Metabolic and Clinical Outcomes in Nondiabetic Individuals With the Metabolic Syndrome Assigned to Chlorthalidone, Amlodipine, or Lisinopril as Initial Treatment for Hypertension

A report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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OBJECTIVE — Optimal initial antihypertensive drug therapy in people with the metabolic syndrome is unknown.

RESEARCH DESIGN AND METHODS — We conducted a subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) to compare metabolic, cardiovascular, and renal outcomes in individuals assigned to initial hypertension treatment with a thiazide-like diuretic (chlorthalidone), a calcium channel blocker (CCB; amlodipine), or an ACE inhibitor (lisinopril) in nondiabetic individuals with or without metabolic syndrome.

RESULTS — In participants with metabolic syndrome, at 4 years of follow-up, the incidence of newly diagnosed diabetes (fasting glucose ≥126 mg/dl) was 17.1% for chlorthalidone, 16.0% for amlodipine ($P = 0.49$, chlorthalidone vs. amlodipine) and 12.6% for lisinopril ($P < 0.05$, lisinopril vs. chlorthalidone). For those without metabolic syndrome, the rate of newly diagnosed diabetes was 7.7% for chlorthalidone, 4.2% for amlodipine, and 4.7% for lisinopril ($P < 0.05$ for both comparisons). There were no differences in relative risks (RRs) for outcomes with amlodipine compared with chlorthalidone in those with metabolic syndrome; in those without metabolic syndrome, there was a higher risk for heart failure (RR 1.55 [95% CI 1.25–1.35]). In comparison with lisinopril, chlorthalidone was superior in those with metabolic syndrome with respect to heart failure (1.31 [1.04–1.64]) and combined cardiovascular disease (CVD) (1.19 [1.07–1.32]). No significant treatment group–metabolic syndrome interaction was noted.

CONCLUSIONS — Despite a less favorable metabolic profile, thiazide-like diuretic initial therapy for hypertension offers similar, and in some instances possibly superior, CVD outcomes in older hypertensive adults with metabolic syndrome, as compared with treatment with CCBs and ACE inhibitors.

Diabetes Care **31:353–360, 2008**

The metabolic syndrome is a clustering of clinical and biochemical characteristics related to insulin resistance (1). It is characterized by hypertension, central obesity, dyslipidemia (high triglycerides, low HDL cholesterol levels), and elevated glucose levels. This syndrome is most commonly found in older adults, in whom obesity and insulin resistance are at their highest prevalence. It is estimated that upwards of 40% of U.S. adults aged >60 years now have this disorder (2). To date, there is no consensus

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Received for publication 26 July 2007 and accepted in revised form 26 October 2007.

Published ahead of print at http://care.diabetesjournals.org on 13 November 2007. DOI: 10.2337/dc07-1452. Clinical trial reg. no. NCT00000542, clinicaltrials.gov.

Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/dc07-1452.

J.Bar. has received honoraria/consulting fees from Boehringer Ingelheim. J.Bas. has received honoraria/consulting fees from Astra-Zeneca, Novartis, Pfizer, and Sankyo. H.R.B. has received honoraria/consulting fees from Abbott Laboratories, Astra-Zeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daichi Sankyo, Forest Pharmaceuticals, Gilead (Myogen), GlaxoSmithKline, InterCure, Merck, Novartis, Pfizer, and sanofi aventis. B.D. has received honoraria/consulting fees from Biomarin, GlaxoSmithKline, Proctor and Gamble, and Takeda. C.N. is employed by Astra-Zeneca. U.T. holds stock in Bayer, has received financial support from Bristol-Myers Squib and Novartis, and has received honoraria/consulting fees from Pfizer and Sanofi Synthelabo. N.D.W. has received financial support from Merck and Pfizer and honoraria/consulting fees from Novartis, Pfizer, sanofi aventis, and Takeda. J.T.W. has received honoraria/consulting fees from GlaxoSmithKline, Novartis, Pfizer, and Sanofi Synthelabo and financial support from GlaxoSmithKline and Novartis.

