Original Paper

Heart Failure in ALLHAT: Did Blood Pressure Medication at Study Entry Influence Outcome?

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Lower heart failure (HF) rates in individuals taking chlorthalidone vs amlodipine, lisinopril, or doxazosin were unanticipated in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). HF differences appeared early, leading to questions about the possible influence of pre-enrollment antihypertensive drugs. A post hoc study evaluated hospitalized HF events. During year 1479 individuals had HF, with pre-entry antihypertensive medication data obtained on 301 patients (63%). Case-only analysis examined interactive effects (interaction odds ratio [OR, ratio of ORs]) of previous medication and ALLHAT treatment on HF outcomes, eg, did treatment effect differ by pre-entry antihypertensive class? Among cases, 39%, 37%, 17%, and 47% were taking pre-entry diuretics, angiotensin-converting enzyme inhibitors, β-blockers, and calcium channel blockers, respectively. Interaction OR for year 1 HF for amlodipine vs chlorthalidone for patients taking vs not taking diuretics pre-entry was 1.08 (95% confidence interval [CI], 0.53–2.21; P=.83); for lisinopril vs chlorthalidone, 1.33 (95% CI, 0.65–2.74; P=.44); and for doxazosin vs chlorthalidone, 1.13 (95% CI, 0.57–2.25; P=.73). Controlling for other pre-entry antihypertensives yielded similar results. There was no significant evidence that pre-entry drug type explained observed hospitalized HF differences by ALLHAT treatment. J Clin Hypertens (Greenwich). *2009;11:466–474.* ©*2009 Wiley Periodicals, Inc.*

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**See* JAMA. *2000;283:1973–1975.*
Manuscript received April 24, 2009; accepted May 28, 2009

doi: 10.1111/j.1751-7176.2009.00149.x

Clinical trials designed to assess the efficacy of antihypertensive agents (placebo- or active-controlled) have frequently enrolled hypertensive patients on prior drug therapy. Patients typically have their blood pressure (BP) drugs withdrawn prior to randomization and are given the study drugs on study entry. In the Systolic Hypertension in the Elderly Program (SHEP),

33.3% of participants were taking BP-lowering drugs at entry,[1] as were 61% in the Treatment of Mild Hypertension Study (TOMHS).[2] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[3,4] and the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial of cardiovascular events in hypertension, more than 90% were taking drugs prior to enrollment.[5] Little is known about the subsequent effects on cardiovascular (CV) outcomes of withdrawing antihypertensive drugs in this setting.

The interest in persistent effects of antihypertensive drugs is relevant to the hypertension trials in which drugs have been withdrawn prior to study entry. This concern arose in speculation about the heart failure (HF) results in ALLHAT.[4,6–9] ALLHAT was a National Heart, Lung, and Blood Institute (NHLBI)–sponsored trial comparing first-step treatment with a diuretic with each of 3 antihypertensive agents from different classes (angiotensin-converting enzyme [ACE] inhibitor, calcium channel blocker, and α-blocker) for preventing fatal and nonfatal coronary heart disease (CHD).[10] A prominent result in ALLHAT was that participants randomized to the α-blocker, calcium channel blocker, and ACE inhibitor developed HF at a significantly higher rate compared with their counterparts assigned to the diuretic chlorthalidone, especially in the first year after randomization.[4,6,7,9] A major criticism of these HF results has been that since more than 90% of ALLHAT participants were taking BP medication at the time of randomization, the observed outcome differences in the treatment groups might have been influenced by discontinuation of a participant's prior antihypertensive drug therapy (especially diuretics and ACE inhibitors used to treat HF) in patients with "subclinical HF," thereby unmasking the condition.[7,8] For example, discontinuing a diuretic might cause an increase in plasma volume and converting to an α-blocker could further increase plasma volume, resulting in fluid overload and manifesting HF. This could have occurred despite exclusion from ALLHAT of potential participants with a history of symptomatic heart failure, ejection fraction known to be <35%, or required treatment for heart failure with one of the study drugs.

