

# Relationship of Antihypertensive Treatment Regimens and Change in Blood Pressure to Risk for Heart Failure in Hypertensive Patients Randomly Assigned to Doxazosin or Chlorthalidone: Further Analyses from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial

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**Background:** The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial reported that treatment initiated with doxazosin compared with chlorthalidone doubled the risk for heart failure in high-risk hypertensive patients (relative risk, 2.04 [95% CI, 1.79 to 2.32]). Patients assigned to doxazosin therapy had a mean in-trial systolic/diastolic blood pressure 3/0 mm Hg higher than that in patients assigned to chlorthalidone. Sixty-eight percent (6167 of 9061) of the former patients and 59% (9081 of 15 256) of the latter patients were given additional medications to achieve a target blood pressure of less than 140/90 mm Hg.

**Objective:** To ascertain the influence of open-label antihypertensive drugs and subsequent blood pressure on relative risk for heart failure.

**Design:** Randomized, double-blind, active-controlled clinical trial.

**Setting:** 623 sites in the United States and Canada.

**Patients:** Hypertensive patients 55 years of age or older with at least one additional risk factor for cardiovascular disease.

**Intervention:** Chlorthalidone (12.5 to 25 mg/d) or doxazosin (2 to 8 mg/d) for a planned follow-up of 4 to 8 years.

**Measurements:** Data on blood pressure, medication, and incident heart failure (treated outside hospital, hospitalized, or fatal) from February 1994 through December 1999.

**Results:** After the treatment groups were categorized as having no exposure to open-label medications (monotherapy) or exposure to open-label therapy, the relative risk for heart failure with doxazosin versus chlorthalidone was 3.10 (CI, 2.51 to 3.82) and 1.42 (CI, 1.20 to 1.69), respectively. After adjustment for follow-up systolic/diastolic blood pressure, the overall relative risk was 2.00 (CI, 1.72 to 2.32).

**Conclusion:** In high-risk patients with hypertension, the higher risk for heart failure while taking doxazosin compared with chlorthalidone is attenuated but not eliminated by adding other antihypertensive drugs. The small observed difference in systolic blood pressure does not explain this increased risk.

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The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, multicenter clinical trial including 42 418 participants at 623 clinical sites, is designed to determine whether treatment begun with a calcium-channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), or an  $\alpha$ -adrenergic blocker (doxazosin) compared to treatment with a diuretic (chlorthalidone) reduces the incidence of fatal coronary heart disease or nonfatal myocardial infarction in high-risk patients with hypertension (1). Secondary end points are all-cause mortality, stroke, and other cardiovascular events. A lipid-lowering trial in a subset of 10 356 participants is designed to determine whether decreasing cholesterol levels with a hydroxymethyl glutamyl coenzyme A reductase inhibitor (pravastatin) compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic patients.

In January 2000, the doxazosin arm of the trial was discontinued (2) because major cardiovascular disease (relative risk, 1.25 [95% CI, 1.17 to 1.33];  $P < 0.001$ ), especially heart failure (relative risk, 2.04 [95% CI, 1.79 to

2.32];  $P < 0.001$ ), was significantly increased compared with the chlorthalidone arm. Equally important, a low probability existed that doxazosin would show benefit over chlorthalidone for the primary end point by the scheduled study end, given the lack of difference (relative risk, 1.02 [95% CI, 0.90 to 1.17];  $P > 0.2$ ) at that time. These intention-to-treat analyses compared patients assigned to chlorthalidone with patients assigned to doxazosin.

In this article, we analyze how treatment changes may have affected the comparison of doxazosin with chlorthalidone in terms of heart failure. Our major objectives are to ascertain to what extent the relative risk with doxazosin versus chlorthalidone depends on 1) whether the assigned drugs were used as monotherapy or in combination with other agents and 2) the difference in decreases in systolic and diastolic blood pressure.

## METHODS

### Study Design

The rationale and design of ALLHAT are described in detail elsewhere (1). In brief, eligible participants were men

**Context**

Previously published results of this randomized, double-blind trial showed that hypertensive patients treated with doxazosin rather than chlorthalidone more often developed heart failure. Did differences in blood pressure control or treatment with other drugs explain these findings?

**Contribution**

This analysis shows that the slightly worse blood pressure control achieved with doxazosin did not explain higher risks for heart failure. Risks with doxazosin versus chlorthalidone were highest among patients who received monotherapy (relative risk, 3.10) and lowest among patients who received stepped care with additional drugs (relative risk, 1.42).