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; MI, myocardial infarction; SBP, systolic blood pressure.

as to which class of antihypertensive medications, if any, is preferred for the treatment of hypertension in patients with the metabolic syndrome (3). Concerns have been raised that diuretics should not be used because they have unfavorable effects on insulin sensitivity and increase the risk of new-onset diabetes and adverse clinical outcomes (4–7). Calcium channel blockers (CCBs), which are metabolically neutral, and ACE inhibitors and angiotensin receptor blockers (ARBs), which improve insulin action (8–10), are considered by many to be the initial drugs of choice. Alternatively, the adverse metabolic effects of thiazide diuretics may have little clinical relevance, and it may be that blood pressure reduction is the most important factor in treating hypertension in all patients, regardless of whether they have metabolic syndrome (11).

We addressed these issues in a subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT was a multicenter randomized clinical trial designed to determine whether the occurrence of fatal coronary heart disease (CHD) or nonfatal myocardial infarction (MI) is lower in high-risk hypertensive patients whose antihypertensive treatment began with a CCB (amlodipine) or an ACE inhibitor (lisinopril) compared with a thiazide-like diuretic (chlorthalidone). Because many of the participants enrolled in ALLHAT met the criteria for the metabolic syndrome, we did a post hoc analysis to evaluate differences in risk of metabolic, cardiovascular disease (CVD), and renal outcomes in nondiabetic participants with or without metabolic syndrome, according to their initial antihypertensive medication assignment.

RESEARCH DESIGN AND METHODS

— The ALLHAT cohort consists of men and women aged ≥55 years who had stage 1 or stage 2 hypertension and at least one additional risk factor for CHD. Of the 42,418 ALLHAT participants, 33,357 were randomly assigned to therapy with chlorthalidone (n = 15,255), amlodipine (n = 9,048), or lisinopril (n = 9,054). A fourth arm of the study, which included 9,061 participants assigned to an α-blocker (doxazosin), was terminated early (12) and is not considered for these analyses. Details of the ALLHAT study design have been published (13).

For this analysis, metabolic syndrome at baseline was defined as the presence of hypertension, which all participants had at study entry, plus the presence of at least two of the following: BMI ≥30 kg/m^2, fasting glucose 100–125 mg/dl, fasting triglycerides ≥150 mg/dl, or HDL cholesterol <40 mg/dl in men and <50 mg/dl in women (1). BMI was chosen because ALLHAT did not collect data on waist circumference. Other studies of the metabolic syndrome have used this approach (14). We excluded participants with a history of diabetes (n = 12,063) and those with baseline fasting glucose levels ≥126 mg/dl (n = 1,105), although these are considered to be part of the metabolic syndrome by Adult Treatment Panel guidelines (3). Also excluded were 2,674 participants in whom the baseline metabolic syndrome status was undetermined. It was our intent to examine the study questions in those without diabetes at baseline because we felt that including those with known diabetes would largely reflect the findings we have already reported for the diabetic subgroup in ALLHAT (15).

Study medications were identically appearing chlorthalidone, lisinopril, or amlodipine capsules. Blood pressure lowering was achieved by titrating the dose of the blinded study drug and adding open-label step 2 (atenolol, clonidine, or reserpine) or step 3 (hydralazine) agents as necessary to obtain a blood pressure of <140/90 mmHg (13).

Follow-up visits were conducted at 1, 3, 6, 9, and 12 months and every 4 months thereafter. The primary outcome was a composite of fatal CHD or nonfatal MI. Four major prespecified secondary outcomes included all-cause mortality, fatal and nonfatal stroke, combined CHD (primary outcome, coronary revascularization, or hospitalized angina), and combined CVD (combined CHD, stroke, treated angina, heart failure [fatal, hospitalized, or treated nonhospitalized], or peripheral arterial disease). End-stage renal disease (dialysis, renal transplant, or kidney disease death) and individual components of the major outcomes, including heart failure, were also prespecified. Standardized procedures were used for reporting and validating study outcomes and have been published previously in detail (16). Although not prespecified, we also calculated changes in fasting glucose levels and the incidence of diabetes (fasting glucose ≥126 mg/dl) in the three treatment groups during follow-up. Glomerular filtration rate (GFR) was estimated using the simplified Modification of Diet in Renal Disease (MDRD) Study equation (17).

