Annals of Internal Medicine

REVIEW

Effects of Blood Pressure Reduction in Mild Hypertension

A Systematic Review and Meta-analysis

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Background: Effects of blood pressure reduction in persons with grade 1 hypertension are unclear.

Purpose: To investigate whether pharmacologic blood pressure reduction prevents cardiovascular events and deaths in persons with grade 1 hypertension.

Data Sources: Trials included in the BPLTTC (Blood Pressure Lowering Treatment Trialists' Collaboration) and trials identified from a previous review and electronic database searches.

Study Selection: Patients without cardiovascular disease with blood pressures in the grade 1 hypertension range (140 to 159/90 to 99 mm Hg) who were randomly assigned to an active (antihypertensive drug or more intensive regimen) or control (placebo or less intensive regimen) blood pressure–lowering regimen.

Data Extraction: Individual-patient data from BPLTTC trials and aggregate data from other trials were extracted. Risk of bias was assessed for all trials.

Data Synthesis: Individual-patient data involved 10 comparisons from trials where most patients had diabetes, and aggregate data involved 3 comparisons from trials of patients without diabetes. The average blood pressure reduction was about 3.6/2.4 mm Hg. Over 5 years, odds ratios were 0.86 (95% CI, 0.74 to 1.01) for total cardiovascular events, 0.72 (CI, 0.55 to 0.94) for strokes, 0.91 (CI, 0.74 to 1.12) for coronary events, 0.80 (CI, 0.57 to 1.12) for heart failure, 0.75 (CI, 0.57 to 0.98) for cardiovascular deaths, and 0.78 (CI, 0.67 to 0.92) for total deaths. Results were similar in secondary analyses. Withdrawal from treatment due to adverse effects was more common in the active groups.

Limitation: Blood pressure reductions and numbers of events were small.

Conclusion: Blood pressure–lowering therapy is likely to prevent stroke and death in patients with uncomplicated grade 1 hypertension.

Primary Funding Source: Swedish Heart-Lung Foundation, Swedish Research Council, Australian Research Council, and National Health and Medical Research Council of Australia.

Ann Intern Med. doi:10.7326/M14-0773 **www.annals.org**

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* For a list of the members of the Blood Pressure Lowering Treatment Trialists' Collaboration, see the **Appendix** (available at www.annals.org).

This article was published online first at www.annals.org on 23 December 2014.

High blood pressure is the most important risk factor for premature death globally (1). The number of persons with blood pressure defined as clinically abnormal (hypertension) is increasing, with 1 billion currently affected worldwide (2). Most of these have grade 1 hypertension (systolic blood pressure of 140 to 159 mm Hg and/or diastolic blood pressure of 90 to 99 mm Hg) and no overt cardiovascular disease (3). The management of this large group is controversial because no trial of blood pressure reduction in uncomplicated grade 1 hypertension has provided clear evidence of benefit (4).

Most trials of blood pressure–lowering drugs have enrolled persons with grade 2 or 3 hypertension or focused on high-risk persons with established cardiovascular disease. Extrapolation of the findings from these trials to the setting of grade 1 hypertension and primary prevention has been questioned, although the relative risk reductions achieved with blood pressure–lowering therapy are similar across a broad range of hypertensive and nonhypertensive persons at elevated cardiovascular risk (5). Likewise, epidemiologic data suggest a log-linear association between blood pressure and cardiovascular events at lower blood pressures (6). A recent systematic review directly addressing the effects of blood pressure reduction in grade 1 hypertension (7) was based on 4 trials, 8912 participants, and 167 primary outcome events. That review did not detect a treatment benefit, but the analysis was limited by the exclusion of many recent relevant trials, use of second-line treatment regimens, and low study power.

The BPLTTC (Blood Pressure Lowering Treatment Trialists' Collaboration) has completed a series of reviews of blood pressure–lowering drug trials and has access to individual-participant data that allow investigation of effects in participant subgroups. Several trials in the BPLTTC include many participants who have blood pressures in the grade 1 hypertension range but do not have preexisting cardiovascular disease. We used these data to update the evidence provided by a recent systematic review (7). We hypothesized that pharmacologic blood pressure reduction would prevent major cardiovascular events in persons with grade 1 hypertension without preexisting manifest cardiovascular disease.

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METHODS

We conducted a systematic literature review and meta-analysis of published and individual-level data from randomized, controlled trials to determine the most likely effects of blood pressure reduction on the risk for cardiovascular events and death in patients enrolled with blood pressures in the grade 1 hypertension range but without manifest cardiovascular disease.

Data Sources and Searches

We built on a systematic review recently published by others (7), and we considered that review complete up to the last date of the last literature search done in May 2011. We applied the same search terms and protocol used in that review to the Cochrane Central Register of Controlled Trials, MEDLINE, and CINAHL and limited the search to May 2011 to June 2014.

Study Selection

Studies were included in the systematic review we updated (7) if they were randomized, controlled trials of at least 1 year's duration; involved patients aged 18 years or older, at least 80% of whom had grade 1 hypertension and no previous cardiovascular disease (myocardial infarction, angina pectoris, coronary bypass surgery, percutaneous coronary intervention, stroke, transient ischemic attack, carotid surgery, peripheral arterial surgery, intermittent claudication, or renal failure); and compared an antihypertensive drug provided as monotherapy or a stepped-care algorithm against placebo or another control regimen. Trials were excluded if they did not contribute an event for any of the outcomes of interest.

Additional Data From the BPLTTC

We examined the available sets of trials with individual-participant data included in the BPLTTC to identify subgroups of participants meeting the review inclusion criteria. These trials also met the original inclusion criteria for participation in the BPLTTC (8). Data from 4 sets of comparisons were included in these analyses: angiotensin-converting enzyme (ACE) inhibitors versus placebo, calcium-channel blockers versus placebo, diuretics versus placebo, and more intensive versus less intensive blood pressure–lowering regimens. To maximize power, we combined these 4 sets of comparisons in our analyses. These comparisons were used because the primary research question was about the effects of blood pressure reduction and the difference between blood pressures for these comparisons is generally moderate to large. Furthermore, prior analyses have shown that most of the treatment effect observed for these comparisons in the present database is determined by the blood pressure reduction achieved, with little attributable to drug-specific, blood pressure–independent effects (9, 10). In a sensitivity analysis, we investigated a subsample by including only data from the placebo-controlled trials. The inclusion criteria for trials and participants sourced from the BPLTTC were otherwise the same as those for trials identified though the literature search. All trials were approved by at least 1 ethics committee.

We investigated the outcomes specified in the original BPLTTC study protocol (8): total major cardiovascular events, comprising stroke (nonfatal stroke or death from cerebrovascular disease), coronary events (nonfatal myocardial infarction or death from coronary heart disease, including sudden death), heart failure (causing death or resulting in hospitalization), or cardiovascular death; each of these outcomes independently; and total deaths. Only the first event for a participant was used for the analysis of each outcome, but a participant who had more than 1 outcome type could contribute to more than 1 analysis. We also tabulated overall withdrawals and withdrawals due to adverse events.

In secondary analyses, we investigated the effects of treating a subset according to recommendations 1, 2, 3, and 5 in the recent guidelines from the Eighth Joint National Committee (JNC 8) (11), thereby excluding 75 persons who were aged 60 years or older and had a systolic blood pressure less than 150 mm Hg and no diabetes. To investigate the potential effect of covariates on the treatment effects, we also performed adjusted analyses in the BPLTTC subsample, adding fixed effects for study type (calcium-channel blocker vs. placebo, ACE inhibitor vs. placebo, or more vs. less intensive blood pressure–lowering regimen), age, sex, smoking status, body mass index, and baseline systolic and diastolic blood pressures.

