Original Investigation

Blood Pressure Lowering in Type 2 Diabetes
A Systematic Review and Meta-analysis

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IMPORTANCE Lowering blood pressure (BP) is widely used to reduce vascular risk in individuals with diabetes.

OBJECTIVE To determine the associations between BP-lowering treatment and vascular disease in type 2 diabetes.

DATA SOURCES AND STUDY SELECTION We searched MEDLINE for large-scale randomized controlled trials of BP-lowering treatment including patients with diabetes, published between January 1966 and October 2014.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted study characteristics and vascular outcome data. Estimates were stratified by baseline BP and achieved BP, and pooled using fixed-effects meta-analysis.

MAIN OUTCOMES AND MEASURES All-cause mortality, cardiovascular events, coronary heart disease events, stroke, heart failure, retinopathy, new or worsening albuminuria, and renal failure.

RESULTS Forty trials judged to be of low risk of bias (100 354 participants) were included. Each 10-mm Hg lower systolic BP was associated with a significantly lower risk of mortality (relative risk [RR], 0.87; 95% CI, 0.78-0.96); absolute risk reduction (ARR) in events per 1000 patient-years (3.16; 95% CI, 0.90-5.22), cardiovascular events (RR, 0.89 [95% CI, 0.83-0.95]; ARR, 3.90 [95% CI, 1.57-6.06]), coronary heart disease (RR, 0.88 [95% CI, 0.80-0.98]; ARR, 1.81 [95% CI, 0.35-3.11]), stroke (RR, 0.73 [95% CI, 0.64-0.83]; ARR, 4.06 [95% CI, 2.53-5.40]), albuminuria (RR, 0.83 [95% CI, 0.79-0.87]; ARR, 9.33 [95% CI, 7.13-11.37]), and retinopathy (RR, 0.87 [95% CI, 0.76-0.99]; ARR, 2.23 [95% CI, 0.15-4.04]). When trials were stratified by mean baseline systolic BP at greater than or less than 140 mm Hg, RRs for outcomes other than stroke, retinopathy, and renal failure were lower in studies with greater baseline systolic BP (*P* interaction <0.1). The associations between BP-lowering treatments and outcomes were not significantly different, irrespective of drug class, except for stroke and heart failure. Estimates were similar when all trials, regardless of risk of bias, were included.

CONCLUSIONS AND RELEVANCE Among patients with type 2 diabetes, BP lowering was associated with improved mortality and other clinical outcomes with lower RRs observed among those with baseline BP of 140 mm Hg and greater. These findings support the use of medications for BP lowering in these patients.

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By 2030, it is estimated that there will be at least 400 million individuals with type 2 diabetes mellitus worldwide, with many of those affected being relatively young and living in low- or middle-income countries.[1] Type 2 diabetes is associated with a substantially increased risk of macrovascular events such as myocardial infarction (MI) and stroke.[2] It is also now the leading cause of blindness in developed countries and is a leading cause of end-stage kidney disease through its effects on the microvasculature.[3,4] Blood pressure (BP) levels are on average higher among individuals with diabetes and increased BP is a well-established risk factor for people with diabetes.[5,6]

In general adult populations, the association of BP with disease outcomes is continuous, with increasing risks of events occurring in parallel with increasing BP levels from as low as 115 mm Hg for systolic and 75 mm Hg for diastolic.[7,8] A similar association has been reported for BP and the risks of macrovascular[9] and microvascular[10] disease in patients with type 2 diabetes. Although data for every population subset and every outcome are not available, the nature of the association of BP appears consistent across large and diverse population groups including men and women, different ethnicities, older and younger people, and among individuals with and without established vascular disease.[7,11]

Lowering BP in individuals with diabetes is an area of current controversy, with particular debate surrounding who should be offered therapy and the BP targets to be achieved. A number of recent guidelines (eTable 1 in the Supplement) have focused entirely on individuals with diabetes who have been diagnosed with hypertension and have established target levels for BP lowering that are less aggressive than previous recommendations. It is unclear whether the new guidelines have used the entire evidence base with respect to recommendations for BP lowering in patients with type 2 diabetes. To address this question, we conducted a comprehensive overview of the effects of BP-lowering treatment in patients with diabetes (regardless of the presence or absence of defined hypertension). We aimed to determine the extent to which BP-lowering treatment is associated with a lower risk of macrovascular outcomes and microvascular outcomes, with a specific focus on areas of current controversy using the totality of the applicable evidence.

Methods

Search Strategy

We conducted a systematic review and meta-analysis, using the approach recommended by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for meta-analyses of interventional studies.[12] Relevant studies were identified using the following search terms: *anti-hypertensive agents* or *hypertension* or *diuretics*, *thiazide* or *angiotensin-converting enzyme* or *receptors, angiotensin/antagonists & inhibitors* or *tetrazoles* or *calcium channel blockers* or *vasodilator agents* or the names of all BP-lowering drugs listed in the *British National Formulary* as keywords or text words or the MeSH (Medical Subject Headings [of the US National Library of Medicine]) term *blood pressure/drug effects*.[13] We used this existing strategy to identify BP-lowering trials published on MEDLINE, from January 1, 1966, to October 28, 2014, restricted to those published in MEDLINE-defined core clinical journals. The initial search was conducted by an experienced research librarian and no language restrictions were applied. Studies were restricted to clinical trials, controlled clinical trials, randomized controlled trials, or meta-analyses. Bibliographies of included studies and bibliographies of identified meta-analyses were searched by hand. We then manually examined whether each trial included patients with diabetes and searched for any reporting of results for the diabetic subgroup.

Eligibility

We included all randomized controlled trials of BP-lowering treatment in which the entire trial population comprised patients with diabetes or in which the results of a diabetic subgroup were able to be obtained. Randomized trials published between January 1966 and March 2014 were included. No trial was excluded due to the presence of comorbidities at baseline. Trials conducted in type 2 diabetic patients with heart failure and after MI were included. However, trials that were conducted in patients predominantly with type 1 diabetes were excluded. Studies that did not make a specific reference to diabetes type were included, assuming that the great majority of patients in these studies had type 2 diabetes. For inclusion, all trials were required to have greater than 1000 patient-years of follow-up in each randomized group to minimize risk of bias associated with small trials.[14]

Search and Extraction

Two researchers screened all abstracts identified in the initial search, excluding studies that violated inclusion criteria (presented in Eligibility). Following the initial abstract screen, full texts of all identified studies were acquired. Two researchers (C.E. and T.C.) then screened full-text studies in duplicate, with differences resolved by consensus. Once all eligible trials were identified, macrovascular and microvascular outcomes for diabetic subgroups were extracted independently by 2 researchers (C.E. and T.C.). Data regarding the patient population, drug or intervention in the treatment group, drug or intervention in the control group, sample size, duration, baseline BP, achieved BP in the treatment group, and mean reduction in BP (difference between achieved BP and baseline BP in the treated group minus the same difference in the control group) were extracted. If the baseline BP, each treatment group BP, or difference in BP levels between groups was unavailable for the subgroup with diabetes, we recorded the value for the entire trial.

