.3 vs. 166.5/90.4	145.2/79.9 vs. 148.5/81.6	Proportion using: Study drug only: 25% vs. 16% Study drug + hydrochlorothiazide: 26% vs. 18% Add-on treatment: 49% vs. 66% Diuretic: 33% vs. 44% β -Blocker: 17% vs. 26% CCB: 18% vs. 28% ACEI: 8% vs. 11% ARB: 3% vs. 4%
71.6 (6.7)	64.5	DM: 10.1 CAD: 4.9 CVD: 1.4	170.5/76.7 vs. 170.1/76.4	143/68 vs. 155/72	Proportion using: No active drug: 9% vs. 53% Chlorthalidone: 46% of treatment group Chlorthalidone + atenolol: 23% of treatment group Other active medication: 21% of treatment group Proportion meeting escape criteria: 3% vs. 15% Proportion prescribed active hypertensive therapy in placebo group: 13% at year 1, 33% at year 3, and 44% at year 5
70.25 (6.7)	33.2	DM: 10.5 CAD: 29.8	173.8/85.5 overall; $P =$ NS for T vs. C	NR	Proportion using: 0 drugs: 14.9% of placebo group 1 drug: 55.0% of treatment group 2 drugs: 26.1% of treatment group 3 drugs: 16.4% of treatment group Proportion using drug vs. corresponding placebo at 2-y follow-up: Nitrendipine: 84.4% vs. 92.4% Enalapril: 32.6% vs. 55.1% Hydrochlorothiazide: 16.2% vs. 34.2%

treatment (SBP targets <120 and <150 mm Hg and achieved SBP <150 mm Hg) did not increase risk for fracture (43, 44). We found low-strength evidence that more aggressive BP control did not consistently increase risk for falls. Two of the trials found that very aggressive BP lowering (SBP <120 mm Hg) did not increase risk for falls (3, 43), whereas a third trial found that moderate BP control (SBP <150 mm Hg) was associated with a small increase in risk for falls (26). We found low-strength evidence of increased risk for syncope from more aggressive BP control across 3 trials with achieved SBP ranging from 121.5 to 143 mm Hg (RR, 1.52 [CI, 1.22 to 2.07]) (Figure 3 of the Supplement).