**Implications**

Increased risks for heart failure with doxazosin versus chlorthalidone are attenuated but not eliminated when additional antihypertensive drugs are used.

—The Editors

and women 55 years of age or older who had systolic or diastolic hypertension ( $\geq 140/90$  mm Hg or hypertension controlled with medication) plus at least one additional risk factor for coronary heart disease events. The risk factors included previous ( $>6$  months) myocardial infarction or stroke, left ventricular hypertrophy on electrocardiography or echocardiography, history of type 2 diabetes, current cigarette smoking, and a low high-density lipoprotein cholesterol level. Persons with a history of hospitalized or treated symptomatic heart failure or a known ejection fraction less than 0.35 were excluded.

Unless the drug regimen required tapering for safety, participants who had been taking antihypertensive medications continued to do so until the day of randomization, at which point they stopped taking all previous medications. On the day after randomization, treatment with the study drug was initiated.

Enrollment occurred from February 1994 through January 1998. The original reported number of 42 448 participants and 625 sites changed because 30 patients with poor documentation of informed consent were excluded (2). Participants were assigned by a computer-generated randomization schedule in a ratio of 1.7:1 to receive chlorthalidone or doxazosin. Randomization was stratified by center and blocked over time to maintain the ratio. All participants gave written informed consent, and all centers obtained institutional review board approval.

**Ascertainment of Outcomes**

At each clinic visit, occurrence of study end points was assessed by the clinical investigator. A hospital discharge summary was required for each hospitalized study outcome, and a death certificate was required for each death.

ALLHAT defined symptomatic heart failure as clear-cut signs or symptoms of left or right ventricular dysfunction that cannot be attributed to other causes. A patient had to have at least one symptom (paroxysmal nocturnal dyspnea, dyspnea at rest, New York Heart Association class III dyspnea or other symptoms [on less than ordinary exertion], or orthopnea) and one sign (rales, ankle edema, tachycardia, cardiomegaly or characteristic pulmonary pattern on chest radiography,  $S_3$  gallop, or jugular venous distention) (3). Symptoms and signs were determined by the clinic investigator through patient history, chart review, or consultation with the treating physician, but such data were not collected centrally.

A one-time sample of 24 hospitalized or fatal heart failure events was reviewed in a blinded manner by the ALLHAT Endpoints Subcommittee; 20 of 24 (83%) were deemed to have complete data for a definitive diagnosis. Of the 20 cases, the agreement rate between the subcommittee and the clinic investigators was 90% (18 of 20) and similar in both treatment groups. Details on the validity of diagnosis of heart failure will be provided in a future report.

