REVIEW

Antihypertensive Treatment and Secondary Prevention of Cardiovascular Disease Events Among Persons Without Hypertension

A Meta-analysis

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Context Cardiovascular disease (CVD) risk increases beginning at systolic blood pressure levels of 115 mm Hg. Use of antihypertensive medications among patients with a history of CVD or diabetes and without hypertension has been debated.

Objective To evaluate the effect of antihypertensive treatment on secondary prevention of CVD events and all-cause mortality among persons without clinically defined hypertension.

Data Sources Meta-analysis with systematic search of MEDLINE (1950 to week 3 of January 2011), EMBASE, and the Cochrane Collaboration Central Register of Controlled Clinical Trials and manual examination of references in selected articles and studies.

Study Selection From 874 potentially relevant publications, 25 trials that fulfilled the predetermined inclusion and exclusion criteria were included in the meta-analysis.

Data Extraction Information on participant characteristics, trial design and duration, treatment drug, dose, control, and clinical events were extracted using a standardized protocol. Outcomes included stroke, myocardial infarction (MI), congestive heart failure (CHF), composite CVD outcomes, CVD mortality, and all-cause mortality.

Results Compared with controls, participants receiving antihypertensive medications had a pooled relative risk of 0.77 (95% confidence interval [CI], 0.61 to 0.98) for stroke, 0.80 (95% CI, 0.69 to 0.93) for MI, 0.71 (95% CI, 0.65 to 0.77) for CHF, 0.85 (95% CI, 0.80 to 0.90) for composite CVD events, 0.83 (95% CI, 0.69 to 0.99) for CVD mortality, and 0.87 (95% CI, 0.80 to 0.95) for all-cause mortality from random-effects models. The corresponding absolute risk reductions per 1000 persons were –7.7 (95% CI, –15.2 to –0.3) for stroke, –13.3 (95% CI, –28.4 to 1.7) for MI, –43.6 (95% CI, –65.2 to –22.0) for CHF events, –27.1 (95% CI, –40.3 to –13.9) for composite CVD events, –15.4 (95% CI, –32.5 to 1.7) for CVD mortality, and –13.7 (95% CI, –24.6 to –2.8) for all-cause mortality. Results did not differ according to trial characteristics or subgroups defined by clinical history.

Conclusions Among patients with clinical history of CVD but without hypertension, antihypertensive treatment was associated with decreased risk of stroke, CHF, composite CVD events, and all-cause mortality. Additional randomized trial data are necessary to assess these outcomes in patients without CVD clinical recommendations.

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CARDIOVASCULAR DISEASE (CVD) is the leading cause of death in the United States and globally, representing 30% of all deaths worldwide.[1] Prospective cohort studies have established a strong, graded, and independent positive association between blood pressure levels and risk of CVD, stroke, and premature death.[2,3] Increased CVD risk begins at systolic blood pressure levels as low as 115 mm Hg, with 54% of stroke and 46% of ischemic heart disease events occurring in persons with blood pressures in this range.[4] In persons with prehypertension, 90% have at least 1 risk factor above optimal levels for heart disease or stroke, and 68% have at least 1 clinically high-risk factor for heart disease or stroke.[5]

Among adults 35 years and older, more than 17% of those with normal blood pressure and 37% of those with blood pressure in the prehypertensive range (130-139 mm Hg systolic, 86-89 mm Hg diastolic) progress to overt hypertension within 4 years without changes in lifestyle or pharmacological intervention.[6] In adults 55 years and older, lifetime risk of developing hypertension is greater than 90%.[7] Recent national surveys report that more than 30% of the general adult population in the United States, Korea, and China has prehypertension.[8-10]

For editorial comment see p 940.

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Clinical trials have documented that lowering blood pressure reduces cardiovascular mortality among patients with hypertension.[3,11] Several randomized controlled trials of blood pressure lowering for the prevention of CVD have demonstrated benefit among persons with prehypertension or normal blood pressures,[12,13] while others have not shown benefit.[14,15] Given these conflicting results, a meta-analysis of randomized controlled trials that examine antihypertensive treatment among persons with blood pressures in the prehypertensive or normal range for the primary or secondary prevention of CVD may help clarify this issue. The objective of this meta-analysis is to evaluate the association between antihypertensive treatment and secondary prevention of CVD events and all-cause mortality among persons without clinically defined hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic and/or use of antihypertensive medications or history of hypertension).

METHODS

Study Selection

We searched online databases including MEDLINE (1950 to week 3 of January 2011), EMBASE, and the Cochrane Collaboration Central Register of Controlled Clinical Trials using the following terms as Medical Subject Headings and keywords: *hypertension* or *blood pressure* or *normal blood pressure* or *prehypertension* or *pre-hypertension* or *pre-hypertensive* or *normotensive* and *antihypertensive agents*, and *cardiovascular disease*. No language restrictions were applied. Searches were limited to randomized clinical trials in human participants 19 years or older. A manual examination of references in selected articles was also performed.

The titles and abstracts of 874 potentially relevant references were identified through the literature search and reviewed independently by 3 investigators (A.M.T., T.H., C.L.E.) to determine whether they met eligibility criteria for inclusion. Discrepancies regarding whether to include or exclude a study were resolved by consensus with other investigators (J.H., L.A.B.).

Studies were eligible for inclusion if they were randomized controlled trials of antihypertensive treatment among persons with blood pressure less than 140 mm Hg systolic or less than 90 mm Hg diastolic for the prevention of CVD events (fatal or nonfatal stroke, fatal or nonfatal myocardial infarction [MI], congestive heart failure [CHF], or CVD mortality). For studies that produced multiple publications, data from the most recent or most complete publication were included in the analysis.

Studies were excluded if CVD events were not reported by hypertension status in studies that included participants with and without hypertension; the study population did not include persons with blood pressure in the normal or prehypertensive ranges; the study population did not include persons with preexisting CVD or CVD equivalents, such as diabetes; antihypertensive treatment was not part of the intervention; treatment allocation was not random; a measure of variance (*P* value or confidence interval [CI]) was not reported or could not be calculated from the information provided; participants were younger than 18 years; or there were differences between intervention and control groups other than antihypertensive treatment.