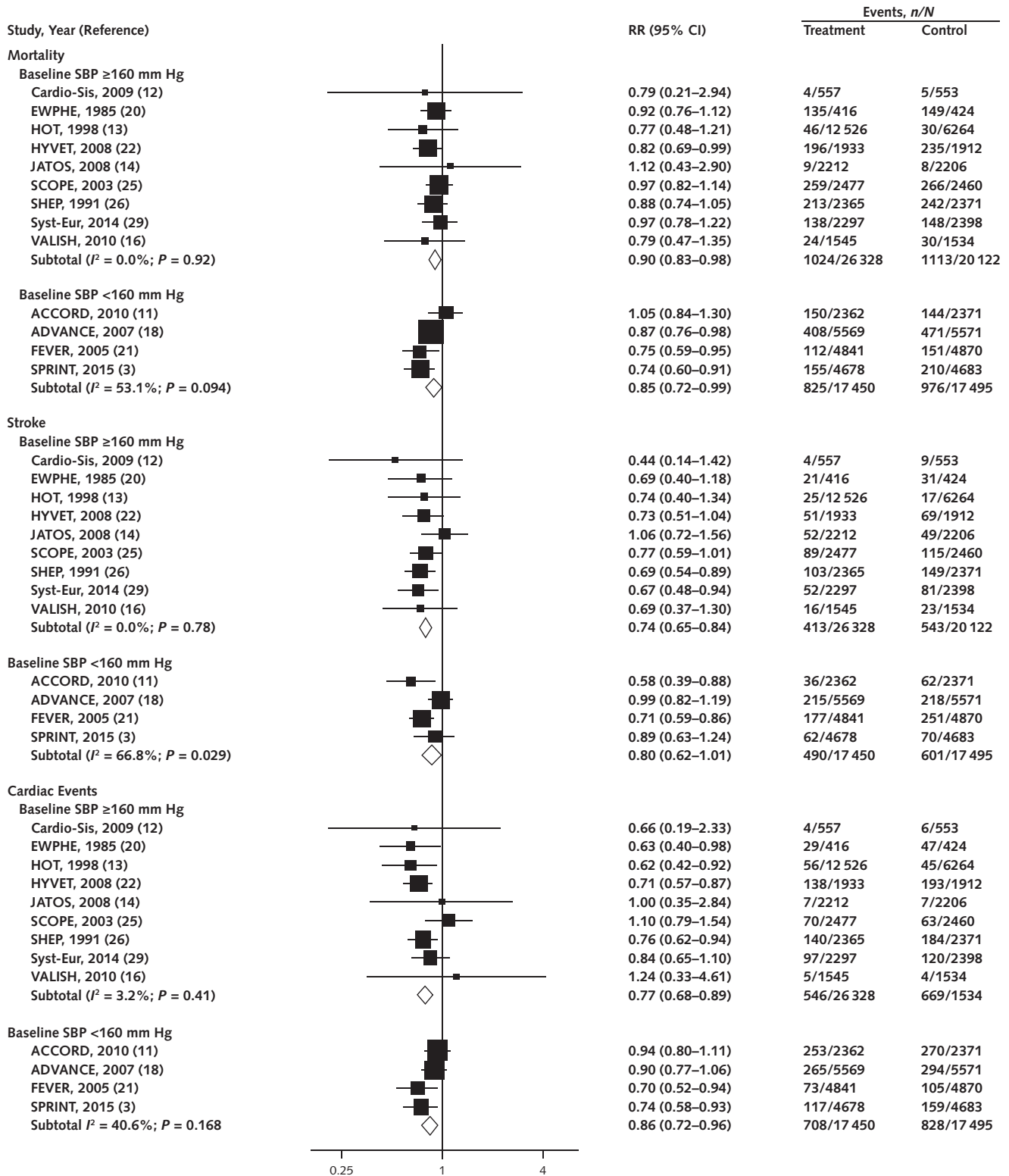
The Role of DBP

In 15 trials, patients had isolated systolic hypertension (SBP >140 mm Hg with DBP \leq 90 mm Hg); there were no trials in which patients had isolated diastolic hypertension (mean DBP >90 mm Hg and mean SBP <140 mm Hg). The achieved DBP was less than 90 mm Hg in all trials. The HOT (Hypertension Optimal Treatment) trial enrolled patients with high DBP (>100 mm

Hg) and compared 3 DBP targets (\leq 80, \leq 85, and \leq 90 mm Hg) (13). Compared with patients assigned to the target of 90 mm Hg or lower, patients assigned to lower targets had reduced risk for cardiac events (RR, 0.62 [CI, 0.42 to 0.92]) but not for stroke (RR, 0.74 [CI, 0.40 to 1.36]) or death (RR, 0.77 [CI, 0.48 to 1.21]). Of note, achieved DBP was still greater than 80 mm Hg in each group in the HOT trial. Overall, patients with DBP greater than 90 mm Hg seem to benefit from BP-lowering treatment, but these patients also had marked systolic hypertension at baseline (13, 20–22, 25, 27). There was no evidence to assess whether treatment of diastolic hypertension in the absence of systolic hypertension is beneficial.

