

# Clinical Outcomes by Race in Hypertensive Patients With and Without the Metabolic Syndrome

## Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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**Background:** Antihypertensive drugs with favorable metabolic effects are advocated for first-line therapy in hypertensive patients with metabolic/cardio-metabolic syndrome (MetS). We compared outcomes by race in hypertensive individuals with and without MetS treated with a thiazide-type diuretic (chlorthalidone), a calcium channel blocker (amlodipine besylate), an  $\alpha$ -blocker (doxazosin mesylate), or an angiotensin-converting enzyme inhibitor (lisinopril).

**Methods:** A subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind hypertension treatment trial of 42 418 participants. We defined MetS as hypertension plus at least 2 of the following: fasting serum glucose level of at least 100 mg/dL, body mass index (calculated as weight in kilograms divided by height in meters squared) of at least 30, fasting triglyceride levels of at least 150 mg/dL, and high-density lipoprotein cholesterol levels of less than 40 mg/dL in men or less than 50 mg/dL in women.

**Results:** Significantly higher rates of heart failure were consistent across all treatment comparisons in those with MetS. Relative risks (RRs) were 1.50 (95% confidence interval, 1.18-1.90), 1.49 (1.17-1.90), and 1.88 (1.42-2.47) in black participants and 1.25 (1.06-1.47), 1.20

(1.01-1.41), and 1.82 (1.51-2.19) in nonblack participants for amlodipine, lisinopril, and doxazosin comparisons with chlorthalidone, respectively. Higher rates for combined cardiovascular disease were observed with lisinopril-chlorthalidone (RRs, 1.24 [1.09-1.40] and 1.10 [1.02-1.19], respectively) and doxazosin-chlorthalidone comparisons (RRs, 1.37 [1.19-1.58] and 1.18 [1.08-1.30], respectively) in black and nonblack participants with MetS. Higher rates of stroke were seen in black participants only (RR, 1.37 [1.07-1.76] for the lisinopril-chlorthalidone comparison, and RR, 1.49 [1.09-2.03] for the doxazosin-chlorthalidone comparison). Black patients with MetS also had higher rates of end-stage renal disease (RR, 1.70 [1.13-2.55]) with lisinopril compared with chlorthalidone.

**Conclusions:** The ALLHAT findings fail to support the preference for calcium channel blockers,  $\alpha$ -blockers, or angiotensin-converting enzyme inhibitors compared with thiazide-type diuretics in patients with the MetS, despite their more favorable metabolic profiles. This was particularly true for black participants.

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**H**YPERTENSIVE PATIENTS with the metabolic/cardio-metabolic syndrome (MetS) are at especially high risk for complications of cardiovascular disease (CVD).<sup>1-3</sup> In addition, racial differences in the presentation of MetS are well documented. For example, when compared with white patients, black patients with MetS have a higher prevalence of elevated blood pressure, type 2 diabetes mellitus, and obesity but lower levels of triglycerides and higher levels of high-density lipoprotein chole-

sterol.<sup>1</sup> The primary management strategy for MetS includes lifestyle changes, optimization of blood pressure (BP) control, and reduction of other cardiovascular risk factors.<sup>1,2</sup>

Despite the lack of supportive clinical outcome data, the use of antihypertensive drugs with a favorable metabolic profile (eg,  $\alpha$ -blockers, angiotensin-converting enzyme [ACE] inhibitors, and calcium channel blockers [CCBs]) has been advocated over classes of antihypertensive drugs with a less favorable profile (eg,  $\beta$ -blockers and thiazide-type diuretics).<sup>4-7</sup> Results from the

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)<sup>8-11</sup> showed that an  $\alpha$ -blocker, an ACE inhibitor, and a CCB were not superior to a thiazide-type diuretic in preventing cardiovascular or renal events in the entire trial cohort or in subgroups stratified by race, diabetic status, or level of renal function. Furthermore, ACE inhibitors were significantly less effective in preventing several cardiovascular outcomes, particularly in black participants.<sup>9</sup> However, it is unclear whether these agents might be more effective than diuretics in patients with MetS. ALLHAT enrolled participants with hypertension and at least 1 additional risk factor for coronary heart disease (CHD), resulting in more than half meeting the definition for MetS. This report focuses on the effects by treatment group and race on cardiovascular and renal outcomes in ALLHAT participants with MetS.

## METHODS

The ALLHAT cohort consisted of men and women 55 years or older with hypertension and at least 1 additional risk factor for CHD. The ALLHAT participants (N=42 418) were randomly assigned to therapy with chlorthalidone (n=15 255), amlodipine besylate (n=9048), lisinopril (n=9054), or doxazosin mesylate (n=9061). Details of the ALLHAT study design have been published previously.<sup>12</sup> The study received appropriate review board approval, and all participants provided written informed consent.

For the purposes of this report, MetS at baseline was defined as hypertension, which all participants had at study entry, plus at least 2 of the following factors: glycemic disorder (fasting glucose level  $\geq 100$  mg/dL [to convert glucose to millimoles per liter, multiply by 0.0555], nonfasting glucose level of  $\geq 200$  mg/dL, or a history of diabetes), body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of at least 30, fasting triglyceride level of at least 150 mg/dL (to convert triglycerides to millimoles per liter, multiply by 0.0113), or high-density lipoprotein cholesterol level of less than 40 mg/dL in men or less than 50 mg/dL in women (to convert cholesterol to millimoles per liter, multiply by 0.0259). This definition is consistent with that of the National Cholesterol Education Program except that BMI was substituted for waist circumference, which was not collected during the trial. This is a validated substitution allowed by the World Health Organization definition, previously used in publications, including a post hoc analysis of a clinical trial.<sup>2,13,14</sup> A fasting glucose level of at least 100 mg/dL rather than 110 mg/dL was used to reflect the changing definition of diabetes mellitus and impaired fasting glucose level as reflected in the International Diabetes Federation definition of MetS.<sup>15</sup>

Lowering of BP was achieved by titrating the dose of the randomized study drug (step 1) and adding open-label step 2 (atenolol, clonidine hydrochloride, or reserpine) or step 3 (hydralazine hydrochloride) agents, as necessary, to obtain a systolic BP of less than 140 mm Hg and diastolic BP of less than 90 mm Hg.<sup>12</sup> All step 1 (blinded) medications were identical in appearance. Follow-up visits were conducted at 1, 3, 6, 9, and 12 months, and then every 4 months thereafter for an average follow-up of 4.9 years for the diuretic vs ACE inhibitor and CCB comparisons. However, on the recommendation of an independent review panel, the  $\alpha$ -blocker arm of the trial was discontinued early, resulting in a 3.2-year average follow-up for the diuretic vs  $\alpha$ -blocker comparison.<sup>16</sup>

The primary outcome of the study was fatal CHD or nonfatal myocardial infarction. Major secondary outcomes in-

cluded all-cause mortality, fatal and nonfatal stroke, combined CHD (primary outcome, coronary revascularization, or hospitalized angina), and combined CVD (combined CHD, stroke, other treated angina, heart failure [fatal, hospitalized, or treated nonhospitalized], or peripheral arterial disease). End-stage renal disease (ESRD) (dialysis, renal transplantation, or death from kidney disease) and components of the major secondary outcomes were also prespecified. Although not a prespecified end point, we calculated changes in fasting glucose levels and the incidence of diabetes (fasting glucose level  $>125$  mg/dL) in the 4 treatment groups. We used standardized procedures for reporting and validating study outcomes.

Data were summarized as mean (SD) for continuous variables and number of subjects (percentage) for categorical variables. Baseline characteristics were compared in black and nonblack participants with and without MetS using the  $z$  test for significance testing of continuous covariates and contingency table analyses for categorical data. Outcomes were analyzed using an intention-to-treat approach. The Cox proportional hazards model was used to determine time-to-event hazard ratios (HRs) with 95% confidence intervals (CIs). Cox test assumptions were examined using log-log plots and tests of treatment  $\times$  time (time-dependent) interaction terms. When the assumptions were violated, a  $2 \times 2$  table was used to estimate relative risk (RR).

