Diuretic Versus α-Blocker as First-Step Antihypertensive Therapy

Final Results From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group

Abstract—The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, double-blind, active, controlled clinical trial conducted to determine whether newer antihypertensive agents, including doxazosin, an α-blocker, differ from chlorthalidone, a diuretic, with respect to coronary heart disease (CHD) and other cardiovascular disease (CVD) events in hypertensive patients at high risk of CHD. In February 2000, the doxazosin treatment arm was discontinued, and findings through December 1999 were reported. This report includes an additional 9232 participant-years and 939 CVD events. At 623 clinical centers, patients (aged ≥55 years) with hypertension and at least 1 other CHD risk factor were randomly assigned to either chlorthalidone or doxazosin. The primary outcome measure was the combined occurrence of fatal CHD or nonfatal myocardial infarction (MI), analyzed by intent to treat; prespecified secondary outcome measures included all-cause mortality, stroke, combined CHD (fatal CHD, nonfatal MI, hospitalized angina, and coronary revascularization), and combined CVD (combined CHD, stroke, angina treated outside the hospital, heart failure, and peripheral arterial disease). Mean follow-up was 3.2 years. There was no difference in primary outcome between the arms (relative risk [RR], 1.02; 95% confidence interval [CI], 0.92 to 1.15). All-cause mortality also did not differ (RR, 1.03; 95% CI, 0.94 to 1.13). However, the doxazosin arm compared with the chlorthalidone arm had a higher risk of stroke (RR, 1.26; 95% CI, 1.10 to 1.46) and combined CVD (RR 1.20; 95% CI, 1.13 to 1.27). These findings confirm the superiority of diuretic-based over α-blocker–based antihypertensive treatment for the prevention of CVD. **(*Hypertension*. 2003;42:239-246.)**

Key Words: hypertension, detection and control ■ antihypertensive therapy ■ clinical trials ■ diuretics ■ adrenergic receptor blockers

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is the largest double-blind, antihypertensive trial designed to determine whether a newer agent is superior to standard therapy in reducing coronary events. Because of their favorable effects on several surrogate end points (eg, cholesterol and glucose), an α-blocker, doxazosin, was 1 of 3 newer agents selected for comparison with a diuretic (chlorthalidone).[1] An angiotensin-converting enzyme inhibitor (lisinopril) and a calcium channel blocker (amlodipine) were also tested in the 42 418 ALLHAT hypertensive participants. In February 2000, the doxazosin component of the study was terminated because of a 25% greater incidence of combined cardiovascular disease (CVD) events compared with the chlorthalidone arm. Termination based on a secondary end point was justified because there was no significant difference in either the primary end point (fatal coronary heart disease [CHD] and nonfatal myocardial infarction [MI]) or in all-cause mortality, and it was highly unlikely that such differences would appear. Rapid analysis and prompt presentation of the first findings of ALLHAT were deemed appropriate in view of their public health and clinical significance.[2] Unavoidably, the original report was based on incomplete outcome data. We now present the final data, which complement the final results for the other 2 comparisons recently published.[3] In particular, we provide more information about the validity and interpretation of the central finding of a 2-fold increase in heart failure (HF) in participants randomized to doxazosin. The present report includes additional end-point data and further subgroup analyses of particular relevance to the HF experience and stroke, as well as the first presentation of information on renal function and global measures of quality of life.

Methods

Study Participants

The rationale and design of ALLHAT have been presented in detail elsewhere.[1,3] Recruitment was designed to generate a sample reflecting patients actually seen in the kind of practice settings where most care is provided.[4] Men and women ≥55 years of age with systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure

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(DBP) ≥90 mm Hg or on medications for hypertension and an additional risk factor for CHD were eligible to participate in ALLHAT. The risk factors could include previous MI or stroke, left ventricular hypertrophy by electrocardiogram or echocardiogram, previously diagnosed type 2 diabetes, current cigarette smoking, low HDL cholesterol level, or certain other manifestations of CVD.[3,5] Patients with HF or known low ejection fraction were excluded. There were 15 255 participants randomized to chlorthalidone and 9061 participants randomized to doxazosin from February 1994 to January 1998 in 623 centers in the United States, Canada, Puerto Rico, and the US Virgin Islands. All participants signed an informed consent form, and all centers received Institutional Review Board approval.