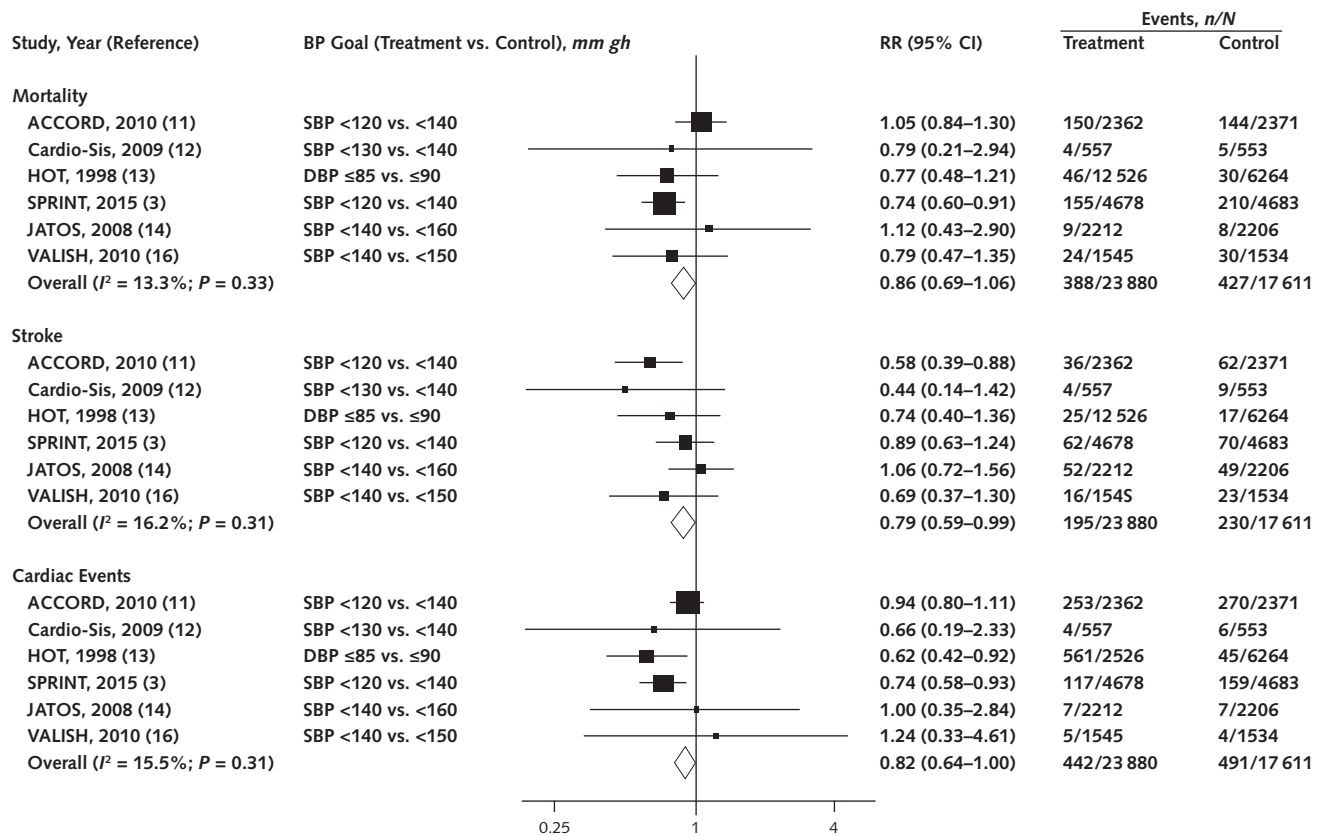
The only 2 studies of patients with an achieved DBP less than 70 mm Hg found no increased risk for falls, fractures, or cognitive impairment. However, there was an increased risk for symptomatic hypotension in both trials (3, 11) and an increased risk for syncope in 1 trial (3). Whether these effects were seen primarily in patients with very low DBP, SBP, or both is unclear.

Figure 1. RRs for death, stroke, and cardiac events, with trials combined by mean baseline SBP ≥ 160 or < 160 mm Hg.



ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicon - MR Controlled Evaluation; Cardio-Sis = Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control; EWPHE = European Working Party on High Blood Pressure in the Elderly; FEVER = Felodipine Event Reduction; 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.

Figure 2. RRs for death, stroke, and cardiac events in trials in which the intervention group had a target of SBP <140 mm Hg or DBP ≤85 mm Hg and the control group had a less strict target.



ACCORD = Action to Control Cardiovascular Risk in Diabetes; BP = blood pressure; C = control group; Cardio-Sis = Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control; 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; SPRINT = Systolic Blood Pressure Intervention Trial; T = treatment group; VALISH = Valsartan in Elderly Isolated Systolic Hypertension.

Modifications by Age and Comorbidity

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 persons aged 75 years or older and those younger than 75 years (Table 5 of the Supplement). One study found that the direction of association with age varied by outcome (45).

We found low-strength evidence of greater absolute treatment effects among patients with high cardiovascular risk and similar relative treatment effects across risk groups. Three of 4 studies reported outcomes according to cardiovascular risk strata and found higher absolute risk reduction in patients in the highest-risk strata (46–48). A fourth study found no interaction between risk profile and treatment effect (3).