In addition to all-cause mortality, data regarding 4 macrovascular outcomes were extracted: cardiovascular disease

(CVD) events (defined as myocardial infarction, sudden cardiac death, revascularization, fatal and nonfatal stroke and fatal and nonfatal heart failure); major coronary heart disease (CHD) events (defined as fatal and nonfatal MI and sudden cardiac death, with silent MI excluded[13]); stroke (fatal and nonfatal); and heart failure (both new diagnosis of heart failure for those without heart failure at baseline and hospitalization for individuals with heart failure at baseline). For microvascular outcomes, 3 outcomes were extracted: retinopathy (defined as progress of 3 or more steps on the Early Treatment of Diabetic Retinopathy Scale [ETDRS] [15]); renal failure (defined as end-stage renal disease requiring dialysis or transplantation or death due to renal disease); and albuminuria (development of microalbuminuria, as well as the composite of new or worsening albuminuria). For one trial, retinopathy was identified as participants requiring laser therapy for treatment of retinopathy rather than progression on the ETDRS; this was included in the meta-analysis.[16] For 6 trials, peripheral artery disease was included in the reported cardiovascular composite; these were included in the meta-analysis.[17-22]

For each outcome, both the total number of events and the summary statistic (either relative risk or hazard ratio with 95% CIs) were extracted if available. If a hazard ratio was provided, we utilized that ratio as a relative risk for the meta-analysis because hazard ratios avoid censoring associated with use of tabular data and have greater statistical power. However, if a hazard ratio was not provided, a relative risk ratio from the total number of events was calculated and used. If the total number of events was not provided, but a summary relative risk or hazard ratio was provided, the total number of events was derived from the reported relative risk or hazard ratio, to allow for the calculation of a pooled event rate.

Assessment of Methodological Quality

We used the Cochrane risk of bias tool to evaluate this risk of methodological quality within included trials.[23] Selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and investigators), detection bias (blinding of evaluators), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting) were judged to be of either low, unclear or high risk. The trial, as a whole, was then judged to be of low, unclear, or high risk of bias, based on whether the level of bias in domains may have led to material bias in the outcomes of interest.

Statistical Analysis

For all analyses, overall estimates of association were calculated using inverse variance weighted fixed-effects analysis with 95% CIs. Fixed-effects analysis was used because heterogeneity was low to moderate[24] and random-effects analysis, in certain circumstances, can give inappropriate weight to smaller studies.[25] Heterogeneity was characterized using the I^2 statistic. Tests of interaction between subgroups were performed using Cochran Q statistic. For our primary analysis, we restricted meta-analysis to trials judged to be of low risk of bias (total, 40).

Analyses were performed to determine: (1) whether BP-lowering treatment is associated with lower risks of all-cause mortality, macrovascular outcomes, and microvascular outcomes, and the magnitude of any such associations; (2) the associations between BP-lowering treatment and these outcomes stratified by initial BP level; (3) the associations between BP-lowering treatment and these outcomes stratified by achieved BP level; and (4) the associations between BP-lowering treatment and these outcomes based on different classes of BP-lowering medication used.

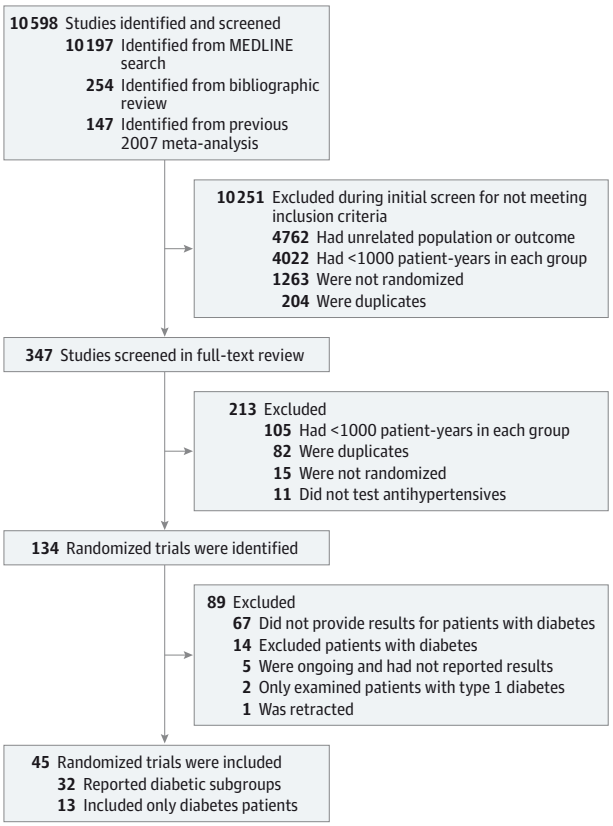
For the first objective, we included all trials that assigned individuals to a BP-lowering medication vs placebo or assigned individuals to higher or lower BP targets. For 2 trials that had 3 groups including a placebo, and for 1 trial that had 4 groups including a placebo, the active groups were combined for analysis by adding together all events and taking a weighted average of baseline BP, achieved BP, and BP reduction.[26-28]

To determine the standardized associations of BP-lowering treatment for every 10-mm Hg reduction in systolic BP, our primary analysis, the log of the summary statistic of each trial (relative risk or hazard ratio) and the standard error of the log was multiplied by 10-mm Hg/systolic BP reduction. For example, if the log-hazard ratio was −0.1 and the BP reduction was 5 mm Hg, the standardized log-hazard ratio was calculated to be −0.1 (10 mm Hg/ 5 mm Hg) = −0.2. If a standardized association was significant, we additionally calculated the absolute risk reduction (ARR) for each significant outcome in events per 1000 patient-years of follow-up. We derived the ARR for each outcome using the formula ARR = (1-RR [relative risk per 10-mm Hg lower SBP])(ACR [assumed control risk]).[23] We used the pooled event rate (in events per 1000 patient-years) in the control groups of meta-analyzed trials for each outcome as the ACR. The number needed to treat over 10 years (NNT) was derived from the inverse of the ARR (per 10 patient-years) and its 95% CI. For trials that did not report the number of events (and only reported an RR), we derived the number of events from the reported RR to allow for calculation of ARR.

Because many trials conducted in patients with diabetes and heart failure did not report the magnitude of BP reduction, and therefore could not be standardized, we examined whether there was heterogeneity between heart failure trials and non-heart failure trials in nonstandardized analyses.