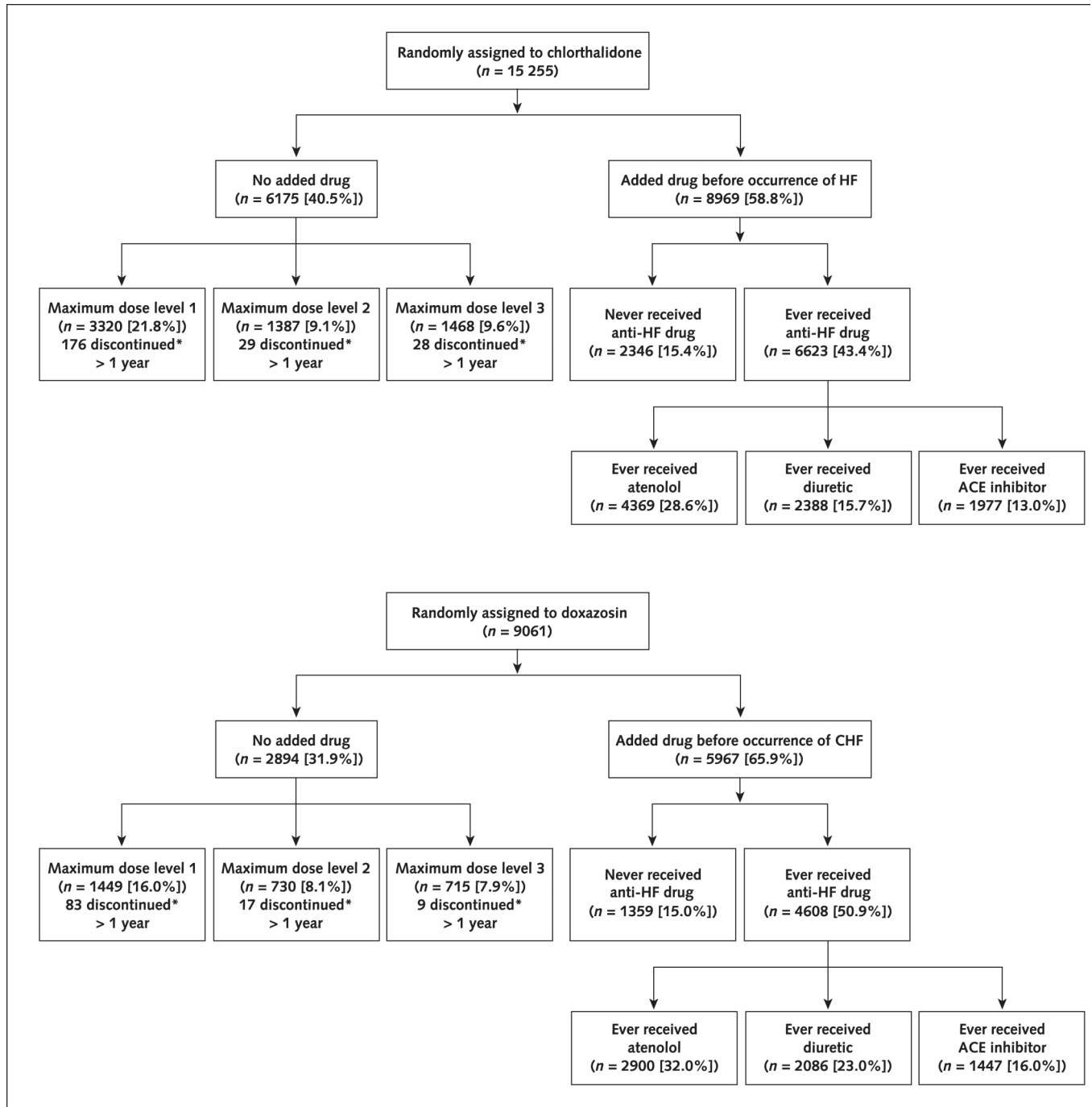
**Measurement and Treatment of Blood Pressure**

The ALLHAT protocol specified a stepped-care treatment program for hypertension. Trained observers using standardized techniques measured blood pressures during the trial (1, 2). All blood pressures were calculated as the average of two measurements obtained with a 30-second interval between them. The blood pressure goal in all four study arms was less than 140/90 mm Hg. This level was to be achieved with the lowest possible dose of blinded first-line drug, with addition of second- and third-line open-label therapy as needed after reaching the maximal dose of first-line drug.

Chlorthalidone and doxazosin were to be taken once daily in the morning. By design, doses were selected to achieve equivalent blood pressure control in the treatment groups. The first, second, and third dosage levels were 12.5 mg/d, 12.5 mg/d (sham titration), and 25 mg/d, respectively, for chlorthalidone and 2 mg/d, 4 mg/d, and 8 mg/d for doxazosin. Double-blinded 1-mg and 12.5-mg doses of doxazosin and chlorthalidone, respectively, were used for the first week to minimize the frequency of postural hypotension associated with doxazosin. The identity of drugs was masked at each dosage level, but dosage level was not.

After randomization, patients were seen for dose titration as needed at 1 and 3 months per the protocol, but they could return more often until target blood pressure was reached. Subsequently, required visits occurred at 3-month intervals during the first year and at 4-month intervals thereafter. Open-label second-step drugs were added as needed and tolerated. These agents were reserpine (0.05 to 0.2 mg/d), clonidine (0.1 to 0.3 mg twice daily), and atenolol (25 to 100 mg/d). The choice of second-step drug was at the discretion of the treating clinician-investigator. The third-step agent was hydralazine (25 to 100 mg

Figure. Participants who underwent randomization and were followed in the monotherapy and open-label therapy analyses, by study treatment group.



Values in parentheses are percentages of total participants. \*Patients discontinued from therapy with randomly assigned drug. ACE = angiotensin-converting enzyme; HF = heart failure.

twice daily). Details of these therapies are provided elsewhere (1).