It is difficult to draw conclusions about treatment effects in diabetic and nondiabetic patients by using study-level comparisons because relatively few studies included only diabetic patients or excluded them and because there are major differences among these studies other than diabetes status. Subgroup analyses from

7 studies suggest that diabetic patients are at least as likely to benefit from BP lowering (Table 6 of the Supplement).

No studies examined how comorbidity burden modifies BP treatment effects. Patients with a high burden of comorbidity were probably not included in the overall group of studies (Table 7 of the Supplement). Because we excluded trials examining BP medications for treatment of systolic heart failure or acute myocardial infarction, it is not surprising that 14 trials excluded patients with heart failure and 11 excluded patients with recent cardiovascular events. However, 17 trials excluded patients on the basis of abnormal renal function criteria; 12 excluded patients with cancer or other life-limiting illness; 9 excluded patients according to presence or severity of diabetes; and 15 used criteria that would implicitly or explicitly exclude patients with dementia, diminished functional status, or both. In 2 trials (49, 50), treatment effects did not differ according to frailty status, but these were post hoc analyses and a large amount of data were missing in 1 of the trials (49).

DISCUSSION

Overall, we found high-strength evidence that treatment to current BP targets (<150/90 mm Hg) in patients older than 60 years substantially reduces mortality, stroke, and cardiac events (Table 2). Many of these data come from trials in which the mean baseline SBP was greater than 160 mm Hg. We also found evidence, driven mainly by 1 large trial (3), that lower targets (SBP <140 mm Hg or DBP ≤85 mm Hg) reduced stroke (moderate-strength evidence) and cardiac events (low-strength evidence) compared with higher targets; mortality was also reduced, but not significantly (low-strength evidence). There are few data to directly help distinguish benefits of SBP of 140 versus 150 mm Hg. Most of the trials of patients achieving SBP less than 140 mm Hg were treat-to-target trials. Only 1 trial included patients with baseline SBP of 140 to 150 mm Hg, and it found an improvement in mortality but not in other outcomes (18). We found moderate-strength evidence that more aggressive BP control (SBP <140 mm Hg) in patients with prior stroke substantially reduced rates of recurrent stroke.

Overall, the treat-to-target trials support a lower BP target in some patients. Several issues must be considered in the choice of a lower treatment target. First, there are tradeoffs that patients may weigh differently based on their values and preferences. Tighter control may prevent, on average, roughly 10 to 20 events for every 1000 high-risk patients treated over 5 years across a population (Table 2), but more aggressive treatment is likely associated with greater medication burden and higher risk for adverse effects, such as hypotension and syncope. On the other hand, we found that lower targets are unlikely to increase the risk for dementia, fractures, and falls or reduce quality of life.

Second, inconsistent findings make it more difficult to apply trial results broadly. The most important inconsistencies are between the ACCORD trial and SPRINT, both of which enrolled patients at high cardiovascular risk and targeted SBP less than 120 mm Hg but reached different conclusions (3, 11). It is unclear which differences in study design or patient population are responsible for the discrepant findings: The ACCORD trial included only diabetic patients whereas SPRINT excluded them, and SPRINT was a larger study with older patients but was stopped early for benefit.

Third, there is little direct evidence to guide choice of target within the SBP range of 120 to 140 mm Hg. A substantial proportion of intervention patients in SPRINT achieved an SBP of 120 to 130 mm Hg, though the target was less than 120 mm Hg and the mean achieved SBP was 121.4 mm Hg.

Fourth, the evidence for lower treatment targets applies to patients at high cardiovascular risk. SPRINT enrolled only patients with known cardiovascular disease or a 10-year Framingham risk score of at least 15%. Individual patient-level data suggest that the absolute treatment benefits are substantially larger in those with higher cardiovascular risk (6, 51). The degree to which an individual patient will benefit from

more intensive treatment likely depends on their risk profile, but existing risk calculators may substantially overestimate risk and, therefore, the absolute expected benefit (52).

