Race and Ethnicity in Trials of Antihypertensive Therapy to Prevent Cardiovascular Outcomes: A Systematic Review

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ABSTRACT

PURPOSE We wanted to systematically review (1) the participation of racial and ethnic minorities in clinical trials of antihypertensive drug therapy and (2) racial differences in the efficacy of these therapies for the prevention of cardiovascular outcomes.

METHODS MEDLINE, EMBASE, LILACS, African Index Medicus, and the Cochrane Library were searched from their inception to December 2005 for randomized controlled trials testing the efficacy of antihypertensive drug therapy in preventing myocardial infarction, stroke, revascularization, or cardiovascular death. MEDLINE was also searched from 2005 through 2006. The 2 authors independently assessed studies for inclusion and quality.

RESULTS Twenty-eight studies met inclusion criteria. Eight trials reported results by racial subgroup. Trials with black and Hispanic participants (ALLHAT, INVEST, VALUE) found similar primary outcomes, but ALLHAT found a greater magnitude of benefit for blacks on diuretic therapy compared with nonblacks. One trial (PROGRESS) compared Asians with non-Asians, reporting that angiotensin-converting enzyme inhibitors (vs placebo) were equally effective for preventing stroke in both groups. In the LIFE trial, post hoc analyses showed different outcomes for blacks and nonblacks, raising questions about the usefulness of angiotensin-receptor blockers as first-line antihypertensive agents in blacks. In 3 studies conducted exclusively in Asians (JMIC-B, FEVER, NICS-EH), calcium channel blockers were effective in preventing cardiovascular outcomes. No trials described cardiovascular outcomes in Native Americans.

CONCLUSIONS Five trials made interethnic group comparisons; 4 had similar primary outcomes for ethnic minorities and whites. Increased minority participation in future studies is needed to determine optimal prevention therapies, especially in outcome-driven trials comparing multidrug antihypertensive treatment regimens.

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INTRODUCTION

The high prevalence of hypertension in minority communities is a major contributor to the disproportionate degree of premature cardiovascular mortality (cardiovascular death when younger than 65 years) observed in Asian/Pacific Islanders, blacks, Hispanics, and Native Americans.[1] There is consensus that lowering blood pressure confers reductions in cardiovascular morbidity and mortality in all hypertensive populations, and the current Joint National Committee VII guidelines recommend diuretics as first-line antihypertensive agents regardless of race.[2] Questions arise, however, when selecting antihypertensive regimens for the many minority patients who require multiple classes of medication to achieve adequate blood pressure control. Currently it is unclear how dif-

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ferent antihypertensive therapies should be prioritized to enhance prevention of cardiovascular outcomes in minority populations.

Prevention of cardiovascular morbidity and mortality outcomes in minorities is a salient issue, as several minority groups have a higher prevalence of hypertension and cardiovascular morbidity than whites. Blacks suffer earlier onset, greater severity, and more end-organ damage as a result of hypertension than whites, contributing to a twofold higher rate of stroke and 50% higher mortality from heart disease.[3] Hispanics have a similar prevalence of hypertension but poorer blood pressure control and have not shared the declines in rates of stage 2 hypertension (>160/100 mm Hg) seen in whites during the past decade.[4,5]

Racial or ethnic differences in response to antihypertensive therapies may contribute to the disparities observed in those with hypertension and cardiovascular disease. Identifying population differences in outcomes of hypertension clinical trials may help address disparities and provide valuable clues for future pharmacogenomic or mechanistic research. Doing so, however, would require sufficient participation of minorities to allow for race- or ethnicity-based comparisons of a therapy's efficacy. It is unclear whether minorities have participated in outcomes-based clinical trials at a level that allows for conclusions to be made about specific racial groups. We therefore conducted a systematic review of the literature with 2 aims. First, we quantified the number and proportion of Asians, blacks, Hispanics, and Native Americans participating in randomized, controlled trials of antihypertensive drug therapy to prevent cardiovascular disease. Second, we critically appraised these trials and summarized racial and ethnic differences in the efficacy of antihypertensive therapies for the prevention of cardiovascular outcomes.