Although ALLHAT did not initially record the type of BP drugs being prescribed at baseline, this information was obtained at the end of the trial by reviewing clinical center records from the time of randomization. This effort was facilitated by an ongoing ALLHAT Heart Failure Validation Study, which identified all cases of hospitalized (fatal and nonfatal) HF events. The Validation Study provided conclusive evidence that ALLHAT findings of chlorthalidone-based treatment's superiority over amlodipine-, lisinopril-, and doxazosin-based strategies in preventing the transition from hypertension to symptomatic HF were not due to misdiagnosis of HF by ALLHAT site physicians.[11] The purpose of this paper is to evaluate whether the type of pre-ALLHAT BP medication influenced the relationship of randomized drug treatment to hospitalized HF rates in ALLHAT.

METHODS

ALLHAT Study Design

The rationale and design of ALLHAT have been presented elsewhere.[10] Briefly, eligible participants had untreated hypertension (≥140/90 mm Hg and ≤180/110 mm Hg) or treated hypertension (eligible if BP <160/100 mm Hg treated with <3 medications) and were men and women, 55 years and older, who had at least 1 additional risk factor for CHD events. These risk factors included prior myocardial infarction (MI) or stroke (>6 months or age-indeterminate), history of coronary revascularization procedure, other documented atherosclerotic CVD, major ST depression or T-wave inversion on electrocardiography within past 2 years, type 2 diabetes mellitus, left ventricular hypertrophy (LVH), current cigarette smoking, and low high-density lipoprotein cholesterol (HDL-C) (<0.9 mmol/L [35 mg/dL]). Individuals with a history of symptomatic HF and/or known left ventricular ejection fraction <35% and/or required treatment for HF with one of the study drugs were excluded. The primary study end point was a composite of fatal CHD and nonfatal MI.

Unless the pre-randomization drug regimen required tapering for safety reasons, individuals continued any prior antihypertensive medications until randomization, at which point they stopped taking all previous medications. Double-blind treatment with the study drug was initiated the day after randomization. Participants (n=42,418) were recruited and randomly assigned to chlorthalidone, amlodipine, lisinopril, or doxazosin in a ratio of 1.7:1:1:1.

Termination of Doxazosin Arm

The doxazosin arm was terminated early because of futility in finding a primary outcome difference and an increased incidence of CVD, especially HF, relative to chlorthalidone. The HF results for this arm have been presented in detail elsewhere.[6,9] Following termination of the doxazosin group, 33,357 participants remained in the antihypertensive study.

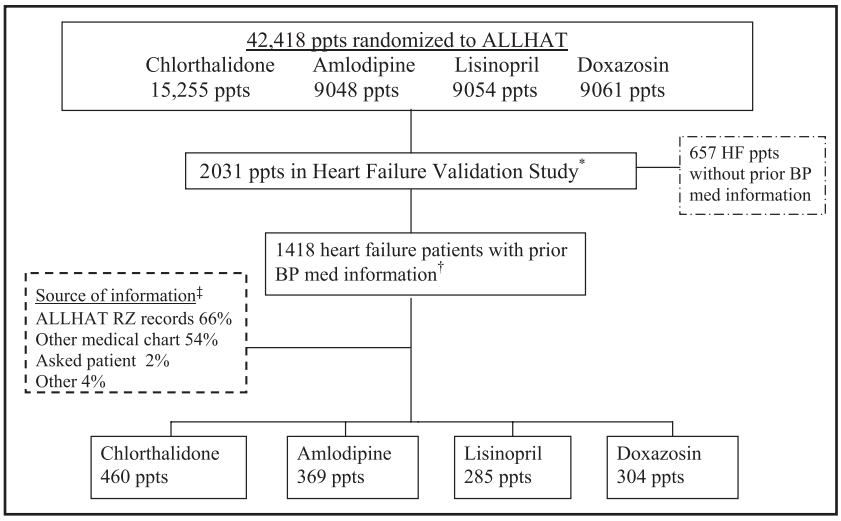

*Figure 1. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Participants in Prior Blood Pressure Medication Study: Population for this study, by assigned treatment group, who were hospitalized for heart failure (HF) while in ALLHAT and for whom information on pre-randomization blood pressure (BP) medication is available. RZ indicates randomization. *Approximately 95% of ALLHAT participants (ppts) with hospitalized HF were part of the Heart Failure Validation Study (HFVS). †HFVS requested HF records for 2031 participants with HF during ALLHAT. Of those, 1374 participants had prior BP medication information; 657 participants did not have prior BP medication information. Prior BP medication information for an additional 44 HF participants in the doxazosin treatment was subsequently received, for a total of 1418 HF participants with prior BP medication information. ‡More than one source of BP information was used for some patients.*