Data were summarized as means ± SD for continuous variables and number of subjects (percentage) for categorical variables. Baseline characteristics were compared in participants with and without metabolic syndrome 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 proportional hazards model was used to determine time-to-event hazard ratios (hereafter called relative risks [RRs]) and 95% CIs. Cox test assumptions were examined using log-log plots and tests of treatment-by-time (time-dependent) interaction terms. When the assumptions were violated, a two-by-two table was used to estimate RR. Heterogeneity of treatment effects across metabolic syndrome was examined by testing for treatment-covariate interaction using a P value <0.05. Given the many subgroup and interaction analyses performed, statistical significance at the $P < 0.05$ level should be interpreted with caution. All statistical analyses were carried out using STATA version 9.0.

RESULTS

— Baseline characteristics of the cohort, categorized by the presence and absence of metabolic syndrome, are shown in Table 1. Compared with those without metabolic syndrome, participants with metabolic syndrome were younger and were more likely to be white, female, and on antihypertensive treatment and to have prevalent CHD or prior coronary revascularization. They had slightly more years of education, lower systolic blood pressure (SBP), higher BMI, lower HDL cholesterol, and higher fasting glucose and triglyceride levels. They were less likely to smoke or to have electrocardiographic left ventricular hypertrophy. The mean duration of follow-up was 4.9 years (maximum 8.1 years). Losses to follow-up were minimal; 99% of expected person-years were observed (online appendix Fig. 1 [available at http://dx.doi.org/10.2337/dc07-1452]).

Blood pressure control

Among participants with metabolic syndrome, SBP at years 1–4 were higher for those on amlodipine than those on chlorthalidone by ~1–1.5 mmHg, a statistically significant difference only at year 1 (P = 0.007) (online appendix Fig. 2). Diastolic blood pressure (DBP) was 0.5-

Table 1—*Baseline characteristics of the ALLHAT antihypertensive component participants, excluding those with diabetes at baseline*

	Participants with metabolic syndrome	Participants without metabolic syndrome
Number randomized	8,013	9,502
Age*	66.0 ± 7.3	68.0 ± 8.1
<65 years	3,770 (47.1)	3,555 (37.4)
≥65 years	4,243 (52.9)	5,947 (62.6)
Black*	1,932 (24.1)	3,607 (38.0)
Women†	3,652 (45.6)	4,157 (43.7)
Years of education*	11.3 ± 3.9	11.0 ± 4.1
Antihypertensive treatment†	7,188 (89.7)	8,400 (88.4)
SBP (mmHg)*	145.6 ± 15.6	146.5 ± 15.8
DBP (mmHg)	84.7 ± 10.1	84.7 ± 9.9
Eligibility risk factors‡		
Cigarette smoker*	1,937 (24.2)	2,849 (30.0)
Atherosclerotic CVD§	4,898 (61.1)	5,942 (62.5)
History of MI or stroke	2,124 (26.5)	2,554 (26.9)
History of coronary revascularization*	1,291 (16.1)	1,267 (13.3)
Other ASCVD	2,339 (29.2)	2,801 (29.5)
ST-T wave	976 (12.2)	1,199 (12.6)
HDL cholesterol <35 mg/dl*	1,727 (21.5)	647 (6.8)
Left ventricular hypertrophy*	1,688 (21.1)	2,650 (27.9)
History of CHD at baseline†	2,451 (30.8)	2,691 (28.5)
n	7,955	9,435
BMI (kg/m²)*	31.5 ± 5.9	26.5 ± 4.7
Fasting glucose*	97.3 ± 12.1	89.4 ± 9.9
n	6,993	7,850
<100 mg/dl*	3,941 (56.4)	7,019 (89.4)
100–125 mg/dl*	3,052 (43.6)	831 (10.6)
Cardiovascular metabolic syndrome risk factors		
Fasting glucose ≥100 mg/dl*	3,052 (43.6)	831 (10.6)
n	6,993	7,850
BMI ≥30 kg/m²*	4,835 (60.4)	1,334 (14.1)
n	8,001	9,489
Fasting triglycerides ≥150 mg/dl*	5,349 (74.1)	1,074 (13.1)
n	7,214	8,168
Low HDL cholesterol*‖	6,348 (79.2)	1,266 (13.3)
n	8,012	9,502
High blood pressure	8,013 (100.0)	9,502 (100.0)
Lipid trial participants†	2,041 (25.5)	2,560 (26.9)