Investigators could choose to prescribe open-label antihypertensive drugs other than those provided by the study. However, use of the drug classes under study—thiazide diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, and  $\alpha$ -adrenergic blockers—was

strongly discouraged to avoid dilution of treatment comparisons. When clinical conditions other than uncontrolled hypertension (for example, angina or heart failure) were present, drugs from any study class could be used. If a step 1 drug was specifically required for blood pressure control while blinded drug treatment was continued, the step 1 drug could be added as open-label therapy but the dose

Table 1. Baseline Characteristics of Participants

Characteristic	No Exposure to Open-Label Drugs (Monotherapy)		Exposure to Open-Label Therapy	
	Chlorthalidone Group	Doxazosin Group	Chlorthalidone Group	Doxazosin Group
Participants, <i>n</i>	6175	2894	8969	5967
Age, <i>y</i> *	66.8 ± 7.9	66.8 ± 8.0	67.0 ± 7.5	66.8 ± 7.6
Ethnicity, %				
White, non-Hispanic	37.5	37.8	53.8	50.5
Black, non-Hispanic	33.4	28.3	30.9	35.1
White Hispanic	18.8	22.5	8.3	7.9
Black Hispanic	5.1	6.0	2.0	2.2
Other	3.9	5.5	4.9	4.3
Women, %	51.3	50.7	44.1	44.4
Level of education, <i>y</i>	10.50 ± 4.1	10.4 ± 4.5	11.3 ± 4.0	11.3 ± 3.7
Current cigarette smoking, %	24.5	23.4	20.2	20.9
Receiving antihypertensive treatment before study entry, %	85.5	84.9	93.3	92.8
Atherosclerotic cardiovascular disease, %	39.9	42.1	48.8	47.3
ST-T wave, %	9.9	8.5	10.2	10.5
Type 2 diabetes, %	35.4	35.0	36.2	35.1
Low high-density lipoprotein cholesterol level, %	11.9	11.5	12.7	12.2
Left ventricular hypertrophy, %				
On electrocardiography	15.0	14.3	16.4	16.7
On echocardiography	3.5	3.2	4.6	4.6
Blood pressure, <i>mm Hg</i> *				
Systolic	143.9 ± 15.3	144.4 ± 15.4	147.8 ± 15.7	147.2 ± 15.8
Diastolic	83.8 ± 9.8	83.9 ± 9.9	84.1 ± 10.3	83.9 ± 10.1
Serum potassium level, <i>mmol/L</i> *	4.4 ± 0.7	4.4 ± 0.8	4.3 ± 0.7	4.3 ± 0.6
Fasting serum glucose level, <i>mmol/L (mg/dL)</i> *	6.9 ± 3.4 (124 ± 61)	6.8 ± 3.3 (126 ± 59)	6.9 ± 3.1 (124 ± 56)	6.8 ± 3.0 (126 ± 54)
Serum creatinine concentration, <i>μmol/L (mg/dL)</i> *	77.8 ± 23.3 (0.8 ± 0.3)	77.8 ± 23.3 (0.8 ± 0.3)	77.8 ± 23.6 (0.8 ± 0.3)	77.8 ± 22.9 (0.8 ± 0.3)
Serum cholesterol level, <i>mmol/L (mg/dL)</i> *				
Total cholesterol	5.6 ± 1.1 (216 ± 42)	5.6 ± 1.1 (216 ± 42)	5.6 ± 1.1 (216 ± 42)	5.6 ± 1.1 (216 ± 42)
Low-density lipoprotein cholesterol	3.5 ± 1.0 (135 ± 37)	3.5 ± 1.0 (135 ± 37)	3.5 ± 1.0 (135 ± 37)	3.5 ± 0.9 (135 ± 35)
High-density lipoprotein cholesterol	1.2 ± 0.4 (46 ± 15)	1.2 ± 0.4 (46 ± 15)	1.2 ± 0.4 (46 ± 15)	1.2 ± 0.4 (46 ± 15)
Fasting triglycerides	2.0 ± 1.5 (177 ± 133)	1.9 ± 1.9 (168 ± 168)	2.0 ± 1.5 (177 ± 133)	1.9 ± 1.3 (168 ± 115)

\* Values with the plus/minus sign are the mean ± SD.

could not exceed one half the maximum recommended by the Fifth Joint National Committee (4). In most such cases, unblinding the patient or the investigator to treatment assignment was not necessary. (Overall, <1% of drug identities were provided to either participant or investigator.) Any of nine possible open-label drug types—diuretic, calcium-channel blocker, angiotensin-converting enzyme inhibitor,  $\alpha$ -adrenergic blocker, atenolol, reserpine, clonidine, hydralazine, and other antihypertensive drug (which could include nonatenolol  $\beta$ -blockers, although drug name was not logged)—could be recorded at each visit. Because diuretics, angiotensin-converting enzyme inhibitors, and  $\beta$ -blockers are beneficial in preventing or treating heart failure, we call these *antihypertensive heart failure drugs*. Data on antihypertensive drug use before study enrollment were collected, but not by drug class.