Treatment

Randomization was stratified by center and blocked over time to maintain the ratio of 1.7:1. The BP treatment goal was SBP/DBP <140/90 mm Hg. Dosages for doxazosin were 2, 4, or 8 mg/d and for chlorthalidone were 12.5, 12.5 (sham titration), or 25 mg/d. Blinded 1 mg and 12.5 mg does of doxazosin and chlorthalidone, respectively, were used during the first week to minimize postural hypotension associated with doxazosin. Participants meeting the BP goal at maximal tolerated doses of these agents could receive open-label drugs, including study-provided atenolol, reserpine, clonidine, and/or hydralazine. However, use of open-label medications from 1 of the masked classes of drugs was to be avoided unless SBP was >160 mm Hg and/or DBP was >100 mm Hg after maximum tolerated titration of drugs from each of the 3 steps or a compelling indication, such as HF, arose. Open-label drugs of the same classes as study agents could be added to half-maximal dose; these were not supplied by the study. Detection of a serum potassium value <3.5 mmol/L required addition of potassium supplements. After initial monthly titration visits, protocol visits were prescribed every 3 months for the first year and every 4 months thereafter.

Outcomes

The primary outcome was the combined incidence of fatal CHD or nonfatal MI. The prespecified secondary end points included all-cause mortality, combined CHD (fatal CHD, nonfatal MI, hospitalized angina, and coronary revascularization procedures), stroke, and combined CVD. The outcomes added here (696 combined CHD, 939 combined CVD, and 662 deaths) occurred before February 15, 2000, but for which complete information was not available for inclusion in the preliminary report. Details of event ascertainment have been reported elsewhere.[1,3] In brief, study clinical outcomes were based on clinic investigator reports, combined with the collection of death certificates and hospital discharge summaries. This report also presents data on end-stage renal disease and quality-of-life outcomes. Quality of life was ascertained at baseline and every 2 years by asking the participant "In general, would you say your health is excellent, very good, good, fair, or poor?" and by requesting that the participant rate his/her health on a 0 to 100 scale.

Statistical Analysis

Data were analyzed according to participants' treatment assignments. Comparability of baseline characteristics and outcomes were assessed by χ^2 tests for categorical variables and standard normal (z) tests for continuous variables. Cumulative event rates were calculated by the Kaplan-Meier procedure. Although rates are presented only through 4 years, both the log-rank test and the Cox proportional-hazards (PH) model incorporated the participant's entire trial experience to evaluate differences between cumulative event curves and to obtain 2-sided probability values. Only the PH results are presented, because probability values were essentially identical. Hazard ratios (hereafter called relative risks, RRs) and 95% confidence intervals (CIs) were obtained from the PH model.[6] For the primary end point, given the expected event rate, treatment crossovers, and losses to follow-up, ALLHAT had an 83% power to detect a 16% reduction between chlorthalidone and doxazosin at a 2-sided $\alpha=0.0178$ ($z=2.37$) to account for the 3 original comparisons

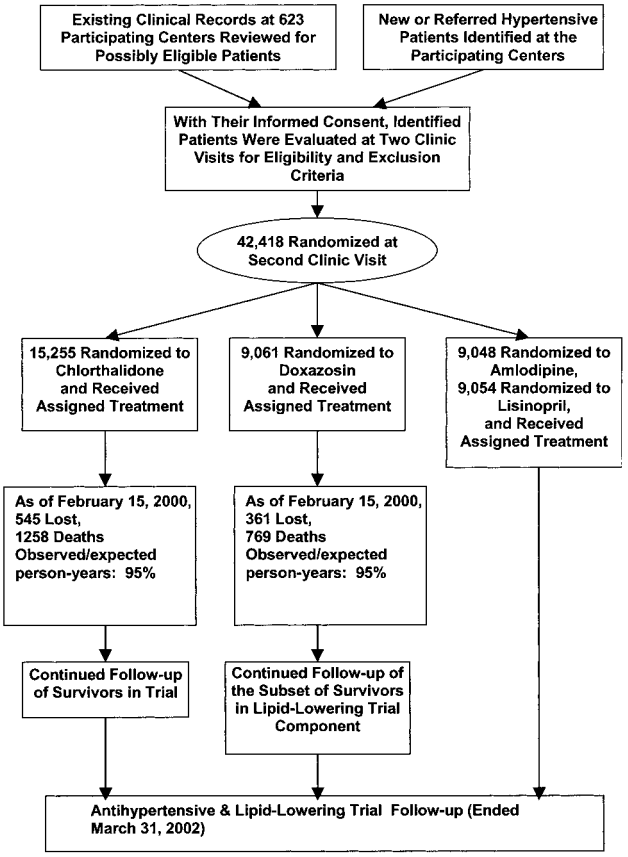

Figure 1. ALLHAT profile.

(equivalent to a 98.2% CI).[7] A 95% CI may be converted to a 98.2% CI by multiplying the upper limit and dividing the lower limit by $RR^{(0.41/z)}$, where z is the value of the test statistic for the RR estimate. The PH assumption was examined by using log-log plots and testing a treatment-by-time (time-dependent) interaction term; if it was violated, RR estimates from a 2×2 table were used.[6] Subgroups were examined by testing for treatment-covariate interaction with the PH model at a value of $P<0.05$.