Data Abstraction

All data were independently abstracted by 3 investigators (A.M.T., T.H., C.L.E.) using a standardized data collection form. Discrepancies were resolved through discussion with other investigators (J.H., L.A.B.) and through reference to the original articles. We attempted to contact study authors for additional information when necessary. Trial characteristics abstracted included design of the randomized controlled trial, type of control, number of treatment groups, description of treatment regimens, description of inclusion and exclusion criteria, numbers of fatal and nonfatal events, definition of participants without hypertension, and demographic characteristics of study populations at baseline. The outcomes recorded included incidence of stroke, MI, CHF events, composite CVD events (as defined by the study), CVD mortality, and all-cause mortality.

The definition of nonhypertensive varied in each study; however, all studies included in this analysis had populations with blood pressure less than 140 mm Hg systolic, less than 90 mm Hg diastolic, or no clinical history of hypertension at baseline. The study-specific definitions of persons without hypertension and outcomes included in this analysis are provided in eTable 1 and eTable 2, available at http://www.jama.com.

Quality Assessment

Two authors (A.M.T., T.H.) independently evaluated quality of each study using an established tool.[16] Nine domains were assessed: randomization, concealment of treatment allocation, similarity of groups at baseline, eligibility criteria, blinding of outcome assessor, patient and care provider, point estimates, and intention-to-treat analysis. Disagreement was resolved through consensus and discussion.

Statistical Analysis

For studies that provided an effect estimate such as a relative risk (RR) or hazard ratio, the study-provided effect estimate was directly used in the pooled meta-analysis calculations. For studies that published number of events but did not publish an effect estimate, this information was used to calculate the RR of each outcome for the intervention compared with the placebo group. We logarithmically transformed the RR and corresponding standard error to stabilize the variance and normalize the distribution. We calculated the overall pooled-effect estimates using inverse-variance weighting to calculate both fixed-effects and DerSimonian and Laird random-effects models.[17] The Q test was used to assess the presence of heterogeneity and the I^2 index to quan-

tify the extent of heterogeneity.[18,19] Fixed- and random-effects models yielded similar findings, but we detected between-study heterogeneity for several outcomes; therefore, results from the random-effects models are presented. Absolute risk reductions for individual studies were calculated as the difference in event rates between treatment and control groups based on the reported or estimated number of events for each outcome. Pooled absolute risk reductions were calculated using inverse-variance weighted DerSimonian and Laird random-effects models.

To assess for publication bias, we constructed funnel plots for each outcome in which the ln(RR) was plotted against its standard error. The Begg rank correlation test was used to examine the asymmetry of the funnel plot,[20] and the Egger weighted linear regression test was used to examine the association between mean effect estimate and its variance.[21] Prestated subgroup analyses were conducted to assess the influence of the presence or absence of comorbid conditions at baseline and class of antihypertensive treatment. We then conducted sensitivity analyses to examine the robustness of the results and restricted analyses by antihypertensive medication use at baseline, definition of persons without hypertension, trial size, duration of follow-up, and year of publication. Additionally, we conducted sensitivity analyses whereby each study was excluded in turn to evaluate the relative influence of each trial on the pooled estimates. $P < .05$ was considered statistically significant, and all tests were 2-sided. All analyses were conducted in STATA version 9.2 (StataCorp, College Station, Texas).

RESULTS

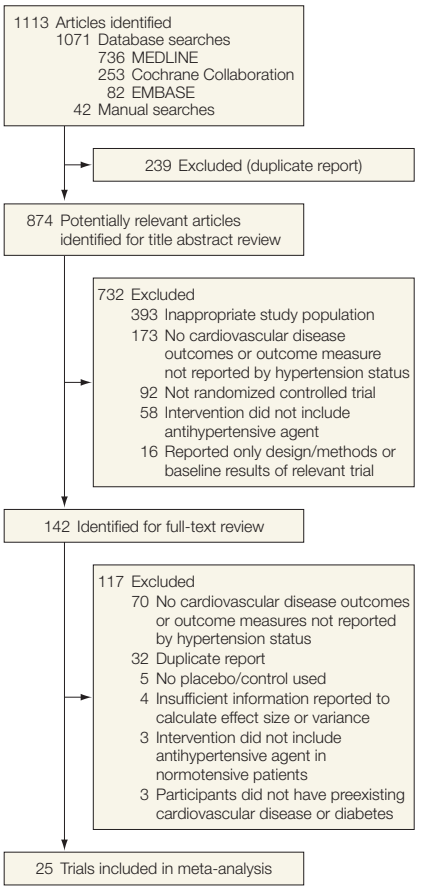
Of 874 potentially relevant studies identified in the initial literature search, 25 were included in the meta-analysis (FIGURE 1). TABLE 1 describes the characteristics of trials included in the meta-analysis. The class and dose of medication administered in the antihypertensive treatment group varied between studies, but for most studies it progressively increased to a defined target dose. Study duration ranged from a mean length of 1.5 to 63 months. Entry criteria also varied between studies; however, all studies required a history of CVD; clinical evidence of recent MI, CHF, coronary artery disease, or stroke; or CVD equivalent such as type 2 diabetes.

The 25 studies included in the meta-analysis incorporated data from 64 162 participants without hypertension (TABLE 2). The mean age of participants in the studies ranged from 55.0 to 68.0 years, and 76% of study participants were men. Clinical history of MI, CHF, diabetes, stroke, and coronary artery disease at baseline varied between studies.

Pooled overall RRs and absolute risk reductions per 1000 persons are presented in FIGURE 2 and FIGURE 3 for all study outcomes. There was a 23% reduction in risk of stroke (RR, 0.77 [95% CI, 0.61 to 0.98]), 20% reduction in risk of MI (RR, 0.80 [95% CI, 0.69 to 0.93]), 29% reduction in risk of CHF events (RR, 0.71 [95% CI, 0.65 to 0.77]), 15% reduction in risk of composite CVD events (RR, 0.85 [95% CI, 0.80 to 0.90]), 17% reduction in risk for CVD mortality (RR, 0.83 [95% CI, 0.69 to 0.99]), and a 13% reduction in risk for all-cause mortality (RR, 0.87 [95% CI, 0.80 to 0.95]). The absolute risk reduction per 1000 persons was –7.7 (95% CI, –15.2 to –0.3) for stroke, –13.3 (95% CI, –28.4 to 1.7) for MI, –43.6 (95% CI, –65.2 to –22.0) for CHF events, –27.1 (95% CI, –40.3 to –13.9) for composite CVD events, –15.4 (95% CI, –32.5 to 1.7) for CVD mortality, and –13.7 (95% CI, –24.6 to –2.8) for all-cause mortality.