Data Extraction and Bias Assessments

We used individual-participant data from the BPLTTC trials. To incorporate the 3 non-BPLTTC trials into the analysis, we constructed data sets for each trial with 1 row per participant and the correct number of treated cases, nontreated cases, treated noncases, and nontreated noncases for all reported outcomes. In these data sets, we also constructed variables for diabetes and blood pressure–lowering treatment status because patients with diabetes or prior blood pressure–lowering treatment were excluded from the non-BPLTTC trials (**Appendix Table 1**, available at www.annals.org). These 3 data sets were then merged with the BPLTTC database and used as individual-participant data. Quality of the included trials was gauged as in the previous systematic review (7) by using the Cochrane Collaboration's risk-of-bias tool.

Data Synthesis and Analysis

We used a 1-step, individual-patient data meta-analysis approach (12) with a 2-level mixed-effects logistic regression model, with patient as the unit of analysis and trial modeled on a second level with a random intercept. Models with a random coefficient for trial did not have a better fit than models with only a random intercept ($P > 0.12$ for all likelihood-ratio tests) and were not pursued further. We calculated absolute risk reductions by applying the relative risks to the observed 5-year Kaplan–Meier risk estimates in 3 samples: the control groups in the BPLTTC trials; the control groups in the non-BPLTTC trials; and a subsample of a contemporary primary care–based sample (13) of 7241 patients starting treatment with an ACE inhibitor or

Table 1. Baseline Characteristics*

Characteristic	Active Groups	Control Groups	Total
BPLTTC trials			
Patients, *n*	3364	2997	6361
Mean age (SD), *y*	63.1 (8.6)	64.0 (8.2)	63.5 (8.4)
Female, *n (%)*	1341 (40)	1203 (40)	2544 (40)
Mean total cholesterol level (SD)			
mmol/L	5.4 (1.2)	5.4 (1.2)	5.4 (1.2)
mg/dL	208.5 (46.3)	208.5 (46.3)	208.5 (46.3)
Mean HDL cholesterol level (SD)			
mmol/L	1.27 (0.52)	1.28 (0.51)	1.27 (0.51)
mg/dL	49.03 (20.08)	49.42 (19.69)	49.03 (19.69)
Smokers, *n (%)*	481 (15)	462 (16)	943 (16)
Previous antihypertensive treatment, *n (%)*	1819 (62)	1686 (61)	3505 (61)
Diabetes mellitus, *n (%)*	3225 (96)	2871 (96)	6096 (96)
Mean BMI (SD), kg/m^2	29.2 (5.1)	29.2 (5.2)	29.2 (5.2)
Mean systolic blood pressure (SD), *mm Hg*	146 (7)	146 (7)	146 (7)
Mean diastolic blood pressure (SD), *mm Hg*	84 (8)	83 (8)	84 (8)
Non-BPLTTC trials			
Patients, *n*	4478	4427	8905
Previous antihypertensive treatment, *n (%)*	0 (0)	0 (0)	0 (0)
Diabetes mellitus, *n (%)*	0 (0)	0 (0)	0 (0)
Total patients, *n*	7842	7424	15 266

BMI = body mass index; BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration; HDL = high-density lipoprotein.
* Data in active and control groups are slightly unbalanced because participants in some trials were not randomly assigned in a 1:1 ratio.

angiotensin-receptor blocker between 1999 and 2007, with a systolic blood pressure of 140 to 159 mm Hg, a diastolic blood pressure of 90 to 99 mm Hg, and no prior cardiovascular disease. We included this cohort, which is set in a country with a modern universal health care system and has no loss to follow-up, to obtain absolute risks that were as clinically relevant as possible. The published manuscript (13) is for a subsample of patients receiving candesartan–losartan. In that cohort, cardiovascular disease was defined as heart failure (International Classification of Diseases [ICD] code I50 or ICD-9 code 428), cardiac arrhythmias (ICD-10 codes I46 to I48 or ICD-9 code 427), peripheral artery disease (ICD-10 codes I70, I71, or I74 or ICD-9 codes 440, 441, or 444), chronic ischemic heart disease (ICD-10 codes I20.9 or I25.1 or ICD-9 codes 413 or 414), myocardial infarction (ICD-10 codes I21 to I23 or ICD-9 codes 410, 411, or 429), stroke (ICD-10 codes I61, I63, I64, or G45 or ICD-9 codes 431 to 435), unstable angina (ICD-10 code I20.0 or ICD-9 code 411), or coronary revascularization. We calculated symmetrical 95% CIs for the absolute risk reductions as $(p1 - p2) \pm 1.96 * ([p1 * \{1 - p1\}/n1] + [p2 * \{1 - p2\}/n2])^{1/2}$, where p1 and p2 were the 5-year risks in the active treatment and control groups, respectively, and n1 and n2 were the number of participants in each group. Multiplicative interaction terms were investigated in the mixed-effects logistic regression models for all outcomes between treatment and sex, diabetes status, background antihypertensive treatment, BPLTTC versus non-BPLTTC trial, and groups defined by the median values of age (67 years) and 5-year risk for cardiovascular disease (11%, estimated with a calibrated Framingham equation [14]) among patients with cardiovascular disease. Consistency of treatment effects across trials and subgroups was described by using the I^2 statistic from a random-effects, inverse variance–weighted, tabular data meta-analysis. We used Stata, version 13 (StataCorp), for all analyses. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (15) in the reporting of this systematic review.

Role of the Funding Source

The funding sources had no role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to approve publication of the finished manuscript.

RESULTS

Included Trials

Three (16–18) of the 4 trials that were included in the recent systematic review contributed 8905 patients (1 trial with 7 participants had zero events and was excluded [7]). Our search strategy (**Appendix Figure 1**, available at www.annals.org) did not identify any eligible articles published since the previous systematic review. From the BPLTTC database, we identified 10 comparisons (19–27) with 6361 eligible patients who had grade 1 hypertension without evidence of manifest cardiovascular disease. This resulted in a total study sample of 15 266 patients.

Baseline Characteristics

Patient characteristics are described in **Table 1**. The total sample included 7842 patients receiving active therapy and 7424 control participants. Of these, 14 457 (95%) were from trials comparing a drug versus placebo and 809 (5%) were from trials comparing a more intensive blood pressure–lowering regimen against a

less intensive one. Most of the 6361 additional participants drawn from the BPLTTC data sets had diabetes, and their mean baseline blood pressure was 146/84 mm Hg. Mean values of baseline variables for the participants from trials outside the BPLTTC were mostly unknown because they were from subsamples of the published studies, but all of the trials excluded persons with diabetes or background antihypertensive treatment (16–18). Distributions of available baseline characteristics and follow-up by trial are presented in **Appendix Table 1**. The interventions tested in the BPLTTC sample were primarily ACE inhibitor–based with a few calcium-channel blocker groups, whereas the non-BPLTTC trials tested primarily diuretics and β-blockers (**Appendix Table 1**). The average achieved blood pressure difference between the active and control groups was 3.6/2.4 mm Hg in the BPLTTC (**Appendix Table 2**, available at www.annals.org) but is unknown for the other contributing trial subgroups.