Results

Participant Characteristics

Of the 24 316 participants, at the end of follow-up there were 481 (3.2%) lost to follow-up in the chlorthalidone group and 447 (4.9%) in the doxazosin group (Figure 1). By February 15, 2000, 9232 years of additional follow-up were included in this analysis compared with the original report.[2] Person-years of observation were 95% of those expected and were similar in both arms of the trial. Table 1 demonstrates the similarity of the chlorthalidone and doxazosin groups at baseline, both of which comprised an almost equal percentage of women and men, more than one third blacks, and 16% Hispanics. Mean age was 67 years, and mean BP at baseline was 146/84 mm Hg. Of note was the finding that nearly 90% of the study participants had received antihypertensive therapy before randomization.

Medication Adherence and Course in Treatment

Of those who attended a study visit (4836/6059, or 80%) at 4 years of follow-up, 78% of the chlorthalidone group and 71%

TABLE 1. Baseline Characteristics of ALLHAT Antihypertensive Component Participants: Chlorthalidone vs Doxazosin

Characteristic	Chlorthalidone	Doxazosin	*P*
No. randomized	15 255	9061	
Age, mean (SD), y	66.9 (7.7)	66.8 (7.7)	0.27
55–59, n (%)	2873 (18.9)	1720 (19.0)	0.18
60–69, n (%)	6954 (45.6)	4229 (46.8)	
70–79, n (%)	4410 (28.9)	2501 (27.7)	
80+, n (%)	1000 (6.6)	591 (6.5)	
Race/ethnicity			
White, non-Hispanic, n (%)	7202 (47.2)	4209 (46.5)	0.32
Black, non-Hispanic, n (%)	4871 (31.9)	2984 (32.9)	
White Hispanic, n (%)	1913 (12.5)	1138 (12.6)	
Black Hispanic, n (%)	498 (3.3)	308 (3.4)	
Other, n (%)	771 (5.1)	421 (4.6)	
Women, n (%)	7171 (47.0)	4203 (46.4)	0.35
Education, mean (SD), y	11.0 (4.0)	11.0 (4.0)	0.77
Smoking status			
Current smoker, n (%)	3342 (21.9)	1966 (21.7)	0.63
Past smoker, n (%)	6180 (40.5)	3634 (40.1)	
Never smoked cigarettes, n (%)	5733 (37.6)	3461 (38.2)	
Antihypertensive treatment			
Treated, n (%)	13 754 (90.2)	8175 (90.2)	0.89
Untreated, n (%)	1500 (9.8)	886 (9.8)	
Eligibility risk factors*			
Atherosclerotic cardiovascular disease, n (%)†	6991 (45.8)	4158 (45.9)	0.93
ST-T wave abnormality, n (%)	1572 (10.4)	920 (10.2)	0.70
Type 2 diabetes, n (%)	5529 (36.2)	3220 (35.5)	0.27
HDL cholesterol <35 mg/dL, n (%)	1801 (11.8)	1048 (11.6)	0.57
LVH by ECG within 2 years, n (%)	2464 (16.2)	1478 (16.3)	0.74
LVH by echocardiogram, n (%)	695 (4.6)	405 (4.5)	0.75
BP, mean (SD), mm Hg	146 (16)/84(10)	146 (16)/84(10)	0.73/0.47
Serum potassium, mean (SD), mmol/L	4.3 (0.7)	4.4 (0.7)	0.07
Fasting serum glucose, mean (SD), mg/dL	123.4 (58.3)	122.4 (56.2)	0.25
Serum creatinine, mean (SD), mg/dL	1.0 (0.3)	1.0 (0.3)	0.25
Total cholesterol, mean (SD), mg/dL	216.1 (43.8)	215.0 (42.4)	0.08
LDL cholesterol, mean (SD), mg/dL	135.8 (37.4)	135.5 (36.4)	0.49
HDL cholesterol, mean (SD), mg/dL	46.8 (14.8)	46.6 (14.4)	0.39
Fasting triglycerides, mean (SD), mg/dL	172.8 (131.2)	169.9 (135.2)	0.15

LVH indicates left ventricular hypertrophy; ECG, electrocardiogram.

*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 might not represent prevalence.

†History of MI or stroke; history of coronary revascularization; 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 thallium or dipyridamole thallium testing, ST depression ≥1 mm for ≥1 minute on exercise testing or Holter monitoring; reversible wall motion abnormality on stress echocardiogram; ankle-arm index <0.9; abdominal aortic aneurysm detected by ultrasonography, CT scan, or x-ray; carotid or femoral bruits).

of the doxazosin group had remained on their assigned treatment. Most of that difference occurred by the end of the first year. A detailed description of drug therapy has been reported.[8] Exclusive use of assigned medication observed at the 4-year follow-up visit was 34% for chlorthalidone and 23% for doxazosin, whereas dual medication use was 35% for chlorthalidone and 37% for doxazosin (≈17% to 18% of the chlorthalidone group and 18% of the doxazosin group were on atenolol). Conversely, 23% of the doxazosin participants were prescribed a diuretic, and 4% of chlorthalidone participants were prescribed an α-blocker. About 19% of those in the chlorthalidone group were prescribed 3 or more medica-