Data are means ± SD or *n* (%). *$P < 0.001$; †$P < 0.05$. ‡For trial eligibility, participants had to have at least one other risk factor in addition to hypertension. Thus, the indicated risk factors are not mutually exclusive or exhaustive and may not represent prevalence. §History of MI or stroke; history of coronary revascularization; major ST-segment depression on T-wave inversion on any electrocardiogram in the past 2 years; other ASCVD (history of angina pectoris; history of intermittent claudication, gangrene, or ischemic ulcers; history of transient ischemic attack; coronary, peripheral vascular, or carotid stenosis 50% or more documented by angiography or Doppler studies; ischemic heart disease documented by reversible or fixed ischemia on stress thalium or dipyridamole thalium, ST depression ≥1 mm for ≥1 min on exercise testing or Holter monitoring; reversible wall motion abnormality on stress echocardiogram; ankle-arm index <0.9; abdominal aortic aneurysm detected by ultrasonography, computed tomography scan, or X-ray; carotid or femoral bruits). ‖HDL <40 mg/dl in men, <50 in women.

to 0.9-mmHg lower at all annual visits in the group assigned to amlodipine. Participants assigned to lisinopril had 1.5- to 3-mmHg higher SBP than those assigned to chlorthalidone at all annual visits (statistically significant at year 1, $P < 0.001$; year 2, $P < 0.001$; and year 3, $P = 0.03$). DBP was nonstatistically significantly higher at years 1–3.

Among participants without metabolic syndrome, SBP was consistently higher among those assigned to amlodipine versus chlorthalidone (statistically significant except at year 2, $P = 0.44$). SBP was also higher among those assigned to lisinopril versus chlorthalidone ($P < 0.001$ for all years). DBP tended to be slightly higher among those assigned to lisinopril, and the differences were statistically significant at year 1 ($P = 0.001$) and year 2 ($P = 0.02$). DBP was slightly lower among those assigned to amlodipine versus chlorthalidone ($P < 0.02$ at all years except for year 2 [$P = 0.06$]).

Biochemical changes

At the end of 4 years, there were no statistically significant differences in total cholesterol between treatment groups among those with metabolic syndrome (Table 2). Among those without metabolic syndrome, total cholesterol levels were lower in the amlodipine (mean 194.7 mg/dl) and lisinopril (mean 195.8 mg/dl) groups compared with the chlorthalidone (mean 199.2 mg/dl) group ($P < 0.001$ and $P < 0.05$, respectively). For those with and those without metabolic syndrome, potassium levels were on average higher at both 2 and 4 years in the amlodipine and lisinopril groups than in the chlorthalidone group ($P < 0.001$). Fasting glucose levels rose in all three treatment groups during the trial. In those with metabolic syndrome, fasting glucose levels at year 2 were 3- to 7-mg/dl lower in the amlodipine and lisinopril groups than in the chlorthalidone group (by 2–3 mg/dl in those without metabolic syndrome). At year 4, those on lisinopril still had a lower fasting glucose than those on chlorthalidone. These findings translated into a diabetes incidence (fasting glucose ≥126 mg/dl) at 4 years of 17.1% in those assigned to chlorthalidone therapy who had metabolic syndrome and 16.0% for those assigned to amlodipine ($P = 0.49$). For those treated with lisinopril, the corresponding diabetes incidence was 12.6% ($P < 0.05$ vs. chlorthalidone). For those without metabolic syndrome, incident diabetes at year 4 of follow-up was lower in those treated with amlodipine (4.2%) and lisinopril (4.7%) than in those treated with chlorthalidone (7.7%, $P < 0.05$ for both comparisons). Estimated GFR was generally slightly lower for participants with metabolic syndrome than for those without metabolic syndrome. For participants with metabolic syndrome, estimated GFR was higher at 2 and 4 years among participants assigned to amlodipine compared with those assigned to chlorthalidone. Estimated GFR was similar at 2 and 4 years for participants assigned to lisinopril compared with those assigned to chlorthalidone. Treatment group comparisons were similar in those without metabolic syndrome.