The median follow-up for the doxazosin comparison with chlorthalidone was only 3.2 years because the doxazosin arm was terminated early in light of an increased cardiovascular risk compared with chlorthalidone (stroke, 26% [ $P=.001$ ]; heart failure, 80% [ $P<.001$ ]) and the futility of achieving a statistically significant difference in the primary end point by the scheduled end of the trial. The shortened duration of follow-up for the diuretic vs  $\alpha$ -blocker comparison required a separate determination of the diuretic event rate for this comparison. Heterogeneity of treatment effects across MetS status and race was examined by testing for treatment  $\times$  covariate interaction with the proportional hazards model using  $P<.05$ . Analyses were unadjusted. Given the many subgroup and interaction analyses performed, statistical significance at the .05 level should be interpreted with caution. All statistical analyses were performed using STATA statistical software (version 9.0; StataCorp, College Station, Texas).

## RESULTS

The baseline characteristics of the cohort group by MetS status, race, and treatment group are outlined in **Table 1**, and the follow-up is described in **Figure 1**. The criteria for MetS were met by 54.4% of ALLHAT participants (n=23 077). Although counterintuitive, ALLHAT participants without MetS were more likely to qualify for the trial based on the presence of CVD. This is because participants without diabetes at baseline (and less likely to be classified as having MetS) had to have other CHD risk factors to qualify for ALLHAT. Participants with MetS from both race subgroups across randomized comparisons were more likely to be younger and female, and—as a result of the ALLHAT recruitment criteria—they were less likely to smoke, to have left ventricular hypertrophy, or to have a history of atherosclerotic CVD. In black participants with MetS, those randomized to amlodipine had a significantly higher BMI and were more likely to be receiving aspirin therapy than those in the chlorthalidone subgroup. Otherwise, baseline characteristics were similar across treatment groups. The ratio of observed to expected person-years in the trial was about 99% for comparisons of amlodipine and lisinopril with

**Table 1. Baseline Characteristics by Race and Metabolic Syndrome<sup>a</sup>**

Characteristic	Black Participants		Nonblack Participants	
	With MetS (n=7327)	Without MetS (n=5491)	With MetS (n=15 750)	Without MetS (n=8723)
Age, mean (SD), y	65.4 (7.2)	67.2 (8.1) <sup>b</sup>	66.4 (7.3)	68.4 (8.0) <sup>b</sup>
Age range, y				
55-59	1750 (23.9)	1032 (18.8) <sup>b</sup>	3021 (19.2)	1304 (14.9) <sup>b</sup>
60-69	3575 (48.8)	2475 (45.1)	7617 (48.4)	3616 (41.5)
70-79	1710 (23.3)	1530 (27.9)	4386 (27.8)	2975 (34.1)
≥ 80	292 (4.0)	454 (8.3)	726 (4.6)	828 (9.5)
Women	4456 (60.8)	2503 (45.6) <sup>b</sup>	6976 (44.3)	3459 (39.7) <sup>b</sup>
Years of education, mean (SD)	10.2 (3.7)	10.1 (4.0) <sup>c</sup>	11.3 (4.1)	11.6 (4.0) <sup>b</sup>
Cigarette smoking				
Current <sup>d</sup>	1428 (19.5)	1758 (32.0)	2684 (17.0)	2123 (24.3)
Past	2667 (36.4)	1818 (33.1)	7137 (45.3)	3609 (41.4)
Never	3232 (44.1)	1914 (34.9)	5929 (37.6)	2991 (34.3)
BMI, mean (SD)	33.3 (6.5)	27.0 (5.0) <sup>b</sup>	31.4 (5.9)	26.2 (3.9) <sup>b</sup>
Aspirin use	1832 (25.0)	1420 (25.9)	6431 (40.8)	3870 (44.4) <sup>b</sup>
Antihypertensive treatment				
Treated	6757 (92.2)	4907 (89.4)	14 295 (90.8)	7724 (88.5)
Untreated	570 (7.8)	584 (10.6)	1455 (9.2)	999 (11.5)
Atherosclerotic CVD	2348 (32.0)	2306 (42.0) <sup>b</sup>	7238 (46.0)	5011 (57.5) <sup>b</sup>
History of MI or stroke <sup>d</sup>	1287 (17.6)	1236 (22.5) <sup>b</sup>	3691 (23.4)	2425 (27.8) <sup>b</sup>
History of coronary revascularization <sup>d</sup>	358 (4.9)	307 (5.6)	2607 (16.6)	1569 (18.0) <sup>c</sup>
Other atherosclerotic CVD <sup>d,e</sup>	1217 (16.6)	1206 (22.0) <sup>b</sup>	3695 (23.5)	2684 (30.8) <sup>b</sup>
ST-T wave abnormality <sup>d</sup>	824 (11.3)	725 (13.4) <sup>c</sup>	1272 (8.1)	872 (10.0) <sup>b</sup>
LVH by ECG or echocardiography <sup>d</sup>	1523 (20.8)	1886 (34.4) <sup>b</sup>	2049 (13.0)	1760 (20.2) <sup>b</sup>
Glycemic status <sup>f</sup>				
Diabetes mellitus	4860 (67.6)	1045 (19.1)	8040 (51.8)	1516 (17.5)
Impaired fasting glucose	402 (5.6)	122 (2.2)	1064 (6.9)	173 (2.0)
Normoglycemic	1932 (26.9)	4308 (78.7)	6420 (41.4)	7000 (80.6)
History of CHD at baseline <sup>d,g</sup>	1180 (16.1)	1041 (19.0) <sup>b</sup>	4490 (28.5)	2849 (32.7) <sup>b</sup>
Lipid trial participants	1985 (27.1)	1474 (26.8)	3761 (23.9)	2249 (25.8) <sup>c</sup>
Blood pressure				
Systolic, mean (SD), mm Hg <sup>h</sup>	146.2 (15.7)	146.2 (16.0)	146.0 (15.5)	146.8 (15.5) <sup>b</sup>
Diastolic, mean (SD), mm Hg	84.4 (10.1)	85.4 (10.1) <sup>b</sup>	83.5 (10.0)	83.7 (9.8)
Serum potassium level, mean (SD), mEq/L	4.26 (0.76)	4.29 (0.73)	4.39 (0.64)	4.41 (0.67)
Fasting serum glucose level, mean (SD), mg/dL	144.2 (68.6)	103.4 (45.5) <sup>b</sup>	131.2 (57.1)	101.8 (38.8) <sup>b</sup>
Serum creatinine level, mean (SD), mg/dL	1.05 (0.35)	1.08 (0.32) <sup>b</sup>	0.99 (0.27)	1.00 (0.26) <sup>c</sup>
TC level, mean (SD) mg/dL	219.7 (46.1)	214.4 (41.3) <sup>b</sup>	217.0 (43.6)	212.4 (40.0) <sup>b</sup>
LDL-C level, mean (SD), mg/dL	141.8 (40.5)	136.2 (37.8) <sup>b</sup>	134.6 (35.8)	134.1 (34.1)
HDL-C level, mean (SD), mg/dL	47.1 (13.4)	57.2 (16.2) <sup>b</sup>	40.1 (10.8)	51.7 (14.6) <sup>b</sup>
HDL-C level, < 35 mg/dL <sup>d</sup>	591 (8.1)	271 (4.9) <sup>b</sup>	2804 (17.8)	745 (8.5) <sup>b</sup>
Fasting triglyceride level, mean (SD), mg/dL	156.3 (109.2)	102.3 (52.2) <sup>b</sup>	224.3 (159.2)	133.2 (94.5) <sup>b</sup>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiography; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MetS, metabolic/cardiometabolic syndrome; MI, myocardial infarction; TC, total cholesterol.