Effects of Blood Pressure–Lowering Drugs on Cardiovascular Events and Death

Patients were followed for a median of 4.4 years (interquartile range, 0.5 years) in the BPLTTC sample and for 4 to 5 years in the non-BPLTTC trials (7). Numbers of events by trial group are presented in **Appendix Table 3** (available at www.annals.org). For the 12 981 patients with available data on cardiovascular outcomes, 661 (5.1%) developed cardiovascular disease, with cumulative event rates of 2.8% for coronary events and 1.8% for stroke. During follow-up, 665 of the 15 266 patients died (4.4%). Data on heart failure and cardiovascular deaths were only available in the BPLTTC trials; among the 5631 patients with such data, 2.5% developed heart failure and 3.9% died from a cardiovascular cause.

Blood pressure–lowering therapy was associated with favorable point estimates of effect for all 6 outcomes studied (**Figure**). However, the 95% CIs crossed unity for total cardiovascular events, coronary events, and heart failure, with only stroke, cardiovascular deaths, and total deaths showing statistically significant reductions (**Figure**). Corresponding absolute risk reductions are presented in **Table 2**.

Data on withdrawals from treatment were limited. In studies with available data, withdrawals were equally common in the active (337 of 1582) and control groups (357 of 1583) (**Appendix Table 4**, available at www.annals.org). Withdrawals due to adverse effects were more common in the active group (76 of 1361) than the control group (38 of 1377) in the only study that reported these data.

Secondary Analysis

Heterogeneity of findings for trials was low for all outcomes ($I^2 <= 35.2\%$ for all). There was nominally significant heterogeneity ($P = 0.02$) of the effects of treatment on cardiovascular death in men compared with women, but no other interactions were observed for the 36 sets of subgroups and outcomes investigated (**Appendix Figure 2**, available at www.annals.org). Interactions with diabetes status are not shown because they nearly completely overlap with the interaction analyses of BPLTTC versus non-BPLTTC trials. Risk of bias within trials was judged as low overall (**Appendix Figure 3**, available at www.annals.org); the review included 2 single-blind trials (ANBP [Australian National Blood Pressure Study] and MRC [Medical Research Council Trial of Treatment of Mild Hypertension]) and 1 open trial (UKPDS [U.K. Prospective Diabetes Study]).

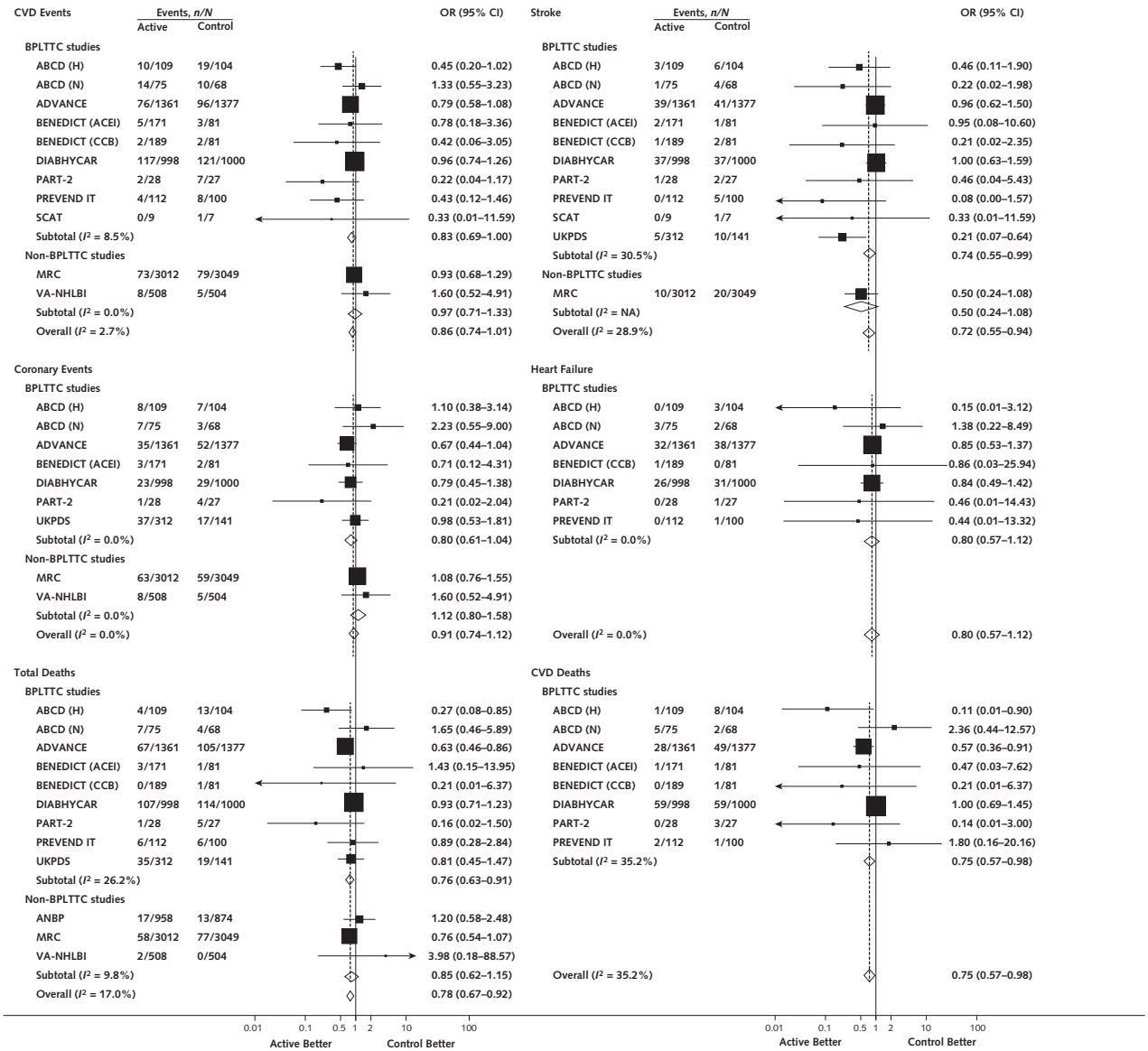
In the subgroup of BPLTTC trials, treating a grade 1 hypertension sample as per the recent JNC 8 guidelines (11) gave results similar to those in the main study sample, with odds ratios of 0.88 (95% CI, 0.75 to 1.04) for total cardiovascular events, 0.72 (CI, 0.55 to 0.95) for strokes, 0.93 (CI, 0.75 to 1.15) for coronary events, 0.82 (CI, 0.58 to 1.16) for heart failure, 0.77 (CI, 0.58 to 1.01) for cardiovascular deaths, and 0.79 (CI, 0.67 to 0.93) for total deaths. In the BPLTTC sample, models that adjusted for study type and baseline age, sex, smoking status, body mass index, and systolic and diastolic blood pressures gave results similar to those of the unadjusted ones. In the adjusted models, treatment led to odds ratios of 0.81 (CI, 0.66 to 0.98) for total cardiovascular events, 0.71 (CI, 0.53 to 0.96) for strokes, 0.79 (CI, 0.60 to 1.04) for coronary events, 0.77 (CI, 0.54 to 1.10) for heart failure, 0.76 (CI, 0.57 to 1.02) for cardiovascular deaths, and 0.75 (CI, 0.61 to 0.91) for total deaths.