Table 2—*Biochemical changes by treatment group and baseline metabolic syndrome, excluding those with diabetes at baseline*

	Baseline		2 Years		4 Years	
	With MetS	Without MetS	With MetS	Without MetS	With MetS	Without MetS
Cholesterol (mg/dl)						
Chlorthalidone	218.6 ± 43.2 (3,689)	214.9 ± 39.9 (4,357)	205.4 ± 40.7 (2,650)	206.6 ± 40.1 (3,033)	197.0 ± 41.0 (2,295)	199.2 ± 39.6 (2,535)
Amlodipine	220.8 ± 44.9 (2,112)	213.2 ± 40.7 (2,595)	204.5 ± 43.1 (1,507)	201.4 ± 40.2 (1,802)*	197.0 ± 40.9 (1,315)	194.7 ± 37.8 (1,525)*
Lisinopril	219.8 ± 42.5 (2,212)	212.9 ± 39.3 (2,550)†	204.6 ± 41.7 (1,467)	201.2 ± 40.2 (1,698)*	196.6 ± 38.5 (1,248)	195.8 ± 37.6 (1,381)†
Potassium (mmol/l)						
Chlorthalidone	4.3 ± 0.7 (3,689)	4.3 ± 0.7 (4,353)	4.0 ± 0.7 (2,566)	4.0 ± 0.7 (2,949)	4.1 ± 0.6 (2,246)	4.1 ± 0.8 (2,489)
Amlodipine	4.3 ± 0.7 (2,111)	4.3 ± 0.7 (2,594)	4.3 ± 0.6 (1,476)*	4.3 ± 0.7 (1,737)*	4.4 ± 0.7 (1,297)*	4.4 ± 0.8 (1,494)*
Lisinopril	4.3 ± 0.6 (2,210)	4.4 ± 0.7 (2,550)†	4.5 ± 0.7 (1,413)*	4.5 ± 0.6 (1,617)*	4.5 ± 0.7 (1,228)*	4.5 ± 0.6 (1,361)*
Fasting glucose (mg/dl)						
Chlorthalidone	97.4 ± 12.1 (3,185)	89.3 ± 9.9 (3,587)	108.1 ± 31.4 (1,664)	96.5 ± 21.0 (1,812)	110.3 ± 32.9 (1,404)	100.2 ± 24.5 (1,541)
Amlodipine	97.2 ± 11.9 (1,849)	89.3 ± 9.7 (2,113)	104.9 ± 28.8 (928)†	94.3 ± 16.4 (1,096)†	110.0 ± 34.0 (833)	96.7 ± 17.8 (918)*
Lisinopril	97.5 ± 12.4 (1,959)	89.5 ± 9.9 (2,150)	101.5 ± 22.7 (906)*	93.7 ± 18.0 (1,027)*	105.7 ± 26.0 (779)*	96.2 ± 17.4 (832)*
Fasting glucose ≥126 mg/dl (%)						
Chlorthalidone	0.0	0.0	14.8	4.6	17.1	7.7
Amlodipine	0.0	0.0	12.9†	3.6	16.0	4.2†
Lisinopril	0.0	0.0	9.9*	2.7†	12.6†	4.7†
Estimated GFR (ml/min per 1.73 m^2)‡						
Chlorthalidone	74.4 ± 17.3 (3,689)	77.0 ± 18.7 (4,353)	71.9 ± 17.8 (2,566)	72.9 ± 19.0 (2,949)	69.2 ± 18.3 (2,246)	70.7 ± 18.8 (2,489)
Amlodipine	75.2 ± 17.8 (2,111)	77.2 ± 18.1 (2,594)	75.9 ± 18.4 (1,476)*	77.5 ± 19.1 (1,737)*	74.0 ± 19.5 (1,298)*	75.0 ± 19.2 (1,495)*
Lisinopril	75.1 ± 18.1 (2,210)	76.8 ± 18.6 (2,550)	72.1 ± 18.2 (1,413)	73.8 ± 19.4 (1,617)	69.8 ± 18.5 (1,230)	71.1 ± 18.8 (1,361)

Data are means ± SD (*n*) unless otherwise indicated. *$P < 0.001$ compared with chlorthalidone; †$P < 0.05$ compared with chlorthalidone. ‡Simplified four-variable MDRD study formula (ref. 17). MetS, metabolic syndrome.