SI unit conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.259; creatinine to micromoles per liter, multiply by 88.4; glucose to millimoles per liter, multiply by 0.0555; potassium to millimoles per liter, multiply by 1; and triglycerides to millimoles per liter, multiply by 0.0113.

<sup>a</sup>Data are given as number (percentage) unless otherwise indicated. Because of missing data, some denominators may be slightly different from what is shown in the column heading.

<sup>b</sup> $P < .001$ , comparison of participants with vs those without MetS.

<sup>c</sup> $P < .05$ , comparison of participants with vs those without MetS.

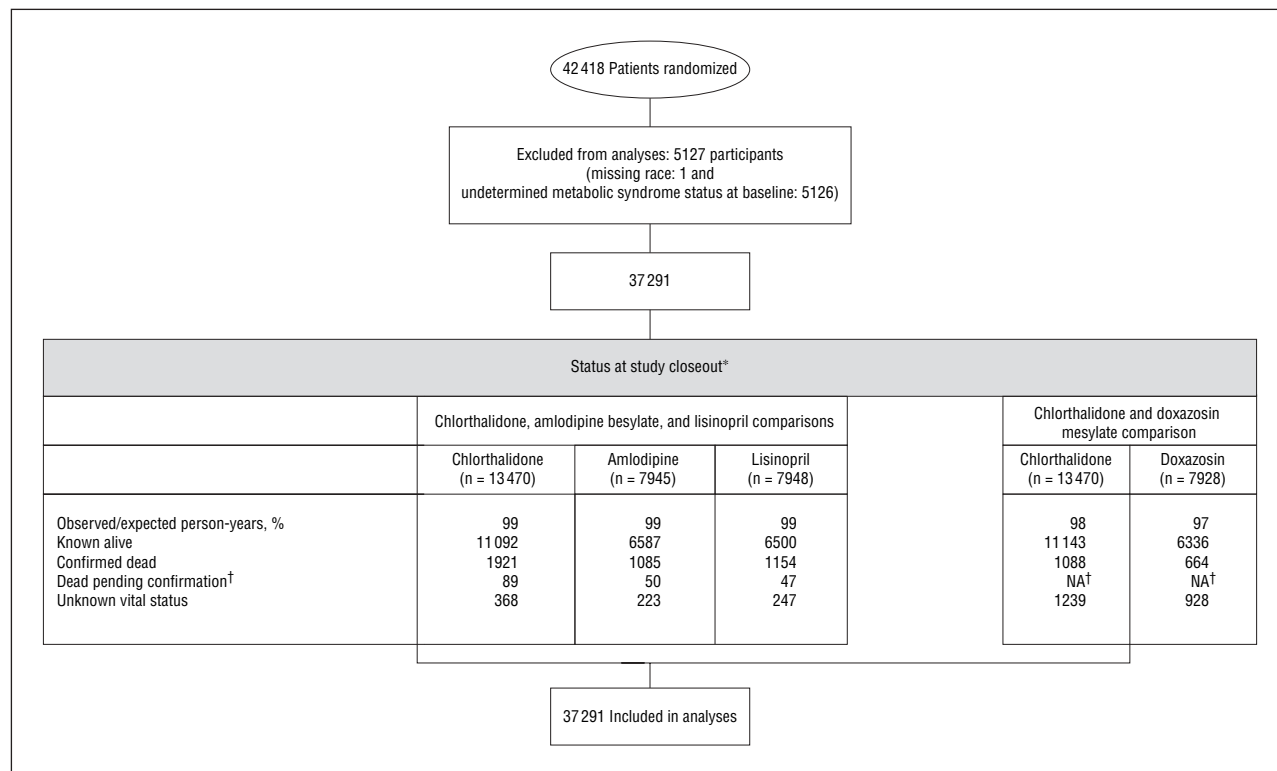
<sup>d</sup>Indicates eligibility risk factors. For trial eligibility, participants had to have at least 1 other risk factor in addition to hypertension. Thus, the indicated risk factors are not mutually exclusive or exhaustive and may not represent prevalence.

<sup>e</sup>Indicates a history of angina pectoris; a history of intermittent claudication, gangrene, or ischemic ulcers; a history of transient ischemic attack; coronary, peripheral vascular, or carotid stenosis of 50% or more documented by angiography or Doppler studies; ischemic heart disease documented by reversible or fixed ischemia on stress thallium or dipyridamole thallium test results, ST depression of at least 1 mm for at least 1 minute on exercise testing or Holter monitoring results; reversible wall motion abnormality on stress ECG; ankle-arm index of less than 0.9; abdominal aortic aneurysm detected by ultrasonography, computed tomography, or radiography; or carotid or femoral bruits.

<sup>f</sup>Diabetes mellitus indicates a history of diabetes at baseline or a fasting glucose level of at least 126 mg/dL; impaired fasting glucose level, no history and a baseline fasting glucose level of 110 to 125 mg/dL inclusive; normoglycemic, not classified as impaired fasting glucose level, no history, and a fasting glucose and/or nonfasting glucose level of less than 110 mg/dL.

<sup>g</sup>Indicates known previous MI, angina, primary cardiac arrest, coronary stenosis of more than 50%, reversible perfusion defect, or prior coronary revascularization procedure. The baseline CHD variable was not collected on all participants from the beginning, but was added after some patients had already been randomized. Therefore, the denominators for black participants with and without MetS are 7214 and 5413, respectively; for nonblack participants with and without MetS, 15 682 and 8695, respectively.

<sup>h</sup>Systolic blood pressure ( $P = .72$ ) is the only variable herein for which the black vs nonblack comparison is not statistically significant. For each of the other variables,  $P \leq .001$  for the black vs nonblack comparison.



**Figure 1.** Randomization and follow-up of participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. NA indicates not applicable. \*Numbers for the chlorthalidone, amlodipine, and lisinopril comparisons are as of September 30, 2002; this period includes an effort to locate as many participants as possible during scheduled study closeout. Numbers for the chlorthalidone and doxazosin comparison are as of February 15, 2000, and reflect the early termination of the doxazosin arm. †The “dead pending confirmation” classification was not used during the doxazosin closeout period.

chlorthalidone, and 97% to 98% for comparisons of doxazosin with chlorthalidone.

### BP CONTROL

Mean baseline systolic and diastolic BPs and the percentage of individuals with BP controlled to less than 140/90 mm Hg were similar across all treatment, race, and metabolic status subgroups (**Table 2** and **Table 3**). Among black participants with MetS, systolic and diastolic BPs were 4/1 mm Hg higher at 4 years in those randomized to lisinopril ( $P < .001$  and  $P = .03$ , respectively) and 2/1 mm Hg higher at 4 years in those randomized to doxazosin ( $P = .02$  and  $P = .36$ , respectively). Approximately 1 mm Hg separated the BPs between the chlorthalidone and amlodipine treatment groups ( $P < .05$  for systolic BP and  $P = .67$  for diastolic BP). In black participants without MetS, BPs at 4 years in those randomized to chlorthalidone were 3/1 mm Hg lower than in those randomized to lisinopril ( $P < .001$  and  $P = .11$ , respectively) and 6/1 mm Hg lower at 4 years than in those randomized to doxazosin ( $P < .001$  and  $P = .06$ , respectively). In nonblack participants at 4 years, systolic BP differed by 0 to 3 mm Hg among all treatment groups, and 0 to 1 mm Hg of difference separated the diastolic BP, regardless of MetS status.