I^2 values were calculated to quantify heterogeneity between studies. The I^2 values were 26.5% ($P = .24$) and 0.0% ($P = .85$) for MI and CHF events, indicating low heterogeneity between studies. Moderate heterogeneity was detected for stroke events ($I^2 = 61.9\%$ [$P = .02$ from Q test]), composite CVD events ($I^2 = 35.4\%$ [$P = .10$]), CVD mortality ($I^2 = 43.6\%$ [$P = .12$]), and all-cause mortality ($I^2 = 46.1\%$ [$P = .03$]).

Figure 1. Selection Process for Studies Included in the Meta-analysis.



We found no evidence of publication bias as indicated by Begg rank correlation test for any outcome examined. However, possible publication bias was detected for stroke ($P = .04$) using Egger linear regression tests. Applying the trim and fill adjustment method produced no change in the overall effect estimate for stroke. Exclusion of any single study did not change the significance of the pooled estimates for CHF events, composite CVD outcomes, and all-cause mortality. After individual exclusion of the SOLVD, ABCD, PEACE, PROGRESS, or PATS studies, treatment with antihypertensive medications no longer showed a statistically significant benefit for the outcome of stroke. After exclusion of the SOLVD study, antihypertensive

Table 1. Characteristics of Randomized Clinical Trials of Antihypertensive Medications Included in the Meta-analysis (N = 25)[a]

Trial[b]	Treatment Regimen			Participant Population	Duration of Follow-up, Mean (Range), Mo
	Medication	Drug Class	Dose/Titration		
MIS,[22] 1975	Practolol	β-Blocker	100 mg/d	7-28 d post-MI	14 (1-36)
MPI,[23] 1980	Propranolol	β-Blocker	40 mg ×3/d	2-14 d post-MI (anterior infarction)	5.6 (1-9)
BHAT,[24] 1982	Propranolol	β-Blocker	180 mg/d or 240 mg/d	5-21 d post-MI	25.1 (1-36)
ASPS,[25] 1983	Pindolol	β-Blocker	15 mg/d	0-21 d post-MI (with electrical and/or mechanical complications)	24 (1-24)
CONSENSUS II,[26,27] 1992	Enalapril	ACEI	20 mg/d	Presented within 24 h of onset of acute MI	6 (1-20)[c]
SOLVD,[28-31] 1995	Enalapril	ACEI	2.5 or 5 mg ×2/d titrated to 10 mg ×2/d	CHF and LVEF ≤35%	40 (15-62)[d]
USCHF,[32] 1996	Carvedilol	β-Blocker	12.5 mg ×2/d increased to 25 or 50 mg ×2/d	LVEF ≤35%, not receiving CCB, α- or β-adrenergic agonists or antagonists, or class IC or III antiarrhythmic agents	6.5 (0-15)[e]
TRACE,[33,34] 1997	Trandolapril	ACEI	1 mg, titrated to 4 mg/d	LVEF ≤35%, 3-7 d post-MI	26 (24-50)
AIRE,[35,36] 1999	Ramipril	ACEI	1.25, 2.5, or 5.0 mg ×2/d	Transient or persistent CHF, 2-9 d post-MI	15 (6-20)
SMILE,[37-39] 1999	Zofenopril calcium	ACEI	7.5 mg ×2/d titrated to 30 mg/d	Presented within 24 h of onset of MI	1.5 (0-1.5)[f]
MERIT-HF,[40] 2000	Metoprolol CR/XL	β-Blocker	25 or 12.5 mg/d to 200 mg	Symptomatic CHF for at least 3 mo, LVEF ≤40%	12 (0-18)
CCS-1,[41,42] 2001	Captopril	ACEI	6.25 mg initial dose + 12.5 mg 2 h later, 12.5 mg ×3/d thereafter	Post-MI (acute MI in past 36 h)	23.4 (6.5-40.3)
HOPE,[43-46] 2001	Ramipril	ACEI	2.5 mg initial dose progressively increased to 10 mg/d	History of CAD, stroke or PAD, or diabetes plus 1 additional risk factor	54 (0-60)
ABCD,[14,47] 2002	Nisoldipine or enalapril	CCB or ACEI	Nisoldipine 10 mg titrated to 60 mg/d or enalapril 5 mg/d titrated to 40 mg/d	Type 2 diabetes, DBP 80-89 mm Hg, not receiving antihypertensive medications	63.6 (0-63.6)
CAMELOT,[12] 2004	Amlodipine	CCB	10 mg/d	LVEF ≥40%, CAD >20% stenosis by coronary angiography, and DBP <100 mm Hg	24 (0-24)
COPERNICUS,[48,49] 2004	Carvedilol	β-Blocker	3.125 mg titrated to 25 mg ×2/d	LVEF <25% despite conventional therapies, dyspnea or fatigue at rest or with minimal exertion	10.4 (0-28.7)
DIABHYCAR,[50] 2004	Ramipril	ACEI	1.25 mg/d	Type 2 diabetes, persistent microalbuminuria or proteinuria, serum creatinine ≤150 μmol/L, no MI in past 3 mo	47 (36-72)[e]
PEACE,[51-53] 2004	Trandolapril	ACEI	2 mg/d increased to 4 mg/d	History of major CVD (if MI, at least 3 mo prior), LVEF >40%	57.6 (0-84)[e]
SAVE,[54,55] 2004	Captopril	ACEI	12.5 mg titrated to target dose of 25 mg ×3/d, maximum 50 mg ×3/d	3-16 d post-MI with LVEF ≤40%	42 (24-60)
PROGRESS,[56-58] 2006	Perindopril + indapamide	ACEI +diuretic	4 mg perindopril + 2.5 mg indapamide daily (2.0 mg indapamide in Japan)	History of stroke or TIA within previous 5 y	46.8 (0-54)
ADVANCE,[59,60] 2007	Perindopril + indapamide	ACEI + diuretic	2 mg/d perindopril + 0.625 mg indapamide; 4mg/d perindopril + 1.25 mg/d indapamide after 3 mo	Type 2 diabetes, ≥1 CVD risk factor, or history of microvascular or macrovascular disease	51.6 (0-60)
PRoFESS,[61,62] 2008	Temisartan	ARB	80 mg/d	Stroke within previous 90 d if ≥55 y; stroke within previous 120 d if 50-54 y	30 (18-52)
TRANSCEND,[15] 2008	Temisartan	ARB	80 mg/d	History of CAD, PVD, stroke, or diabetes with end-organ damage; intolerance to ACEIs	56 (IQR, 51-64)[e]
EUROPA,[13,63,64] 2009	Perindopril	ACEI	8 mg/d	Documented CAD (MI >3 mo prior to enrollment) in men or women, history of angina, and confirmed ischemia on stress testing in men	50.4 (0-60)
PATS,[65] 2009	Indapamide	Diuretic	2.5 mg/d	History of stroke or TIA (qualifying cerebrovascular event ≥4 weeks prior to enrollment)	24 (0-45)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PVD, peripheral vascular disease; TIA, transient ischemic attack.