### Statistical Analysis

Data were analyzed for use of additional drugs according to participants' randomized treatment assignments and regardless of continuation of blinded study treatment. The outcomes "all heart failure" (treated outside hospital, hospitalized, or fatal) and "hospitalized or fatal heart failure" were examined by treatment group for the entire cohort. The time to event for the previously published "as-

randomized" analyses was the interval from randomization to first diagnosis of heart failure for patients who had an outcome, or from randomization to study end or loss to follow-up for those without an outcome. In this study, outcome rates were compared by treatment group for participants with no exposure to open-label medication, and results of this comparison were contrasted with rates in the respective treatment groups with such exposure. Similar comparisons were done for patients with exposure and those with no exposure to antihypertensive heart failure medications. Dose-exposure analyses were done to compare the influence of the two doses of chlorthalidone with that of the three doses of doxazosin (six possible comparisons) on the observed relative risk.

Cumulative event rates were calculated by using the Kaplan-Meier procedure (5). Relative risks (hazard ratios) with 95% CIs and two-sided *P* values were calculated by using a proportional hazards model (5). The drug-exposure and no-drug-exposure analyses were also performed by using Cox regression with a time-dependent covariate representing exposure and an interaction term representing the product of this term and drug assignment. Cox regression analyses limited to the duration of receipt of the various doses of doxazosin and chlorthalidone were also per-

formed. Because these time-dependent analyses are subject to statistical and epidemiologic biases, the *P* values, relative risks, and confidence intervals for them should be interpreted with caution (6).

To account for differences in systolic blood pressure between the randomized treatment groups as previously reported, two types of analyses were performed. First, participants were stratified by their blood pressure at 9 to 12 months after randomization into categories of systolic blood pressure ( $\geq 140$  mm Hg or  $< 140$  mm Hg), diastolic blood pressure ( $\geq 90$  mm Hg or  $< 90$  mm Hg), and combinations of these blood pressures (eight groupings). Mean differences in systolic and diastolic blood pressure between the treatment groups at this time and event rates, relative risks, and 95% CIs beyond 1 year were calculated. Second, Cox regression analyses of the entire cohort that included fixed covariates of baseline systolic and diastolic blood pressure and time-dependent covariates of follow-up systolic and diastolic blood pressure were performed.

Follow-up blood pressures were obtained at clinic visits. Missed visits resulted in missing blood pressures. Reasons for missing visits were recorded and included loss to follow-up, refusal to return, and intercurrent illness. Analyses were done by using all available information (which decreased sample sizes owing to missing values) and by assigning follow-up blood pressures for the missing observations (a measurement not captured in the last 6 months) according to time period and treatment group by using the method of multiple imputation (7, 8).

**Role of the Funding Source**

The National Heart, Lung, and Blood Institute sponsored the study and was involved in all aspects other than direct operations of the study centers. This included col-

lection, analysis, and interpretation of the data plus the decision to submit the manuscript for publication.

**RESULTS**

The results presented here are restricted to the same data set as the previously published analysis (1). The median duration of follow-up for all participants was 3.3 years. Five hundred (3.3%) patients in the chlorthalidone group and 338 (3.7%) patients in the doxazosin group were lost to follow-up. During the trial, about 59% of patients in the chlorthalidone group and 68% of patients in the doxazosin group were stepped up to additional drugs.

The **Figure** shows the number of patients who were randomly assigned and followed to the time of each analysis. It also shows the number of participants who reached the maximal dose level of blinded step 1 drug and those who were stepped up to any open-label drug or any antihypertensive heart failure open-label drug before heart failure occurred. The relative risk for receiving additional medications before reported onset of heart failure (doxazosin versus chlorthalidone) was 1.31 (95% CI, 1.27 to 1.35) (*P* < 0.001). Of patients who never started taking antihypertensive heart failure medication, about one fourth started therapy with a calcium antagonist; these patients had few heart failure events (7 and 2 in the chlorthalidone and doxazosin groups, respectively).