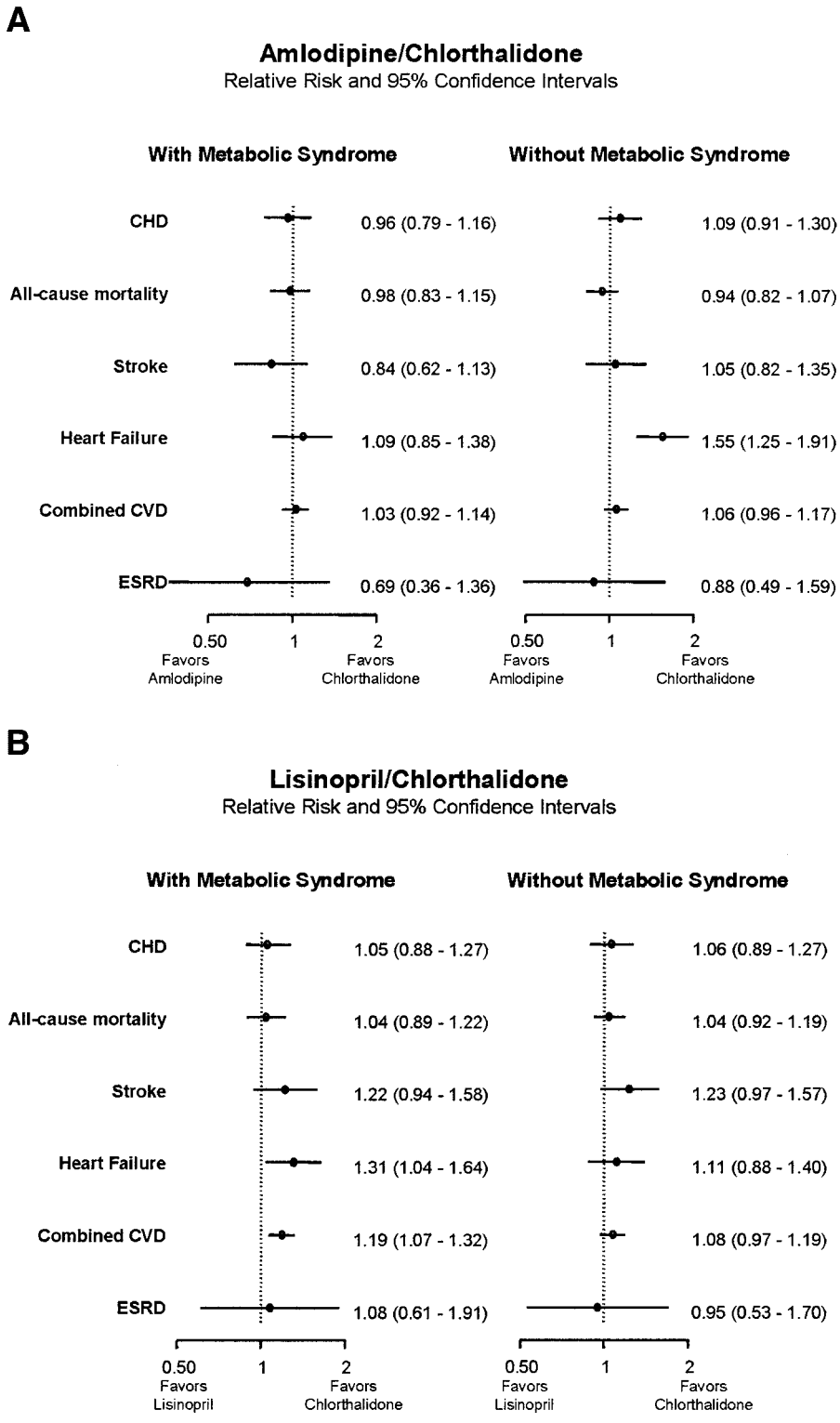

Figure 1—*RRs and 95% CIs for amlodipine/chlorthalidone* (A) *and lisinopril/chlorthalidone* (B) *comparisons in participants with and without metabolic syndrome (excluding those with diabetes at baseline).*

CVD and renal end points by treatment group

Figure 1 shows the unadjusted RRs for each end point comparing the amlodipine to the chlorthalidone group and the lisinopril to the chlorthalidone group for those with and without the metabolic syndrome separately.