[a] All trials were double-blinded with the exception of the ABCD Normotensive Trial, which was single-blinded. Placebo control was used in all studies.

[b] ABCD indicates Appropriate Blood Pressure Control in Diabetes–Normotensive Study; ADVANCE, Action in Diabetes and Vascular Disease: PreterAx and Diamicro N-MR Controlled Evaluation; AIRE, Acute Infarction Ramipril Efficacy; ASPS, Australian and Swedish Pindolol Study; BHAT, β-Blocker Heart Attack Trial Research Group; CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurances of Thrombosis; CCS-1, Chinese Cardiac Study; CONSENSUS II, Cooperative New Scandinavian Enalapril Survival Study II; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; DIABHYCAR, Noninsulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril Study; EUROPA, European trial on Reduction of Cardiac Events With Perindopril in Patients With Stable Coronary Artery Disease:HOPE, Heart Outcomes Prevention Evaluation; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MIS, Multicenter International Study; MPI, Multicenter Post-Infarction Study; PATS, Post-Stroke Antihypertensive Treatment Study; PEACE, Prevention of Events With Angiotensin Converting Enzyme Inhibition Trial; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SAVE, Survival and Ventricular Enlargement Trial; SMILE, Survival of Myocardial Infarction Long-term Evaluation Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Event Study; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; USCHF, US Carvedilol Heart Failure Study Group.

[c] Patients (N=2952) underwent follow-up for 180 days, observation period ranged from 41 to 180 days.[26]

[d] Mean follow-up time was 37.4 (range, 14.6-62.0) months and 41.4 (range, 22-55) months for the SOLVD Prevention and Treatment trials, respectively. Participants from both trials were included in the analysis of nonhypertensive participants.

[e] Median follow-up time reported.

[f] Double-blind treatment period was 6 weeks; maintenance treatment using conventional therapy was continued for 48 additional weeks. Six-week outcomes are evaluated in this meta-analysis.[37]

treatment for the prevention of MI no longer showed statistically significant benefit. For the prevention of CVD mortality, the benefit of antihypertensive treatment among persons without hypertension was no longer statistically significant after omission of TRACE, AIRE, or SAVE.

We conducted sensitivity analyses to examine the robustness of the results for the composite CVD outcome and all-cause mortality (eTable 3). Sensitivity analyses were not conducted for the outcomes of stroke, MI, CHF, and CVD mortality because of the small number of studies and events. Results did not differ according to any of these criteria. On a 9-point scale, our quality assessment scores ranged from 7.0 to 9.0 for all studies included. The median score was 9.0 points, and these studies were considered to be excellent quality. There was no difference in the association of antihypertensive

Table 2. Baseline Characteristics of Participants Without Hypertension in Randomized Controlled Trials of Antihypertension Medications