TABLE 2. Number of Subjects, Mean BP, Percent at Goal, and BP Difference at Baseline and Annual Visits

	Baseline	12 Months	24 Months	36 Months	48 Months
Chlorthalidone					
n	15 255	12 829	11 690	8052	4224
SBP/DBP, mm Hg	146.2/84.0	136.9/79.3	135.9/78.3	135.5/77.3	135.3/76.5
% at <140/90 mm Hg	27.2	57.8	61.0	62.0	62.6
Doxazosin					
n	9061	7513	6725	4570	2424
SBP/DBP, mm Hg	146.3/83.9	140.1/79.5	138.2/78.4	137.6/76.9	137.4/76.6
% at <140/90 mm Hg	27.3	50.4	54.8	56.8	57.6
SBP/DBP Δ, mm Hg (compared with chlorthalidone group)	0.1/−0.1	3.2/0.2	2.3/0.1	2.1/−0.4	2.1/0.1

tions to lower their BP, compared with 27% of participants in the doxazosin group. In both groups, unspecified refusals were the most common reason (more than one third) for discontinuing the blinded study medication.

Intermediate Outcomes

Mean BP at randomization was 146/84 mm Hg for both groups, and after the first year, it was 137/79 mm Hg for the chlorthalidone group and 140/80 mm Hg for the doxazosin group (Table 2). Starting at 24 months, the systolic difference narrowed to 2 mm Hg, with concomitant narrowing of differences in the percentage at goal. Nevertheless, more chlorthalidone than doxazosin subjects were at goal pressure at their 4-year follow-up visit (63% vs 58%).

Serum cholesterol, initially 216 mg/dL for the chlorthalidone group and 215 mg/dL for the doxazosin group, fell to 197 and 187 mg/dL, respectively, at 4 years ($P<0.001$). About 25% of each group had participated in the lipid-lowering trial. Serum potassium, initially 4.3 mmol/L in the chlorthalidone group and 4.4 mmol/L in the doxazosin group, was 4.1 and 4.4 mmol/L at 4 years, respectively ($P<0.001$). Fasting serum glucose, initially 123 mg/dL in the chlorthalidone group and 122 mg/dL in the doxazosin group, was 125 and 117 mg/dL, respectively, at the fourth-year visit ($P<0.001$).

Baseline serum creatinine was 1.0 mg/dL in the 2 groups. After 4 years of follow-up, creatinine level rose to 1.2 mg/dL in the chlorthalidone group and to 1.1 mg/dL in the doxazosin group ($P<0.001$). Serum creatinine doubled during treatment in 0.8% of the chlorthalidone and in 0.5% of the doxazosin participants ($P=0.02$).

Responses to the question about general health status were similar between the chlorthalidone and doxazosin groups at baseline and at years 2 and 4. About 75% reported excellent, very good, or good health status both at baseline and subsequently. Responses to the question about health status as a continuous value (with 100 being "perfect health") at baseline were 73.9 in both groups, and at year 4, 73.5 and 73.1 for the chlorthalidone and doxazosin groups, respectively.

Primary and Secondary End Points

Table 3 and Figure 2 include 431 and 265 additional combined CHD events, 584 and 355 additional combined CVD events, and 407 and 255 more deaths from all causes than previously reported for the chlorthalidone and doxazosin groups, respectively. There were also 126 and 93 additional HF cases in the chlorthalidone and doxazosin groups, respectively. Altogether, 98.4% (4020/4085) and 98.8% (2670/2703) of the events were confirmed by appropriate documentation (hospital record and/or death certificate).

There was no significant difference between the chlorthalidone and doxazosin groups for the primary CHD end point of combined nonfatal MI and CHD death (Figure 2a), all-cause mortality (Figure 2b), or combined CHD (Figure 2c). Highly significant ($P<0.001$) increases in combined CVD (Figure 2d), HF (Figure 2e), and stroke events (Figure 2f) were experienced by participants randomized to doxazosin compared with the chlorthalidone group. Specifically, participants randomized to doxazosin experienced a 26% higher risk of stroke, an 80% higher risk of HF, a 12% higher risk of coronary revascularization, and a 13% higher risk of hospitalized or treated angina. Thus, the combined CVD risk was 20% higher (4-year rates of 28.6 vs 25.1/100) among participants randomized to doxazosin compared with chlorthalidone. About half of the 20% was accounted for by the increased risk of HF. With a more restrictive outcome measure for HF (only hospitalized or fatal cases; Table 3), the RR for doxazosin compared with chlorthalidone was 1.66 (95% CI, 1.46 to 1.89).