**Table 1** shows baseline characteristics of the chlorthalidone and doxazosin groups, stratified by no exposure to open-label medication and exposure to such drugs. In each stratum, the distribution of characteristics by treatment group was very similar, with a few exceptions. In the

*Table 2. Event Rates and Relative Risks for All Heart Failure and Hospitalized or Fatal Heart Failure*

Heart Failure and Medication Category	Events per 100 Persons at 4 Years*		Patients with Outcomes		Relative Risk (95% CI)	P Value
	Chlorthalidone Group	Doxazosin Group	Chlorthalidone Group	Doxazosin Group		
	←----- n ----->					
All heart failure						
As randomly assigned	4.46 ± 0.26	8.14 ± 0.43	420	491	2.04 (1.79–2.32)	<0.001
No exposure to open-label therapy	2.64 ± 0.31	6.63 ± 0.79	144	227	3.10 (2.51–3.82)	<0.001
Exposure to open-label therapy	6.93 ± 0.59	8.75 ± 0.72	276	264	1.42 (1.20–1.69)	<0.001
Exposure to antihypertensive heart failure open-label therapy	6.90 ± 0.69	9.81 ± 0.95	207	214	1.45 (1.20–1.76)	<0.001
No exposure to antihypertensive heart failure open-label therapy	6.10 ± 1.22	7.43 ± 1.62	69	50	1.25 (0.87–1.80)	>0.2
Hospitalized or fatal heart failure						
As randomly assigned	3.53 ± 0.23	5.77 ± 0.37	327	346	1.83 (1.58–2.13)	<0.001
No exposure to open-label therapy	2.03 ± 0.28	3.69 ± 0.57	109	139	2.52 (1.96–3.24)	<0.001
Exposure to open-label therapy	5.64 ± 0.54	6.77 ± 0.62	218	207	1.39 (1.15–1.68)	<0.001
Exposure to antihypertensive heart failure open-label therapy	5.86 ± 0.64	7.83 ± 0.87	172	172	1.38 (1.12–1.71)	<0.001
No exposure to antihypertensive heart failure open-label therapy	4.01 ± 0.90	4.61 ± 1.22	46	35	1.31 (0.85–2.04)	>0.2

\* Data are presented as the mean ± SE.

**Table 3. Relative Risk for Heart Failure, by Dose of Doxazosin Compared with Chlorthalidone, in Participants Not Exposed to Open-Label Therapy**

Doxazosin Dosage vs. Chlorthalidone Dosage	All Heart Failure		Hospitalized or Fatal Heart Failure	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
2 mg/d vs. 12.5 mg/d	2.81 (2.24–3.53)	<0.001	2.27 (1.73–2.98)	<0.001
4 mg/d vs. 12.5 mg/d	3.51 (2.78–4.43)	<0.001	2.84 (2.15–3.76)	<0.001
8 mg/d vs. 12.5 mg/d	3.25 (2.28–4.64)	<0.001	2.81 (1.84–4.30)	<0.001
2 mg/d vs. 25 mg/d	2.43 (1.73–3.42)	<0.001	1.84 (1.22–2.77)	0.004
4 mg/d vs. 25 mg/d	3.04 (2.10–4.39)	<0.001	2.30 (1.48–3.58)	<0.001
8 mg/d vs. 25 mg/d	2.81 (2.24–3.53)	<0.001	2.27 (1.73–2.98)	0.043

monotherapy stratum, the doxazosin arm included more black patients than white patients compared with the chlorthalidone arm, whereas in the open-label therapy stratum, the chlorthalidone arm included more black patients than white patients. In addition, in the monotherapy stratum, the doxazosin arm included more Hispanic patients and more persons with atherosclerotic cardiovascular disease but fewer persons with ST-T wave abnormalities. About 30% of participants who had been taking antihypertensive therapy before study entry had a blood pressure less than 140/90 mm Hg. Overall, the mean blood pressures for persons receiving previous therapy (90.2%) and those not receiving previous therapy were 145/83 mm Hg and 156/89 mm Hg, respectively.

Table 2 shows results of Cox regression analyses comparing the treatment groups with respect to heart failure outcomes for all patients as randomly assigned, those with no exposure to open-label medication, and those with exposure to such medication. The 4-year event rates are higher among participants exposed to open-label medication than in those not exposed. For both outcomes, the risk with doxazosin treatment compared with chlorthalidone treatment is substantial, in patients without and with exposure to open-label drugs. The risk ratios in the monotherapy groups (3.1 for all cases of heart failure and 2.5 for hospitalized or fatal heart failure) are greater than those in the as-randomized groups. The risk ratios for participants with exposure to open-label medication are smaller (about 1.4) but still statistically significant ( $P < 0.001$ ).