			No. (%)[b]		BP or Cutpoint for Nonhypertensive, Mean, mm Hg[c]		Clinical History, No. (%)[b]				
Trial	No.[a]	Age, Mean (SD), y	Men	Nonwhite Race	Systolic	Diastolic	MI	CHF	Diabetes	Stroke	CAD
MIS,[22] 1975[d]	1334	55.0 (NR)	1154 (86.5)	NR	NR	<78.0	1334 (100)	0	40 (3.0)	NR	NR
MPI,[23] 1980[d]	292	54.9 (NR)	247 (84.5)	NR	NR	<79.7	292 (100)	5 (1.5)	11 (3.6)	NR	NR
BHAT,[24] 1982[d]	2715	54.8 (NR)	2294 (84.5)	304 (11.2)	NR	≤76.0	2715 (100)	250 (9.2)	313 (11.5)	NR	NR
ASPS,[25] 1983[d]	390	58.0 (NR)	324 (83.0)	NR	NA[e]	NA[e]	390 (100)	NR	27 (6.8)	NR	NR
CONSENSUS II,[26,27] 1992[d]	4437	65.8 (NR)	3262 (73.5)	NR	NA[e]	NA[e]	4437 (100)	271 (6.1)	497 (11.2)	NR	NR
SOLVD,[28-31] 1995[d]	4145	59.1 (NR)	3673 (88.6)	485 (11.7)	NA[e]	NA[e]	3312 (79.9)	4145 (100)	634 (15.3)	NR	NR
USCHF,[32] 1996[d]	547	58.0 (12.2)	419 (76.6)	NR	115.0	73.0	NR	547 (100)	NR	NR	261 (47.6)
TRACE,[33,34] 1997	1349	68.0 (NR)	1000 (74.1)	NR	119.0	75.0	1349 (100)	285 (21.1)	157 (11.6)	NR	NR
AIRE,[35,36] 1999	1432	64.4 (11.0)	1117 (78.0)	NR	NA[e]	NA[e]	1432 (100)	1432 (100)	145 (10.1)	NR	NR
SMILE,[37-39] 1999	876	63.3 (10.0)	701 (80.0)	NR	132.1	81.8	876 (100)	0	158 (18.0)	NR	NR
MERIT-HF,[40] 2000[d]	2235	63.8 (NR)	1732 (77.5)	135 (6.0)	NA[e]	NA[e]	1078 (48.2)	2235 (100)	552 (24.7)	NR	NR
CCS-1,[41,42] 2001[d]	4760	63.5 (10.8)	3627 (76.2)	4760 (100)	<140.0	NR	4760 (100)	929 (19.5)	405 (8.5)	NR	NR
HOPE,[43-46] 2001[d]	4673	66.0 (7.0)	3425 (73.3)	NR	<138.0	NR	2458 (52.6)	0	4712 (38.5)	510 (10.9)	3739 (80.0)
ABCD,[14,47] 2002	480	59.1 (0.6)	262 (54.5)	NR	136.4	84.4	NR	10 (2.0)	480 (100)	17 (3.5)	NR
CAMELOT,[12] 2004[d]	699	57.3 (9.6)	522 (74.7)	76 (10.8)	<129.5	NR	263 (37.6)	0	130 (18.6)	28 (3.9)	699 (100)
COPERNICUS,[48,49] 2004[f]	1336	62.4 (12.4)	1082 (81.0)	NR	85-125	71.6	NR	1336 (100)	NR	NR	NR
DIABHYCAR,[50] 2004[d]	2177	65.1 (8.4)	1516 (69.9)	NR	<140.0	<90.0	131 (6.0)	0	2177 (100)	92 (4.2)	NR
PEACE,[51] 2004[d]	6050	64.0 (8.0)	4961 (82.0)	454 (7.5)	<140.0	<90.0	3328 (55.0)	0	1029 (17.0)	394 (6.5)	6050 (100)
SAVE,[54,55] 2004	1325	58.0 (10.9)	1141 (86.1)	116 (8.7)	108.0	68.0	1325 (100)	0	223 (16.8)	NR	NR
PROGRESS[56-58] 2006[f]	2137	61.7 (10.0)	1554 (72.7)	962 (45.0)	127.4	78.9	349 (16.3)	NR	229 (10.7)	NR	2137 (100)[g]
ADVANCE,[59,60] 2007[d]	1939	66.0 (6.5)	1106 (57.0)	NR	<140.0	<90.0	233 (12.0)	NR	1939 (100)	1939 (9.0)	NR
PRoFESS,[61,62] 2008[d]	6822	66.2 (8.6)	4366 (64.0)	2900 (42.5)	≤135.0	NR	NR	NR	1924 (28.2)	6822 (100)	NR
TRANSCEND,[15] 2008[d]	1955	66.9 (7.4)	1115 (57.0)	761 (38.9)	≤133.0	NR	906 (46.3)	0	698 (35.7)	1459 (74.6)	430 (22.0)
EUROPA,[13,63,64] 2009[d]	9154	60.0 (9.0)	7818 (85.4)	NR	<140.0	NR	5923 (64.7)	0	1126 (12.3)	302 (3.3)	9154 (100)
PATS,[65] 2009	903	60.2 (6.5)	651 (72.0)	903 (100)	<140.0	<90.0	NR	NR	NR	903 (100)[h]	NR

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic blood pressure; MI, myocardial infarction; NA, not applicable; NR, not reported; SBP, systolic blood pressure.

[a] Number of participants meeting the definition of normotensive or prehypertensive and included in the analyses.

[b] In studies in which the number is not overtly given, the number of men is estimated from the total proportion of men and the number of participants without hypertension included in the analysis assuming that the proportion remained consistent between those with and without hypertension.

[c] Mean blood pressures or cutpoint indicating those without hypertension for participants included in the data analysis. Five studies included subgroup analyses of participants with no history of hypertension; however, SBP or DBP were not provided for these participants. Mean of SBP or DBP is provided for studies in which this could be determined in the population without hypertension. For studies that defined the nonhypertensive participants using a cutpoint, this has been denoted in the blood pressure data as an inequality. For studies in which the population without hypertension was defined as having no clinical history of hypertension, this has been denoted as no history of hypertension.

[d] Proportion at baseline includes data from normotensive and hypertensive study participants.

[e] No history of hypertension; see footnote "c."

[f] Weighted average or proportion, data pooled from multiple normotensive and prehypertensive categories.

[g] Within previous 5 years.

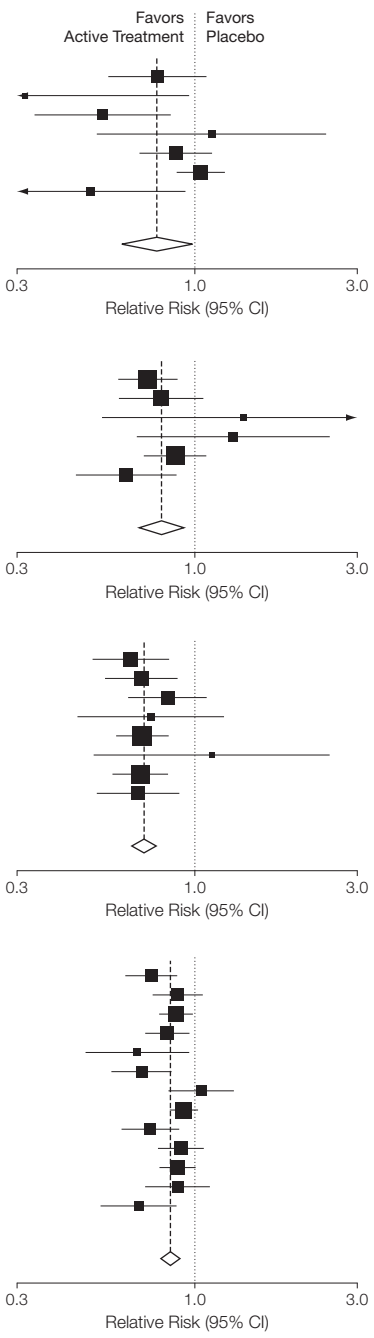
[h] All participants had a history of either transient ischemic attack or stroke.

treatment and composite CVD outcome or all-cause mortality after exclusion of studies that scored fewer than 9 points (MIS and BHAT received 8 points each; MPI, ASPS, and ABCD received 7 points each).