To elucidate the nature of the PH assumption for the HF outcomes analyses, we used a 2-time-interval (baseline to year 1 and year 1 to end of study) analysis wherein RRs were constant within each interval.[6] For all HF, participants assigned to doxazosin compared with those assigned to chlorthalidone had a 259% increased risk during year 1, which diminished to a 36% increased risk thereafter; for hospitalized/fatal HF, there was a 222% increased risk during year 1 and a 30% increased risk thereafter. These increased risks were statistically significant in both intervals.

The HF findings were generally reflected in all predefined subgroups, including black and nonblack participants, men and women, diabetic and nondiabetic persons, those older and younger than 65, and in post hoc defined groups, including antihypertensive drug treatment status at entry and prior CHD. (Figure 3 displays similarity across subgroups for combined CVD and HF). In subjects who had or had not been

TABLE 3. Outcomes in the BP Component of ALLHAT by Treatment Group as of February 15, 2000

Outcomes	Total No. of Patients With Outcomes		4-Year Rate Per 100 (SE)		RR (D/C), 95% CI	z Score	P*
	Chlorthalidone Group	Doxazosin Group	Chlorthalidone Group (n=15 255)	Doxazosin Group (n=9061)			
CHD (nonfatal MI+fatal CHD)	818	499	7.76 (0.30)	7.91 (0.39)	1.03 (0.92–1.15)	0.49	0.62
All-cause mortality	1258	769	10.51 (0.32)	11.04 (0.43)	1.03 (0.94–1.13)	0.68	0.50
Cardiovascular	551	377	4.74 (0.22)	5.60 (0.32)	1.15 (1.01–1.32)	2.15	0.03
MI	184	105	1.65 (0.13)	1.76 (0.19)	0.96 (0.76–1.22)	−0.32	0.75
Definite CHD	57	39	0.54 (0.08)	0.54 (0.10)	1.16 (0.77–1.74)	0.70	0.49
Possible CHD	62	43	0.50 (0.08)	0.63 (0.11)	1.17 (0.79–1.73)	0.79	0.43
Stroke	92	76	0.79 (0.10)	1.25 (0.16)	1.39 (1.03–1.89)	2.14	0.03
Congestive HF	59	42	0.60 (0.09)	0.65 (0.11)	1.20 (0.81–1.78)	0.91	0.36
Other cardiovascular	97	72	0.88 (0.10)	1.12 (0.15)	1.25 (0.92–1.70)	1.44	0.15
Noncardiovascular	561	317	4.82 (0.23)	4.72 (0.30)	0.95 (0.83–1.09)	−0.67	0.50
Cancer	314	162	2.78 (0.18)	2.43 (0.21)	0.87 (0.72–1.05)	−1.43	0.15
Kidney disease	12	12	0.11 (0.04)	0.24 (0.09)	1.69 (0.76–3.77)	1.29	0.20
Accident/suicide/homicide	39	28	0.33 (0.06)	0.40 (0.09)	1.21 (0.75–1.97)	0.78	0.44
Other noncardiovascular	196	115	1.75 (0.14)	1.84 (0.19)	0.99 (0.79–1.25)	−0.08	0.93
Unknown	146	75	1.37 (0.13)	1.18 (0.16)	0.87 (0.66–1.15)	−1.00	0.32
Combined CHD†	1642	1040	14.87 (0.39)	16.00 (0.53)	1.07 (0.99–1.16)	1.82	0.07
Stroke	434	325	4.08 (0.22)	5.49 (0.35)	1.26 (1.10–1.46)	3.20	0.001
Combined CVD‡	2829	1947	25.09 (0.48)	28.56 (0.64)	1.20 (1.13–1.27)	6.13	<0.001
Congestive HF (fatal, hospitalized, treated)	546	584	5.35 (0.26)	8.89 (0.42)	1.80 (1.61–2.02)§	10.27	<0.001
Congestive HF (fatal, hospitalized)	440	434	4.41 (0.24)	6.63 (0.37)	1.66 (1.46–1.89)§	7.72	<0.001
Coronary revascularization	770	508	7.08 (0.28)	8.02 (0.40)	1.12 (1.00–1.25)	1.97	0.05
Hospitalized or treated angina	1227	811	10.81 (0.33)	11.82 (0.45)	1.13 (1.03–1.23)	2.65	0.01
Lower-extremity peripheral arterial disease	376	217	3.68 (0.21)	3.49 (0.27)	0.97 (0.82–1.15)	−0.31	0.76
Cancer	758	408	7.37 (0.30)	6.53 (0.36)	0.91 (0.80–1.02)	−1.58	0.11
End-stage renal disease	104	64	1.10 (0.13)	1.08 (0.17)	1.04 (0.76–1.42)	0.26	0.80

*To adjust for multiple comparisons, compare the *P* value to 0.018 rather than 0.05.