Cox regression with a time-dependent covariate representing exposure to open-label therapy (or antihypertensive heart failure open-label therapy) plus the interaction term of exposure and treatment assignment yielded nearly identical results. When race, Hispanic ethnicity, presence of atherosclerotic cardiovascular disease, and presence of ST-T wave abnormalities were added as covariates, the findings were essentially unchanged.

Table 3 shows the relative risk for all heart failure and hospitalized or fatal heart failure in the treatment groups, according to dose levels of doxazosin and chlorthalidone. This analysis is limited to duration of follow-up with no exposure to open-label therapy. The increased risk was apparent at all dose levels of doxazosin. At a fixed dose of chlorthalidone, an increase in relative risk was noted when

the dose of doxazosin was increased from 2 mg to 4 mg but not when it was increased from 4 mg to 8 mg. For a fixed dose of doxazosin, relative risks were decreased when the dose of chlorthalidone was increased from 12.5 to 25 mg. However, all relative risks were substantial and consistent with the overall results.

The results of the two outcome comparisons for the entire cohort shown in Table 2 are not controlled for follow-up blood pressure. Throughout the trial, systolic blood pressure was 2 to 3 mm Hg higher in the doxazosin group than the chlorthalidone group, but diastolic blood pressure did not differ substantially between the groups (2). The proportions of missing blood pressure measurements were 7% at 1 month, 16% at 6 months, 16% at 1 year, 20% at 3 years, and 16% at 5 years.

Table 4 shows event rates and relative risks of the treatment groups for heart failure outcomes beyond 1 year, with stratification to control for blood pressure at 1 year. The stratum with the lower systolic or diastolic blood pressure had a higher relative risk and a smaller difference in mean systolic blood pressure for doxazosin versus chlorthalidone. In the combination groupings, the stratum with the best control (blood pressure < 140/90 mm Hg) had the greatest relative risk and only a small difference in mean systolic blood pressure. After adjustment for baseline and follow-up blood pressures, the results were essentially unchanged for all heart failure (relative risk, 2.04 [CI, 1.79 to 2.32] vs. 2.00 [CI, 1.76 to 2.28];  $P < 0.001$ ) and hospitalized or fatal heart failure (relative risk, 1.83 [CI, 1.58 to 2.13] vs. 1.80 [CI, 1.54 to 2.09];  $P < 0.001$ ).

## DISCUSSION

We found that doxazosin is less effective than chlorthalidone in preventing major cardiovascular events, especially heart failure. Because this was an active control trial, we cannot determine whether chlorthalidone was beneficial, doxazosin was harmful, or both. Chlorthalidone has been shown to prevent and treat heart failure (9), whereas doxazosin has not been shown to do either. In the Systolic Hypertension in the Elderly Program, risk for heart failure was reduced by 50% with use of chlorthalidone compared with placebo (9).

In ALLHAT, not all participants continued to take

their assigned treatment, and reasons for stepping up to open-label medication might have differed between the randomized groups. These reasons may have had a differential effect on subsequent risk for heart failure. A major finding of the current study is that higher risk for heart failure with doxazosin compared with chlorthalidone was attenuated but not eliminated by the addition of other antihypertensive drugs.

The current analyses are subject to indication and diagnostic bias (10). Indication bias happens when the investigator gives additional medication on the basis of signs and symptoms, for example, to control blood pressure or reduce perceived side effects. Diagnostic bias can occur when the investigator or patient is influenced by knowledge about treatment. Participants in the doxazosin group were significantly more likely (relative risk, 1.31) than those in the chlorthalidone group to receive other drugs, and administration of other drugs tended to occur earlier in the doxazosin group. Since time to heart failure was shorter in the doxazosin group than the chlorthalidone group, a greater proportion (46%) of all heart failure events occurred before use of open-label therapy in the doxazosin group compared with the chlorthalidone group (34%), resulting in an exaggeration of the relative risk. Diagnostic bias should not have occurred because open-label therapy had not yet been given. Indication bias is possible because blood pressures and side effects may have influenced why certain participants were stepped up to additional medication but others were not.

On the basis of this reasoning, participants with exposure to open-label medication should have had an attenuated relative risk. This effect was seen for all cases of heart failure and hospitalized or fatal heart failure. In addition, the presence of other drugs could have further influenced the differences because of blood-pressure-related and unrelated effects. Diagnostic and indication bias could have played some role, since participants and investigators knew which open-label drugs were being taken and why. The postexposure results indicate that open-label therapy, in-

cluding antihypertensive heart failure therapy, diminished but did not eliminate the relative risks of both outcomes in the two treatment groups. The incidence of these outcomes in each treatment group was higher after exposure to other drugs than before such exposure. Perhaps participants with hypertension that was harder to control were at greater risk for heart failure.