METHODS

We searched the literature for published reports of randomized clinical trials that tested the effect of antihypertensive drug therapy—diuretics, β-blockers, α-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers—on outcomes related to cardiovascular disease morbidity and mortality. The specific criteria for a trial's inclusion in our review were prespecified as follows: (1) primary endpoint related to cardiovascular morbidity and mortality (fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, cardiovascular death, revascularization, or a composite of these endpoints); (2) random allocation of subjects to single-drug therapy vs placebo, single-drug-based combination of drugs vs placebo, or single-drug-based combinations vs other combinations of drugs; (3) double-blind design or prospective, randomized, open-label, blinded endpoint (PROBE) design; and (4) follow-up of at least 1 year. We excluded trials that examined only surrogate endpoints for cardiovascular disease (such as blood pressure lowering), studies with primary outcomes other than cardiovascular disease, and studies that excluded hypertensive subjects.

To identify relevant trials, we searched MEDLINE, EMBASE, African Index Medicus, LILACS (Literatura Latino-America y del Caribe en Ciencias del la Salud), and the Cochrane Clinical Trials Database from their inception to December 2005. We also searched MEDLINE from 2005 through 2006. We did not restrict our search to specific languages.

We applied 3 electronic search strategies. The first strategy utilized terms published by the Cochrane Collaboration Hypertension Group[6] and restricted to the Major Subject Heading (MeSH) heading "treatment outcome." The second strategy included the term "hypertension" combined with terms for continental ancestry groups (eg, African Continental Ancestry Group) and with specific terms for US racial ethnic minority groups (eg, African Americans). The final strategy utilized the MeSH headings "cardiovascular disease," "myocardial infarction," or "cerebrovascular disease," with "prevention and control." We supplemented our search of electronic databases by hand, searching other systematic reviews and national practice guidelines and by speaking with experts.

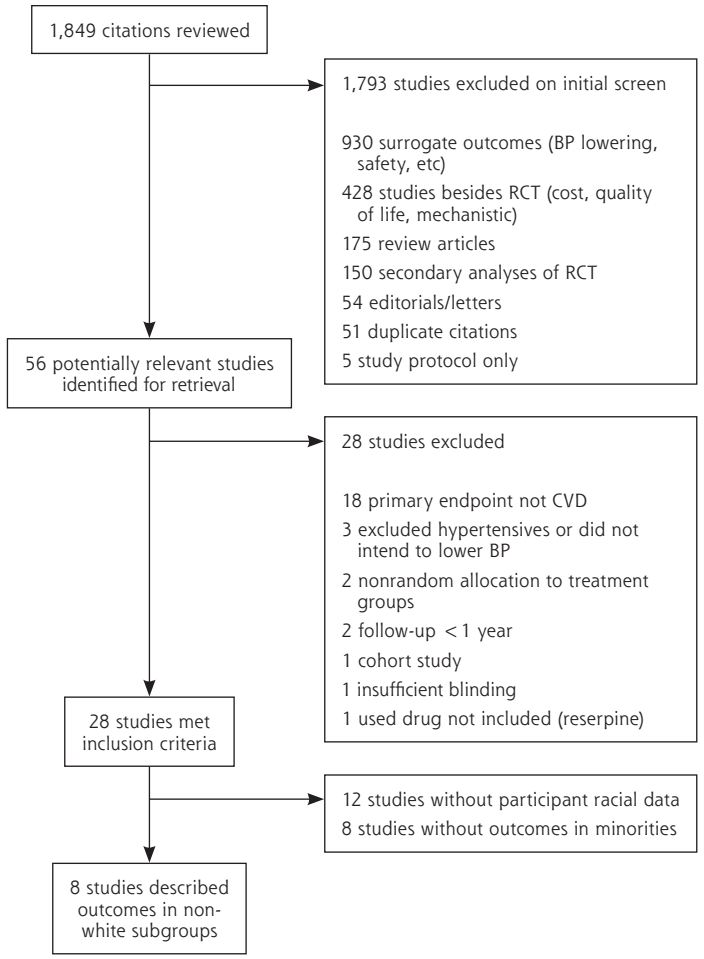
Each trial's study design, population characteristics, outcomes, and subgroup analyses were assessed independently by the 2 authors. Disagreements over trial eligibility were resolved after discussion between the authors. Eligible trials were assigned a Jadad score from 0 to 5 based on reporting of randomization, blinding, withdrawals, and losses to follow-up.[7] We extracted data on race and ethnicity and outcomes for each trial. If no such data were published, we contacted principal investigators twice in an attempt to gather missing information. For trials with available subgroup analyses, we recorded race-specific differences in baseline characteristics, blood pressure control, cardiovascular outcomes, and adverse events.