†Combined CHD=CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina.

‡Combined CVD=CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized congestive HF, and peripheral arterial disease (hospitalized or outpatient revascularization).

§PH assumption violated; numbers given are RRs.

regularly taking antihypertensive medications before enrollment in ALLHAT, the respective RRs of combined CVD for doxazosin compared with chlorthalidone were each significant at 1.18 and 1.39, respectively. The test for interaction was not significant ($P=0.13$). For HF, RRs were 1.87 and 1.54 for those treated and untreated, respectively. Again, there was no evidence of an interaction ($P=0.41$). Although the 95% CI for the untreated subjects was 0.98 to 2.42, the intervals for the treated and untreated groups were broadly overlapping.

Noncardiovascular end points occurred at similar rates in the 2 groups. Cancer incidence did not differ significantly between chlorthalidone and doxazosin subjects (7.37 vs 6.53 per 100; $P=0.11$). End-stage renal failure, as defined by initiation of dialysis, transplantation, or renal disease death, occurred in 1.1% of both groups.

Discussion

These more complete final results extend and further confirm the previously reported analysis of the doxazosin/chlorthalidone comparison in ALLHAT by adding 9232 person-years of experience and increasing the number of combined CVD end points by 24%. In no instance have these additional data materially altered any finding or conclusion previously presented.[2] Altogether, 98.6% of events have been validated by examination of hospital charts or death certificates. The results provide compelling confirmation that chlorthalidone provides cardiovascular protection superior to that of doxazosin when used as first-line antihypertensive therapy in patients who are at appreciable risk of CVD events. Specifically, we now confirm a 20% excess in all cardiovascular events (25% in preliminary data), including an 80% increase in HF (104% in preliminary data) and a significant 26% excess in stroke (19% in preliminary data) for participants randomized to doxazosin compared with chlorthalidone. At the same time, there were no differences in the primary end point of fatal and nonfatal CHD, in all-cause mortality, in the incidence of end-stage renal disease, in peripheral vascular disease, in noncardiovascular events, or in "quality of life."