Diastolic blood pressure reductions were greatest in the 3 trials that tested more versus less intensive blood pressure–lowering regimens (**Appendix Table 2**). We therefore performed a sensitivity analysis that included only placebo-controlled trials, in which treatment led to odds ratios of 0.88 (CI, 0.74 to 1.03) for total cardiovascular events, 0.82 (CI, 0.62 to 1.09) for strokes, 0.86 (CI, 0.68 to 1.09) for coronary events, 0.81 (CI, 0.58 to 1.16) for heart failure, 0.77 (CI, 0.58 to 1.02) for cardiovascular deaths, and 0.79 (CI, 0.67 to 0.94) for total deaths.

DISCUSSION

In this systematic review and meta-analysis of patients who were enrolled with blood pressures in the grade 1 hypertension range and were free of overt cardiovascular disease, blood pressure–lowering therapy tended to lead to beneficial cardiovascular effects, with statistically significant reductions observed for stroke, cardiovascular deaths, and total deaths. The modest blood pressure reductions achieved and the moderate numbers of events recorded meant that CIs were wide for all outcomes and the power to test the hypothesis of protection was limited in every case. Nonetheless, the findings suggest that blood pressure reduction is likely to provide benefit among patients with grade 1 hypertension and that these benefits could be substantial, particularly among patients at elevated absolute cardiovascular risk. Data on withdrawals from treatment were limited, but withdrawals were equally common in active and control groups, although withdrawals due to adverse effects were more common in the former.

Figure. Main treatment effects.



The average achieved blood pressure difference between active and control groups in the BPLTTC studies was 3.6/2.4 mm Hg. ABCD = Appropriate Blood Pressure Control in Diabetes; ACEI = angiotensin-converting enzyme inhibitor; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ANBP = Australian National Blood Pressure Study; BENEDICT = Bergamo Nephrologic Diabetes Complications Trial; BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration; CCB = calcium-channel blocker; CVD = cardiovascular disease; DIABHYCAR = Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril; H = hypertensive sample; MRC = Medical Research Council Trial of Treatment of Mild Hypertension; N = normotensive sample; NA = not applicable; OR = odds ratio; PART-2 = Prevention of Atherosclerosis with Ramipril; PREVEND IT = Prevention of Renal and Vascular End-Stage Disease Intervention Trial; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; UKPDS = U.K. Prospective Diabetes Study; VA-NHLBI = Veterans Administration-National Heart, Lung, and Blood Institute Feasibility Trial.

These findings are in line with those from definitive large-scale trials of blood pressure reduction conducted among patients with higher blood pressures and/or preexisting cardiovascular disease (28). The proportional reductions in risk that we observed for patients who were enrolled with blood pressures in the grade 1 hypertension range and were free of overt cardiovascular disease are similar to those for other population subsets, and these observations provide further support for the notion that the relative effects of blood pressure–lowering treatments on cardiovascular events are highly generalizable across diverse patient groups (5).

Besides the inclusion of persons with diabetes or prior antihypertensive treatment, the disparity between the conclusions of this review and the one immediately preceding it (7) is primarily attributable to statistical power. The present review nearly doubled the number of patients, quadrupled the number of cardiovascular events, and provides data on end points not available

Table 2. Effects of Blood Pressure–Lowering Drugs on Absolute Risk for Cardiovascular Events and Death

Outcome, by Data Source	5-y Risk, %	ARR (95% CI), %
BPLTTC control groups		
Cardiovascular events	7.4	1.0 (−0.1 to 1.9)
Strokes	2.8	0.8 (0.2 to 1.3)
Coronary events	4.6	0.4 (−0.6 to 1.2)
Heart failure	2.4	0.5 (−0.3 to 1.0)
Total deaths	6.6	1.4 (0.5 to 2.2)
Cardiovascular deaths	3.1	0.8 (0.1 to 1.3)
Non-BPLTTC control groups		
Cardiovascular events	2.4	0.3 (0.0 to 0.6)
Total deaths	2.0	0.4 (0.2 to 0.7)
Contemporary primary care–based cohort*		
Cardiovascular events	11.6	1.6 (−0.1 to 3.0)
Strokes	4.2	1.2 (0.3 to 1.9)
Coronary events	5.1	0.5 (−0.6 to 1.3)
Heart failure	3.0	0.6 (−0.4 to 1.3)
Total deaths	4.3	1.0 (0.3 to 1.4)
Cardiovascular deaths	2.5	0.6 (0.1 to 1.1)

ARR = absolute risk reduction; BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration.
* Patients with grade 1 hypertension without previous cardiovascular disease from a contemporary cohort study (13).

in the prior meta-analysis. Consequently, it is better able to elucidate the likely real effects of blood pressure–lowering treatment on major health outcomes. In addition, most patients in the prior review were from trials that included β-blocker regimens, which are no longer recommended as first-line therapy by most guidelines (29). Of note, we found no evidence that the relative risk reductions achieved with active therapy differed substantially between the BPLTTC and non-BPLTTC trials (**Appendix Figure 2**) or for the other subgroups studied; the statistically significant heterogeneity we observed in 1 subgroup is probably a chance finding because 36 tests were done and the *P* value was not extreme.

Although the participants included in this review did not have preexisting manifest cardiovascular disease, their 5-year risk for cardiovascular events and death was not trivial. This is because most patients with blood pressures in the grade 1 hypertension range without overt cardiovascular disease included in the contributing trials were probably enrolled on the basis of other risk factors being present. For the approximately 50% of patients drawn from studies included in the BPLTTC, at least part of this risk is probably attributable to the effects of diabetes, which was highly prevalent, whereas diabetes was an exclusion criterion for the non-BPLTTC trials (16–18). Of note, the relative risk reductions achieved with blood pressure–lowering therapy have previously been shown to be similar in persons with and without diabetes (30), and this was also true for our study. Likewise, relative risk reductions were similar in patient subsets defined by different levels of baseline absolute cardiovascular risk estimated with the Framingham equation.

Patients in this study may have had subclinical cardiovascular damage at baseline that was not captured in the BPLTTC data set or the reports of the other trials. Therefore, although it is reasonable to assume that the relative risk reductions in the present study can be generalized to a broader population group with grade 1 hypertension, there is uncertainty about the wider applicability of the absolute risk reductions observed. For that reason, we have presented estimated absolute risk reductions calculated by using data from 3 different settings, including a contemporary primary care–based cohort (**Table 2**). In each case, the estimates must be interpreted with caution because the CIs are wide and the point estimates of absolute effect are probably unreliable. Nonetheless, these data highlight the potentially sizeable risk reductions that might be achieved by the treatment of grade 1 hypertension, particularly among persons with multiple cardiovascular risk factors. A definitive, adequately powered, large-scale trial among patients with uncomplicated grade 1 hypertension would be an important addition to the evidence base, but the likelihood that such a trial will be done seems small. In the meantime, decision making based on absolute risk assessment may be the best approach for the prescription of blood pressure–lowering treatment to patients with grade 1 hypertension (31–34).

The use of data from many trials with different inclusion criteria and treatment regimens enhances the generalizability of our conclusions, although the ability to explore effects in subgroups was limited by sample size and we did not have the statistical power to investigate effects of the individual drugs. Both larger and smaller effects than might have been expected for the achieved blood pressure reduction were observed and are probably explained by the limited statistical power of this review. The focus on only the major benefits and harms is a constraint introduced by the lack of reported data on less serious outcomes. Again, the relative effects of blood pressure reduction on the risks for these outcomes can probably be inferred from other studies, although there will be the same uncertainty about the absolute effects. Our study was also limited by the relatively short duration of follow-up of participants in the included trials. Finally, although all study participants had blood pressures in the grade 1 hypertension range at enrollment, some were receiving background antihypertensive treatment at baseline and their untreated blood pressures may have been above the grade 1 hypertension range in some cases.