Participant Population for Prior Drug Study

At randomization it was noted whether participants had previously taken antihypertensive medications, but specific information as to the type of medications was not collected. Following termination of the doxazosin arm of the study, a validation study was undertaken in which all hospitalized (fatal and nonfatal) HF events in all 4 arms were centrally reviewed by independent reviewers blinded to treatment assignment.[11] Using lists of cases identified for the purpose of the HF Validation Study, at the end of the participant close-out phase, the clinic investigators and study coordinators were asked to go back to their records and retrieve information on specific antihypertensive medications (and doses, if known) used prior to enrollment in ALLHAT and to complete a study form with that information. Only one mailing of the form was undertaken. Prestudy antihypertensive medication information was received for approximately two thirds (1418) of the 2031 HF participants for whom it was requested. These 1418 participants comprise the participant population for this paper (Figure 1).

Statistical Analyses

Percent of hospitalized HF patients on class of prior (pre-randomization) antihypertensive drug (diuretics, ACE inhibitors, calcium channel blockers, and β-blockers) was tabulated for the entire study and for those with HF during the first year. The interaction of randomized drug group and class of prior antihypertensive drug as they influenced the occurrence of hospitalized HF during the first year was examined using a case-only analysis, with a case defined as an HF event with pre-enrollment BP medication information.[12] In complete (cases and non-cases) analyses, treatment–covariate interactions as well as the individual influences of treatment and covariate can be examined with regard to the odds or risk of disease occurrence using logistic regression. A case-only analysis can be used to examine such treatment–covariate interactions but this approach cannot assess the individual influences of treatment or a covariate. As a form of methodologic validation, we present both analyses to see that they yield quite similar results for the interaction of prior treatment using any antihypertensive medication with effect of treatment assignment. In a case-only analysis, 2 assumptions are implicit: (1) the covariate and treatment are independent, and (2) the outcome is rare (<5%–10%). These assumptions are a prerequisite of using an OR as an estimate of the relevant risk ratio. In a large randomized clinical trial such as ALLHAT, randomization ensures the independence of covariates and study treatment. In addition, the assumption of low disease risk is not needed, as the interaction measure on a multiplicative scale is a ratio of risk ratios.[13]

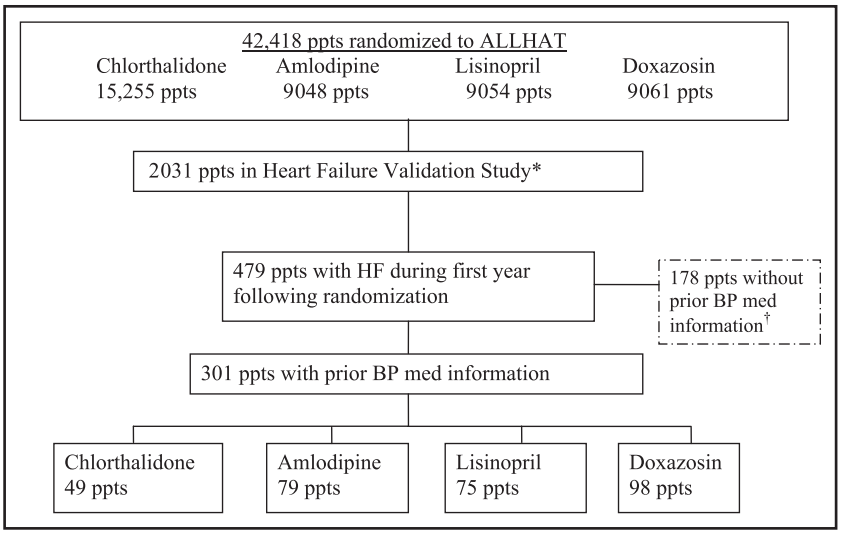

*Figure 2. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Participants in Prior Blood Pressure Medication Study with heart failure (HF) during year one: Subgroup of population for this study, by assigned treatment group, hospitalized for HF during the "first year" following randomization and for whom information on pre-randomization BP medication is available. *Approximately 95% of ALLHAT participants (ppts) with hospitalized HF were part of the Heart Failure Validation Study. †Participants were excluded if they developed HF after year 1 or if their prior medication data was received after study data cut-off deadline.*

