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

Ina U. Park, MD
Anne L. Taylor, MD

1Department of Family Medicine and Community Health, University of Minnesota, Minneapolis, Minn
2Department of Medicine, Division of Cardiology, University of Minnesota, Minneapolis, Minn

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 (JMIG-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.

Ann Fam Med 2007;5:444-452. DOI: 10.1370/afm.708.

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-

Conflicts of interest: none reported

CORRESPONDING AUTHOR
Ina U. Park, MD
California Department of Health Services
STD Control Branch
850 Marina Bay Parkway, Bldg P, 2nd Fl
Richmond, CA 94804
parki@obgyn.ucsf.edu
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. 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.

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 de 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 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. 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.

**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. Of the 16 studies with racial data, 8 studies did not describe outcomes in minority subgroups. Characteristics of the 8 trials with racial subgroup analyses are summarized in Table 1, 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) and the International Verapamil-Trandolapril Study (INVEST) 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) 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) and Valsartan Long-term Use Evaluation (VALUE). Three trials were conducted exclusively in Asian populations: the Japanese Multicenter Investigation of Cardiac Disease (JMIC-B), the National Intervention Cooperative Study in Elderly Hypertensives (NICS-EH), and the Felodipine Event Reduction Study (FEVER). 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 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...
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 ventricular hypertrophy. TIA = transient ischemic attack.

### 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) |
|------------|--------------------------|-------------|-------------------|------------------|-------------------|--------------------|-------------------------------|
| ALLHAT, 2002 | White 19,977 (47) | USA, Canada | Chlorthalidone vs doxazosin, amlo-dipine, 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, 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 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, 2001 | White 3,770 (62) | Europe, China, Japan | Perindopril + indapamide vs placebo | 3.9 | No age limits, previous CVA or TIA ± HTN | Asians, westerners | Blacks: age, baseline CVD, DM, LVH (\( P < .001 \)) |
| INVEST, 2004 | White 3,7707 (62) Black 658 (4.3) Asian 353 (3.5) Other 474 (3.1) | USA, Europe | Valsartan-based vs valsartan-based | 4.2 | Aged >50 y, HTN, 2-3 CV risk factors | Asian, blacks, white, other | Blacks: age, baseline CVD, DM, LVH (\( P < .001 \)) |
| LIFE, 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, baseline CVD, DM, smoking (\( P < .001 \)) |

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.
**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  | Intervention | Race-treatment Interaction |
|------------|---------|----------------------|---------|----------|--------------|---------------------------|
| PROGRESS  | All strokes | Asian Westerners | 0.61 (0.48-0.78) | N/A | Favors Perindopril | Favors Placebo  |
|           |         |                     | 0.78 (0.65-0.95) | N/A | Favors Felodipine with HCTZ | Favors HCTZ Alone  |
| FEVER     | All strokes | Chinese             | 0.73 (0.60-0.95) | .002 | Favors Nifedipine | Favors ACE Inhibitor  |
| JMIC-8    | Composite CV Events | Japanese | 1.05 (0.81-1.37) | .75 | Favors Nicardipine | Favors Trichlormethiazide  |
| NICS-EH   | Composite CV Events | Japanese | 0.97 (0.51-1.83) | .93 |

| Study Name | Outcome | Racial/Ethnic Groups | RR      | P Value  | Intervention | Race-treatment Interaction |
|------------|---------|----------------------|---------|----------|--------------|---------------------------|
| PROGRESS  | All strokes | Asian Westerners | 0.61 (0.48-0.78) | N/A | Favors Perindopril | Favors Placebo  |
|           |         |                     | 0.78 (0.65-0.95) | N/A | Favors Felodipine with HCTZ | Favors HCTZ Alone  |
| FEVER     | All strokes | Chinese             | 0.73 (0.60-0.95) | .002 | Favors Nifedipine | Favors ACE Inhibitor  |
| JMIC-8    | Composite CV Events | Japanese | 1.05 (0.81-1.37) | .75 | Favors Nicardipine | Favors Trichlormethiazide  |
| 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  | Intervention | Race-treatment Interaction |
|------------|---------|----------------------|---------|----------|--------------|---------------------------|
| ALLHAT     | Fatal/Non-fatal CHD | Blacks | 1.10 (0.94-1.28) | .24 | Favors Lisinopril | Favors Chlorthalidone  |
| ALLHAT     | Stroke | Non-blacks | 0.94 (0.85-1.05) | .29 | Favors Chlorthalidone  |
|           |         | Blacks | 1.40 (1.17-1.68) | <.001 | Favors Lisinopril | Favors Chlorthalidone  |
|           |         | Non-blacks | 1.00 (0.85-1.17) | .97 | Favors Lisinopril  |
|           | Combined CVD | Blacks | 1.19 (1.09-1.30) | <.001 | Favors Lisinopril  |
|           |         | Non-blacks | 1.06 (1.00-1.13) | .05 | Favors Lisinopril  |
| ALLHAT     | Fatal/Non-fatal CHD | Blacks | 1.01 (0.86-1.18) | .95 | Favors Amlodipine | Favors Chlorthalidone |
| ALLHAT     |         | Non-blacks | 0.97 (0.87-1.08) | .57 | Favors Amlodipine  |
| LIFE       | Fatal CVD | US Blacks | 1.66 (1.04-2.66) | .033 | Favors Losartan | Favors Atenolol  |
| LIFE       |         | US Non-blacks | 0.72 (0.53-0.99) | .046 | Favors Losartan  |