In conclusion, the effective treatment of patients with blood pressures in the grade 1 hypertension range in the primary preventive setting is likely to reduce the risk for several important adverse health outcomes. As for other groups, the magnitude of the benefit depends primarily on the size of the blood pressure reduction achieved and the level of baseline risk. Ultimately, resourcing will determine how large a proportion of the population with uncomplicated grade 1 hypertension can be treated, and estimation of cardiovascular risk may aid prioritization in this patient group.

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Note: The authors had access to all of the study data, take responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

Financial Support: Dr. Sundström was funded by the Swedish Heart-Lung Foundation (grant 20041151) and the Swedish Research Council (grants 2007-5942 and 2010-1078). Dr. Rahimi was funded by the U.K. National Institute for Health Research (NIHR Oxford Biomedical Research Centre and NIHR Career Development Fellowship). Dr. Neal is supported by an Australian Research Council Future Fellowship and National Health and Medical Research Council of Australia Senior Research Fellowship. This work received partial funding support from a National Health and Medical Research Council of Australia Program Grant.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-0773.

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Obtaining of funding: J. Sundström.
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Collection and assembly of data: J. Sundström, H. Arima, F. Turnbull, M. Woodward.

Appendix: The Blood Pressure Lowering Treatment Trialists' Collaboration

Collaborating trialists: Lawrence Agodoa (AASK [African American Study of Kidney Disease and Hypertension]), Raymond Estacio (ABCD [Appropriate Blood Pressure Control in Diabetes]), Robert Schrier (ABCD), Jacobus Lubsen (ACTION [A Coronary Disease Trial Investigating Outcome with Nifedipine GITS]), John Chalmers (ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation]), Jay Cutler (ALLHAT [Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial]), Barry Davis (ALLHAT), Lindon Wing (ANBP2 [The Second Australian National Blood Pressure Study]), Neil Poulter (ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial]), Peter Sever (ASCOT), Giuseppe Remuzzi (BENEDICT [Bergamo Nephrologic Diabetes Complications Trial]), Piero Ruggenenti (BENEDICT), Steven Nissen (CAMELOT [Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis]), Lars Lindholm (CAPPP [Captopril Prevention Project], STOP2 [Swedish Trial in Old Patients with Hypertension-2], and NORDIL [Nordic Diltiazem]), Tsuguya Fukui (CASE-J [Candesartan Antihypertensive Survival Evaluation in Japan]), Toshio Ogihara (CASE-J), Takao Saruta (CASE-J), Henry Black (CONVINCE [Controlled Onset Verapamil Investigation of Cardiovascular End Points]), Peter Sleight (CONVINCE, HOPE [Heart Outcomes Prevention Evaluation], TRANSCEND [Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease], and ONTARGET [Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial]), Michel Lièvre (DIABHYCAR [Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril]), Hiromichi Suzuki (ECOST [Efficacy of Candesartan on Outcome in Saitama Trial]), Kim Fox (EUROPA [European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease]), Lisheng Liu (FEVER [Felodipine Event Reduction]), Takayoshi Ohkubo (HOMED-BP [Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure]), Yutaka Imai (HOMED-BP), Salim Yusuf (HOPE, ONTARGET, and TRANSCEND), Christopher Bulpitt (HYVET [Hypertension in the Very Elderly Trial]), Edmund Lewis (IDNT [Irbesartan Diabetic Nephropathy Trial]), Morris Brown (INSIGHT [International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment]), Chris Palmer (INSIGHT), Jiguang Wang (NICOLE [Nisoldipine in Coronary Artery Disease in Leuven]), Carl Pepine (INVEST [International Verapamil SR-Trandolapril Study]), Masao Ishii (JATOS [Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients] and JMIC-B [Japan Multicenter Investigation for Cardiovascular Diseases-B]), Yoshiki Yui (JMIC-B), Kizuku Kuramoto (NICS-EH [National Intervention Cooperative Study in Elderly Hypertensives]), Marc Pfeffer (PEACE [Prevention of Events With Angiotensin-Converting Enzyme Inhibition]), Folkert W. Asselbergs (PREVEND IT [Prevention of Renal and Vascular End-Stage Disease Intervention Trial] and renal analyses), Wiek van Gilst (PREVEND IT and renal analyses), Robert Byington (PREVENT [Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial]), Bertram Pitt (QUIET [Quinapril Ischemic Event Trial]), Barry Brenner (RENAAL [Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan]), Willem J. Remme (renal analyses), Dick de Zeeuw (renal trials), Mahboob Rahman (renal trials), Giancarlo Viberti (ROADMAP [Randomised Olmesartan and Diabetes Microalbuminuria Prevention]), Koon Teo (SCAT [Simvastatin/Enalapril Coronary Atherosclerosis Trial]), Alberto Zanchetti (SCOPE [Study on Cognition and Prognosis in the Elderly], VHAS [Verapamil in Hypertension and Atherosclerosis Study], and ELSA [European Lacidipine Study on Atherosclerosis]), Ettore Malacco (SHELL [Systolic Hypertension in the Elderly: Lacidipine Long-Term Study]), Giuseppe Mancia (SHELL), Jan Staessen (SYST-EUR [Systolic Hypertension in Europe]), Robert Fagard (SYST-EUR), and Rury Holman (UKPDS [U.K. Prospective Diabetes Study]).

Other members: L. Hansson (deceased), John Kostis, Yoshihiko Kanno, Stephan Lueders, Masunori Matsuzaki, P. Poole-Wilson (deceased), and Joachim Schrader.

Secretariat: Kazem Rahimi (Coordinator), Craig Anderson, John Chalmers, Neil Chapman, Rory Collins, Stephen MacMahon, Bruce Neal, Anthony Rodgers, Paul Whelton, Mark Woodward, and Salim Yusuf.