To determine if the associations between BP-lowering treatment and outcomes varied by initial systolic BP, we stratified trials into categories of 140 mm Hg and greater and less than 140 mm Hg, according to the mean baseline BP of participants. Similarly, to determine if the associations between BP-lowering treatment and outcomes varied by achieved BP, we stratified trials into categories of 130 mm Hg and greater and less than 130 mm Hg according to the mean systolic BP achieved in the intervention group. As a sensitivity analysis, we: (1) excluded trials (total, 12) from relevant analyses in which it was necessary to impute BP data (either baseline, follow-up, or difference between groups) for the diabetic subgroup from the entire population; (2) examined nonstandardized associations by baseline

Figure 1. Flowchart of Trial Identification for Meta-analysis



and achieved BP; and (3) included 5 trials that were judged to be of unclear or high risk of bias.

Possible variation in the associations between BP-lowering treatment and outcomes by class of medication was examined by comparing all trials that tested a given class of medication (angiotensin-converting enzyme [ACE] inhibitor, angiotensin II receptor blocker [ARB], β-blocker, diuretic, calcium channel blocker [CCB]) against another class. One trial comparing classes of medication had 3 groups, but only provided summary statistics (RR reductions) for macrovascular outcomes.[22] Because inclusion of both comparisons would have led to duplicate counting of participants, we randomly selected a group for inclusion in the analysis. We did not include microvascular outcomes in the analysis by class of medication because there were not enough trials to allow for meta-analysis.

Analyses were performed using STATA statistical software version 12 (StataCorp) and R version 3.0 (R Project).

Results

Study Characteristics

In total, 10 598 abstracts were screened and 10 251 excluded (**Figure 1**). Next, 347 studies were screened in a full-text review and of these, an additional 213 were excluded. Of the 134 randomized trials identified, 89 trials were excluded, the majority because they did not provide separate results for patients with diabetes.

Thirty-three were considered trials that tested BP lowering, by either comparing a BP-lowering drug against a placebo (26 trials) or comparing BP lowering to different target levels (7 trials) (**Table**). Seventeen trials compared different classes of drugs against each other. At minimum, all 45 trials included a report about all-cause mortality or 1 prespecified macrovascular outcome, and 16 trials included a report about 1 of the 3 prespecified microvascular outcomes. Twelve BP-lowering trials reported only a baseline BP or achieved BP for the entire study population, but not separately for the diabetic subgroup. One trial was judged to be of high risk of bias due to evidence of poor allocation concealment, while 4 trials were judged to be of unclear risk of bias, and 40 trials of low risk of bias (eTable 2 in the Supplement). Therefore, 40 trials involving 100 354 participants formed the primary analysis, with an additional 5 trials (at unclear or high risk of bias) involving 4232 participants included in secondary analyses.

Associations Between BP-Lowering Treatment and Macrovascular and Microvascular Outcomes

A 10-mm Hg reduction in systolic BP was associated with a significantly lower risk of all-cause mortality (RR, 0.87 [95% CI, 0.78-0.96]), CVD events (RR, 0.89 [95% CI, 0.83-0.95]), CHD events (RR, 0.88 [95% CI, 0.80-0.98]), and stroke events (RR, 0.73 [95% CI, 0.64-0.83]). The associations for heart failure events (RR, 0.86 [95% CI, 0.74-1.00]) and renal failure (RR, 0.91 [95% CI, 0.74-1.12]) were not significant (**Figure 2**, eFigures 1-8 in the Supplement). For microvascular outcomes, a 10 mm Hg-lower systolic BP was associated with a lower risk of retinopathy (RR, 0.87 [95% CI, 0.76-0.99]) and albuminuria (RR, 0.83 [95% CI, 0.79-0.87]) (Figure 2). The corresponding ARRs, in events per 1000 patient-years of follow-up, were 3.16 (95% CI, 0.90-5.22) for all-cause mortality (number needed to treat [NNT] over 10 years = 32 [95% CI, 19-111]); ARR was 3.90 for CVD events (95% CI, 1.57-6.06; NNT = 26 [95% CI, 17-64]); ARR was 1.81 for CHD events (95% CI, 0.35-3.11; NNT = 55 [95% CI, 32-284]); ARR was 4.06 for stroke events (95% CI, 2.53-5.40; NNT = 25 [95% CI, 19-40]); ARR was 2.23 for retinopathy events (95% CI, 0.15-4.04; NNT = 45 [95% CI, 25-654]); and ARR was 9.33 for albuminuria (95% CI, 7.13-11.37; NNT = 11 [95% CI, 9-14]).

Analyses not standardized to a 10-mm Hg BP reduction showed broadly similar results to standardized analyses (eFigures 9-16 in the Supplement) except that associations between BP-lowering treatment and the risk of heart failure (RR, 0.81 [95% CI, 0.76-0.86]) and renal failure (RR, 0.88 [95% CI, 0.79-0.99]) were statistically significant. Estimates were also similar in trials that were conducted in heart failure/left ventricular systolic dysfunction (HF/LVSD) patients and non-HF/LVSD patients, with the exception of heart failure as the outcome, where the RR was significantly lower in patients with HF/LVSD (eFigure 17 in the Supplement).