### Outcomes in Multiple Ethnic Groups

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

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

ACE = angiotensin-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.\(^{30}\)

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.\(^{31}\) Despite US guidelines that specify both the inclusion and analysis of outcomes for minorities in federally funded clinical trials,\(^{32}\) 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.\(^{33}\)

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.\(^{34}\) 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 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.\(^{35}\) 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.54 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, althoughblinding 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.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/current/full/5/5/444.

Submitted September 7, 2006; submitted revised January 31, 2007; accepted March 17, 2007.

Key words: Hypertension; drug therapy; antihypertensive agents; ethnic groups; cardiovascular diseases; evidence-based medicine; minority groups

A summary of this work was disseminated as a podium presentation at the North American Primary Care Research Group Annual Meeting, Tucson, Arizona, October 15-18, 2006.

Funding support: This study was supported in part by a faculty development grant from the Health Resources and Services Administration, T0HP05168-01-00.

Acknowledgments: We thank Anne Marie Weber-Main, PhD, for her critical review and editing of manuscript drafts. We also thank James Neaton, PhD, for his review and suggestions on this manuscript.

References

1. Disparities in premature deaths from heart disease—50 States and the District of Columbia, 2001. MMWR Morb Mortal Wkly Rep. 2004;53(6):121-125.

2. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206-1252.
3. American Heart Association. Heart disease and stroke statistics: 2006 update. 2006. http://www.americanheart.org.

4. Qureshi AI, Suri MF, Kirmani JF, Divani AA. Prevalence and trends of prehypertension and hypertension in United States: National Health and Nutrition Examination Surveys 1976 to 2000. Med Sci Monit. 2005;11(9):CR403-409.

5. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA. 2003;290(2):199-206.

6. Cochrane Library. Cochrane Review Groups (CRG), Hypertension Group. http://www.mrw.interscience.wiley.com/cochrane/clabuff/articles/HTN/frame.html. Accessed: February 23 2006.

7. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

8. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997;350(9080):757-764.

9. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351(9118):1755-1762.

10. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care. 1998;21(4):597-603.

11. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet. 2000;356(9227):366-372.

12. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342(3):145-153.

13. Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) Study. Lancet. 2000;356(9227):359-365.

14. Gayet JL. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens. 2003;21(9):1771; author reply 1771-1772.

15. Malacco E, Mancia G, Rappelli A, Menotti A, Zuccaro MS, Coppini A. Treatment of isolated systolic hypertension: the SHELL study results. Blood Press. 2003;12(3):160-167.

16. Schrader J, Luders S, Kulchewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nifedipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke. 2005;36(6):1218-1226.

17. Pitt B, O’Neill B, Feldman R, et al. The QLunapir Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. Am J Cardiol. 2001;87(9):1058-1063.

18. Hansson L, Lindholm LH, Ekblom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet. 1999;353(9142):1751-1756.

19. Dahlof B, Hansson L, Lindholm LH, Schersten B, Ekblom T, Wester PO. Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) analyses performed up to 1992. Clin Exp Hypertens. 1993;15(6):925-939.

20. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. N Engl J Med. 2003;348(7):583-592.

21. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlopidine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895-906.

22. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA. 2003;289(16):2073-2082.

23. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362(9386):782-788.

24. Five-year findings of the Hypertension Detection and Follow-up Program: mortality by race-sex and blood pressure level. A further analysis. Hypertension Detection and Follow-up Program Cooperative Group. J Community Health. 1989;4(9):314-327.

25. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004;351(20):2058-2068.

26. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA. 1998;276(23):1886-1892.

27. Neaton JD, Grimm RH Jr, Prineas RJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA. 1993;270(6):713-724.

28. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288(23):2981-2997.

29. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. JAMA. 2000;283(15):1967-1975.

30. Davis BR, Cutler JA, Gordon DJ, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. Am J Hypertens. 1996;9(4 Pt 1):342-360.

31. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension. 2004;43(2):239-246.

32. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003;290(21):2805-2816.

33. Pepine CJ, Handberg-Thurmond E, Marks RG, et al. Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): an Internet-based randomized trial in coronary artery disease patients with hypertension. J Am Coll Cardiol. 1998;32(9):1229-1237.