RESULTS

Electronic searches yielded 1,849 unique citations with abstracts, from which we selected 56 potential studies. Fifty were identified from MEDLINE; an additional 6 were found through hand searching those studies or other systematic reviews. In the initial evaluation, we excluded 28 studies: 18 for having surrogate outcomes or primary outcomes other than cardiovascular disease morbidity or mortality, and 10 for failing to meet other

inclusion or exclusion criteria (Figure 1). Thus, 28 studies met initial inclusion criteria and received a detailed evaluation.

Figure 1. Flow diagram of systematic literature search and assessment.



BP = blood pressure; CVD = cardiovascular disease; RCT = randomized controlled trial.

Participation of Minority Subgroups

We reviewed multiple publications from each study including articles on design and rationale, outcomes, and subgroup analyses. Twelve of 28 studies (43%) did not have any retrievable information on subjects' racial characteristics.[8-19] Of the 16 studies with racial data, 8 studies did not describe outcomes in minority subgroups.[20-27] Characteristics of the 8 trials with racial subgroup analyses are summarized in Table 1,[28-44] including sample size, number of subjects by racial category, study site location, drug intervention and comparison treatment, duration of follow-up, inclusion criteria, racial subgroups compared (if any), and baseline differences between minority groups and whites.

The Antihypertensive Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[45] and the International Verapamil-Trandolapril Study (INVEST)[32] were the only 2 trials with greater than 50% minority participation. Each had large numbers of blacks and Hispanics. The Protection Against Recurrent Stroke Study (PROGRESS)[46] reported the largest analysis comparing Asians (38%) with non-Asians. Two trials of angiotensin II receptor blockers conducted subgroup analyses of blacks: the Losartan Intervention For Endpoint Prevention (LIFE)[47] and Valsartan Long-term Use Evaluation (VALUE).[48] Three trials were conducted exclusively in Asian populations: the Japanese Multicenter Investigation of Cardiac Disease (JMIC-B),[43] the National Intervention Cooperative Study in Elderly Hypertensives (NICS-EH),[42] and the Felodipine Event Reduction Study (FEVER).[44] No trials described cardiovascular outcomes in Native Americans.

Cardiovascular Outcomes

Results for the 8 studies that reported cardiovascular outcomes in nonwhite populations are summarized in Figure 2. The Jadad scores for methodologic quality of these studies ranged from 3 to 5. Both JMIC-B and INVEST utilized an open-label design[49] and lost 2 points for description and method of blinding. The NICS-EH and FEVER trials lost 1 point for description of withdrawals/dropouts. ALLHAT, LIFE, PROGRESS, and VALUE received the maximum score of 5. In all studies, subjects were randomly allocated to treatment (or placebo) groups. With the exception of the NICS-EH, all studies used intention-to-treat analyses. Because these studies had widely differing designs and primary outcomes, formal statistical procedures and meta-analyses could not be performed.