### BIOCHEMICAL CHANGES

The mean serum cholesterol levels in participants with and without MetS (approximately 25% of whom were randomized in the ALLHAT lipid component, half of

whom received pravastatin sodium) decreased more in the amlodipine, lisinopril, and doxazosin groups compared with the chlorthalidone group at 4 years. The difference in achieved levels was largest in those randomized to doxazosin by 8 to 14 mg/dL (Tables 2 and 3). Serum potassium levels for those with and without MetS were also slightly but significantly higher for the amlodipine, lisinopril, and doxazosin groups vs the chlorthalidone group at year 4. Compared with those receiving chlorthalidone, fasting glucose levels at 4 years were lower for participants with MetS receiving amlodipine (by 2-5 mg/dL), lisinopril (by 6-7 mg/dL), and doxazosin (by 8-13 mg/dL). In those without MetS, glucose levels at 4 years were 1 to 4 mg/dL higher among participants in the chlorthalidone group than among the other treatment groups. The differences in glucose levels at 4 years were significant only for the lisinopril and doxazosin vs chlorthalidone comparisons in nonblack participants with MetS ( $P < .05$ ).

### CARDIOVASCULAR AND RENAL END POINTS

**Figures 2, 3, and 4** show the event rates and HRs or RRs for the prespecified outcomes by race, metabolic status, and treatment group. No differences were noted among the 4 treatment groups, regardless of race or MetS status for the primary end point (nonfatal myocardial infarction and fatal CHD).

**Table 2. BP and Biochemical Changes by Race and Treatment Group in Participants With MetS<sup>a</sup>**

Variable	Black Participants				Nonblack Participants			
	Chlorthalidone <sup>b</sup>	Amlodipine Besylate	Lisinopril	Doxazosin Mesylate <sup>c</sup>	Chlorthalidone <sup>b</sup>	Amlodipine Besylate	Lisinopril	Doxazosin Mesylate <sup>c</sup>
Fasting glucose level, mg/dL								
Baseline	145.5 (70.7)	141.6 (66.0)	145.5 (69.6)	143.2 (66.7)	131.5 (57.8)	131.9 (58.1)	130.7 (55.6)	130.5 (56.2)
2 y	150.1 (73.1)	147.1 (72.3)	139.2 (68.0) <sup>d</sup>	137.2 (66.9) <sup>d</sup>	137.2 (60.1)	130.2 (53.3) <sup>e</sup>	130.1 (54.6) <sup>e</sup>	126.9 (53.3) <sup>e</sup>
4 y	146.3 (72.7)	141.8 (61.9)	139.3 (72.0)	130.1 (54.8)	134.5 (56.8)	132.3 (52.6)	128.5 (50.5) <sup>d</sup>	124.9 (52.2) <sup>d</sup>
6 y	133.0 (60.3)	130.8 (55.1)	135.9 (59.3)		130.8 (48.5)	130.9 (46.8)	127.2 (46.7)	
Potassium level, mEq/L								
Baseline	4.27 (0.76)	4.24 (0.77)	4.28 (0.75)	4.25 (0.74)	4.37 (0.64)	4.40 (0.66)	4.40 (0.59) <sup>d</sup>	4.41 (0.69) <sup>d</sup>
2 y	3.98 (0.67)	4.26 (0.62) <sup>e</sup>	4.38 (0.69) <sup>e</sup>	4.28 (0.73) <sup>e</sup>	4.07 (0.71)	4.35 (0.63) <sup>e</sup>	4.52 (0.71) <sup>e</sup>	4.38 (0.59) <sup>e</sup>
4 y	4.10 (0.63)	4.35 (0.73) <sup>e</sup>	4.39 (0.59) <sup>e</sup>	4.25 (0.57) <sup>e</sup>	4.17 (0.65)	4.45 (0.70) <sup>e</sup>	4.61 (0.72) <sup>e</sup>	4.46 (0.79) <sup>e</sup>
6 y	4.12 (0.61)	4.40 (0.85) <sup>e</sup>	4.44 (0.47) <sup>e</sup>		4.24 (0.60)	4.44 (0.49) <sup>e</sup>	4.61 (0.52) <sup>e</sup>	
TC level, mg/dL								
Baseline	220.1 (46.5)	221.6 (47.0)	219.2 (47.1)	218.1 (44.3)	216.7 (43.8)	218.4 (45.2)	217.4 (42.5)	216.0 (42.9)
2 y	209.6 (44.7)	206.3 (45.9)	205.9 (46.3)	197.0 (42.7) <sup>e</sup>	203.2 (41.3)	201.7 (42.5)	202.2 (43.2)	195.2 (41.3) <sup>e</sup>
4 y	201.4 (44.0)	200.2 (46.0)	198.0 (42.3)	189.3 (45.5) <sup>e</sup>	194.3 (42.4)	193.7 (40.7)	193.4 (41.0)	185.1 (36.9) <sup>e</sup>
6 y	191.1 (43.1)	190.4 (43.3)	190.3 (42.0)		182.5 (41.4)	184.3 (39.9)	184.5 (40.8)	
TC change from baseline, mg/dL								
2 y	-10.1 (36.8)	-14.2 (40.3) <sup>d</sup>	-13.2 (41.0)	-21.0 (35.3) <sup>e</sup>	-12.8 (37.9)	-16.1 (39.7) <sup>d</sup>	-14.6 (39.2)	-19.8 (38.6) <sup>e</sup>
4 y	-17.5 (40.5)	-19.7 (43.5)	-21.0 (42.1)	-28.0 (37.6) <sup>e</sup>	-20.5 (41.6)	-23.5 (41.9) <sup>d</sup>	-23.4 (42.5) <sup>d</sup>	-28.9 (37.7) <sup>e</sup>
6 y	-28.3 (43.1)	-32.9 (45.7)	-29.8 (39.2)		-33.4 (45.1)	-33.2 (41.7)	-33.5 (43.6)	
SBP, mm Hg								
Baseline	146.4 (15.6)	146.1 (15.9)	146.2 (15.4)	146.1 (15.9)	146.0 (15.5)	145.9 (15.6)	146.3 (15.4)	146.1 (15.6)
2 y	137.9 (17.1)	139.1 (15.5)	143.4 (19.1) <sup>e</sup>	140.6 (18.5) <sup>e</sup>	135.4 (15.3)	136.4 (14.3) <sup>d</sup>	137.2 (16.9) <sup>e</sup>	137.2 (16.2) <sup>e</sup>
4 y	135.5 (16.5)	136.9 (15.5) <sup>d</sup>	139.5 (18.7) <sup>e</sup>	138.9 (17.7) <sup>d</sup>	133.7 (15.0)	134.5 (14.0) <sup>d</sup>	134.1 (15.9)	136.3 (16.5)
6 y	134.8 (17.3)	136.8 (16.5)	137.9 (19.6) <sup>d</sup>		133.5 (15.3)	134.1 (14.7)	131.8 (16.6) <sup>d</sup>	
DBP, mm Hg								
Baseline	84.5 (10.0)	84.3 (10.3)	84.3 (10.2)	84.5 (10.0)	83.5 (10.0)	83.3 (10.2)	83.7 (9.9)	83.4 (10.0)
2 y	79.6 (10.1)	79.3 (10.0)	80.9 (10.7) <sup>e</sup>	79.8 (10.6)	77.7 (9.2)	76.7 (8.9) <sup>e</sup>	77.5 (9.8)	77.3 (9.5)
4 y	77.5 (9.9)	77.7 (10.1)	78.5 (10.7) <sup>d</sup>	78.0 (11.0)	75.7 (9.5)	74.8 (9.0) <sup>e</sup>	75.4 (9.9)	75.0 (10.4)
6 y	75.1 (10.8)	75.2 (9.6)	75.2 (10.2)		73.3 (9.7)	72.3 (9.6) <sup>d</sup>	72.5 (10.3)	
At goal BP, No. (%) <sup>f</sup>								
Baseline	729 (27.7)	454 (29.2)	421 (26.7)	435 (27.8)	1549 (27.3)	933 (27.8)	910 (27.0)	954 (28.7)
2 y	1096 (55.9)	570 (50.1) <sup>d</sup>	464 (42.3) <sup>e</sup>	525 (47.7) <sup>e</sup>	2862 (63.0)	1578 (60.8)	1514 (58.6) <sup>e</sup>	1483 (57.6) <sup>e</sup>
4 y	984 (63.3)	552 (60.2)	430 (51.0) <sup>e</sup>	240 (54.4) <sup>d</sup>	2525 (68.7)	1451 (67.2)	1429 (68.5)	530 (60.4)
6 y	336 (67.2)	178 (60.5)	149 (58.4) <sup>d</sup>		756 (70.3)	441 (68.4)	444 (72.9)	

Abbreviations: BP, blood pressure; DBP, diastolic BP; TC, total cholesterol; SBP, systolic BP; MetS, metabolic/cardiomatabolic syndrome.