Table. Summary of Baseline Characteristics of Included Trials

Source	Main Inclusion Criteria	Intervention	Control	No. Participants With Diabetes	Mean Age, y	Men, No. (%)	Mean Duration of Follow-up, y	Mean BP, Systolic/Diastolic, mm Hg	
								Baseline	Intervention Group, Over Follow-up
BP-Lowering Drug vs Placebo									
ADVANCE,[29,30] 2007	Diabetes mellitus	ACE + diuretic (perindopril + indapamide)	Placebo	11 140	66	6405 (57)	4.3	145/81	136/73
ALTITUDE,[31] 2012	Diabetes mellitus with either albuminuria (micro or macro) or cardiovascular disease	Aliskiren	Placebo	8561	65	5826 (68)	2.7	137/74	139/75
BENEDICT,[28] 2004	Diabetes mellitus without microalbuminuria	ACE (trandolapril) + CCB (verapamil)	Placebo	600	63	314 (52)	3.6	151/88	139/80
		ACE (trandolapril)	CCB (verapamil)	604	63	321 (53)	3.6	151/88	139/81
BEST,[32] 2003	Heart failure	β-Blocker (bucindolol)	Placebo	964	61	750 (78)	2	120/72	NA
CIBIS-2,[33] 2001	Heart failure	β-Blocker (bisoprolol)	Placebo	312	NA	250 (80)[a]	NA	130/80	NA
CONSENSUS II[34] 1992	ST-elevated acute myocardial infarction	ACE (enalapril)	Placebo	685	66	500 (73)[a]	0.5	134/80	NA
DIABHYCAR,[35] 2004	Diabetes mellitus with high urinary albuminum secretion	ACE (rampiril)	Placebo	4912	65	3432 (70)	3.9	145/82	142/80
DIRECT-protect-2,[36-38] 2008	Diabetes mellitus	ARB (candesartan)	Placebo	1905	57	948 (50)	4.7	133/77	NA
EUROPA (PERSUADE),[39] 2005	Coronary artery disease	ACE (perindopril)	Placebo	1502	62	1231 (82)	4.3	140/82	135/80
FEVER,[19] 2011	Hypertension + cardiovascular risk factor	CCB (felodipine)	Placebo	1241	62	757 (61)[a]	3.3	154/91	139/82
HOPE,[16] (MICRO-HOPE) 2000	Cardiovascular disease history with an additional cardiovascular risk factor	ACE (rampiril)	Placebo	3577	65	2255 (63)	4.5	142/80	140/77
IDNT,[40,41] 2001	Diabetes mellitus	ARB (irbesartan)	Placebo	1148	59	781 (68)	2.6	159/87	140/77
		CCB (amlodipine)	Placebo	1136	59	762 (67)	2.6	159/87	141/77
MERIT-HF,[42,43] 2005	Heart failure (NYHA II-IV)	β-Blocker (metoprolol)	Placebo	985	65	714 (78)	1	132/78	NA
Norwegian-1,[44] 1983	Acute myocardial infarction	β-Blocker (timolol)	Placebo	99	NA	60 (61)	1.4	NA	NA
PRoFESS,[45] 2008	History of cerebrovascular events	β-Blocker (telmisartan)	Placebo	5743	66	3676 (64)[a]	2.5	144/88	135/79
PROGRESS,[46,47] 2001	History of cerebrovascular events	ACE (perindopril)	Placebo	761	64	548 (72)	3.9	149/84	NA
RENAAL,[18] 2001	Diabetes mellitus	ARB (losartan)	Placebo	1513	60	956 (63)	3.4	153/82	140/74
ROADMAP,[17] 2011	Diabetes mellitus	ARB (olmesartan)	Placebo	4447	58	2052 (46)	3.2	136/81	126/74
SAVE,[48,49] 1992	Myocardial infarction with left ventricular dysfunction	ACE (captopril)	Placebo	492	59	408 (83)[a]	3.5	113/70	NA
SCOPE,[50] 2005	Elderly with hypertension	ARB (candesartan)	Placebo	599	76	216 (36)[a]	3.7	166/90	145/80

(continued)

Table. Summary of Baseline Characteristics of Included Trials (continued)

Source	Main Inclusion Criteria	Intervention	Control	No. Participants With Diabetes	Mean Age, y	Men, No. (%)	Mean Duration of Follow-up, y	Mean BP, Systolic/Diastolic, mm Hg	
								Baseline	Intervention Group, Over Follow-up
SHEP,[51] 1996	Elderly with systolic hypertension	Diuretic (chlorthalidone) with addition of β-blocker (atenolol)	Placebo	583	70	289 (50)	4.5	170/76	143/68
SOLVD treatment,[52,53] 1991	Signs of heart failure and ventricular dysfunction after myocardial infarction	ACE (enalapril)	Placebo	663	61	506 (76)	3.4	125/77	NA
SOLVD prevention,[52,54] 1992	Ventricular dysfunction after myocardial infarction without signs of heart failure	ACE (enalapril)	Placebo	647	59	552 (85)	3.1	125/78	NA
Syst-Eur,[55,56] 1997	Elderly patients with isolated systolic hypertension	CCB (nitrendipine) ± ACE (enalapril) ± diuretic (hydrochlorothiazide)	Placebo	492	70	162 (33)[a]	2	175/85	153/78
TRACE,[57] 1999	Left ventricular systolic dysfunction after myocardial infarction	ACE (trandolapril)	Placebo	237	70	142 (60)	2.2	126/77	NA
VA NEPHRON-D,[58] 2013	Diabetes mellitus	ACE (lisinopril) + ARB (losartan)	ARB (losartan)	1448	65	1436 (99)	2.2	137/73	132/NA[b]
More-Intensive Lowering vs Less-Intensive Lowering									
ACCORD,[59,60] 2010	Diabetes mellitus	Intense	Usual	4733	62	2475 (52)	4.7	139/76	119/64
HDFP,[61,62] 1979	Hypertension	Stepped care	Referred care	772	51	NA	NA	159/101	NA
HOT,[27] 1998	Hypertension	Intense (<85 mm Hg)	Usual (<90 mm Hg)	1002	62	531 (53)[a]	3.8	170/105	141/83
		Intense (<80 mm Hg)	Usual (<90 mm Hg)	1000	62	530 (53)[a]	3.8	170/105	140/81
SPS3,[63] 2013	History of cerebrovascular events	Intense	Usual	1106	63	697 (63)[a]	3.7	143/79	127/NA[b]
UKPDS,[64,65] 1998	Diabetes mellitus with hypertension	Intense	Usual	1148	56	637 (55)	8.4	160/94	144/82
		ACE (captopril)	β-blocker (atenolol)	758	56	410 (54)	8.4	159/94	144/83
BP-Lowering Drug vs Another Drug									
ACCOMPLISH,[66] 2010	Hypertension	CCB (amlodipine + benazepril)	Diuretic (hydrochlorothiazide + benazepril)	6946	68	3954 (57)	2.5	145/79	132/73
ALLHAT,[22] 2002	Hypertension + cardiovascular risk factor	CCB (amlodipine)	Diuretic (chlorthalidone)	8851	67	4691 (53)[a]	4.9	146/84	135/75
		ACE (lisinopril)	Diuretic (chlorthalidone)	8740	67	4632 (53)[a]	4.9	146/84	136/75
ASCOT,[21] 2008	Hypertension + 3 cardiovascular risk factors	CCB (amlodipine)	β-Blocker (atenolol)	5137	63	3723 (73)	5.5	165/93	136/75
CAPPP,[67,68] 1999	Hypertension	ACE (captopril)	Conventional treatment (diuretics or β-blockers)	572	55	354 (62)	6.2	164/97	156/89
CASE-J,[20] 2010	Hypertension + cardiovascular risk factor	ARB (candesartan)	CCB (amlodipine)	2018	64	1126 (56)	3.3	160/88	136/77
INSIGHT,[69] 2003	Hypertension + cardiovascular risk factor	CCB (nifedipine)	Diuretic (co-amilozide)	1302	66	624 (48)	4	176/98	144/82

(continued)

Table. Summary of Baseline Characteristics of Included Trials (continued)