In participants with metabolic syndrome, there were no significant differences in the primary end point (CHD [nonfatal MI or CHD death]) for either amlodipine versus chlorthalidone (RR 0.96 [95% CI 0.79–1.16]) or lisinopril versus chlorthalidone (1.05 [0.88–1.27]). These results were similar to those for participants without metabolic syndrome (*P* for interaction, NS). The 6-year

CHD rates (per 100) for those in the chlorthalidone, amlodipine, and lisinopril groups among those with metabolic syndrome were 9.6, 8.8., and 10.5, and among those without metabolic syndrome were 9.0, 9.6, and 9.6, respectively. For the amlodipine versus chlorthalidone comparison, there were no treatment group differences in the secondary end points of combined CVD, all-cause mortality, stroke, or end-stage renal disease, and the results were similar in those with and without metabolic syndrome (*P* for interaction, NS). In those without the metabolic syndrome, amlodipine versus chlorthalidone treatment was associated with significantly more heart failure (1.55 [1.25–1.91]), whereas for those with metabolic syndrome there was no difference (1.09 [0.85–1.38]) (*P* for interaction = 0.03). Those with the metabolic syndrome assigned to lisinopril compared with chlorthalidone were significantly more likely to experience heart failure (1.31 [1.04–1.64]) and combined CVD (1.19 [1.07–1.32]). These results were not statistically different for those without metabolic syndrome (*P* for interaction, NS).

Within each treatment group (chlorthalidone, lisinopril, or amlodipine) there were no statistically significant differences in combined CVD between those who developed incident diabetes versus those who did not in those with and without metabolic syndrome (online appendix Fig. 3). However, there appeared to be a greater separation between those with and without incident diabetes in the amlodipine and lisinopril groups versus those in the chlorthalidone group.

CONCLUSIONS — In this study of nondiabetic hypertensive adults with and without the metabolic syndrome, we found that CHD, all-cause mortality, stroke, and renal outcome rates did not differ significantly between those whose initial treatment was a thiazide-type diuretic compared with those treated first with a CCB or an ACE inhibitor. However, in participants with metabolic syndrome, those treated with a diuretic had a lower risk of heart failure and combined CVD than those treated with an ACE inhibitor. There were no differences in outcomes between diuretic and CCB therapy in those with metabolic syndrome, but participants without metabolic syndrome had a higher risk of heart failure with CCB therapy. These results are consistent with the overall results of ALLHAT (16), as well as those of the diabetic subgroup of ALLHAT participants (15), suggesting that diuretics are the preferred initial treatment for hypertension in older individuals with the metabolic syndrome compared with ACE inhibitors and CCBs, despite the higher incidence of new diabetes for the chlorthalidone group.

Even without clinical outcome data, several reviews suggest that drugs that block the renin-angiotensin-aldosterone system (ACE inhibitors/ARBs) should be the treatment of choice for hypertension in those with metabolic syndrome (5,18–23). The basis for these recommendations is that the metabolic syndrome is characterized by obesity and insulin resistance, conditions associated with increased inflammatory markers, endothelial dysfunction, and elevated levels of angiotensin. ACE inhibitors/ARBs, which improve endothelial dysfunction (24), block the metabolic effects of angiotensin (25), lower the levels of several inflammatory markers (26), and improve insulin sensitivity, should therefore have theoretical advantages in these patients. Our results show that despite these theoretical considerations, ACE inhibitors provided no advantage over thiazide-type diuretics in prevention of cardiovascular outcomes. These results are consistent with those of the Blood Pressure Lowering Treatment Trialists' Collaboration, which reported no significant differences in CHD, stroke, or CHF outcomes between ACE inhibitor therapy and diuretic therapy (with or without β-blockers) in hypertensive adults with or without diabetes (27). Likewise, the recently reported Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study showed no benefit of ACE inhibitor therapy over placebo for preventing glucose metabolic disturbances (28).