Outcomes in Asians

In PROGRESS, Asians had greater reductions in blood pressure than did Western participants (P = .01); however, there was no significant interaction between race-treatment interactions with perindopril on secondary stroke prevention (P = .1). In the 2 Japan-based trials (JMIC-B, NICS-EH), which compared calcium channel blockers with ACE inhibitors or diuretics, no difference in cardiovascular outcomes

Table 1. Trials of Antihypertensive Agents With Cardiovascular Morbidity and Mortality Outcomes

Trial, year	Racial Subgroups No. (%)	Study Sites	Drug Intervention	Follow-up Mean, y	Inclusion Criteria	Subgroups Compared	Baseline Differences (vs Whites)
Characteristics of studies with racial outcome data							
ALLHAT,[28-31] 2002	White 19,977 (47) Black 15,085 (35.5) Hispanic 5,299 (12.5) Other 2,058 (5)	USA, Canada	Chlorthalidone vs doxazosin, amlodipine, or lisinopril	4.9	Aged >55 y, HTN, prior CAD, or 1 risk factor	Blacks, nonblacks	Blacks: age, baseline CVD, DM, LVH (P <.001)
INVEST,[32,33] 2003	White 10,925 (48.3) Black 3,029 (13.4) Asian 149 (0.8) Hispanic 8,045 (35.6) Other 428 (1.9)	North & Latin America, Europe	Verapamil-based vs atenolol-based	2.7	Aged >50 y, HTN, known CAD	Blacks, Hispanics, white, other	Hispanic & black: age, DM, ASA/statin use (P <.001) Blacks: LVH, BMI, CKD (P <.001)
PROGRESS,[34,35] 2001	White 3,770 (62) Asian 2,335 (38)	Europe, China, Japan	Perindopril ± indapamide vs placebo	3.9	No age limits, previous CVA or TIA ± HTN	Asians, westerners	
VALUE,[36-38] 2004	White 13,643 (89.1) Black 658 (4.3) Asian 535 (3.5) Other 474 (3.1)	USA, Western Europe	Valsartan-based vs amlodipine-based	4.2	Aged >50 y, HTN, 2-3 CV risk factors	Asian, blacks, white, other	
LIFE,[39-41] 2002	White 8,503 (92) Black 533 (6) Asian 43 (1) Hispanic 100 (1)	Europe, USA	Losartan vs atenolol	4.8	Aged 55-80 y, HTN, LVH	Blacks, nonblacks	Blacks: age, DM, CKD, smoking (P <.001)
Studies In single racial/ethnic group							
NICS-EH[42]	Asian 414 (100)	Japan, multiple centers	Nicardipine vs trichlormethiazide	5.0	Aged >60 y, HTN, no prior CVD		
JMIC,[43] 2004	Asian 1,650 (100)	Japan, multiple centers	Nifedipine vs ACE inhibitors (varied types)	3.0	Aged <75 y, HTN, known		
FEVER,[44] 2005	Asian 9,711 (100)	China, multiple centers	Hydrochlorothiazide + feldopine vs hydrochlorothiazide + placebo	3.3	Aged 50-79 y, HTN, 2 CV risk factors		

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; BMI = body mass index; CAD/CHD = coronary artery (heart) disease; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; HTN = hypertension; LVH = left ventricular hypertrophy; TIA = transient ischemic attack.

was found. In the China-based trial (FEVER), a calcium channel blocker plus diuretic was found to be more effective than low-dose diuretic monotherapy.

Outcomes in Blacks

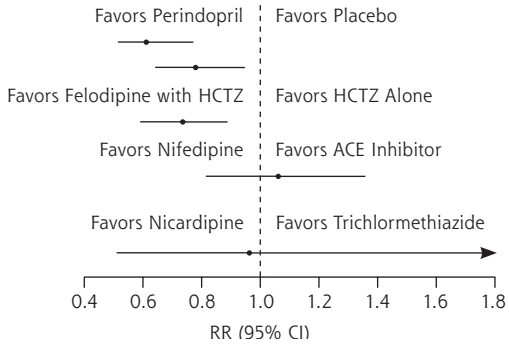
In ALLHAT, there were no racial differences for the primary outcome of fatal or nonfatal coronary heart disease. For stroke and combined cardiovascular disease, however, blacks experienced a greater magnitude of benefit with chlorthalidone than did nonblacks (for interaction P= .01 for stroke, and P = .04 for cardiovascular disease). Although blacks achieved a 4/1 mm Hg greater blood pressure reduction with chlorthalidone than with lisinopril, adjustment for blood pressure did not fully explain differences in outcomes.