Additionally, we conducted subgroup analyses to examine whether the association of antihypertensive treat-

Figure 2. Pooled Relative Risks and Absolute Risk Reductions for Fatal or Nonfatal Stroke, Myocardial Infarction, and Congestive Heart Failure and Composite Cardiovascular Disease Outcomes

Source	Events/Total, No. Placebo	Events/Total, No. Active	Relative Risk (95% CI)	Absolute Risk Reduction per 1000 (95% CI)
Fatal or nonfatal stroke				
SOLVD,[28] 1995	79/2077	62/2068	0.77 (0.56-1.08)	–8.1 (–19.1 to 3.0)
ABCD,[14] 2002	13/243	4/237	0.32 (0.10-0.95)	–36.6 (–69.3 to –3.9)
PEACE,[52] 2004	52/3071	27/2979	0.54 (0.34-0.85)	–7.9 (–13.6 to –2.2)
SAVE,[54] 2004	22/669	25/656	1.12 (0.51-2.44)	5.2 (–14.7 to 25.2)
PROGRESS,[56] 2006	121/1065	107/1072	0.88 (0.69-1.12)	–13.8 (–40.0 to 12.4)
PRoFESS,[61] 2008	259/3409	270/3413	1.04 (0.88-1.22)	3.1 (–9.6 to 15.8)
PATS,[65] 2009	28/470	13/443	0.49 (0.26-0.94)	–30.2 (–56.8 to –3.7)
Total	574/11 004	508/10 868		
Pooled relative risk			0.77 (0.61-0.98)	–7.7 (–15.2 to –0.3)
Heterogeneity: $P = .02$, $I^2 = 61.9\%$				
Fatal or nonfatal myocardial infarction				
SOLVD,[28] 1995	228/2077	172/2068	0.73 (0.60-0.89)	–26.6 (–44.6 to –8.6)
TRACE,[33] 1997	93/675	74/674	0.80 (0.60-1.06)	–28.0 (–63.1 to 7.1)
SMILE,[37] 1999	7/432	10/444	1.39 (0.53-3.61)	6.3 (–11.9 to 24.5)
ABCD,[14] 2002	15/243	19/237	1.30 (0.68-2.49)	18.4 (–27.5 to 64.4)
PEACE,[52] 2004	174/3071	148/2979	0.88 (0.71-1.09)	–7.0 (–18.3 to 4.3)
SAVE,[54] 2004	88/669	57/656	0.63 (0.45-0.89)	–44.6 (–78.1 to –11.2)
Total	605/7167	480/7058		
Pooled relative risk			0.80 (0.69-0.93)	–13.3 (–28.4 to 1.7)
Heterogeneity: $P = .24$, $I^2 = 26.5\%$				
Fatal or nonfatal congestive heart failure				
SOLVD,[28] 1995	501/2077	345/2068	0.65 (0.50-0.84)	–74.4 (–98.8 to –50.0)
TRACE,[33] 1997	131/675	91/674	0.70 (0.54-0.89)	–59.1 (–98.5 to –19.6)
AIRE,[36] 1999	118/717	96/715	0.83 (0.64-1.08)	–30.3 (–67.2 to 6.6)
SMILE,[37] 1999	34/432	26/444	0.74 (0.45-1.21)	–20.1 (53.6 to 13.3)
MERIT-HF,[40] 2000	242/1121	169/1114	0.70 (0.59-0.84)	–64.2 (–96.2 to –32.2)
ABCD,[14] 2002	11/243	12/237	1.12 (0.50-2.49)	5.4 (–32.9 to 43.6)
COPERNICUS,[48] 2004[a]	NR	NR	0.69 (0.57-0.83)	NA
SAVE,[54] 2004	121/669	84/656	0.68 (0.51-0.90)	–52.8 (–91.6 to –14.0)
Total	1158/5934	823/5908		
Pooled relative risk			0.71 (0.65-0.77)	–43.6 (–65.2 to –22.0)
Heterogeneity: $P = .85$, $I^2 = 0.0\%$				
Composite CVD outcomes				
SOLVD,[28] 1995	800/2077	69/2068	0.74 (0.62-0.89)	–81.0 (–109.8 to –52.2)
SMILE,[37] 1999	34/432	31/444	0.89 (0.75-1.05)	–8.9 (–43.6 to 25.9)
MERIT-HF,[40] 2000	414/1121	361/1114	0.88 (0.78-0.99)	–45.3 (–84.7 to –5.8)
HOPE,[43] 2002	370/2322	313/2351	0.83 (0.71-0.96)	–26.2 (–46.5 to –6.0)
CAMELOT,[12] 2004	77/359	51/340	0.68 (0.48-0.96)	–64.5 (–121.4 to –7.4)
COPERNICUS,[48] 2004[a]	NR	NR	0.70 (0.57-0.85)	NA
DIABHYCAR,[50] 2004	137/1112	137/1065	1.04 (0.84-1.30)	5.4 (–22.4 to 33.3)
PEACE,[52] 2004[a]	693/3071	624/2979	0.93 (0.84-1.02)	16.2 (–37.0 to 4.6)
SAVE,[54] 2004	234/669	180/656	0.74 (0.61-0.90)	–75.4 (–125.1 to –25.7)
ADVANCE,[59] 2007[b]	139/986	121/953	0.91 (0.78-1.06)	–11.0 (–41.1 to 19.2)
PRoFESS,[61] 2008	465/3409	414/3413	0.89 (0.79-1.01)	–15.1 (–31.0 to 0.8)
TRANSCEND,[15] 2008[a]	NR	NR	0.89 (0.72-1.11)	NA
EUROPA,[13] 2009[b]	387/4543	306/4611	0.78 (0.64-0.95)	–18.8 (–29.7 to –8.0)
Total	377/20 401	3167/19 994		
Pooled relative risk			0.85 (0.80-0.90)	–27.1 (–40.3 to –13.9)
Heterogeneity: $P = .10$, $I^2 = 35.4\%$				



CI indicates confidence interval; CVD, cardiovascular disease; NA, not applicable; NR, not reported. Sizes of data markers indicate the weight of each study in the analysis. For expansions of study names, see Table 1 footnote.
[a] Number of events could not be calculated from information provided.
[b] Number of events was estimated from information provided.

ment differed among persons with clinical history of MI or coronary artery disease, those with preexisting CHF, and those with history of diabetes or class of antihypertensive medication (eTable 4). There was little change in the overall effect estimates by clinical history for any of the outcomes, with the exception of diabetes. For prevention of composite CVD outcomes and all-cause mortality, no statistically significant benefit of antihypertensive treatment was reported in trials conducted exclusively in patients with diabetes; however, these results should be interpreted cautiously because of the limited number of trials.