Appendix Table 1. Trial Characteristics

Characteristic	BPLTTC Trials										Non-BPLTTC Trials		
	ABCD		ADVANCE	BENEDICT*		DIABHYCAR	PART-2	PREVEND IT	SCAT	UKPDS	MRC	ANBP	VA-NHLBI
	Hypertensive Sample	Normotensive Sample		ACEI	CCB								
Treatment regimen	More vs. less intensive†	More vs. less intensive†	Perindopril + indapamide vs. placebo	Trandolapril vs. placebo	Verapamil vs. placebo	Ramipril vs. placebo	Ramipril vs. placebo	Fosinopril vs. placebo	Enalapril vs. placebo	More vs. less intensive‡	Bendrofluazide or propranolol vs. placebo	Chlorothiazide vs. placebo	Chlorthalidone + reserpine vs. placebo
Median follow-up (IQR), *y*§	5.0 (0.2)	5.1 (0.3)	4.4 (0.3)	3.6 (2.8)	3.5 (3.4)	3.9 (1.8)	4.8 (0.5)	3.9 (0.1)	3.9 (1.3)	8.3 (3.0)	NA	NA	NA
Patients, *n*	213	143	2738	261	272	1998	55	212	16	453	6061	1832	1012
Mean age (SD), *y*	56.6 (8.2)	62.2 (7.1)	65.9 (6.3)	61.4 (8.0)	61.6 (8.1)	64.7 (8.3)	64.0 (6.2)	56.7 (11.0)	61.7 (10.5)	53.6 (8.3)	NA	NA	NA
Women, *n (%)*	71 (33)	71 (50)	1248 (46)	119 (46)	121 (44)	650 (33)	16 (29)	67 (32)	2 (12)	179 (40)	NA	NA	NA
Mean total cholesterol level (SD)													
mmol/L	5.7 (1.6)	5.6 (1.0)	5.3 (1.2)	5.4 (1.0)	5.5 (1.0)	NA	6.5 (1.1)	6.1 (1.0)	5.2 (0.6)	NA	NA	NA	NA
mg/dL	220.1 (61.8)	216.2 (38.6)	204.6 (46.3)	208.5 (38.6)	212.4 (38.6)	NA	251.0 (42.5)	235.5 (38.6)	200.8 (23.2)	NA	NA	NA	NA
Mean HDL cholesterol level (SD)													
mmol/L	1.06 (0.32)	1.05 (0.29)	1.28 (0.36)	1.20 (0.32)	1.22 (0.30)	NA	4.36 (0.95)	1.01 (0.30)	1.04 (0.20)	NA	NA	NA	NA
mg/dL	40.93 (12.36)	40.54 (11.20)	49.42 (13.90)	46.33 (12.36)	47.10 (11.58)	NA	168.34 (36.68)	39.00 (11.58)	40.15 (7.72)	NA	NA	NA	NA
Smokers, *n (%)*	35 (16)	14 (10)	445 (16)	41 (16)	27 (10)	302 (18)	16 (29)	61 (29)	2 (12)	0 (0)	NA	NA	NA
Previous antihypertensive treatment, *n (%)*	78 (37)	51 (36)	1907 (70)	261 (100)	272 (100)	911 (46)	18 (33)	0 (0)	7 (44)	0 (0)	0 (0)	0 (0)	0 (0)
Diabetes mellitus, *n (%)*	213 (100)	143 (100)	2738 (100)	261 (100)	272 (100)	1998 (100)	5 (9)	10 (5)	3 (19)	453 (100)	0 (0)	0 (0)	0 (0)
Mean BMI (SD), kg/m^2	31.8 (5.8)	32.6 (5.8)	28.7 (5.4)	28.8 (4.5)	29.1 (4.6)	29.4 (4.6)	27.2 (4.5)	27.8 (4.2)	30.0 (3.1)	30.1 (5.8)	NA	NA	NA
Mean systolic blood pressure (SD), *mm Hg*	144 (10)	147 (6)	148 (6)	147 (6)	148 (6)	145 (6)	146 (9)	147 (6)	141 (9)	145 (10)	NA	NA	NA
Mean diastolic blood pressure (SD), *mm Hg*	94 (3)	85 (3)	82 (8)	87 (6)	87 (6)	82 (7)	85 (9)	84 (7)	81 (8)	93 (4)	NA	NA	NA

ABCD = Appropriate Blood Pressure Control in Diabetes; ACEI = angiotensin-converting enzyme inhibitor; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ANBP = Australian National Blood Pressure Study; BENEDICT = Bergamo Nephrologic Diabetes Complications Trial; BMI = body mass index; BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration; CCB = calcium-channel blocker; DIABHYCAR = Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril; HDL = high-density lipoprotein; MRC = Medical Research Council Trial of Treatment of Mild Hypertension; NA = not available; PART-2 = Prevention of Atherosclerosis with Ramipril; PREVEND IT = Prevention of Renal and Vascular End-Stage Disease Intervention Trial; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; UKPDS = U.K. Prospective Diabetes Study; VA-NHLBI = Veterans Administration-National Heart, Lung, and Blood Institute Feasibility Trial.

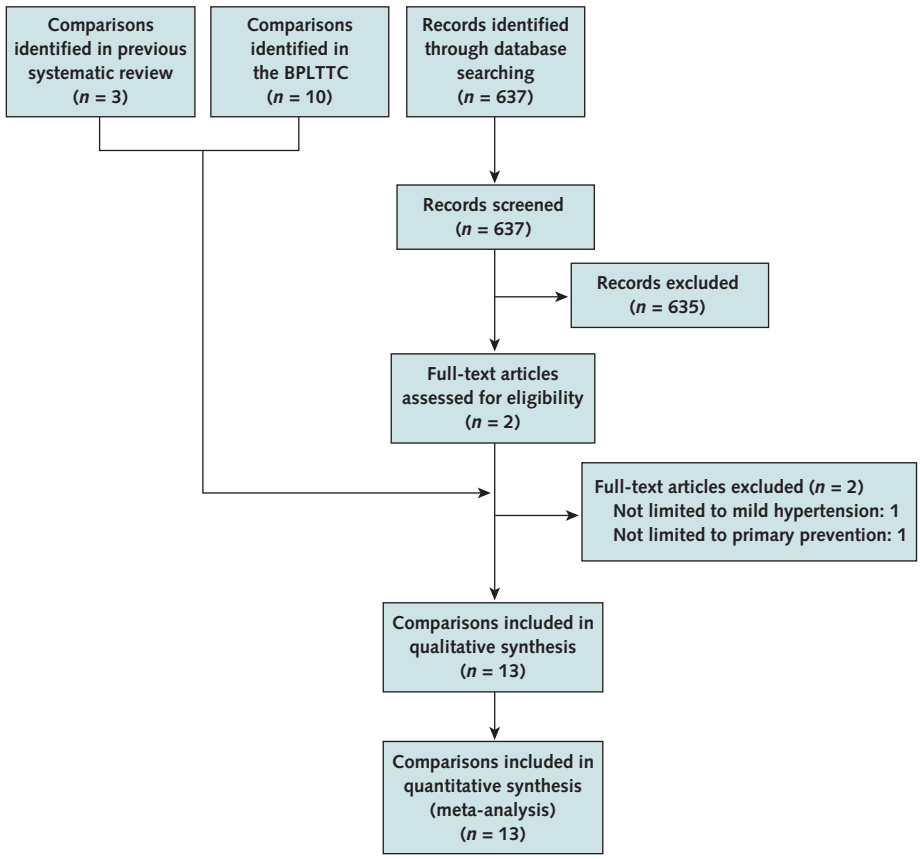
* We randomly allocated half of the placebo recipients to each regimen.

† Nisoldipine or enalapril.

‡ Captopril or atenolol.

§ Treatment was intended for the full duration of follow-up in all studies.

Appendix Figure 1. Summary of evidence search and selection.



BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration.