34. Chalmers J, Neal B, MacMahon S. PROGRESS (Perindopril Protection Against Recurrent Stroke Study): regional characteristics of the study population at baseline. PROGRESS Management Committee. J Hypertens Suppl. 2000;18(1):S13-19.

35. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358(9287):1033-1041.
36. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363(9426):2022-2031.

37. Kjeldsen SE, Julius S, Brunner H, et al. Characteristics of 15,314 hypertensive patients at high coronary risk. The VALUE trial. The Valsartan Antihypertensive Long-term Use Evaluation. Blood Press. 2001;10(2):83-91.

38. Mann J, Julius S. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of cardiovascular events in hypertension. Rationale and design. Blood Press. 1998;7(3):176-183.

39. Dahlof B, Devereux RB, de Faire U, et al. The Losartan Intervention For Endpoint Reduction in Hypertension study: rationale, design, and methods. The LIFE Study Group. Am J Hypertens. 1997;10(7 Pt 1):705-713.

40. Dahlof B, Devereux RB, Julius S, et al. Characteristics of 9194 patients at high cardiovascular risk treated with regimens based on valsartan and amlodipine: the VALUE randomised trial. J Hum Genet. 2005;50(12):2157-2172.

41. Lindholm LH, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9111):1004-1010.

42. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Hypertension. 1999;34(5):1129-1133.

43. Yui Y, Sumiyoshi T, Kodama K, et al. Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multi-center Investigation for Cardiovascular Diseases-B (JMICH-B) randomised trial. Hypertens Res. 2004;27(3):181-191.

44. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A. The Felodipine and Amlodipine Randomized Evaluation (VALUE) trial of cardiovascular events in hypertension. JAMA. 2004;293(13):1595-1608.

45. Rodgers A, Chapman N, Woodward M, et al. Perindopril-based blood pressure lowering in individuals with cerebrovascular disease: consistency of benefits by age, sex and region. J Hypertens. 2004;22(3):653-659.

46. Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy: the LIFE study. J Am Coll Cardiol. 2004;43(8):1047-1055.

47. Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. J Hypertens. 2006;24(11):2163-2168.

48. Smith DH, Neutel JM, Lacourciere Y, Kemptorone-Rawson J, Prospective, randomized, open-label, blinded-endpoint (PROBE) designed trials yield the same results as double-blind, placebo-controlled trials with respect to ABPM measurements. J Hypertens. 2003;21(7):1291-1298.

50. Cooper-DelHoff RM, Aranda JM, Jr., Gaxiola E, et al. Blood pressure control and cardiovascular outcomes in high-risk Hispanic patients—findings from the International Verapamil SR/Trandolapril Study (INVEST). Am Heart J. 2006;151(5):1072-1079.

51. Sheikh A, Netuveli G, Kai J, Panesar SS. Comparison of reporting of ethnicity in US and European randomised controlled trials. BMJ. 2004;329(7457):87-88.

52. National Institutes of Health. NIH Policy and guidelines on the inclusion of women and minorities as subjects in clinical research. Amended, October 2001. http://grants.nih.gov/grants/women_min/guidelines_amended_10_2001.htm. Accessed: June 30 2006.

53. Corbie-Smith G, St George DM, Moody-Ayers S, Ransohoff DF. Adequacy of reporting race/ethnicity in clinical trials in areas of health disparities. J Clin Epidemiol. 2003;56(3):416-420.

54. Tang H, Quertermous T, Rodriguez B, et al. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. Am J Hum Genet. 2005;76(2):268-275.

55. Gadegbeku CA, Lea JP, Jamerson KA. Update on disparities in the pathophysiology and management of hypertension: focus on African Americans. Med Clin North Am. 2005;89(5):921-933, 930.

56. Wright JT, Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002;288(19):2421-2431.

57. Douglas JC, Bakris GL, Epstein M, et al. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. Arch Intern Med. 2003;163(5):525-541.

58. Matsuoka H. [Treatment of elderly hypertension based on various hypertension management guidelines—comparison between European and American guidelines and Japanese guidelines]. Rinsho. 2005;63(6):945-951.

59. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA. 2003;289(19):2534-2544.

60. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. J Am Coll Cardiol. 2002;39(2):315-322.

61. Lawes CM, Rodgers A, Bennett DA, et al. Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens. 2003;21(4):707-716.

62. Berlin JA. Does blindedness of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. Lancet. 1997;350(9072):185-186.

63. Taylor AL, Wright JT, Jr. Should ethnicity serve as the basis for clinical trial design? Importance of race/ethnicity in clinical trials: lessons from the African-American Heart Failure Trial (A-HeFT), the African-American Study of Kidney Disease and Hypertension (AASK), and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Circulation. 2005;112(23):3654-3660; discussion 3666.