In the LIFE trial, statistical tests for interaction of race and treatment on outcome showed a trend toward significance (P = .057), prompting a post hoc analysis, which found that nonblacks on losartan-based therapy had a reduction in cardiovascular events, whereas blacks on losartan-based therapy had an increase in cardiovascular events despite greater regression of left

Figure 2. Effect of treatment strategies on cardiovascular outcomes in racial/ethnic subgroups.

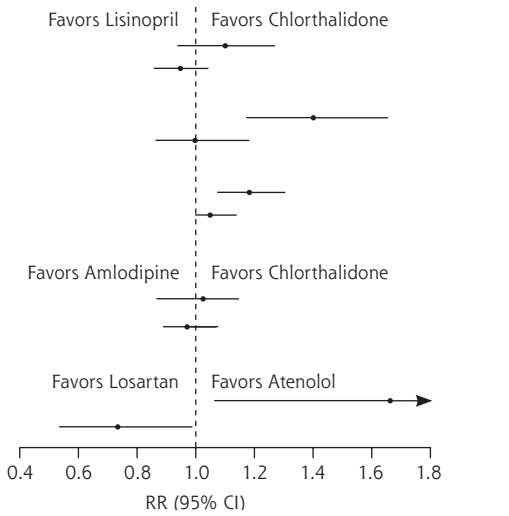
Outcomes in Asians

Study Name	Outcome	Racial/ Ethnic Groups	RR	*P* Value	Race-treatment Interaction
PROGRESS	All strokes	Asian	0.61 (0.48-0.78)	N/A	*P* = .1
		Westerners	0.78 (0.65-0.95)	N/A	
FEVER	All strokes	Chinese	0.73 (0.60-0.95)	.002	
JMIC-8	Composite CV Events	Japanese	1.05 (0.81-1.37)	.75	
NICS-EH	Composite CV Events	Japanese	0.97 (0.51-1.83)	.93	



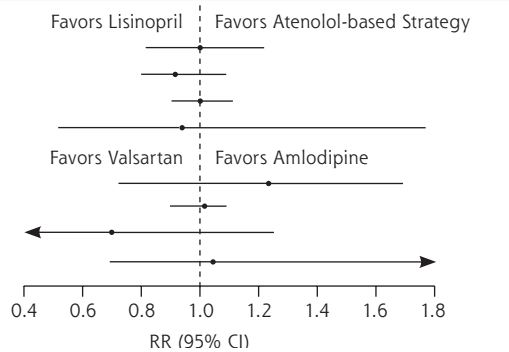
Outcomes in Blacks

Study Name	Outcome	Racial/ Ethnic Groups	RR	*P* Value	Race-treatment Interaction
ALLHAT	Fatal/Non-fatal CHD	Blacks	1.10 (0.94-1.28)	.24	
		Non-blacks	0.94 (0.85-1.05)	.29	
	Stroke	Blacks	1.40 (1.17-1.68)	<.001	*P* = .01
		Non-blacks	1.00 (0.85-1.17)	.97	
	Combined CVD	Blacks	1.19 (1.09-1.30)	<.001	*P* = .04
		Non-blacks	1.06 (1.00-1.13)	.05	
ALLHAT	Fatal/Non-fatal CHD	Blacks	1.01 (0.86-1.18)	.95	
		Non-blacks	0.97 (0.87-1.08)	.57	
LIFE	Fatal CVD	US Blacks	1.66 (1.04-2.66)	.033	*P* = .057
		US Non-blacks	0.72 (0.53-0.99)	.046	



Outcomes in Multiple Ethnic Groups

Study Name	Outcome	Racial/ Ethnic Groups	RR	*P* Value	Race-treatment Interaction
INVEST	Composite Death and Non-fatal CVA/MI	Blacks	1.00 (0.82-1.22)	N/A	
		Hispanics	0.92 (0.78-1.08)	N/A	
		Whites	1.00 (0.90-1.10)	N/A	
		Other	0.94 (0.50-1.76)	N/A	
VALUE	Composite Cardiac Events	Blacks	1.22*	.405	
		Hispanics	1.01*	.507	
		Whites	0.69*	.201	
		Other	1.08*	.514	



*Exact 95% CI not provided; range extrapolated from article figure.