Many researchers believe that it is the degree of blood pressure reduction achieved that is the primary determinant of clinical outcomes, not which drug is used to attain the reduction (11). Because the blood pressure differences between treatment groups for those with and without the metabolic syndrome were not greater than those observed over all in ALLHAT, we feel that any differences in benefit attributable to blood pressure reduction is likely to apply equally to both subgroups.

In all treatment groups, with or without metabolic syndrome, fasting glucose levels increased during the trial. Those with metabolic syndrome treated with chlorthalidone had higher FG levels at 2 years than those treated with amlodipine or lisinopril. By Year 4, however, there was no difference between those treated with amlodipine and those treated with chlorthalidone, while those treated with lisinopril had ~4-mg/dl lower values. In spite of this unfavorable biochemical finding, the change in fasting glucose levels did not adversely impact CVD outcomes, a finding similar to what we found in the nondiabetic cohort of ALLHAT (15). The possibility has been raised that had ALLHAT been extended to 10 or 15 years of follow-up, the negative effect of elevated fasting glucose levels and the dyslipidemia associated with diuretic use would have become evident (29). The recent report from the 14-year follow-up of the Systolic Hypertension in the Elderly Program (SHEP) does not support this argument (30). Glucose elevation observed during chlorthalidone therapy in that study was minimal. In participants assigned to chlorthalidone who developed diabetes, the risk of CVD mortality was similar to that in those who did not develop diabetes (HR 1.04 [95% CI 0.75–1.46]), whereas in participants assigned to placebo who developed diabetes, the CVD mortality risk was higher than in those who did not develop diabetes (1.56 [1.12–2.18]).

The current study has important strengths. Compared with other hypertension trials, ALLHAT is the largest and provides much greater statistical power to recognize associations and differences. Considerable attention was paid to quality assurance. All laboratory tests were done in a certified central laboratory. The study was conducted in a variety of practice environments (academic, HMO, private practice, and Veterans Administration clinics), reflective of medical practice across the U.S. The cohort for this analysis was created so as to exclude people with diabetes, thereby excluding the confounding effects of elevated glucose levels on clinical outcomes. There are, of course, limitations. Our analyses are post hoc, since the metabolic syndrome was not a predesignated subgroup analysis. Because entry into ALLHAT required the presence of hypertension and one other CVD risk factor, participants not having an eligibility risk factor that is a metabolic syndrome component (low HDL) were inevitably more likely to have other eligibility risk factors (e.g., left ventricular hypertrophy or smoking). This may explain

why the rates of some of the end points were lower in participants with the metabolic syndrome than in those without it, something we would not have expected. Because of its large simple trial design, several factors that are part of the definition of metabolic syndrome or segregate with the metabolic syndrome, such as inflammatory factors, waist circumference, and urinary albumin, were not recorded in ALLHAT. Last, there is lack of uniformity and consensus on the definition of the metabolic syndrome, making it difficult to directly compare our results to those of other studies using different definitions.

In conclusion, thiazide-like diuretic initial therapy for hypertension offers similar and in some instances possibly superior CVD and renal outcomes in older hypertensive adults with metabolic syndrome, compared with treatment with CCBs and ACE inhibitors. This was true in spite of the mildly increased fasting glucose levels and higher level of incident diabetes in those treated with the thiazide-like diuretics compared with the other two medications. These findings are consistent with those in the overall ALLHAT cohort and in the subgroup with diabetes, as previously reported (15,16).

Acknowledgments— This study was supported by contract N01-HC-35130 from the National Heart, Lung, and Blood Institute. The Institute's role included involvement in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. The ALLHAT investigators acknowledge contributions of study medications supplied by Pfizer, Inc. (amlodipine and doxazosin), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin) and financial support provided by Pfizer, Inc.

B.D., C.B., and S.P. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

These data were presented in part at the Consortium for Southeastern Blood Pressure Control (Coral Gables, FL, 2003, and Nashville, TN, 2005), the American Heart Association (New Orleans, LA, 2004), the European Society of Hypertension (Milan, Italy, 2005), and the American Osteopathic Association (Orlando, FL, 2005).

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