Univariate analyses and multivariate analyses controlling for the use of open-label antihypertensive drugs were performed. In performing multivariate case-only analyses, we assessed a specified treatment–covariate interaction (eg, "prior diuretic use"–"ALLHAT treatment" interaction) while accounting for other possible treatment–covariate interactions (eg, "prior ACE inhibitor use"–"ALLHAT treatment" interaction or "prior calcium channel blocker use"–"ALLHAT treatment" interaction). In addition, multiple imputation[14] was used to examine whether the one third of participants who developed hospitalized heart failure within the first year and for whom we could not obtain type of prior BP medication might have influenced the results. The imputation was accomplished by imputing a class or prior drug use from sampling from the known distribution of such within each of the ALLHAT randomized treatment groups.

RESULTS

Baseline Characteristics and Use of Prior BP Medications

Figure 1 and Figure 2 describe the population for this study. During ALLHAT, 2207 individuals developed fatal/hospitalized HF. Of those, hospital records were requested for 2031 patients with hospitalized (fatal and nonfatal) events as part of the HF Validation Study.[11] Of these, 479 occurred during the first year following randomization. We were able to obtain information on BP medication use prior to ALLHAT enrollment for 1418 (69%) of the 2031 HF cases, including 301 (63%) of the 479 events that occurred during the first year following randomization. Table I shows the baseline characteristics of the participants who developed hospitalized HF within the first year and for whom we subsequently obtained type of prior BP medication (n=301) vs those in whom we did not (n=178). With the exception of race (P=.02) and other CV disease (P<.01), these groups' other 25 baseline characteristics were similar. Examining data on all hospitalized HF cases, means and distributions of the participants with data on type of prior BP medication were similar to the 657 with no data (data not shown).

Participants could have been taking one, multiple, or no medications for BP prior to study entry (Table II). At the time of randomization, about 47% of participants who developed HF during ALLHAT were taking a calcium channel blocker, 39% a diuretic, 37% an ACE inhibitor, and 17% a β-blocker. Among participants who developed hospitalized HF during the first year after randomization, percentages on prior diuretic therapy were similar in the treatment groups: chlorthalidone (45%), amlodipine (47%), lisinopril (52%), and doxazosin (48%). The chlorthalidone group also had the largest percentage of participants taking ACE inhibitors (43%), vs 42% in the amlodipine

Table I. Baseline Characteristics of Participants With HF During the First Year Following Randomization:[a] Participants With Prior BP Medication Data vs Participants Without Prior BP Medication Data

Patients With HF	Prior BP Medication Information 301	No Prior BP Medication Information 178	*P* Value
Age, mean (SD), y	70.9 (8.9)	70.9 (7.8)	NS
Race, No. (%)			.02
Black	107 (35.5)	79 (44.4)	
White	189 (62.8)	92 (51.7)	
Other	5 (1.7)	7 (3.9)	
Female, No. (%)	142 (47.2)	80 (44.9)	NS
Taking BP medications at baseline, No. (%)	284 (94.4)	170 (95.5)	NS
SBP, mm Hg, mean (SD)	150.0 (16.4)	148.8 (17.0)	NS
DBP, mm Hg, mean (SD)	83.0 (11.4)	81.6 (10.9)	NS
Cigarette smoking, No. (%)			NS
Current	64 (21.3)	26 (14.6)	
Past	135 (44.9)	79 (44.4)	
Never	102 (33.9)	73 (41.0)	
ASCVD,[b] No. (%)	200 (66.5)	106 (59.6)	NS
Eligibility criteria,[c] No. (%)			
History of MI or stroke	110 (36.5)	58 (32.6)	NS
History of coronary revascularization	61 (20.3)	31 (17.4)	NS
Other ASCVD	107 (35.6)	42 (23.6)	<.01
History of diabetes	137 (45.5)	86 (48.3)	NS
Major ST-wave abnormality	32 (10.7)	19 (10.9)	NS
HDL-C <35	24 (7.8)	22 (12.4)	NS
LVH by ECG	72 (23.9)	40 (22.5)	NS
LVH by ECHO	23 (7.7)	7 (4.0)	NS
History of CHD, No. (%)	121 (40.5)	59 (33.7)	NS
BMI, kg/m^2, mean	29.8 (6.7)	30.1 (7.5)	NS
Aspirin use, No. (%)	123 (40.9)	73 (41.0)	NS
Estrogen use (women), No. (%)	14 (9.9)	11 (13.8)	NS
Serum potassium, mEq/L, mean (SD)	4.3 (0.5)	4.4 (0.7)	NS
Fasting glucose, mg/dL, mean (SD)	127.6 (59.4)	129.5 (57.8)	NS
Total cholesterol, mg/dL, mean (SD)	215.9 (47.9)	212.6 (48.8)	NS
HDL-C, mg/dL, mean (SD)	44.8 (14.5)	45.4 (13.6)	NS
LDL-C, mg/dL, mean (SD)	135.4 (40.8)	135.6 (40.5)	NS
Fasting triglycerides, mg/dL, mean (SD)	181.3 (138.6)	161.3 (165.8)	NS
Serum creatinine, mg/dL, mean (SD)	1.1 (0.4)	1.2 (0.4)	NS