SI unit conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.259; glucose to millimoles per liter, multiply by 0.0555; and potassium to millimoles per liter, multiply by 1.

<sup>a</sup>Data are given as mean (SD) unless otherwise indicated.

<sup>b</sup>Values for chlorthalidone are as of September 30, 2002 (comparisons with amlodipine and lisinopril), and are comparable but may not be identical to those in the comparison with doxazosin, which was terminated early.

<sup>c</sup>Comparisons are vs chlorthalidone values as of February 15, 2000.

<sup>d</sup> $P < .05$  for comparison vs chlorthalidone.

<sup>e</sup> $P < .001$  for comparison vs chlorthalidone.

<sup>f</sup>Indicates SBP of less than 140 mm Hg and DBP of less than 90 mm Hg.

### AMLODIPINE-CHLORTHALIDONE COMPARISON

In black participants with MetS, those assigned to amlodipine compared with those assigned to chlorthalidone were more likely to have higher rates of combined CVD (HR, 1.14 [95% CI, 1.00-1.29]) and heart failure (HR, 1.50 [95% CI, 1.18-1.90]); ESRD also trended higher but the difference was not statistically significant (HR, 1.50 [95% CI, 0.99-2.28]). Nonblack participants with MetS who were randomized to amlodipine had higher rates of heart failure compared with those randomized to chlorthalidone (RR, 1.25 [95% CI, 1.06-1.47]) but lower rates of stroke (HR, 0.80 [95% CI, 0.64-0.99]). Participants without MetS randomized to amlodipine had similar rates of all outcomes compared with those randomized to chlorthalidone but higher rates of heart failure in black (RR, 1.39 [95% CI, 1.01-1.91]) and nonblack (RR, 1.48 [95% CI, 1.18-1.87]) participants. In black participants, although the comparisons of amlodipine with

chlorthalidone for ESRD were not statistically significant for participants either with or without MetS, there was a statistically significant difference in treatment effect by MetS for ESRD (HR, 1.50 [95% CI, 0.99-2.28] for those with MetS; HR, 0.67 [95% CI, 0.35-1.28] for those without MetS;  $P = .04$  for interaction). In nonblack participants with MetS, we found a statistically significant difference between amlodipine and chlorthalidone for stroke (HR, 0.80 [95% CI, 0.64-0.99]). However, this could be by chance because the  $P$  value for interaction comparing the results in participants with and without MetS was not statistically significant ( $P = .051$  for interaction).

### LISINOPRIL-CHLORTHALIDONE COMPARISON

Black participants with MetS who were randomized to lisinopril compared with chlorthalidone were more likely to have higher rates of combined CHD (HR, 1.19 [95% CI, 1.01-1.40]), combined CVD (HR, 1.24 [95% CI, 1.09-

**Table 3. BP and Biochemical Changes by Race and Treatment Group in Participants Without MetS<sup>a</sup>**

Variable	Black Participants				Nonblack Participants			
	Chlorthalidone <sup>b</sup>	Amlodipine Besylate	Lisinopril	Doxazosin Mesylate <sup>c</sup>	Chlorthalidone <sup>b</sup>	Amlodipine Besylate	Lisinopril	Doxazosin Mesylate <sup>c</sup>
Fasting glucose level, mg/dL								
Baseline	103.0 (46.6)	105.0 (46.7)	102.5 (41.0)	103.7 (46.9)	102.7 (40.9)	101.2 (36.9)	101.8 (38.4)	100.9 (37.3)
2 y	107.7 (43.8)	107.1 (47.1)	108.5 (50.2)	107.9 (44.4)	108.4 (46.3)	103.3 (34.1) <sup>d</sup>	102.5 (37.0) <sup>d</sup>	103.5 (36.4) <sup>d</sup>
4 y	109.3 (39.2)	105.0 (37.2)	109.4 (40.0)	105.2 (38.7)	108.3 (36.6)	107.4 (42.9)	106.9 (37.1)	104.8 (36.5)
6 y	106.0 (37.9)	115.0 (47.7)	111.3 (46.1)		113.1 (36.5)	103.4 (30.6) <sup>d</sup>	107.2 (35.6)	
Potassium level, mEq/L								
Baseline	4.27 (0.70)	4.28 (0.70)	4.31 (0.79)	4.30 (0.76)	4.40 (0.68)	4.39 (0.67)	4.43 (0.68)	4.41 (0.65)
2 y	3.99 (0.62)	4.24 (0.73) <sup>e</sup>	4.37 (0.65) <sup>e</sup>	4.27 (0.77) <sup>e</sup>	4.07 (0.70)	4.34 (0.62) <sup>e</sup>	4.55 (0.62) <sup>e</sup>	4.36 (0.58) <sup>e</sup>
4 y	4.07 (0.67)	4.37 (0.92) <sup>e</sup>	4.41 (0.55) <sup>e</sup>	4.41 (0.94) <sup>e</sup>	4.16 (0.78)	4.43 (0.61) <sup>e</sup>	4.60 (0.63) <sup>e</sup>	4.44 (0.90) <sup>e</sup>
6 y	4.10 (0.81)	4.36 (0.69) <sup>e</sup>	4.49 (0.76) <sup>e</sup>		4.18 (0.78)	4.44 (0.64) <sup>e</sup>	4.61 (0.54) <sup>e</sup>	
TC level, mg/dL								
Baseline	214.8 (41.1)	213.2 (41.6)	214.3 (41.1)	214.7 (41.4)	213.6 (41.0)	212.4 (40.6)	211.8 (38.3)	211.1 (39.4) <sup>d</sup>
2 y	207.6 (43.9)	200.0 (39.3) <sup>e</sup>	201.5 (44.4) <sup>d</sup>	196.8 (38.4) <sup>e</sup>	203.7 (39.5)	201.1 (40.8)	199.9 (38.8) <sup>d</sup>	194.0 (36.3) <sup>e</sup>
4 y	201.8 (42.6)	196.3 (41.0) <sup>d</sup>	195.2 (39.6) <sup>d</sup>	187.9 (37.2) <sup>e</sup>	195.0 (39.0)	193.7 (37.6)	194.7 (38.6)	188.3 (35.9) <sup>d</sup>
6 y	195.1 (42.4)	188.1 (37.2) <sup>d</sup>	190.6 (40.4)		187.0 (37.6)	188.5 (38.9)	185.2 (35.8)	
TC change from baseline, mg/dL								
2 y	-8.2 (36.1)	-12.9 (33.5) <sup>d</sup>	-13.1 (35.9) <sup>d</sup>	-18.3 (34.3) <sup>e</sup>	-10.2 (36.7)	-10.9 (35.0)	-12.0 (35.1)	-17.8 (34.4) <sup>e</sup>
4 y	-14.1 (36.5)	-15.9 (36.2)	-20.8 (36.7) <sup>e</sup>	-25.6 (34.1) <sup>e</sup>	-19.1 (38.6)	-18.7 (37.8)	-17.8 (38.2)	-24.3 (36.7)
6 y	-22.9 (38.1)	-19.7 (36.2)	-24.2 (41.8)		-28.0 (39.2)	-24.5 (38.2)	-26.4 (36.7)	
SBP, mm Hg								
Baseline	146.1 (15.7)	145.9 (16.1)	146.5 (16.3)	146.5 (16.0)	146.7 (15.8)	146.7 (15.4)	147.2 (15.2)	146.7 (15.4)
2 y	135.8 (16.2)	138.0 (16.2) <sup>d</sup>	140.1 (18.5) <sup>e</sup>	140.4 (18.0) <sup>e</sup>	135.0 (15.2)	135.9 (14.4)	135.9 (16.8)	136.4 (16.0) <sup>d</sup>
4 y	133.6 (16.9)	135.8 (16.5) <sup>d</sup>	136.6 (18.3) <sup>e</sup>	139.1 (17.6) <sup>e</sup>	132.8 (15.4)	132.7 (14.1)	134.5 (17.2) <sup>d</sup>	136.1 (16.8) <sup>d</sup>
6 y	133.6 (16.1)	135.3 (17.6)	138.3 (19.3) <sup>d</sup>		132.8 (15.6)	131.3 (15.0)	133.2 (16.7)	
DBP, mm Hg								
Baseline	85.3 (10.1)	84.9 (10.2)	85.8 (9.9)	85.7 (10.0)	83.7 (9.7)	83.7 (9.9)	83.8 (9.8)	83.6 (9.8)
2 y	79.3 (9.7)	79.3 (10.0)	81.3 (11.4) <sup>e</sup>	81.0 (10.9) <sup>e</sup>	77.4 (9.3)	76.6 (9.4) <sup>d</sup>	77.1 (9.6)	77.4 (9.5)
4 y	78.2 (9.9)	77.6 (9.6)	79.0 (11.2)	79.3 (10.5)	75.7 (9.2)	74.5 (9.4) <sup>e</sup>	75.6 (10.0)	75.6 (10.5)
6 y	76.2 (10.1)	76.2 (9.7)	77.8 (11.4)		73.2 (10.0)	72.7 (8.9)	73.4 (10.4)	
At goal BP, No (%) <sup>f</sup>								
Baseline	520 (26.5)	327 (28.0)	285 (24.9)	318 (26.2)	864 (27.1)	508 (27.3)	455 (24.6)	465 (25.6)
2 y	884 (60.8)	482 (55.6) <sup>d</sup>	397 (48.0) <sup>e</sup>	393 (46.5) <sup>e</sup>	1577 (63.2)	903 (60.8)	843 (59.8) <sup>d</sup>	860 (61.0)
4 y	769 (65.8)	452 (62.6)	389 (59.2) <sup>d</sup>	175 (51.3) <sup>d</sup>	1418 (70.7)	875 (70.8)	746 (65.6)	310 (62.6)
6 y	250 (66.3)	160 (64.3)	125 (56.3) <sup>d</sup>		379 (72.1)	244 (73.9)	208 (67.5)	