Blood pressure change from baseline to follow-up was available for nonhypertensive participants in 3 studies.[14,37,54] The blood pressure difference between the treatment and placebo groups at the end of the intervention period was significantly different only for those in the ABCD normotensive study.[14]

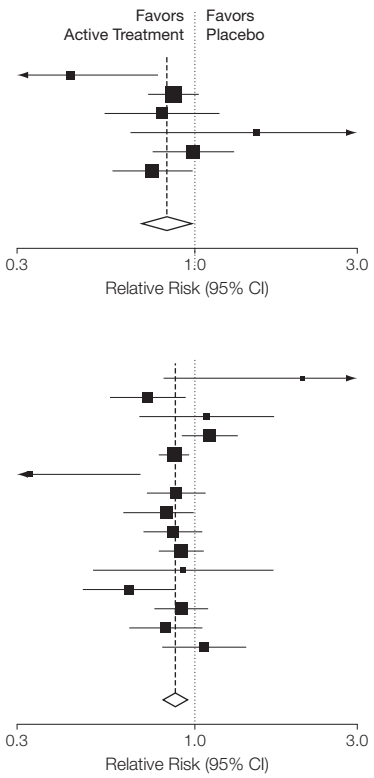
COMMENT

This meta-analysis is unique in that, to our knowledge, it is the first to focus on the association of antihypertensive medication use and secondary prevention of CVD events and all-cause mortality among persons without clinically defined hypertension. Our results show that persons with a history of CVD but with blood pressures in the normal and prehypertensive ranges can obtain significant benefit from antihypertensive treatments. The overall pooled results for antihypertensive treatment compared with control showed a significant reduction in risk for fatal or nonfatal stroke, CHF events, composite CVD events, an all-cause mortality. For fatal and nonfatal MI and for CVD mortality, the pooled relative risk reduction was significant but the pooled absolute risk reduction did not achieve statistical significance. This discrepancy reflects the increased variance of the absolute measures compared with the variance of the relative measures. Results for the outcomes studied were consistent across subgroups and did not differ significantly by trial characteristics.

Risk for CVD increases monotonically at all blood pressure levels in the normotensive and prehypertensive range.[2,3] Although prehypertension affects nearly 70 million adults in the United States and is associated with an increased risk of CVD similar to that seen for those with hypertension, the use of antihypertensive treatment among persons with blood pressures less than 140/90 mm Hg has been debated.[66-72] According to the current al-

Figure 3. Pooled Relative Risks and Absolute Risk Reductions for Cardiovascular and All-Cause Mortality

Source	Events/Total, No. Placebo	Events/Total, No. Active	Relative Risk (95% CI)	Absolute Risk Reduction per 1000 (95% CI)
Cardiovascular mortality				
MIS,[22] 1975	36/678	15/656	0.43 (0.24-0.78)	–30.2 (–50.6 to –9.8)
TRACE,[33] 1997	204/675	176/674	0.86 (0.73-1.03)	–41.1 (–89.1 to 6.9)
AIRE,[36] 1999	48/717	38/715	0.80 (0.54-1.18)	–13.8 (–38.4 to 10.8)
ABCD,[14] 2002	9/243	13/237	1.48 (0.65-3.40)	17.8 (–19.7 to 55.3)
PEACE,[52] 2004	100/3071	96/2979	0.99 (0.75-1.30)	–0.3 (–9.3 to 8.6)
SAVE,[54] 2004	120/669	90/656	0.75 (0.57-0.98)	–42.2 (–81.4 to –3.0)
Total	517/6053	428/5917		
Pooled relative risk			0.83 (0.69-0.99)	–15.4 (–32.5 to 1.7)
Heterogeneity: $P = .12$, $I^2 = 43.6\%$				
All-cause mortality				
MPI,[23] 1980	6/143	13/149	2.07 (0.81-5.29)	45.3 (–10.7 to 101.3)
BHAT,[24] 1982	129/1369	92/1346	0.73 (0.56-0.94)	–25.9 (–46.4 to –5.4)
ASPS,[25] 1983	29/190	33/200	1.08 (0.68-1.71)	12.4 (–60.2 to 84.9)
CONSENSUS II,[26] 1992	190/2259	202/2178	1.10 (0.91-1.33)	8.6 (–8.1 to –25.4)
SOLVD,[28] 1995	501/2077	426/2068	0.87 (0.78-0.96)	–35.2 (–60.6 to –9.9)
USCHF,[32] 1996	19/210	13/337	0.34 (0.17-0.69)	–51.9 (–95.8 to –8.0)
TRACE,[33] 1997	267/675	233/674	0.88 (0.72-1.07)	–49.9 (–101.3 to 1.6)
AIRE,[36] 1999	148/717	116/715	0.78 (0.61-0.99)	–44.2 (–84.3 to –4.1)
SMILE,[37] 1999	25/432	22/444	0.86 (0.70-1.05)	–8.3 (–38.2 to 21.6)
CCS-1,[41] 2001	303/2354	282/2406	0.91 (0.78-1.06)	–11.5 (–30.2 to 7.2)
ABCD,[14] 2002	20/243	18/237	0.92 (0.50-1.70)	–6.4 (–54.6 to 41.9)
COPERNICUS,[48] 2004	NR	NR	0.64 (0.47-0.88)	NA
PEACE,[52] 2004	230/3071	203/2979	0.91 (0.76-1.09)	–6.8 (–19.7 to 6.2)
SAVE,[54] 2004	140/669	115/656	0.82 (0.64-1.05)	–34.0 (–76.4 to 8.4)
PROGRESS,[56] 2006	84/1065	90/1072	1.06 (0.80-1.41)	5.1 (–18.1 to 28.3)
Total	2091/15474	1858/15461		
Pooled relative risk			0.87 (0.80-0.95)	–13.7 (–24.6 to –2.8)
Heterogeneity: $P = .03$, $I^2 = 46.1\%$				