Abbreviations: BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; ECHO, echocardiogram; ECG, electrocardiogram; HF, heart failure; LDL-C, low density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; NS, not significant; SBP, systolic blood pressure. [a]Refers to participants in the Heart Failure Validation Study for whom prior blood pressure (BP) medication data was requested. [b]Atherosclerotic cardiovascular disease (ASCVD) consists of a history of stroke, coronary revascularization, major ST-segment depression or T-wave inversion, and "other ASCVD." [c]For trial eligibility, participants had to have at least 1 other risk factor in addition to hypertension. Thus, the indicated risk factors are not mutually exclusive or exhaustive and may not represent prevalence. To convert high-density lipoprotein (HDL-C) to mmol/L, multiply by 0.0259.

group, 36% in the lisinopril group, and 41% in the doxazosin group. For both first year and the entire duration of follow-up of participants who developed hospitalized HF, there were no significant differences between the randomized drug groups in the proportion of type of BP drugs taken prior to entry.

Interaction of Assigned ALLHAT Treatment and Prior BP Treatment

Table III is used to illustrate the comparability of results in assessing interactions when using the case-only method vs the complete data set method. Herein we examine the interaction of initial (step 1) ALLHAT drug treatment and use of any prior

Table II. Participants With Hospitalized or Fatal HF During ALLHAT: Number (% of Treatment Group) of Patients on Prior BP Medications

Prior BP Medication[a]	Treatment Assignment				
	Chlorthalidone	Amlodipine	Lisinopril	Doxazosin	Total
Participants with HF during ALLHAT[b]					
Diuretics	168 (37)	152 (41)	106 (37)	127 (42)	541 (39)
Calcium channel blocker	211 (46)	173 (47)	129 (45)	149 (49)	641 (47)
ACE inhibitor	177 (38)	145 (39)	99 (35)	103 (34)	513 (37)
β-Blocker	80 (17)	53 (14)	63 (22)	44 (17)	240 (17)
No. of participants with HF during ALLHAT	460	369	285	304	1418
Participants with HF within the first year following randomization[b]					
Diuretics	22 (45)	37 (47)	39 (52)	47 (48)	146 (49)
Calcium channel blocker	17 (35)	35 (44)	38 (51)	46 (47)	136 (45)
ACE inhibitor	21 (43)	33 (42)	27 (36)	40 (41)	121 (40)
β-Blocker	5 (10)	9 (11)	18 (24)	10 (10)	42 (14)
No. of participants with HF during first year	49	79	75	98	301

Abbreviations: ACE, angiotensin-converting enzyme. ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. [a]Participants may have been receiving 1, multiple, or no prior blood pressure (BP) medications. [b]Refers to participants with heart failure (HF) for whom prior BP drug information was available (cases).

BP medication in relation to occurrence of hospitalized HF cases. Specifically, Table III compares the case-only interaction-ORs with the corresponding interaction-OR obtained from an analysis of the complete data set (cases and noncases). Both yielded similar estimates. For the amlodipine-chlorthalidone comparison, the complete data set interaction-OR was 2.04 (*P*=.26) and the case-only interaction-OR was 2.07 (*P*=.25). Here the interaction-OR represents the odds of developing hospitalized HF in the first year for those taking amlodipine vs those taking chlorthalidone among participants who had been taking prior BP medications (OR, 2.91; 95% CI, 2.00–4.25) divided by the odds of developing hospitalized HF during the first year for those taking amlodipine vs those taking chlorthalidone among participants who had not been taking prior BP medications (OR, 1.43; 95% CI, 0.43–4.69). For the lisinopril–chlorthalidone comparison, the complete data set interaction-OR was 5.13 (*P*=.052) (OR, 2.88; 95% CI, 1.97–4.20, for those who took prior BP medications, compared with OR, 0.56; 95% CI, 0.11–2.78, for those who did not take prior BP medications) and case-only interaction-OR was 5.09 (*P*=.052); for the doxazosin–chlorthalidone comparison, the interaction-ORs and *P* values were virtually the same for the complete data set and case-only results (OR, 3.28; *P*=.06–.8). When looking at amlodipine+lisinopril+doxazosin vs chlorthalidone, the ORs and *P* values were very similar for the complete data set