Abbreviations: BP, blood pressure; DBP, diastolic BP; TC, total cholesterol; SBP, systolic BP; MetS, metabolic/cardiomatabolic syndrome.

SI unit conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.259; glucose to millimoles per liter, multiply by 0.0555; and potassium to millimoles per liter, multiply by 1.

<sup>a</sup>Data are given as mean (SD) unless otherwise indicated.

<sup>b</sup>Values for chlorthalidone are as of September 30, 2002 (comparisons with amlodipine and lisinopril), and are comparable but may not be identical to those in the comparison with doxazosin, which was terminated early.

<sup>c</sup>Comparisons are vs chlorthalidone values as of February 15, 2000.

<sup>d</sup> $P < .05$  for comparison vs chlorthalidone.

<sup>e</sup> $P < .001$  for comparison vs chlorthalidone.

<sup>f</sup>Indicates SBP of less than 140 mm Hg and DBP of less than 90 mm Hg.

1.40)), stroke (HR, 1.37 [95% CI, 1.07-1.76]), heart failure (RR, 1.49 [95% CI, 1.17-1.90]), and ESRD (HR, 1.70 [95% CI, 1.13-2.55]), whereas nonblack participants with MetS had higher rates of combined CVD (HR, 1.10 [95% CI, 1.02-1.19]) and heart failure (RR, 1.20 [95% CI, 1.01-1.41]). There were no significant differences in end points for lisinopril compared with chlorthalidone in black or nonblack participants without MetS. In black participants, there was a statistically significant difference in treatment effect for ESRD among those with and without MetS (HR, 1.70 [95% CI, 1.13-2.55] for those with MetS; HR, 0.75 [95% CI, 0.40-1.40] for those without MetS;  $P = .03$  for interaction).

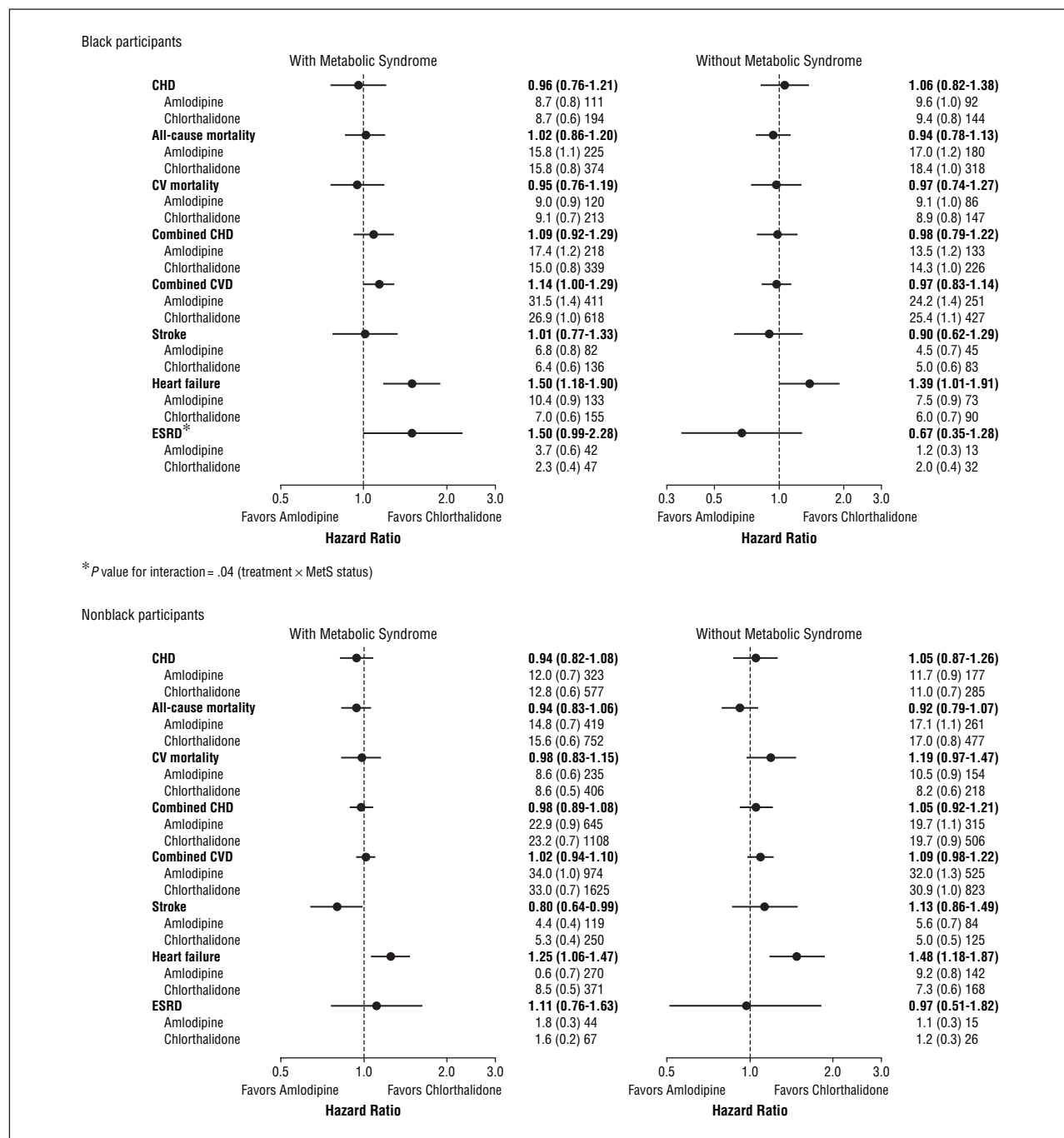
#### DOXAZOSIN-CHLORTHALIDONE COMPARISON