Analyses by dose that were restricted to participants taking monotherapy are subject to the same potential biases described above. For a fixed dose of chlorthalidone, the relative risk tended to increase with increasing doses of doxazosin, whereas for a fixed dose of doxazosin, the relative risk decreased with the increased dose of chlorthalidone. Increasing doses of doxazosin relative to increasing doses of chlorthalidone were associated with shorter duration of treatment with the medication. If doxazosin had no effect on prevention of heart failure, comparison of patients taking a fixed dose of chlorthalidone with patients taking increasing doses of doxazosin might include an increasing proportion of persons at greater risk for heart failure owing to harder-to-control blood pressure. This effect would tend to increase the relative risk.

Finally, the mean systolic blood pressure was 2 to 3 mm Hg lower in the chlorthalidone group than the doxazosin group throughout the trial. However, the relative risks changed little after adjustment for differences in blood pressure throughout the trial. On the basis of results from the Framingham Heart Study (11), this observed difference in systolic blood pressure would be associated with at most a 2% reduction in relative risk, a finding consistent with ours (relative risk, 2.00 after adjustment [reduced from 2.04]). In addition, stratification of participants by blood pressure at 1 year showed that lower blood pressures were associated with greater relative increases in risk. It appears that in ALLHAT, the degree of difference in blood pressure does not explain the increased risk for heart failure in the doxazosin group compared with the chlorthalidone group. Possible limitations of our analyses include measurement error in blood pressure and possible loss of bal-

**Table 4. Event Rates and Relative Risk for Heart Failure after 1 Year of Therapy with Doxazosin or Chlorthalidone, and Differences in Blood Pressure 9 to 12 Months after Randomization**

Blood Pressure	Rate of Heart Failure		Relative Risk with Use of Doxazosin vs. Chlorthalidone (95% CI)	Difference in Systolic/Diastolic Blood Pressure between Doxazosin Group and Chlorthalidone Group
	Chlorthalidone Group	Doxazosin Group		
<i>mm Hg</i>	←———events/100 person-years———→			<i>mm Hg</i>
Systolic				
≥140	1.48	1.93	1.30 (1.05–1.60)	1.6/0.0
<140	0.96	1.51	1.58 (1.18–2.13)	0.4/–1.2
Diastolic				
≥90	1.54	1.79	1.17 (0.88–1.53)	4.3/0.3
<90	1.09	1.76	1.61 (1.29–2.00)	2.4/–0.6
Systolic/diastolic				
≥140/≥90	1.53	1.79	1.17 (0.88–1.55)	2.3/0.0
≥140/<90	1.41	2.10	1.49 (1.08–2.05)	1.2/–0.3
<140/≥90	1.61	1.79	1.11 (0.25–3.98)	0.2/–0.1
<140/<90	0.92	1.50	1.63 (1.20–2.05)	0.5/–1.1

ance of known and unknown characteristics, since we used postrandomization variables.

In patients at very low risk for heart failure, such as young persons with uncomplicated hypertension or those without other risk factors for cardiovascular disease, the findings of ALLHAT neither support nor refute a strategy of initial therapy with  $\alpha$ -adrenergic blockers, allowing addition to or replacement of other antihypertensive drug classes if blood pressure is not well controlled. In older men with benign prostatic hypertrophy in whom an  $\alpha$ -adrenergic blocker seems like the best treatment for the uropathy, coexisting hypertension should be treated with another antihypertensive drug as well. However, our analyses provide no guidance as to selection of a second drug class.

In summary, doxazosin recipients were more likely than chlorthalidone recipients to be given additional drugs. A disproportionately higher rate of heart failure occurred in the doxazosin group than the chlorthalidone group before exposure to additional medication. The data suggest a dose–response relationship for doxazosin compared with chlorthalidone. Stepping up to any drug, even a heart failure prevention drug, decreased but did not eliminate the relative risk for heart failure events. Differences in blood pressure during receipt of study treatment appeared to account for very little of the observed results. The principal finding remains that treatment with doxazosin compared with chlorthalidone carries an excess risk for heart failure in high-risk patients with hypertension, regardless of the dose used or addition of other drugs.

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