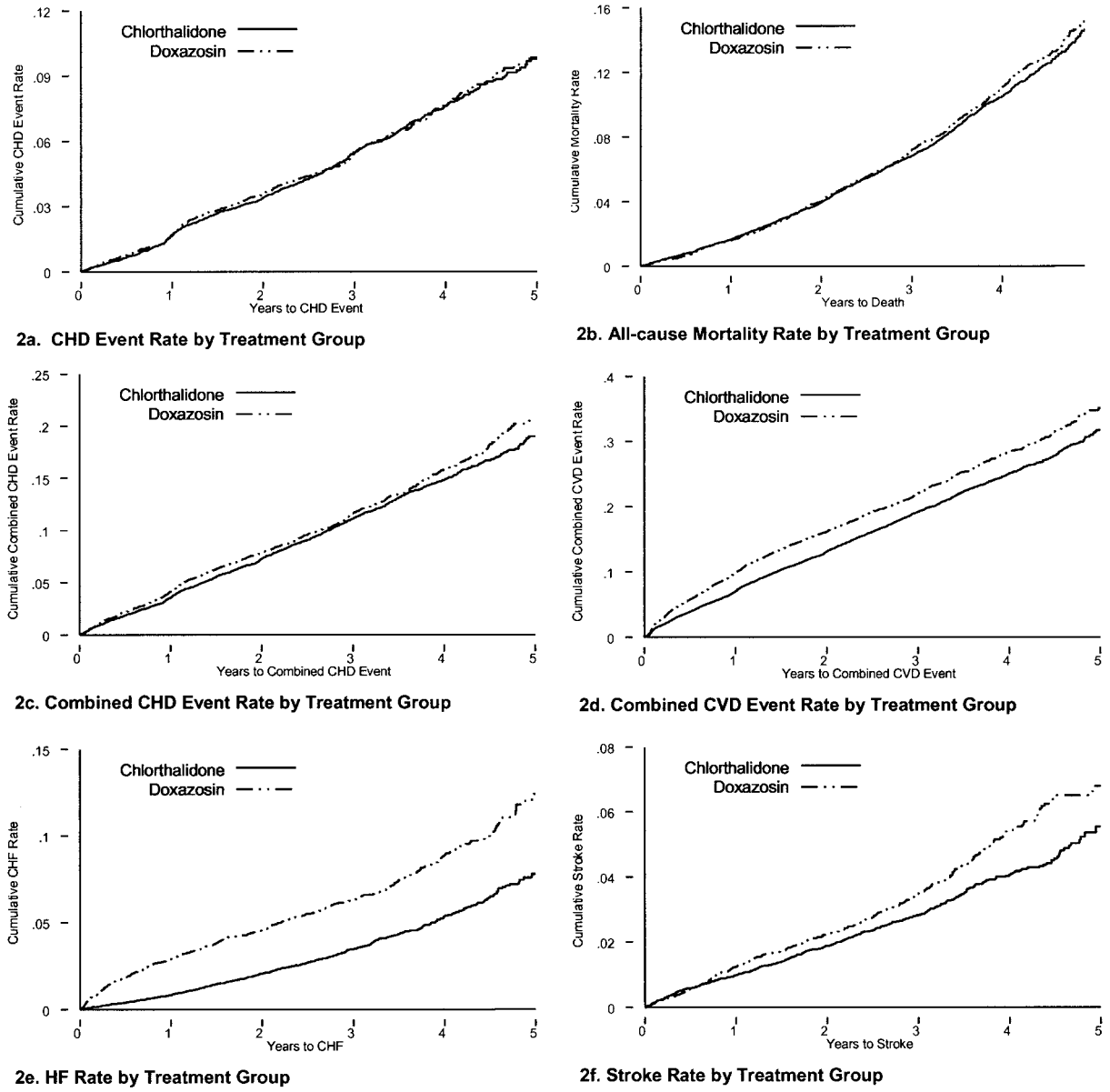

Figure 2. Kaplan-Meier estimates for CHD (primary outcome), all-cause mortality, combined CHD, combined CVD, congestive HF, and stroke.

The striking excess in HF associated with doxazosin use has stimulated wide interest.[9–11] More detailed information and analyses further support and explain these findings. Predetermined diagnostic criteria were well and equally applied to both treatment groups; limiting the comparison to "hard" hospitalized and fatal cases produced results similar to those for the group as a whole.[12] Two-year mortality rates for those who developed HF were, as expected, high and similar for the 2 groups (18.6% and 22.1% for doxazosin and chlorthalidone, respectively).[12] Adjusting for group differences in attained BP had little effect on HF results.[13] The excess HF (hospitalized plus fatal, as well as total) was actually greater when the comparison with chlorthalidone was limited to subjects who had achieved BPs <140/90 mm Hg. Similar results were seen in all gender and race/ethnicity groups as well as in participants above and below age 65, in diabetic and nondiabetic participants, and in those with and without a history of CHD.

It has been suggested that these findings might be due in part to the unmasking of undiagnosed HF in a subset of doxazosin participants after withdrawal of baseline diuretic therapy. To further assess this possibility, we found no interaction by subgroup after stratification by prior treatment status. The minority (10%) who entered without recent therapy had a point estimate for increased HF similar to the group as a whole, although this did not reach statistical significance (RR, 1.54; 95% CI, 0.96 to 2.42). Moreover, although the divergence in HF risk in participants randomized to doxazosin was most pronounced during the initial year, a significant excess for doxazosin compared with chlorthalidone in total, as well as in hospitalized/fatal HF, was also seen when the analysis was limited to events after the first

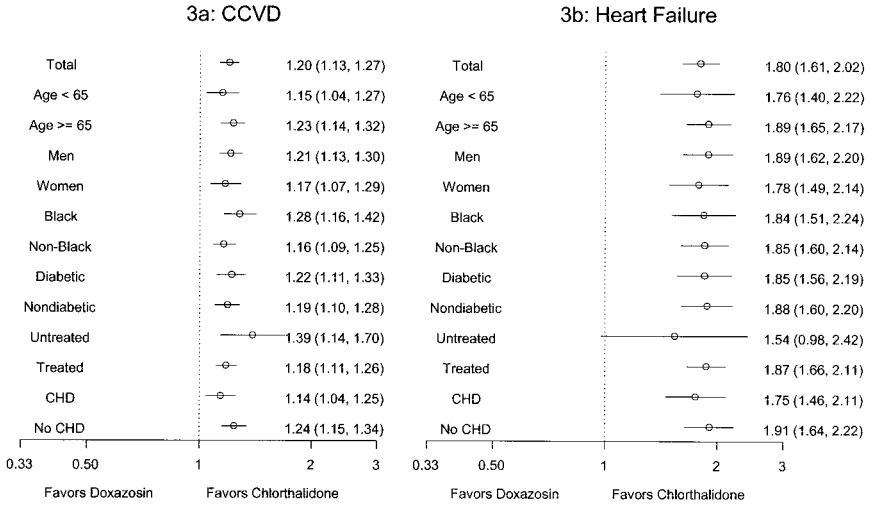

Figure 3. RRs and 95% CIs for doxazosin/chlorthalidone comparisons in subgroups.

year. These findings indicate that although discontinuation of prestudy diuretic therapy might have contributed, it cannot explain the persistent excess in HF associated with doxazosin therapy.