Black participants with MetS randomized to doxazosin vs chlorthalidone had higher rates of combined CVD (HR, 1.37 [95% CI, 1.19-1.58]), stroke (HR, 1.49 [95% CI, 1.09-

2.03]), and heart failure (RR, 1.88 [95% CI, 1.42-2.47]), whereas nonblack participants with MetS had higher rates of combined CVD (HR, 1.18 [95% CI, 1.08-1.30]) and heart failure (RR, 1.82 [95% CI, 1.51-2.19]). Both racial groups without MetS who were treated with doxazosin had similarly higher rates of combined CVD and heart failure.

#### COMMENT

The major finding of this report is that, despite a more favorable metabolic profile, the CCB, the ACE inhibitor, and the  $\alpha$ -blocker were not superior to the thiazide-type diuretic in preventing adverse clinical outcomes in hypertensive patients with MetS. The findings by race and MetS status also parallel the findings in the entire cohort and in all other subgroup analyses from the trial.<sup>8-11,16,17</sup> In no subgroup analysis from ALLHAT has

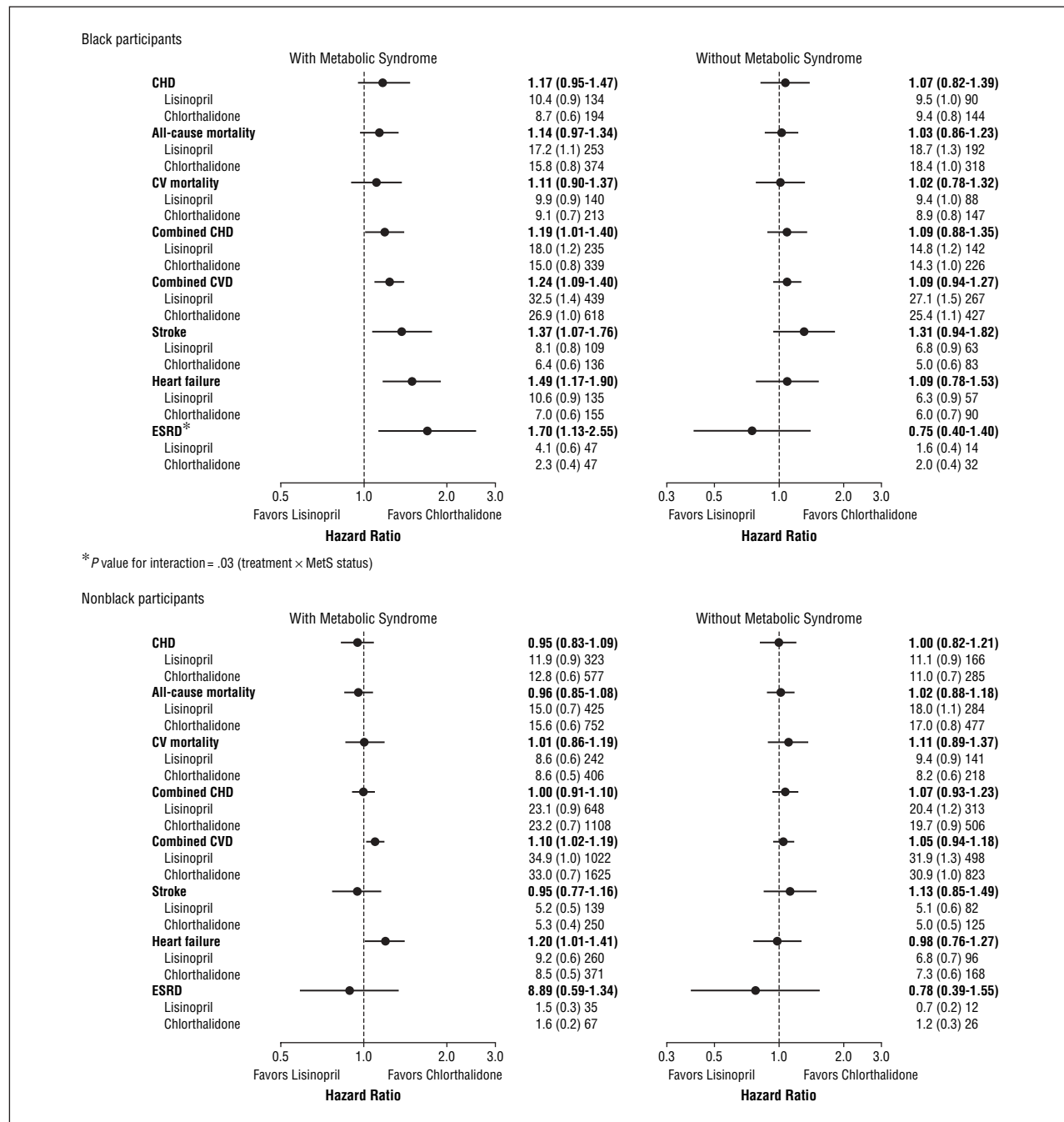


**Figure 2.** Comparisons of amlodipine besylate with chlorthalidone. Data are expressed as hazard ratios (95% confidence intervals) (with event rates [SEs] and numbers of events given for each drug) by race and metabolic/cardiometabolic syndrome (MetS) status. CHD indicates coronary heart disease; CV, cardiovascular; CVD, CV disease; and ESRD, end-stage renal disease.

the CCB, the ACE inhibitor, or the  $\alpha$ -blocker been shown thus far to be more effective than the thiazide-type diuretic in preventing the primary outcome (nonfatal myocardial infarction or CHD death) or any other major cardiovascular or renal outcome. We found a lower rate of stroke in nonblack participants with MetS assigned to amlodipine compared with those receiving chlorthalidone. However, this was not seen in black participants with MetS or in either subgroup without MetS, and did not translate into a lower rate of the composite CVD (presumably because of the excess heart failure). Given the num-

ber of comparisons and a statistical cutoff of  $P = .05$ , the finding is likely due to chance.