ACE = antiotensin-converting enzyme; BP = blood pressure; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; HCTZ = hydrochlorothiazide; MI = myocardial infarction; RR = relative risk.

ventricular hypertrophy ($P = .018$) and similar blood pressure control in blacks on losartan and atenolol.

Outcomes in Multiple Races

In INVEST, there were no racial differences (among blacks, Hispanics, whites, or others) between the verapamil- and atenolol-based strategies for the primary outcome of death and nonfatal myocardial infarction or stroke. Hispanics had a lower overall cardiovascular event rate than non-Hispanics (hazard ratio, 0.87 [0.78-0.97]), but there was no evidence for race-treatment interaction.[50]

Participants in the VALUE trial were predominantly white (89%). No significant racial differences were found (among blacks, whites, Asians, or others) between the valsartan- and amlodipine-based strategies for the primary outcome of composite cardiac events.

DISCUSSION

In attempting to quantify minority participation in hypertension clinical trials, we encountered both a lack of reporting and widely differing reporting methods on the part of investigators. Most of the studies without race or ethnicity data were conducted in the European Union, where trial reports are 5 times less likely to contain data on race or ethnicity than US trials.[51] Despite US guidelines that specify both the inclusion and analysis of outcomes for minorities in federally funded clinical trials,[52] 40% of clinical trials in high-impact US-based journals still lack reporting on race, even in areas of such health care disparities as cardiovascular disease.[53]

Numerous factors complicate the reporting of racial demographic and outcomes data in clinical trials. Although the race and ethnicity categories defined by the National Institutes of Health may be well suited to research in the United States, they can be difficult to apply in large multinational studies, in which participating nations do not routinely collect individual racial data or may classify race in a different manner than in the United States. Race is particularly difficult to define in Latin American countries given the considerable admixing between indigenous peoples and those of European and/or African origins. Allowing trial participants to self-identify their race/ethnicity according to ancient geographic ancestry may partially address this issue. In a US multiethnic cohort, geographic ancestry and self-identified race/ethnicity were almost perfectly correlated to a few distinct genetic clusters.[54] Whether the same would also hold true outside the United States has not yet been investigated. Even if this strategy could be applied globally to improve categorization and reporting of race in clinical trials, factors influencing health extend well beyond the notion of genetics. Social, environmental, and lifestyle factors differ greatly between hypertensive subjects in international trials and US minority subjects with shared geographic ancestry; these factors interact and may importantly influence cardiovascular risk and health outcomes.

In reviewing cardiovascular disease prevention trials of antihypertensive therapies, we identified only 4 trials that included a priori analyses to compare outcomes among minority groups (ALLHAT, INVEST, PROGRESS, VALUE). For each trial's primary outcome, similar treatment efficacy was found for whites and minorities. Blacks in ALLHAT who were treated with the ACE-inhibitor lisinopril, however, had significantly higher blood pressures, a greater incidence of strokes, and a greater incidence of combined cardiovascular disease than blacks treated with diuretics. Previous research has suggested that, because of lower renin levels in black hypertensive patients, ACE-inhibitors are less effective as monotherapy for hypertension in blacks than in whites.[55] Although ALLHAT provided evidence for poorer cardiovascular outcomes for blacks treated with lisinopril than with diuretics, studies such as the African American Study of Kidney disease have since shown that treatment with ACE-inhibitors does reduce the rate of progression of hypertensive nephropathy in blacks.[56] Currently, ACE-inhibitors are not recommended as first-line monotherapy for hypertension in blacks, but they appear to have utility in patients with hypertensive chronic kidney disease or as part of a multiple drug antihypertensive regimen when specific organ sparing is a therapeutic goal.