Therefore, we conclude, in view of the sustained, significant difference in HF, the similarity in point estimates, the overlapping CIs between subgroups, and the absence of an interaction between treatment status at entry and drug use, that the absence of statistical significance in the untreated subgroup is most likely a reflection of the relatively small numbers in that subgroup. Among the nearly 90% of subjects receiving antihypertensive therapy at entry to the study, the RR for HF was 1.87 (95% CI, 1.66 to 2.11) for doxazosin compared with chlorthalidone. Taken together, this new information confirms that the difference in HF was real and accurately reflected the prognostic severity generally associated with this diagnosis. In short, these findings suggest that it is the drug therapy itself that explains the dramatically lower occurrence of HF in those randomized to chlorthalidone.

Renal outcomes will be presented in detail separately for all components of the ALLHAT. It is sufficient to note here that randomization to doxazosin or chlorthalidone did not yield clinically significant differences in serum creatinine or in occurrence of end-stage renal disease. General health perception, assessed by 2 simple global questions asked at baseline and during follow-up, was generally satisfactory for the ALLHAT volunteers. About 75% of our study participants reported a good or better response to the quality-of-life question, and responses did not differ between groups.

Finally, our results provide further evidence that the health effects of antihypertensive agents might not be adequately assessed by surrogate measures, such as changes in risk factor levels.[14] Here, for example, chlorthalidone therapy was associated with a significant advantage in morbidity despite the expected relatively favorable effect of doxazosin on metabolic measures such as glucose and lipids.

As in all clinical trials, limitations are to be noted in the ALLHAT experience. Follow-up was very good, but still, 3.8% of the study participants were lost by the time that the doxazosin arm was terminated. Although event rates in those lost to follow-up cannot be assessed, dropout percentages were similar in the 2 groups, and because of their modest numbers, are extremely unlikely to have altered overall outcomes in any category. Despite a vigorous attempt to achieve equal BP control, those assigned to doxazosin who discontinued the study drug did so more often than their counterparts assigned to chlorthalidone and also had an average 2 to 3 mm Hg higher SBP. There was no difference in DBP throughout follow-up. Based on extrapolation from other studies, this degree of BP difference might have contributed to but does not fully explain the stroke and angina differences.[15–20] It could not begin to account for the near doubling of HF experienced by the doxazosin group.[13] Because of discontinuation of assigned doxazosin therapy in one fourth of participants, the addition of other antihypertensive therapies by most, and the use of a diuretic by a small fraction, it is likely that the results reported here underestimate the true magnitude of the disadvantage borne by participants randomized to doxazosin.

ALLHAT has documented that doxazosin is inferior to chlorthalidone as a first-line drug in the treatment of moderate- to high-risk hypertensive subjects. However, there are at least 2 closely related, relevant issues that cannot be directly addressed by the data. As to the first, it seems reasonable, in the absence of evidence to the contrary, to suspect that these findings might also apply to other α-blockers used in the treatment of hypertension and to hypertensive subjects similar to those meeting the ALLHAT eligibility criteria. Second, although we believe that the decision to include an α-blocker in the management of benign prostatic hypertrophy cannot be derived from the ALLHAT data, these findings should be considered in determining the management of such patients.

ALLHAT, because of its unprecedented size, rigorous design, and clear outcome, is a landmark comparative trial of antihypertensive therapies. Because of superior BP control, enhanced tolerability, reduced cardiovascular morbidity associated with chlorthalidone compared with doxazosin, and lack of evidence that this class of agents provides cardioprotection superior to placebo, an α-blocker can no longer be considered appropriate initial therapy for hypertension. In-

stead, these findings provide strong support for the recommendation that thiazide-type diuretics be the drug of first choice for antihypertensive therapy in patients at appreciable CVD risk.

Perspective

Hypertension is a major contributor to cardiovascular morbidity and morality (CVD). Although it has long been known that pharmacologic intervention can significantly reduce the incidence of CVD, the availability of newer antihypertensive agents has raised the possibility that they might offer greater cardioprotection than traditional diuretic-based therapy. To test that hypothesis, ALLHAT was designed to compare representatives of 3 newer classes of antihypertensive agents with chlorthalidone, the standard used in earlier placebo-controlled trials. That portion of the study comparing doxazosin, an α-blocking agent, with chlorthalidone, a thiazide-type diuretic, was terminated ahead of schedule after finding a substantial excess of cardiovascular events in the doxazosin group and determining that continuation of the study was unlikely to produce evidence of significant benefit for doxazosin. In this final and more complete report, we confirm the initial results showing an excess of 80% for HF and of 26% for stroke in the doxazosin group. These final results now provide further evidence that neither the 2 to 3 mm Hg higher SBP nor the unmasking of latent HF at entry to the study for participants previously treated with a diuretic bore the major responsibility for the additional HF burden of participants randomized to doxazosin. It is likely that these results apply to other α-blockers. In view of superior BP control, greater tolerability, and a significant reduction in cardiovascular events, we believe that these results provide further direct evidence that antihypertensive therapy should routinely be initiated with a thiazide-type diuretic.

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