Table III. Interactions of Step 1 Treatment and Use of Any Prior BP Medications for Occurrence of Fatal and Hospitalized HF During First Year Following Randomization

Randomized Comparison	Complete Data Set (Cases and Non-Cases)		Case[a] Only	
	OR[b]	*P* Value	OR	*P* Value
Amlodipine vs chlorthalidone	2.04[c]	.26	2.07	.25
Lisinopril vs chlorthalidone	5.13[d]	.05*	5.09	.05*
Doxazosin vs chlorthalidone	3.28[e]	.08	3.28	.06
(A+L+D) vs chlorthalidone	3.05[f]	.04	3.06	.04

Abbreviations: A, amlodipine; D, doxazosin; L, lisinopril. *P=.052. [a]Refers to participants with heart failure (HF) for whom prior blood pressure (BP) drug information was available (cases). [b]Odds ratio (OR) for the interaction of step 1 treatment and use of any prior BP medication is derived, for each step 1 treatment comparison, from the quotient of the OR of those who took prior BP medications over the OR of those who did not take prior BP medications. [c]OR (A vs C)=2.91 (2.00 vs 4.25) for those on prior medications; 1.43 (0.43 vs 4.69) for those not on prior medications. [d]OR (L vs C) = 2.88 (1.97 vs 4.20) for those on prior medications; 0.56 (0.11 vs 2.78) for those not on prior medications. [e]OR (D vs C) = 3.71 (2.58 vs 5.33) for those on prior medications; 1.13 (0.32 vs 4.01) for those not on prior medications. [f]OR ([A+L+D] vs C) = 3.17 (2.29 vs 4.38) for those on prior medications; 1.04 (0.38 vs 2.81) for those not on prior medications.

Table IV. Interaction of Treatment and "Specific" Prior BP Medications Used in Participants With Heart Failure During the First Year Following Randomization

Randomized Comparisons Prior Antihypertensive Drug	Univariate		Multivariate[a]	
	OR	95% CI	OR	95% CI
Amlodipine vs chlorthalidone				
Diuretic	1.08	0.53–2.21	1.17	0.56–2.45
ACE inhibitor	0.96	0.47–1.97	1.13	0.51–2.48
Calcium channel blocker	1.50	0.72–3.13	1.60	0.73–3.54
β-Blocker	1.13	0.36–3.60	1.18	0.35–3.94
Lisinopril vs chlorthalidone				
Diuretic	1.33	0.65–2.74	1.52	0.70–3.29
ACE inhibitor	0.75	0.36–1.57	0.83	0.38–1.80
Calcium channel blocker	1.93	0.92–4.06	2.34*	1.06–5.17
β-Blocker	2.78	0.96–8.07	3.16*	1.05–9.51
Doxazosin vs chlorthalidone				
Diuretic	1.13	0.57–2.25	1.55	0.73–3.30
ACE inhibitor	0.92	0.46–1.84	1.03	0.49–2.17
Calcium channel blocker	1.67	0.82–3.39	1.73	0.79–3.81
β-Blocker	1.00	0.32–3.10	1.46	0.41–5.27
(A+L+D) vs chlorthalidone				
Diuretic	1.17	0.63–2.16	1.40	0.72–2.71
ACE inhibitor	0.88	0.47–1.63	1.05	0.54–2.06
Calcium channel blocker	1.68	0.89–3.19	1.66	0.84–3.28
β-Blocker	1.51	0.56–4.07	1.84	0.61–5.60

Abbreviations: A, amlodipine; ACE, angiotensin-converting enzyme; CI, confidence interval; D, doxazosin; L, lisinopril; OR, odds ratio. *$P<.05$. [a]Controlled for use of other classes of blood pressure (BP) drugs.

and case-only analyses (OR, 3.05 and 3.06, respectively; $P=.04$). Thus, the interaction-ORs of step 1 medication and the use of prior BP medication do not differ between the entire data set and case-only analyses.