Finally, it is critically important to consider that small variations in BP measurement technique can have large effects, though the degree to which variations in measurement technique will change BP for an individual patient is impossible to predict (53). Most trial protocols specified measurement of BP while the patient was seated after 5 minutes of rest; clinicians should follow similar procedures.

We found no evidence examining how multiple comorbidities (which may lead to burdensome therapy regimens and adverse medication interactions) modify BP treatment effects. Although recent substudies from SPRINT and HYVET (Hypertension in the Very Elderly Trial) suggest that patient frailty does not modify treatment effects (49, 50), few data remain to apply to patients who are institutionalized, have dementia, or have significant multimorbidity.

Our review adds to the literature by focusing on older adults, comprehensively examining short- and long-term harms, and analyzing studies that directly compared treatment targets. Prior meta-analyses have focused on other populations and have not included newer studies (54, 55). Although these analyses have found benefit from more aggressive BP treatment, they also found that most of the benefit was seen in higher-risk patients or those with higher baseline BPs. A more recent meta-analysis found that treatment with antihypertensive medication improved outcomes down to an SBP less than 130 mm Hg and effects did not differ on the basis of cardiovascular risk, but it included a broad array of studies, including studies of normotensive patients (56).

Several important limitations must be considered. Most important, the differences among trials in treatment, patient population, and secular changes in co-interventions should temper the use of meta-analytic estimates alone to understand treatment effects; it is important to consider summary estimates in addition to a qualitative consideration of trial differences. We emphasized analyses based on baseline BP and treatment target comparisons because we felt that these parallel clinical treatment choices and reliance on analyses based solely on achieved BP can be misleading (57), but we acknowledge differences of opinion with regard to these choices. Finally, we were unable to determine how choice of medication class influenced results, though we did not find a pattern of differential results according to medication type, which is consistent with a prior individual patient-level meta-analysis of BP treatment trials (not confined to older adults) (51).

In conclusion, lowering BP in adults older than 60 years reduces mortality, stroke, and cardiac events. The most consistent and largest effects were seen in studies of patients with higher baseline BP (SBP ≥160 mm Hg) achieving moderate BP control (<150/90 mm Hg). Lower treatment targets (<140/85 mm Hg) are likely to be beneficial for some patients at high cardiovascular

Table 2. Summary of the Evidence on More Versus Less Intensive Treatment for Hypertension in Elderly Adults

Studies, n	Total Patients, n	Combined Estimates	Estimate of Events Prevented per 1000 High-Risk Patients Over 5 y (95% CI)*	Strength of Evidence†	Summary of Findings
Mortality					
9 RCTs‡	46 450	RR: 0.90 (0.83-0.98) ARR: 1.64	34 (7-58)	High§	Consistent benefit of treating BP to levels <150/90 mm Hg.
6 RCTs	41 491	RR: 0.86 (0.69-1.06) ARR: 0.80	18 (NA¶ -40)	Low	Lower treatment targets (SBP <140 mm Hg or DBP ≤85 mm Hg, or lower) associated with nonsignificant mortality reduction compared with higher targets. Findings were inconsistent across studies, and estimate was imprecise.
Stroke					
9 RCTs‡	46 450	RR: 0.74 (0.65-0.84) ARR: 1.13	26 (16-35)	High§	Clear, consistent benefit of treating BP to levels <150/90 mm Hg.
6 RCTs	41 491	RR: 0.79 (0.59-0.99) ARR: 0.49	9 (0-17)	Moderate	Lower treatment targets (SBP <140 mm Hg or DBP ≤85 mm Hg, or lower) reduced the risk for stroke compared with higher targets; some inconsistency, but relatively stable effect across analyses.¶
Cardiac events					
9 RCTs‡	46 450	RR: 0.77 (0.68-0.89) ARR: 1.25	65 (31-90)	High§	Clear, consistent benefit of treating BP to levels <150/90 mm Hg.
6 RCTs	41 491	RR: 0.82 (0.64-1.00) ARR: 0.94	18 (NA¶ -36)	Low	Lower treatment targets (SBP <140 mm Hg or DBP ≤85 mm Hg, or lower) may reduce the risk for cardiac events compared with higher targets. Findings were inconsistent across studies, and estimate was imprecise.
Short-term adverse events					
19 RCTs	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 for syncope was increased in 2 of 3 trials reporting this outcome. Excessive heterogeneity among trials precluded pooling of results.
Renal outcomes					
13 RCTs	66 607	-	-	Low	More intensive BP 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	25 901	Incident dementia in 4 RCTs of patients without prior stroke: odds ratio, 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	11 680	-	-	Moderate (fracture)	Mixed findings: 3 trials found no effect of lower BP targets on risk for fracture. 2 trials with an SBP target of 120 mm Hg found no effect on risk for falls, whereas a third (with achieved SBP <150 mm Hg) found a small increase in risk for falls.
Falls: 3 RCTs	17 196	-	-	Low (falls)	-