In ALLHAT, INVEST, and PROGRESS, there were widespread dissimilarities of potential confounders both between and within minority racial subgroups. Factors such as baseline blood pressure, blood pressure control, diabetes, and baseline medication use widely varied between majority and minority groups. Although randomization in these trials minimized the differences between treatment groups, we feel that subgroup analyses generally should not be overinterpreted beyond showing the consistency of benefit (or detriment) for antihypertensive therapies across racial subgroups, except in the case where there is evidence for significant treatment-subgroup interactions.

Contrary to the similar outcomes described previously, a post hoc analysis of the LIFE data found that losartan therapy improved cardiovascular outcomes for whites and worsened outcomes in blacks despite similar blood pressure control for blacks on losartan or atenolol. This type of qualitative interaction (intervention has opposite effects in subgroups) is unusual and does raise questions regarding the efficacy of angiotensin-receptor blockers as antihypertensive treatment in blacks to prevent cardiovascular outcomes. Given

the post hoc nature of the analysis and the small number of cardiovascular events, however, these results should be interpreted cautiously. The only other outcome-based trial of angiotensin-receptor blockers (VALUE) did not show significant effects of race on outcome, but the proportion of black participants was small (<4%). Current recommendations by the Hypertension in African Americans Working Group state that angiotensin-receptor blockers (and ACE-inhibitors) can be effective initial therapy for hypertension in blacks, although cardiovascular disease outcome data in this population are limited.[57]

In Japan calcium channel blocker therapy is often used as a first-line agent in uncomplicated hypertension.[58] Baseline data from the PROGRESS trial showed that 50% to 60% of hypertensive Asian subjects were being treated with calcium channel blockers.[34] Two recent meta-analyses suggest that antihypertensive therapy with calcium channel blockers likely has an equivalent or only modestly detrimental effect on cardiovascular outcomes compared with other classes of therapy.[59,60] The JMIC-B and NICS-EH studies (Japan) were not adequately powered to detect equivalence between calcium channel blockers and other therapeutic modalities; therefore, the investigators' finding of "no difference" in both of these studies should not be interpreted as true equivalence between calcium channel blockers and ACE inhibitors or diuretics. In FEVER (China), a low-intensity regimen was compared with an intensive blood-pressure–lowering strategy (diuretics with calcium channel blockers), which is already known to reduce cardiovascular outcomes in Asian subjects.[61] Given the differences in intensity of therapy, we cannot discern whether calcium channel blockers have any cardiovascular protective properties in Asians aside from blood pressure lowering.

Our review has several limitations. Because we were unable to retrieve race or ethnicity data from 12 trials, we may be underestimating overall minority participation. We analyzed results only from published trial reports; given the small number of trials with outcomes in minorities, funnel plots for publication bias were not performed. Neither reviewer was blinded to author or to journal of publication during data abstraction, although blinding of reviewers has not been shown to affect the results of published reviews.[62]

The inclusion of minorities and race-specific analyses in clinical trials are essential steps to identify important differences in pathophysiology and treatment response—differences that may lead to a reduction in health care disparities in cardiovascular disease. Standardized reporting of minority participation is also needed. Without this information, it will be impossible to understand disparities in clinical trial participation or the applicability of trial results to nonwhite populations. Certain groups (eg, Native Americans) bear a large burden of cardiovascular disease but have not been represented in clinical trials in numbers sufficient to conduct meaningful subgroup analyses. Understanding outcomes in this group would require pooling of data from multiple studies. Pooling of data would be facilitated if data from cardiovascular disease prevention trials were made available to researchers as public-use data sets.

Because most hypertensive patients will require therapy with 2 or more medications to achieve adequate blood pressure control, future trials should examine cardiovascular outcomes when multiple classes of antihypertensive therapy are combined to achieve common blood pressure goals. Whether future studies should examine outcomes exclusively in a single minority group (ie, African American study of kidney disease) compared with outcomes in multiple racial subgroups (ie, INVEST) is a subject of debate.[63] What is clear is that outcome-based trials on the magnitude of ALLHAT or INVEST will be costly and require large numbers of minority participants to conduct prespecified analyses by race and ethnicity. The translation of these trial results to the care of minority patients in clinical practice will prove invaluable for appropriate therapeutic decision making and improvement of cardiovascular outcomes in an increasingly diverse patient population.

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