Source	Main Inclusion Criteria	Intervention	Control	No. Participants With Diabetes	Mean Age, y	Men, No. (%)	Mean Duration of Follow-up, y	Mean BP, Systolic/Diastolic, mm Hg	
								Baseline	Intervention Group, Over Follow-up
INVEST,[70] 2004	Coronary artery disease with hypertension	CCB (verapamil)	β-Blocker (atenolol)	6400	66	2947 (46)	2.7	151/85	NA
JMIC-B,[71] 2004	Coronary artery disease with hypertension	CCB (nifedipine)	ACE inhibitor	372	64	257 (69)	3	147/82	138/76
LIFE,[72] 2002	Hypertension + left ventricular hypertrophy	ARB (losartan)	β-Blocker (atenolol)	1195	67	561 (47)	4.7	177/96	146/79
MOSES,[73,74] 2005	History of cerebrovascular events	ARB (eprosartan)	CCB (nitrendipine)	498	70	279 (56)	2.5	152/86	140/82
NORDIL,[75] 2000	Hypertension	CCB (diltiazem)	Diuretic/β-blocker	727	60	353 (49)[a]	4.5	173/106	155/89
STOP-2,[76] 2000	Elderly patients with systolic hypertension	ACE (enalapril or lisinopril)	Diuretics/β-blockers	488	76	201 (41)	4	195/96	161/80
		CCB (felodipine or isradipine)	Diuretics/β-blockers	484	76	194 (40)	4	195/96	162/79
Factorial Design									
ABCD (H),[77-80] 1998	Diabetic mellitus + hypertension (DBP>90)	Intense	Usual	470	57	317 (67)	5	155/98	133/78
		CCB (nisoldipine)	ACE (enalapril)	470	57	317 (67)	5	155/98	NA
ABCD (N),[80,81] 2002	Diabetic mellitus + normotension (80-89 mm Hg DBP)	Intense	Usual	480	59	262 (55)	5.3	136/84	128/75
		CCB (nisoldipine)	ACE (enalapril)	480	59	262 (55)	5.3	136/84	132/78

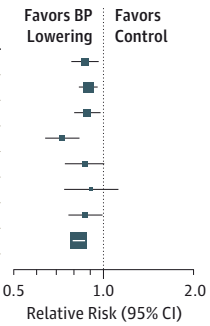
Abbreviations: ACR, assumed control risk; ARB, angiotensin receptor blocker; BB, β-blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; NA, not available; SBP, systolic blood pressure.

[a] For these trials, the number of men or proportion of men in the diabetic subgroup was not available. The number of men was imputed by multiplying the proportion of men for the overall trial by the number of participants in the diabetic subgroup.

[b] Systolic blood pressure available, diastolic blood pressure unavailable.

Figure 2. Standardized Associations Between 10–mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes in Diabetic Patients

Outcome	No. of Studies	BP Lowering		Control		Relative Risk (95% CI)
		Events	Participants	Events	Participants	
Mortality	20	2334	27693	2319	25864	0.87 (0.78-0.96)
Cardiovascular disease	17	3230	25756	3280	24862	0.89 (0.83-0.95)
Coronary heart disease	17	1390	26150	1449	24761	0.88 (0.80-0.98)
Stroke	19	1350	27614	1475	26447	0.73 (0.64-0.83)
Heart failure	13	1235	21684	1348	20791	0.86 (0.74-1.00)
Renal failure	9	596	19835	560	18912	0.91 (0.74-1.12)
Retinopathy	7	844	9781	905	9566	0.87 (0.76-0.99)
Albuminuria	7	2799	13804	3163	12821	0.83 (0.79-0.87)



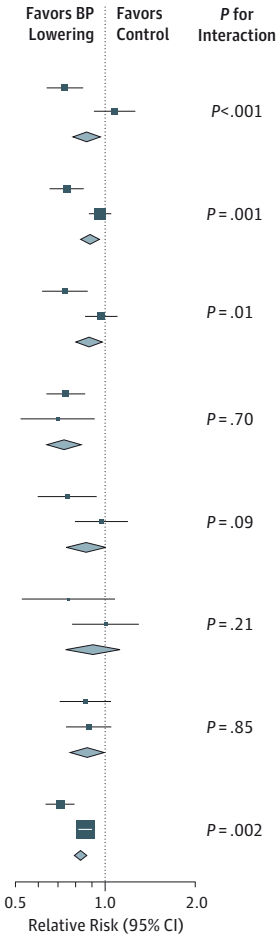
Macrovascular outcomes include cardiovascular events, coronary heart disease, stroke, and heart failure; and microvascular outcomes include renal failure, retinopathy, and albuminuria. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% CIs of the estimate. BP indicates blood pressure.

Associations Between BP-Lowering Treatment and Outcomes Stratified by Initial Systolic BP

Trials were stratified by mean initial systolic BP level (range, ≥140 mm Hg to <140 mm Hg) and the associations of outcomes with a 10-mm Hg systolic BP lowering compared between strata (**Figure 3**). Significant interactions were observed for mortality, CHD, CVD, and heart failure (all $P < .1$), with lower relative risks observed among those trials with mean baseline systolic BP of 140 mm Hg or greater and no significant associations among the group with baseline systolic BP of less than 140 mm Hg. BP-lowering treatment was associated with lower risks of stroke and albuminuria, regardless of initial systolic BP. Excluding trials with imputed BP values did not alter the main findings (eFigure 18 in the Supplement). Conclusions were broadly similar for the nonstandardized analyses (eFigure 19 in the Supple-

Figure 3. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes Stratified by Mean Systolic BP of Trial Participants at Entry

Outcome	No. of Studies	Baseline SBP, Mean, mm Hg	BP Lowering, No. Events	BP Lowering, No. Participants	Control, No. Events	Control, No. Participants	Relative Risk (95% CI)	P for Interaction
Mortality, mm Hg								
≥140[16, 18, 19, 27-30, 35, 39-41, 51, 55, 56, 64, 65, 77-80]	13	149	1614	16418	1626	14580	0.73 (0.64-0.84)	
<140[17, 31, 36-38, 58-60, 80, 81]	7	137	720	1275	693	11284	1.07 (0.92-1.26)	P<.001
Overall							0.87 (0.78-0.96)	
Cardiovascular disease, mm Hg								
≥140[16, 18, 19, 27-30, 35, 39-41, 46, 47, 51-53]	11	148	1861	14976	1918	14068	0.74 (0.65-0.85)	
<140[17, 31, 36-38, 58-60, 80, 81]	6	137	1369	10780	1362	10794	0.96 (0.88-1.05)	P=.001
Overall							0.89 (0.83-0.95)	
Coronary heart disease, mm Hg								
≥140[16, 18, 27, 29, 30, 35, 39-41, 47, 51, 64, 65]	10	148	858	14875	931	13477	0.73 (0.61-0.87)	
<140[17, 31, 36-38, 43, 58-60, 80, 81]	7	137	532	11275	518	11284	0.97 (0.86-1.10)	P=.01
Overall							0.88 (0.80-0.98)	
Stroke, mm Hg								
≥140[16, 18, 19, 27, 29, 30, 35, 39-41, 45-47, 51, 55, 56, 63-65]	14	148	1129	19066	1245	17868	0.74 (0.64-0.86)	
<140[31, 36-38, 58-60, 80, 81]	5	137	221	8548	230	8579	0.69 (0.52-0.92)	P=.70
Overall							0.73 (0.64-0.83)	
Heart failure, mm Hg								
≥140[16, 18, 29, 30, 35, 39-41, 46, 47, 64, 65]	8	146	774	13592	814	12676	0.75 (0.59-0.94)	
<140[31, 42, 43, 58-60, 80, 81]	5	137	461	8092	534	8115	0.97 (0.79-1.19)	P=.09
Overall							0.86 (0.74-1.00)	
Renal failure, mm Hg								
≥140[16, 18, 29, 30, 35, 40, 41, 64, 65]	6	147	389	12475	346	11530	0.75 (0.52-1.08)	
<140[31, 58-60]	3	138	207	7360	214	7382	1.00 (0.77-1.29)	P=.21
Overall							0.91 (0.74-1.12)	
Retinopathy, mm Hg								
≥140[16, 29, 30, 64, 65, 77-80]	4	146	564	7946	586	7753	0.86 (0.70-1.04)	
<140[36-38, 59, 60, 80, 81]	3	137	280	1835	319	1813	0.88 (0.74-1.05)	P=.85
Overall							0.87 (0.76-0.99)	
Albuminuria, mm Hg								
≥140[16, 28-30, 64, 65]	4	146	1681	8447	1898	7647	0.71 (0.63-0.79)	
<140[17, 36-38, 59, 60]	3	137	1118	5357	1265	5174	0.86 (0.81-0.90)	P=.002
Overall							0.83 (0.79-0.87)	