Continued on following page

Table 2—Continued

Studies, n	Total Patients, n	Combined Estimates	Estimate of Events Prevented per 1000 High-Risk Patients Over 5 y (95% CI)*	Strength of Evidence†	Summary of Findings
Quality of life					
4 RCTs	7154	-	-	Moderate (quality of life) Low (functional status)	Moderate BP control (SBP of 140–150 mm Hg) did not affect quality of life. 1 study found no effect on functional status.
Effects of age					
12 RCTs	76 137	-	-	Low	Similar effects across different age groups in age-treatment interaction analyses, but these were 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 frail elderly adults					
2 RCTs	5166	-	-	Insufficient	Treatment effects did not vary with frailty score in post hoc analyses from 2 trials, 1 of which had a 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 patients with stroke					
2 RCTs	9125	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 mm Hg reduced recurrent stroke.

ARR = absolute risk reduction; BP = blood pressure; DBP = diastolic blood pressure; NA = not applicable; RCT = randomized, controlled trial; RR = relative risk; SBP = systolic blood pressure.

* We estimated events prevented by applying the summary RR from meta-analyses to observed control group event rates that were standardized to 5 y. Because poorly controlled BP itself contributes to cardiovascular risk, we used different control group event rate data from the 2 most contemporary trials for each set of analyses. We used data from HYVET (Hypertension in the Very Elderly Trial) (22) to estimate event rates in the higher baseline BP analyses and from SPRINT (Systolic Blood Pressure Intervention Trial) (the older age subgroup, because the mean age was comparable to that in HYVET) for the treat-to-target analyses (50).

† The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence and the internal validity of individual studies. "High" indicates that further research is very unlikely to change our confidence on the estimate of effect. "Moderate" indicates that further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate. "Low" indicates that further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate. "Insufficient" indicates that any estimate of effect is very uncertain.

‡ The analyses presented here are of trials of patients with a baseline SBP ≥160 mm Hg. The achieved SBP in 3 of the trials was <140 mm Hg, but these studies contributed relatively few events. Achieved SBP in all other studies was ≥140 mm Hg.

§ Most of the evidence comes from trials in which the baseline SBP was ≥160 mm Hg and the achieved SBP was 140–150 mm Hg. These are large trials providing consistent evidence and a precise summary estimate.

|| All trials that tested strict vs. less strict BP targets in which the target BP in the intervention group was SBP <140 mm Hg or DBP <85 mm Hg, or even lower.

¶ Because the upper bound of the CI for RR was ≥1.00.

risk, but the results across trials are less consistent. Lower treatment targets are largely supported by findings from 1 trial that targeted SBP less than 120 mm Hg and in which most intervention patients achieved SBP less than 130 mm Hg. In patients with cerebrovascular disease, more aggressive BP lowering (SBP <140 mm Hg) likely reduces recurrent stroke. Lower treatment

targets are associated with higher medication burden and an increased risk for short-term harms, such as hypotension. On the other hand, evidence that there is not an increased risk for cognitive impairment, falls, and reduced quality of life may provide flexibility for providers in crafting an individualized antihypertensive treatment plan. There are few data to assess the risks

and benefits of antihypertensive treatment among institutionalized elderly patients or those with multiple comorbidities.

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Disclaimer: This article is based on research conducted by the Evidence-based Synthesis Program Center located at the Veterans Affairs Portland Health Care System, Portland, Oregon. The findings and conclusions in this article are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the U.S. Department of Veterans Affairs or the U.S. government. Therefore, no statement in this article should be construed as an official position of the U.S. Department of Veterans Affairs.