The lack of benefit of the agents with the most favorable metabolic profile (ie, ACE inhibitors and  $\alpha$ -blockers) was especially marked in the black participants with MetS. The magnitude of the excess risk of ESRD (70%), heart failure (49%), and stroke (37%) and the increased risk of combined CVD and combined CHD strongly argue against the preference of ACE inhibitors over diuretics as the initial therapy in black patients with MetS. Similar higher risk was noted for those random-



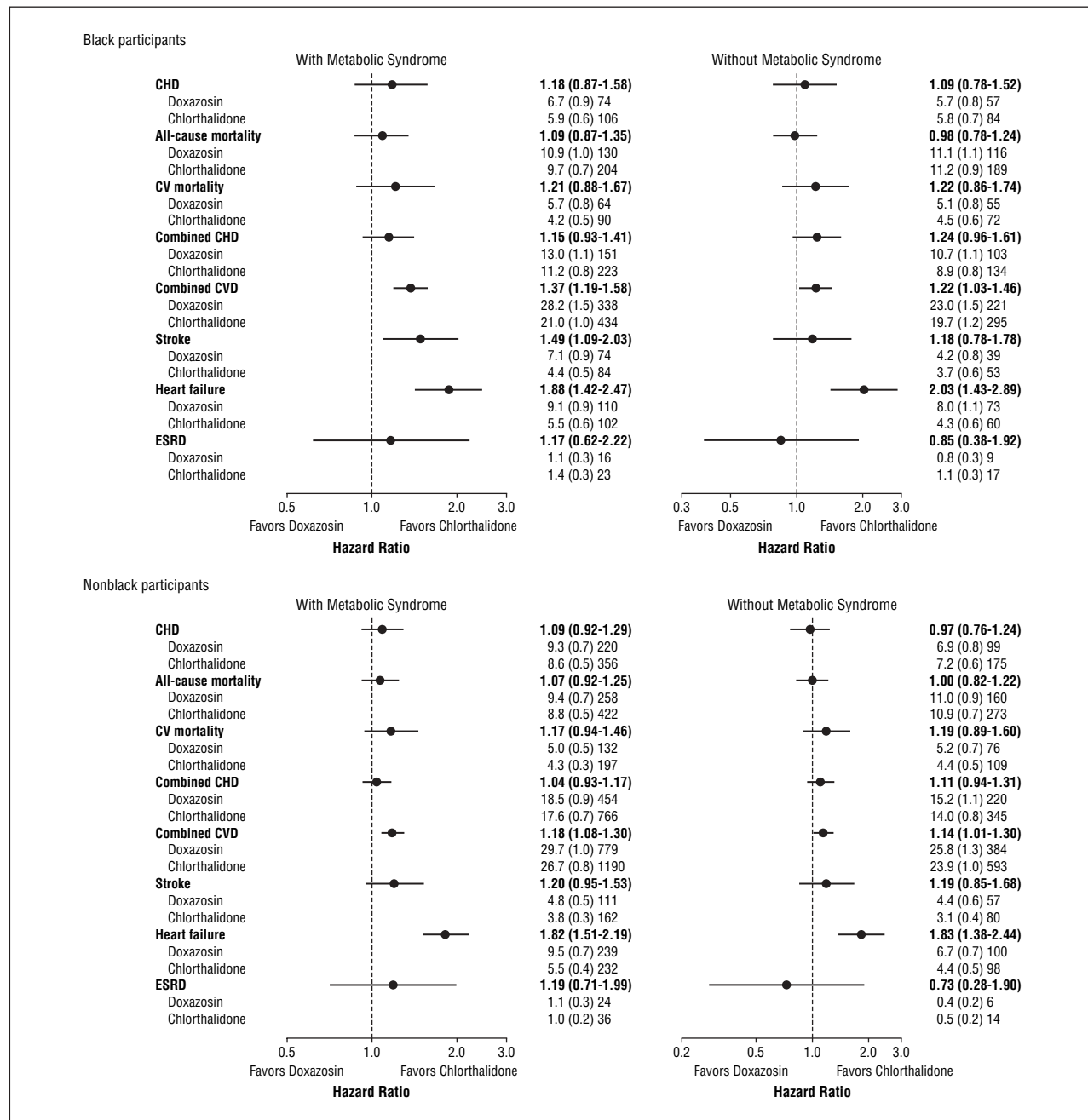
**Figure 3.** Comparisons of lisinopril with chlorthalidone. Data are expressed as hazard ratios (95% confidence intervals) (event rates [SEs] and numbers of events given for each drug) by race and metabolic/cardiomatabolic syndrome (MetS) status. CHD indicates coronary heart disease; CV, cardiovascular; CVD, CV disease; and ESRD, end-stage renal disease.

ized to the  $\alpha$ -blocker vs the diuretic. Although treatment-related differences in cardiovascular and renal outcomes in the lisinopril vs chlorthalidone comparison may in part be attributed to BP differences in black participants with MetS, no such attribution can explain the lack of superiority of amlodipine in either race subgroup or that of doxazosin or lisinopril in nonblack participants with MetS, because BP differences were minimal.

ALLHAT is not only the first large clinical outcome trial, to our knowledge, to report on the comparative effects of different classes of antihypertensive drugs on cardiovascular and renal outcomes in patients with MetS but, re-

markably, it is also powered to do so by race, given the large number of ALLHAT participants meeting the criteria for MetS. Its findings are consistent with published reports from other cohorts (including in diabetic patients) and meta-analyses.<sup>18-24</sup> This report complements the findings in nondiabetic ALLHAT participants with and without MetS.<sup>25</sup> In addition, it extends those findings to include the comparison of an  $\alpha$ -blocker and a diuretic, includes analyses by race, and includes diabetic patients in the definition to be consistent with most definitions of MetS.

The ALLHAT results seem to conflict with expectations. Some authors<sup>6,26,27</sup> have suggested that the fol-



**Figure 4.** Comparisons of doxazosin mesylate with chlorthalidone. Data are expressed as hazard ratios (95% confidence intervals) (with event rates [SEs] and numbers of events given for each drug) by race and metabolic/cardiometabolic syndrome (MetS) status. CHD indicates coronary heart disease; CV, cardiovascular; CVD, CV disease; and ESRD, end-stage renal disease.

low-up was too short for the metabolic effects to manifest themselves as clinical outcomes and may not generalize to younger patients, especially those with MetS. Although longer-term treatment effects will be evaluated in an extended morbidity and mortality follow-up of the ALLHAT participants using national databases, until these data are available, little from this or other studies predicts a future reversal of our findings. First, differences in metabolic changes, while statistically significant, are relatively small. The largest difference in mean fasting glucose levels was between the diuretic and the  $\alpha$ -blocker arms (up to 13 mg/dL [up to 0.7 mmol/L]). This approximates only a 0.16% lower glycosylated hemoglobin level<sup>28</sup> and a small

difference in diabetic outcomes.<sup>29</sup> Second, one would also have to assume that the drug-induced increases in glucose levels carry the same risk as a similar increase due to factors such as weight gain or sedentary lifestyle. Although definitive data are not yet available, analyses of a 14-year extended follow-up of participants in the Systolic Hypertension in the Elderly Program showed a significant increase in both cardiovascular and total mortality in participants assigned to placebo who developed diabetes mellitus during the double-blind phase of the trial.<sup>19</sup> However, no such increase was seen in those who developed diabetes in the chlorthalidone treatment arm (with atenolol added as needed for BP control). An ob-

servational study by Verdecchia et al<sup>30</sup> reported an increase in CVD event rates associated with new-onset diabetes in hypertensive patients, but the increase in CVD risk was not associated with diuretic therapy. Furthermore, neither the ALLHAT data nor meta-analyses involving more than 2800 CHD events, more than 5000 CVD events, and more than 230 000 patient-years (more if the  $\alpha$ -blockers were to be included) suggest even the slightest signal for a lower rate of cardiovascular events with the ACE inhibitors or the  $\alpha$ -blockers, which represent the agents with the most favorable metabolic effects, compared with calcium antagonists and diuretics/ $\beta$ -blockers. This was shown for individuals with and without diabetes.<sup>16,23,24</sup> In fact, we have recently reported not only a similar lack of association between the change in glucose levels and CVD outcomes from ALLHAT in those randomized to chlorthalidone but also significantly higher CVD and CHD event rates associated with elevations of glucose levels in those assigned to lisinopril.<sup>31</sup> Finally, the recently published DREAM trial (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) specifically designed to evaluate the effect of ACE inhibitor treatment in patients with impaired fasting glucose levels or impaired glucose tolerance reported no significant reduction in new-onset diabetes in participants randomized to ramipril compared with placebo.<sup>32</sup>

These findings fail to provide support for the selection of  $\alpha$ -blockers, ACE inhibitors, or CCBs over thiazide-type diuretics to prevent cardiovascular or renal outcomes in patients with MetS, despite their more favorable metabolic profiles.

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