Macrovascular outcomes include cardiovascular events, coronary heart disease, stroke, and heart failure; and microvascular outcomes include renal failure, retinopathy, and albuminuria. Mean baseline blood pressure (BP) is weighted by number of participants. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% CIs of the estimate. SBP indicates systolic blood pressure.

ment), although tests for interactions varied for some outcomes. Nonstandardized estimates were similar when 1 trial at unclear risk of bias was included (eFigure 20 in the Supplement).

Associations Between BP-Lowering Treatment and Outcomes Stratified by Achieved Systolic BP

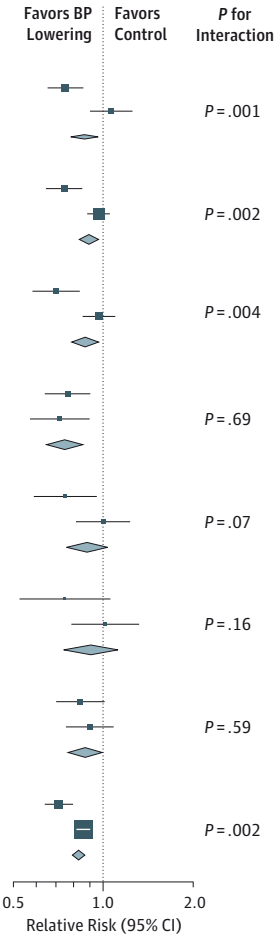
Trials were stratified by the systolic BP achieved in the treatment group (≥130 or <130 mm Hg) and the associations of a 10-mm Hg systolic BP lowering with risk compared between strata (**Figure 4**). Significant interactions were observed for mortality, CHD, CVD, heart failure, and albuminuria (all $P < .1$), with lower relative risks in the 130-mm Hg or greater stratum than the lower than 130-mm Hg stratum. No significant interaction was observed for stroke or retinopathy. The associations between BP-lowering treatment and the risks of stroke and albuminuria were significant for both strata. Standardized estimates made excluding trials with imputed BP values were not substantively different (eFigure 21 in the Supplement). For nonstandardized estimates, there was heterogeneity for CHD and stroke (eFigure 22 in the Supplement).

Associations Between BP-Lowering Treatment and Outcomes by Class of Medication

Few differences were observed in the associations between BP-lowering treatment and outcomes for regimens based on different classes of medication used (**Figure 5**). The key exception was heart failure, in which diuretics were associated with a significantly lower RR (0.83 [95% CI, 0.72-0.95]) than all other forms of medication, driven largely by the results of ALLHAT. ARBs also appeared to be particularly associated with a lower RR of heart failure, although data were only available from 2 trials and the CIs were wide. By contrast, CCBs were associated with a higher RR of heart failure when compared with all other classes of medications. There was also some evidence that CCBs were associated with a lower risk of stroke (RR, 0.86 [95% CI, 0.77-0.97]),

Figure 4. Standardized Associations Between 10–mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes, Stratified by Mean Achieved Systolic BP in the Active Group of Each Trial

Outcome	No. of Studies	Achieved SBP, Mean, mm Hg	BP Lowering, No. Events	BP Lowering, No. Participants	Control, No. Events	Control, No. Participants	Relative Risk (95% CI)	P for Interaction
Mortality, mm Hg								
≥130[16, 18, 19, 27-31, 35-41, 51, 55, 56, 58, 64, 65, 77-80]	16	138	2090	22 367	2079	20 545	0.75 (0.65-0.86)	
<130[17, 42, 43, 59, 60, 80, 81]	4	123	244	5326	240	5319	1.06 (0.90-1.25)	P = .001
Overall							0.87 (0.78-0.96)	
Cardiovascular disease, mm Hg								
≥130[16, 18, 19, 27, 29, 30, 32, 35-41, 51-53, 58]	13	138	2551	20 529	2558	19 668	0.74 (0.64-0.85)	
<130[17, 59, 60, 80, 81]	3	123	597	4831	631	4829	0.96 (0.88-1.05)	P = .002
Overall							0.89 (0.83-0.96)	
Coronary heart disease, mm Hg								
≥130[16, 18, 27, 29, 30, 32, 35-41, 51, 58, 64, 65]	12	138	1055	20 428	1126	19 077	0.70 (0.58-0.83)	
<130[17, 42, 43, 59, 60, 80, 81]	4	123	305	5326	302	5319	0.97 (0.85-1.10)	P = .004
Overall							0.87 (0.78-0.96)	
Stroke, mm Hg								
≥130[16, 18, 19, 27, 29, 30, 32, 35-41, 45, 51, 55, 56, 58, 64, 65]	15	138	1196	24 066	1261	22 915	0.76 (0.64-0.90)	
<130[59, 60, 63, 80, 81]	3	121	106	3152	149	3167	0.72 (0.57-0.90)	P = .69
Overall							0.74 (0.65-0.85)	
Heart failure, mm Hg								
≥130[16, 18, 29, 30, 32, 35, 38-41, 58, 64, 65]	9	138	1043	18 194	1106	17 322	0.75 (0.59-0.95)	
<130[42, 43, 59, 60, 80, 81]	3	121	167	3094	209	3104	1.00 (0.81-1.23)	P = .07
Overall							0.88 (0.75-1.03)	
Renal failure, mm Hg								
≥130[16, 18, 29, 30, 32, 35, 40, 41, 58, 64, 65]	8	139	537	17 473	502	16 541	0.74 (0.52-1.06)	
<130[59, 60]	1	119	59	2362	58	2371	1.01 (0.78-1.32)	P = .16
Overall							0.91 (0.74-1.12)	
Retinopathy, mm Hg								
≥130[16, 29, 30, 36-38, 64, 65, 77-80]	5	137	694	8897	736	8707	0.84 (0.70-1.01)	
<130[59, 60, 80, 81]	2	120	150	884	169	859	0.90 (0.75-1.08)	P = .59
Overall							0.87 (0.76-0.99)	
Albuminuria, mm Hg								
≥130[16, 28-30, 36-38, 64, 65]	5	137	1822	9398	2049	8601	0.71 (0.64-0.79)	
<130[17, 59, 60]	2	122	977	4406	1114	4220	0.86 (0.81-0.90)	P = .002
Overall							0.83 (0.79-0.87)	