Financial Support: This research was funded by the U.S. Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-1754.

Reproducible Research Statement: *Study protocol:* Available at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015017677. *Statistical code:* Available from Dr. Kansagara (e-mail, kansagar@ohsu.edu). *Data set:* Supplementary data are available in the Supplement.

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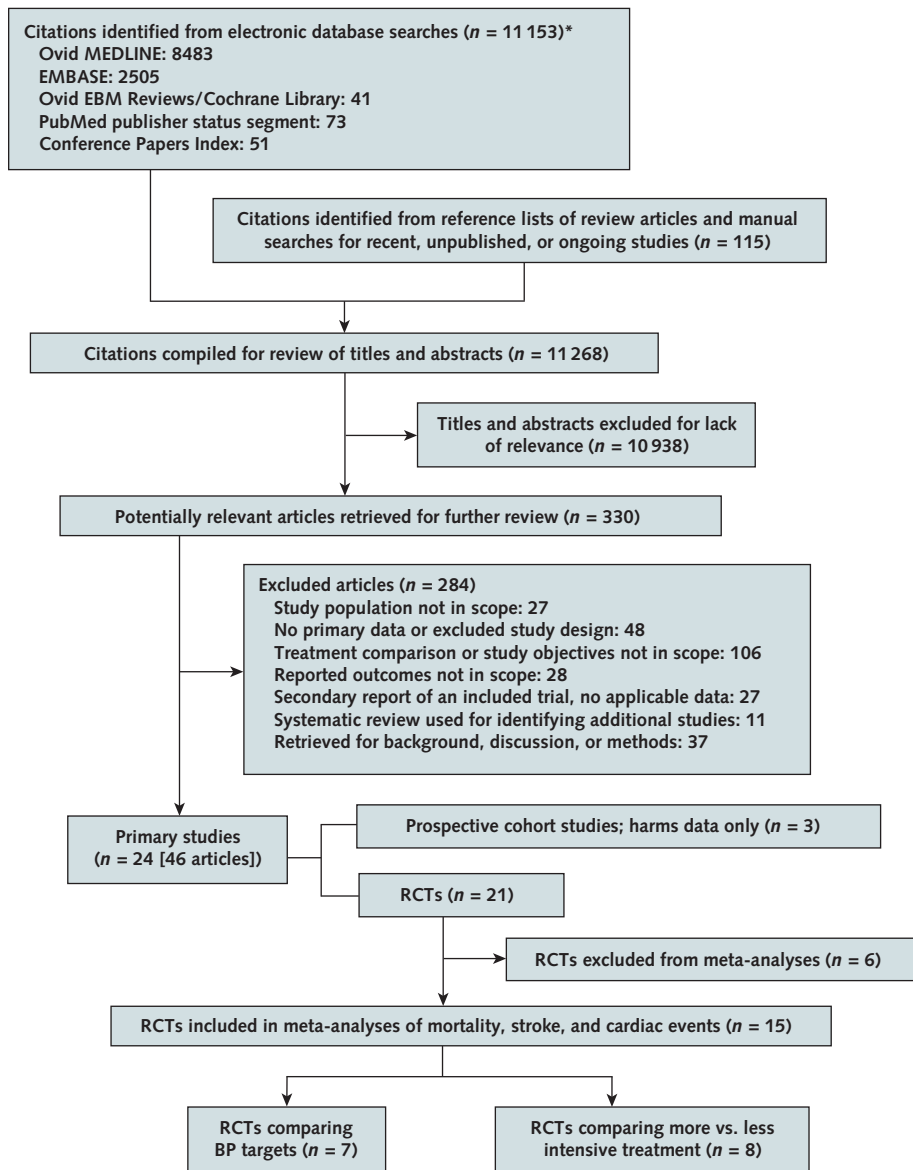
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Appendix Figure. Literature flow diagram.



BP = blood pressure; EBM = Evidence-Based Medicine; RCT = randomized, controlled trial.

* All databases were searched through 30 January 2015. The Ovid MEDLINE search was updated on 15 September 2016.