Appendix Table 2. Blood Pressure Reductions in BPLTTC Trials

Trial	Treatment Regimen	Systolic Blood Pressure Reduction (95% CI), *mm Hg**	Diastolic Blood Pressure Reduction (95% CI), *mm Hg**
ABCD			
Hypertensive sample	More vs. less intensive†	8.7 (6.0 to 11.4)	7.8 (6.6 to 8.9)
Normotensive sample	More vs. less intensive†	7.1 (4.1 to 10.1)	6.0 (4.5 to 7.4)
ADVANCE	Perindopril + indapamide vs. placebo	5.0 (4.1 to 5.9)	1.9 (1.4 to 2.5)
BENEDICT‡			
ACEI	Trandolapril vs. placebo	1.3 (−1.1 to 3.7)	1.2 (−0.4 to 2.8)
CCB	Verapamil vs. placebo	−0.7 (−3.1 to 1.8)	0.5 (−1.1 to 2.1)
DIABHYCAR	Ramipril vs. placebo	1.4 (0.5 to 2.2)	0.6 (0.0 to 1.2)
PART-2	Ramipril vs. placebo	7.6 (1.6 to 13.6)	4.4 (0.4 to 8.4)
PREVEND IT	Fosinopril vs. placebo	7.2 (4.2 to 10.0)	4.6 (3.1 to 6.2)
SCAT	Enalapril vs. placebo	−4.6 (−15.3 to 6.1)	−4.4 (−10.0 to 1.3)
UKPDS	More vs. less intensive§	9.1 (6.7 to 11.6)	6.1 (4.7 to 7.5)
Total sample	–	3.6 (3.1 to 4.1)	2.4 (2.1 to 2.8)

ABCD = Appropriate Blood Pressure Control in Diabetes; ACEI = angiotensin-converting enzyme inhibitor; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; BENEDICT = Bergamo Nephrologic Diabetes Complications Trial; BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration; CCB = calcium-channel blocker; DIABHYCAR = Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril; PART-2 = Prevention of Atherosclerosis with Ramipril; PREVEND IT = Prevention of Renal and Vascular End-Stage Disease Intervention Trial; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; UKPDS = U.K. Prospective Diabetes Study.

* Difference in reduction from baseline between active and control groups.

† Nisoldipine or enalapril.

‡ We randomly allocated half of the placebo recipients to each regimen.

§ Captopril or atenolol.

Appendix Table 3. Numbers of Patients and Events, by Trial Group

Trial, by Data Source	Active Group, *n*							Control Group, *n*						
	Patients	Total Deaths	Cardiovascular Deaths	Cardiovascular Events	Strokes	Coronary Events	Heart Failure	Patients	Total Deaths	Cardiovascular Deaths	Cardiovascular Events	Strokes	Coronary Events	Heart Failure
BPLTTC trials														
ABCD														
Hypertensive sample	109	4	1	10	3	8	0	104	13	8	19	6	7	3
Normotensive sample	75	7	5	14	1	7	3	68	4	2	10	4	3	2
ADVANCE	1361	67	28	76	39	35	32	1377	105	49	96	41	52	38
BENEDICT*														
ACEI	171	3	1	5	2	3	0	90	2	2	3	1	2	0
CCB	189	0	0	2	1	0	1	83	0	0	1	0	1	0
DIABHYCAR	998	107	59	117	37	23	26	1000	114	59	121	37	29	31
PART-2	28	1	0	2	1	1	0	27	5	3	7	2	4	1
PREVEND IT	112	6	2	4	0	NA	0	100	6	1	8	5	NA	1
SCAT	9	0	0	0	0	0	0	7	0	0	1	1	0	0
UKPDS	312	35	NA	NA	5	37	NA	141	19	NA	NA	10	17	NA
Non-BPLTTC trials														
MRC	3012	58	NA	73	10	63	NA	3049	77	NA	79	20	59	NA
ANBP	958	17	NA	NA	NA	NA	NA	874	13	NA	NA	NA	NA	NA
VA-NHLBI	508	2	NA	8	NA	8	NA	504	0	NA	5	NA	5	NA
All trials	7842	307	96	311	99	185	62	7424	358	124	350	127	179	76

ABCD = Appropriate Blood Pressure Control in Diabetes; ACEI = angiotensin-converting enzyme inhibitor; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ANBP = Australian National Blood Pressure Study; BENEDICT = Bergamo Nephrologic Diabetes Complications Trial; BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration; CCB = calcium-channel blocker; DIABHYCAR = Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril; MRC = Medical Research Council Trial of Treatment of Mild Hypertension; NA = not available; PART-2 = Prevention of Atherosclerosis with Ramipril; PREVEND IT = Prevention of Renal and Vascular End-Stage Disease Intervention Trial; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; UKPDS = U.K. Prospective Diabetes Study; VA-NHLBI = Veterans Administration-National Heart, Lung, and Blood Institute Feasibility Trial.

* We randomly allocated half of the placebo recipients to each regimen.

Appendix Table 4. Patients and Withdrawals in the Original Study Samples and the Subsamples Included in This Study, by Trial Group*

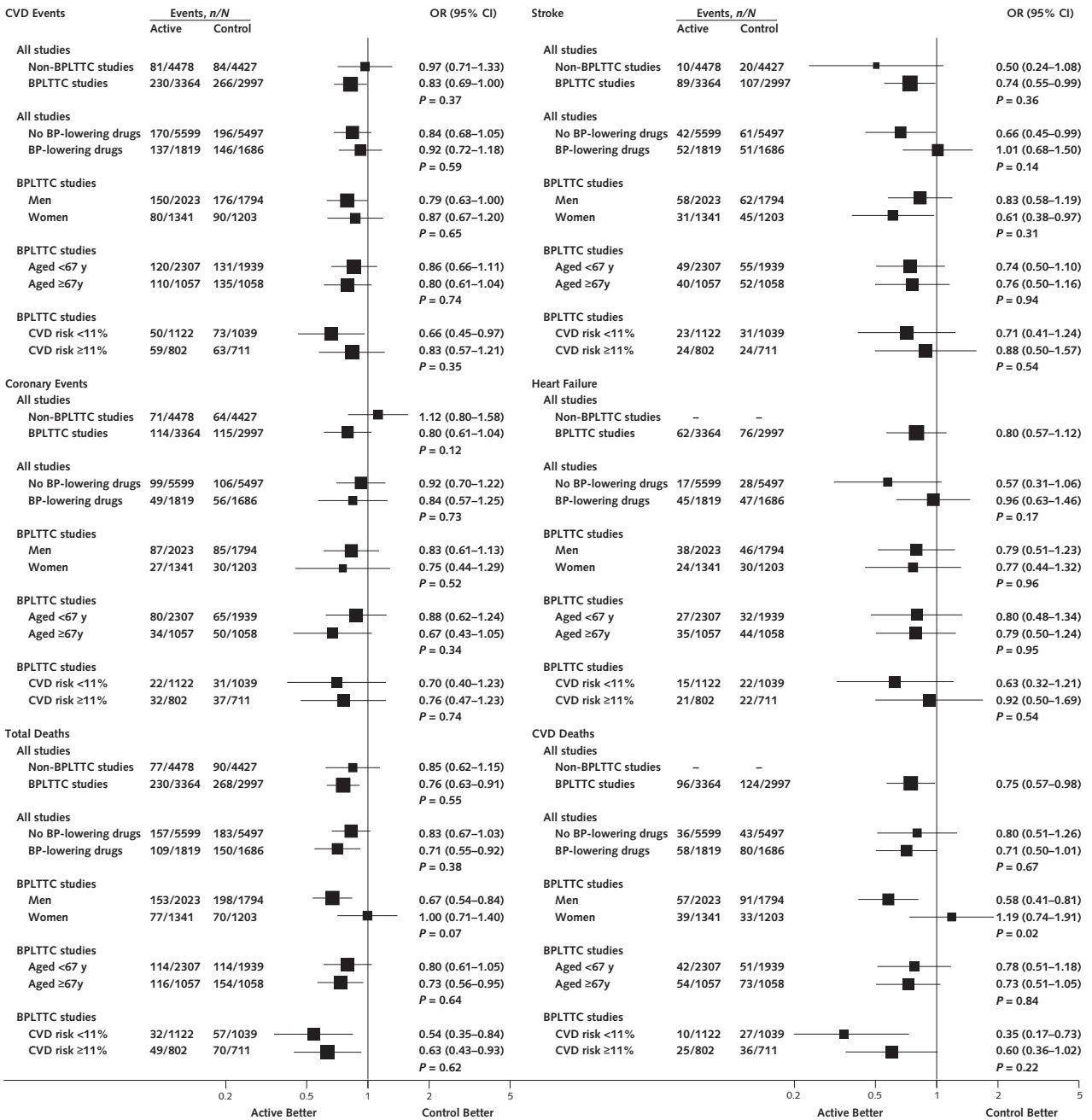
Trial	Active Group						Control Group					
	Original Sample			Studied Subsample			Original Sample			Studied Subsample		
	Patients, *n*	Withdrawals, *n* (%)	Withdrawals Due to AEs, *n* (%)	Patients, *n*	Withdrawals, *n* (%)	Withdrawals Due to AEs, *n* (%)	Patients, *n*	Withdrawals, *n* (%)	Withdrawals Due to AEs, *n* (%)	Patients, *n*	Withdrawals, *n* (%)	Withdrawals Due to AEs, *n* (%)
ABCD												
Hypertensive sample	237	NA	NA	109	19 (17)	NA	233	NA	NA	104	28 (27)	NA
Normotensive sample	237	42 (18)	NA	75	18 (24)	NA	243	41 (17)	NA	68	21 (31)	NA
ADVANCE	5569	1488 (27)	320 (6)	1361	290 (21)	76 (6)	5571	1428 (26)	160 (3)	1377	298 (22)	38 (3)
BENEDICT†												
ACEI	301	NA	NA	171	NA	NA	150	NA	NA	90	NA	NA
CCB	303	NA	NA	189	NA	NA	150	NA	NA	83	NA	NA
DIABHYCAR	2443	344 (14)	NA	998	NA	NA	2469	334 (14)	NA	1000	NA	NA
PART-2	308	86 (28)	NA	28	8 (29)	NA	309	77 (25)	NA	27	8 (30)	NA
PREVEND IT	431	130 (30)	NA	112	NA	NA	433	110 (25)	NA	100	NA	NA
SCAT	229	NA	NA	9	2 (22)	NA	231	NA	NA	7	2 (29)	NA
UKPDS	758	NA	NA	312	NA	NA	390	NA	NA	141	NA	NA
MRC	8700	1056 (12)	980 (11)	3012	NA	NA	8654	1214 (14)	203 (2)	3049	NA	NA
ANBP	1721	NA	NA	958	NA	NA	1706	NA	NA	874	NA	NA
VA-NHLBI	508	NA	NA	508	NA	NA	504	NA	NA	504	NA	NA
All trials	21 745	NA	NA	7842	NA	NA	21 043	NA	NA	7424	NA	NA