Macrovascular outcomes include cardiovascular events, coronary heart disease, stroke, and heart failure; and microvascular outcomes include renal failure, retinopathy, and albuminuria. The mean achieved blood pressure (BP) is weighted by number of participants. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% CIs of the estimate. SBP indicates systolic blood pressure.

while β-blockers were associated with a higher risk (Figure 5). ARBs were associated with a lower risk of mortality relative to other classes of medications, an association was driven by the LIFE study, which compared an ARB against a β-blocker. Estimates were similar when 1 trial judged to be of high risk of bias and 3 trials judged to be of unclear risk of bias were included (eFigure 23 in the Supplement).

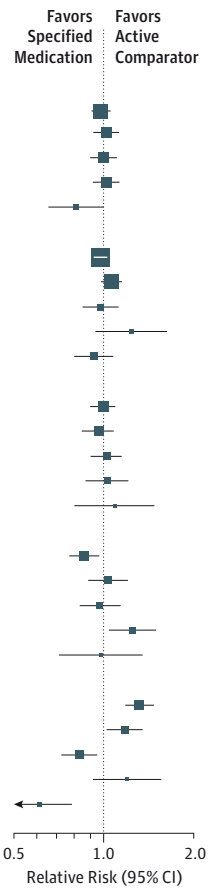
Discussion

In this meta-analysis, BP-lowering treatment was associated with a significantly lower risk of all-cause mortality, CVD events, CHD events, and stroke events in patients with diabetes. Additionally, BP-lowering treatment was associated with a lower risk of retinopathy and albuminuria. Although the associations between BP-lowering treatment and risk of vascular outcomes were largely not significantly different across classes of medication, our results provide evidence of differential associations between classes for heart failure and stroke, as has been previously observed in the general population.[13]

Although we performed both standardized and nonstandardized analyses of the data, we elected to primarily focus on the standardized analyses, which are less influenced by any effects that may not be mediated through BP lowering. However, although there are some differences, the conclusions are broadly similar with and without standardization. Our analyses show evidence that BP-lowering treatment was associated with lower risks of outcomes in trials that included patients with an initial mean BP level of 140 mm Hg or greater, compared with patients with an initial mean BP level of less than 140 mm Hg, with the exception of stroke, albuminuria, and retinopathy. Similarly, when trials were stratified by achieved systolic BP, treatment was associated with lower risks only in the less than 130-mm Hg stratum for stroke and albuminuria in standardized analyses.

Figure 5. Associations of Each Class of Antihypertensives on Mortality, Cardiovascular Events, Coronary Heart Disease Events, Stroke Events, and Heart Failure Events Compared With All Other Classes of Antihypertensives

Medication Class vs All Other Classes of Hypertensives	No. of Studies	Specified Medication, No.		Any Active Comparator, No.		SBP Reduction, Mean (95% CI), mm Hg[a]	Relative Risk (95% CI)
		Events	Participants	Events	Participants		
Mortality							
CCB[21, 22, 28, 40, 41, 66, 69, 70, 75-81]	11	1482	15117	1910	17665	0.5 (-2.0 to 1.1)	0.98 (0.92-1.05)
ACE[22, 28, 64, 65, 76-81]	6	615	4617	972	7154	1.7 (0.8 to 2.6)	1.02 (0.93-1.12)
Diuretics[22, 66, 69]	3	956	9649	634	7339	-1.5 (-2.4 to -0.7)	1.00 (0.91-1.10)
β-Blocker[21, 64, 65, 70, 72]	4	768	6770	753	6720	-0.7 (-1.8 to 0.5)	1.02 (0.92-1.13)
ARB[40, 41, 72]	2	150	1165	187	1176	2.5 (1.5 to 3.5)	0.81 (0.66-0.99)
Cardiovascular disease							
CCB[21, 22, 40, 41, 66, 69, 70, 75-81]	10	2035	14814	2672	17364	0.5 (-1.0 to 1.2)	0.98 (0.93-1.03)
ACE[22, 76-81]	4	862	3916	1406	6493	1.8 (1.0 to 2.6)	1.06 (0.99-1.15)
Diuretics[22, 66, 69]	3	1675	9649	1137	7339	-1.5 (-2.4 to -0.7)	0.98 (0.85-1.12)
β-Blocker[21, 70, 72]	3	792	6412	722	6320	-0.8 (-2.1 to 0.6)	1.24 (0.94-1.62)
ARB[40, 41, 72]	2	275	1165	300	1176	2.5 (1.5 to 3.5)	0.93 (0.80-1.08)
Coronary heart disease							
CCB[21, 22, 40, 41, 66, 69, 70, 75-81]	10	751	14814	1002	17364	0.5 (-1.0 to 1.2)	1.00 (0.91-1.09)
ACE[22, 64, 65, 76-81]	5	404	4316	668	6851	1.6 (0.6 to 2.6)	0.96 (0.85-1.08)
Diuretics[22, 66, 69]	3	635	9649	406	7339	-1.5 (-2.4 to -0.0)	1.02 (0.90-1.15)
β-Blocker[21, 64, 65, 70, 72]	4	308	6770	304	6720	-0.7 (-1.8 to 0.5)	1.03 (0.87-1.20)
ARB[40, 41, 72]	2	85	1165	77	1176	2.5 (1.5 to 3.5)	1.09 (0.80-1.48)
Stroke							
CCB[21, 22, 40, 41, 66, 69, 70, 75-81]	10	484	14814	726	17364	0.5 (-1.0 to 1.2)	0.86 (0.77-0.97)
ACE[22, 64, 65, 76-81]	5	257	4316	412	6851	1.6 (0.6 to 2.6)	1.03 (0.89-1.20)
Diuretics[22, 66, 69]	3	394	9649	270	7339	-1.5 (-2.4 to -0.7)	0.98 (0.84-1.14)
β-Blocker[21, 64, 65, 70, 72]	4	273	6770	220	6720	-0.7 (-1.8 to 0.5)	1.25 (1.05-1.50)
ARB[40, 41, 72]	2	79	1165	80	1176	2.5 (1.5 to 3.5)	0.98 (0.71-1.34)
Heart failure							
CCB[21, 22, 40, 41, 66, 69, 75-81]	9	612	11645	643	14133	0.7 (-1.0 to 1.4)	1.32 (1.18-1.47)
ACE[22, 64, 65, 76-81]	5	317	4316	454	6851	1.6 (0.6 to 2.6)	1.17 (1.02-1.35)
Diuretics[22, 66, 69]	3	448	9649	349	7339	-1.5 (-2.4 to -0.7)	0.83 (0.72-0.95)
β-Blocker[21, 64, 65, 72]	3	129	3539	110	3551	-1.3 (-2.8 to 0.2)	1.20 (0.92-1.56)
ARB[40, 41, 72]	2	92	1165	148	1176	2.5 (1.5 to 3.5)	0.61 (0.48-0.78)



[a] Systolic blood pressure (SBP) reduction is reported as a 95% CI for the mean reduction at the trial level, not a range of reduction among trials.