CI indicates confidence interval; CVD, cardiovascular disease; NA, not applicable; NR, not reported. Sizes of data markers indicate the weight of each study in the analysis. For expansions of study names, see Table 1 footnote.

gorithm for treatment of hypertension in persons with compelling indications (CHF, post-MI, high coronary disease risk, and recurrent stroke prevention), pharmacological treatment is indicated for those whose blood pressure is not controlled to less than 140/90 mm Hg with lifestyle intervention alone.[3] Hypertension precedes the development of CHF in the majority of patients and increases risk for MI and CHF.[3]

The results of this meta-analysis suggest that persons with these compelling indications but without hypertension may also benefit from reduced morbidity and mortality attributable to CVD events when treated with antihypertensive medications. In persons 40 years and older with prehypertension, more than 90% have at least 1 above-optimal risk factor, and more than 68% have at least 1 clinically high risk factor for heart disease or stroke.[5] Although pharmacological treatment for all individuals in this population would not be economically feasible, a more reasonable strategy might be to identify groups within the prehypertensive population who would obtain the greatest benefit from early pharmacological intervention.

For patients with diabetes, the current algorithm for treatment of hypertension indicates pharmacological treatment for those whose blood pressure is not controlled to less than 130/80 mm Hg with lifestyle intervention alone.[3] Recent findings reported from the ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) trial conducted in patients with diabetes demonstrated no reduction in the rate of fatal or nonfatal CVD events when systolic blood pressure was controlled to less than 120 mm Hg compared with less than 140 mm Hg.[73] The ACCORD BP trial included participants with systolic blood pressures of 130 to 180 mm Hg who were taking 3 or fewer antihypertensive medications at baseline. The results of our meta-analysis show that for the prevention of composite CVD outcomes and all-cause mortality, no benefit of antihypertensive treatment was seen in trials conducted in patients with diabetes and without hypertension. Our findings should be interpreted with caution because of the small number of studies in such patients.

We identified only 2 studies of antihypertensive treatment conducted in populations with blood pressures less than 140/90 mm Hg and without a history of CVD or diabetes.[74,75] The primary objective of both trials was to examine the prevention of hypertension in persons with blood pressure in the prehypertensive range, but CVD events were also examined. Although both studies were small and had relatively few events, there was an indication of possible benefit overall. Additional studies are needed to determine if any benefit of antihypertensive treatment would be obtained in populations without hypertension or clinical history of CVD.

We were able to identify no evidence among populations with specific risk factors such as elevated lipid levels, history of smoking, or chronic kidney disease. Additionally, few studies included racial and ethnic minorities or reported results according to race/ethnicity. Because of the increased risk for CVD events in the presence of these risk factors, additional studies should be conducted to determine if there is benefit of treating prehypertension at levels less than 140/90 mm Hg in populations with these risk factors. Although antihypertensive agents, including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers are generally well tolerated, deleterious adverse effects are not uncommon and can be serious.

The primary strength of this meta-analysis was its inclusion of only randomized controlled trials, which are less subject to bias and confounding than observational studies. Additionally, study characteristics were very similar at baseline, lending confidence to the findings.

The primary limitation of this meta-analysis was the dearth of studies reporting the outcomes of interest for normotensive and prehypertensive participants. Few studies included in this meta-analysis presented the results by baseline blood pressure levels and treatment regimen; therefore, it was not possible to determine the dose-response relationship between baseline blood pressure and risk of first occurrence or recurrence of CVD events among persons with blood pressure less than 140/90 mm Hg. Additional studies should be conducted to examine the baseline blood pressure level at which antihypertensive treatment should begin in persons with CVD or CVD equivalents such as diabetes.

Moreover, this meta-analysis is not a mechanistic study; thus, we cannot determine whether the benefit associated with use of antihypertensive treatment was attributable to blood pressure lowering or to other tissue or neurohormonal mechanisms. Additionally, it is possible that misclassification of participants may have occurred owing to variations in methods of blood pressure measurement across studies included in the meta-analysis; however, less stringent methods of measurement may overdiagnose hypertension among participants. Because of the small number of studies included, potential publication bias and the influence of heterogeneity between studies cannot be ruled out.

Although we calculated the effect estimate from available data when it was not provided in the published data, it is possible that confounding occurred owing to differential loss to follow-up by treatment group. In addition, the statistical methods resulted in a discrepancy for the findings of 2 outcomes (MI and CVD mortality), perhaps reflecting the increased variance of the absolute measures compared with the variance of the relative measures, which may be compounded by the effect of pooling. Lastly, the total numbers of events were unavailable in some studies; therefore, the counts of events were estimated from the effect estimate and other information provided in the text

of publications.[13,59] It was not possible to estimate the total number of events in the COPERNICUS or TRANSCEND studies from the information provided in the text.[15,48] A collaborative meta-analysis pooling individual-patient data could serve to eliminate many of these limitations.

CONCLUSION

Prehypertension affects nearly 30% of the adult population and carries an elevated risk for CVD incidence and mortality. To our knowledge, this meta-analysis is the first to examine the association between antihypertensive medications and CVD morbidity and mortality as well as all-cause mortality in individuals without hypertension. Among patients with clinical history of CVD but without hypertension, antihypertensive treatment was associated with decreased risk of stroke, CHF, composite CVD events, and all-cause mortality. Additional randomized trial data are necessary to assess these outcomes in patients without CVD clinical recommendations.

Author Contributions: Ms Thompson and Dr Bazzano 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: Reynolds, He, Bazzano.
Acquisition of data: Thompson, Hu, Eshelbrenner, Bazzano.
Analysis and interpretation of data: Thompson, Hu, He, Bazzano.
Drafting of the manuscript: Thompson, Hu, Bazzano.
Critical revision of the manuscript for important intellectual content: Thompson, Hu, Eshelbrenner, Reynolds, He, Bazzano.
Statistical analysis: Thompson, Eshelbrenner, Bazzano.
Obtained funding: He, Bazzano.
Administrative, technical, or material support: Hu, Eshelbrenner, Bazzano.
Study supervision: He, Bazzano.
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Online-Only Material: eTables 1-4 are available at http://www.jama.com.

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