ABCD = Appropriate Blood Pressure Control in Diabetes; ACEI = angiotensin-converting enzyme inhibitor; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AE = adverse event; ANBP = Australian National Blood Pressure Study; BENEDICT = Bergamo Nephrologic Diabetes Complications Trial; CCB = calcium-channel blocker; DIABHYCAR = Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril; MRC = Medical Research Council Trial of Treatment of Mild Hypertension; NA = not available; PART-2 = Prevention of Atherosclerosis with Ramipril; PREVEND IT = Prevention of Renal and Vascular End-Stage Disease Intervention Trial; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; UKPDS = U.K. Prospective Diabetes Study; VA-NHLBI = Veterans Administration-National Heart, Lung, and Blood Institute Feasibility Trial.

* Information about reasons for withdrawals in the studied subsample was available only for ADVANCE. Withdrawals due to AEs were defined as those due to cough, dizziness, hypotension, or a serious AE.

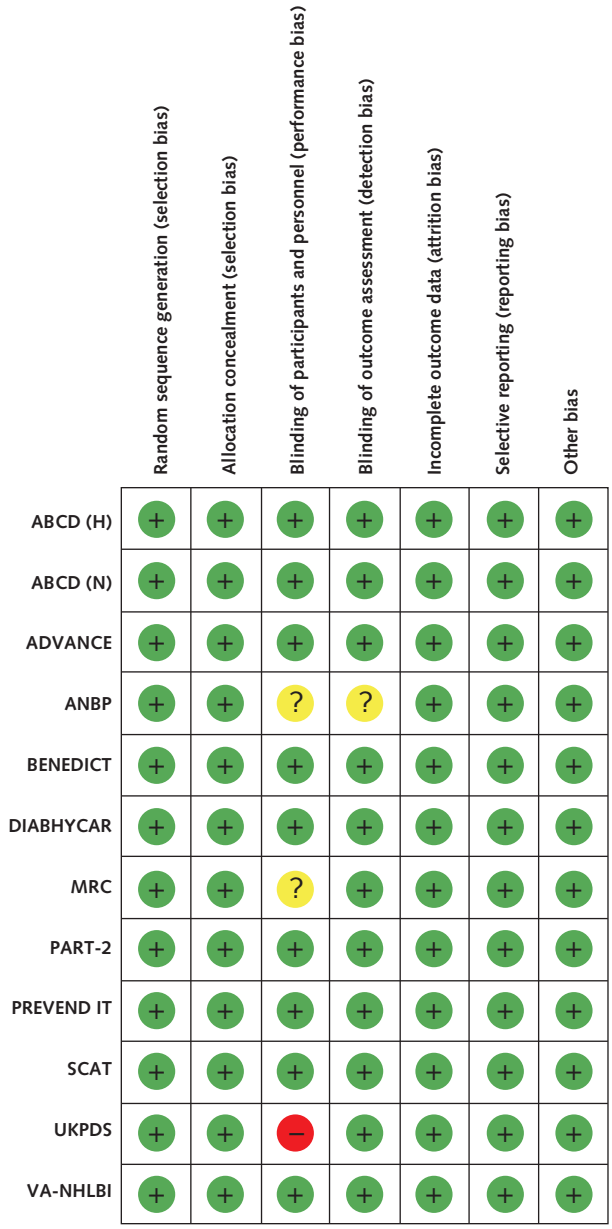
† We randomly allocated half of the placebo recipients to each regimen.

Appendix Figure 2. Treatment effects in subgroups.



Analyses based on BPLTTC status, BP-lowering drugs, and diabetes included all trials; those based on age, sex, and CVD risk included only BPLTTC trials. Data on heart failure and cardiovascular deaths were only available in the BPLTTC trials. BP = blood pressure; BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration; CVD = cardiovascular disease; OR = odds ratio.

Appendix Figure 3. Risk of bias within studies.



Plus sign denotes low risk. Minus sign denotes high risk. Question mark denotes unclear risk. ABCD = Appropriate Blood Pressure Control in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ANBP = Australian National Blood Pressure Study; BENEDICT = Bergamo Nephrologic Diabetes Complications Trial; DIABHYCAR = Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril; H = hypertensive sample; MRC = Medical Research Council Trial of Treatment of Mild Hypertension; N = normotensive sample; PART-2 = Prevention of Atherosclerosis with Ramipril; PREVEND IT = Prevention of Renal and Vascular End-Stage Disease Intervention Trial; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; UKPDS = U.K. Prospective Diabetes Study; VA-NHLBI = Veterans Administration-National Heart, Lung, and Blood Institute Feasibility Trial.