The area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% CIs of the estimate. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

The failure to identify an association between BP-lowering treatment and lower risk of the cardiovascular composite with lower achieved BP levels is contrary to the findings of a large meta-analysis of 147 randomized trials performed in a broader population, which found evidence of a lower risk of CHD and stroke events at much lower achieved BP levels.[13] A key difference between the previous meta-analysis and the current study is the inclusion of large numbers of patients with heart failure or recent MI in the prior overview, among whom mechanisms of action independent of BP lowering have been hypothesized. It is also likely that the inclusion of a number of recent trials of dual renin angiotensin system blockade (particularly the ALTITUDE study[31]) has attenuated the anticipated benefits of achieving lower BP levels. These results also contrast with a previous meta-analysis, which did not observe an association between BP lowering to a target of level of 130 mm Hg or less and risk of retinopathy or an association between BP lowering to any target (≤135 or ≤130 mm Hg) and risk of MI.[82] Our differing results are likely due to the greater power of our meta-analysis (45 trials, 104 586 participants), relative to the previous review, which examined 13 trials enrolling 37 736 participants.

Our results lead to potentially different recommendations from those made in several recent guidelines (eTable 1 in the Supplement). For example, the recent JNC 8 (eighth Joint National Committee) guidelines relaxed the threshold for initiation of BP-lowering treatment from 130 mm Hg to 140 mm Hg in individuals with diabetes.[83] The ACCORD trial, which compared a target of lower than 120 mm Hg to lower than 140 mm Hg, was cited in support of this decision, as no significant reduction in the composite outcome of cardiovascular death, nonfatal MI, and nonfatal stroke was observed.[59] Although we also observed that BP lowering was not associated with a lower risk of CVD or CHD events at a baseline systolic BP of lower than 140 mm Hg, we did observe lower risks of stroke, retinopathy, and progression of albuminuria. Thus, in contrast with the recommendations of the JNC 8 guidelines, for individuals at high risk of these outcomes (eg, individuals with a history of cerebrovascular disease or individuals with mild nonproliferative diabetic retinopathy), the

commencement of BP-lowering therapy below an initial systolic BP level of 140 mm Hg and treatment to a systolic BP level below 130 mm Hg should be considered.

When deciding whether to commence BP-lowering treatment in individuals with systolic BP below 140 mm Hg or whether to aim for systolic BP levels below 130 mm Hg, the risk of adverse events associated with BP-lowering treatments needs to be considered. This requires individualized assessment of the likely absolute benefits and risks with shared decision making between patients and clinicians. Although many trials reported select adverse events, these data were too disparate to allow formal meta-analysis. In ACCORD, the rate of serious adverse events attributed to BP lowering in the intensive treatment group (which reached an achieved BP of 119 mm Hg) was 2.5 times that of the control group (an achieved BP of 133 mm Hg), however, the absolute rate of these adverse events in the intensive group was low, and was substantially lower than that of the primary outcome (0.70% per year vs 1.87% per year).[59] It is possible that there is a higher risk of some important adverse events with large reductions at lower BP levels. Additionally, because many trial participants will have been treated with multiple classes of BP-lowering medications, differences between classes, with regard to efficacy and adverse events, may have been obscured. An individual patient data meta-analysis of efficacy and adverse events, stratified by patient characteristics, baseline BP, and class of medication, is necessary to provide the reliable evidence required to fully evaluate the overall balance of risks and benefits.

Strengths and Limitations

With data from 104 586 patients enrolled in 45 large trials, these analyses included substantially more information than previous published meta-analyses addressing this question (eTable 3 in the Supplement). This was, in large part, due to our efforts to identify all relevant data, by including not just trials performed in patients with diabetes, but also the results reported for the diabetic subgroups in large trials of mixed populations. For the associations with treatment based on initial BP level and target BP levels, we base our interpretation of the data primarily on the presence or absence of statistical heterogeneity across subgroups rather than the significance of the results in each individual subgroup. This approach minimizes the effect of the wide CIs obtained for each individual subgroup consequent on division of the data, and provides for a more robust interpretation. The uncertainty that ensues from the subgroup analyses emphasizes the need for more clinical trial data, particularly in relation to systolic BP targets of less than 130 mm Hg. Further trials that evaluate BP-lowering treatment into the 120- to 130-mm Hg range among hypertensive and nonhypertensive diabetic individuals would clarify whether lowering systolic BP to a target of less than 130/80 mm Hg would further reduce vascular risk relative to a target of less than 140/90 mm Hg, because the reliability of this meta-analysis is limited by the scarcity of large trials with achieved BP levels in the 120- to 130-mm Hg range. Additionally, the relatively short follow-up of included trials may also have prevented associations of BP-lowering treatment with vascular outcomes from being observed, particularly for outcomes such as heart failure and renal failure, which are often a consequence of MI and albuminuria, respectively.

Conclusions

Among patients with type 2 diabetes, BP lowering was associated with improved mortality and other clinical outcomes. These findings support the use of medications for BP lowering in these patients. Although proportional associations of BP-lowering treatment for most outcomes studied were attenuated below a systolic BP level of 140 mm Hg, data indicate that further reduction below 130 mm Hg is associated with a lower risk of stroke, retinopathy, and albuminuria, potentially leading to net benefits for many individuals at high risk for those outcomes.

ARTICLE INFORMATION

Author Contributions: Drs Emdin and Rahimi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Emdin, Rahimi, Neal, Patel.
Acquisition, analysis, or interpretation of data: Emdin, Rahimi, Neal, Callender, Perkovic, Patel.
Drafting of the manuscript: Emdin, Rahimi.
Critical revision of the manuscript for important intellectual content: Emdin, Rahimi, Neal, Callender, Perkovic, Patel.
Statistical analysis: Emdin.
Obtained funding: Rahimi.
Administrative, technical, or material support: Neal, Callender.
Study supervision: Rahimi, Neal, Patel.

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