Table IV shows the interactions of the randomized treatments and the specific type of prior BP medication with respect to its effect on hospitalized HF during the first year. There was no significant interaction between type of prior drug and risk of hospitalized HF in the comparison of amlodipine vs chlorthalidone, lisinopril vs chlorthalidone, and doxazosin vs chlorthalidone for any of the univariate analyses. Multiple imputations were used to impute the type of prior BP medication for the 178 first-year hospitalized HF cases on whom we did not have such data. The results were similar and the conclusion did not change (data not shown). Finally, the interaction analyses were also performed by race: blacks and non-blacks. There were no significant differences from the overall analyses (data not shown).

Multivariate analyses were performed to account for the fact that many individuals had been taking more than 1 medication at baseline. In such analyses, we are assessing a specified treatment–covariate interaction while accounting for other possible treatment–covariate interactions. No significant interactions were noted, except for the lisinopril–chlorthalidone comparison. Here, it appears that individuals who had been taking either a calcium channel blocker or a β-blocker prior to ALLHAT entry had a higher OR than those who had not been taking these types of BP medications.

DISCUSSION

When the main results of ALLHAT were published, one of the most important findings was an increase in treated nonhospitalized, hospitalized, or fatal HF relative risk (1.38 for amlodipine, 1.19 for lisinopril, and 1.80 for doxazosin) compared with chlorthalidone.[4,6] Differences in BP lowering did not account fully for these differences in HF.[7] The validity of HF diagnoses was questioned by some,[8] suggesting the possibility of a large number of false-positives. Further examination of the HF outcome, especially when limiting the evaluation to fatal/hospitalized HF, showed that diuretics were superior to the other drug classes in preventing HF.[7,11,15] Furthermore, the validity of hospitalized HF diagnoses was confirmed in the HF Validation Study.[11]

One major factor surrounding the HF results from ALLHAT was prior BP treatment. Since a

large proportion of trial participants would have likely been taking diuretics and ACE inhibitors previously and withdrawn from these drugs at the time of randomization, this could have unmasked subclinical HF present at the time of randomization. Baseline exclusions would not necessarily identify this group because clinical markers such as echocardiography and chest x-rays were not required to be performed by the study at randomization and many participants may not have had these clinical data available when determining study eligibility. However, the distributions of prestudy diuretics and ACE inhibitors across ALLHAT treatment groups were similar.

In addition, while withdrawal could lead to immediate or short-term reversal of drug effects, there is evidence to show that they can persist after discontinuation well beyond what their half-life would predict. In the Hypertension Control Program (HCP), a follow-up to the Hypertension Detection and Follow-Up Program (HDFP),[16,17] participants who had remained on the diuretic chlorthalidone for 5 years were withdrawn from antihypertensive treatment but continued to benefit from their effects long after stopping the drugs. At 1-year post-drug withdrawal, 50% remained normotensive, at 2 years, 40% remained normotensive, and at 3 years, 18% remained normotensive.[16] These data demonstrate that at least for some antihypertensive patients, the drug effects persist after withdrawal much longer than is predicted by the half-life kinetics of the drugs. Other studies have observed this delay in reaching hypertensive BPs after drug withdrawal during only a few months of follow-up observation.[18,19] Thus, discontinuation of BP medications does not imply the immediate cessation of their effects.

Since the specific entry drug treatment was only ascertained for the hospitalized HF group and not the entire ALLHAT group, we used the case-only method of analysis.[12] Hospitalized HF, which developed during the first year of follow-up, was also examined because it was suggested that this group would be the most likely to experience the postulated unmasking effect. The results show no evidence from either the first year or the full follow-up period that class of prior drug treatment had any role in influencing hospitalized HF incidence in ALLHAT.

This conclusion should be considered in view of several caveats. One possible problem could be confounding by indication. We do not know the reason why the specific drugs were originally prescribed. ALLHAT participants were at high risk for CV disease. It can be assumed that the choice of drug prescription pre-ALLHAT was not random. We have limited ability to adjust for such factors. A similar problem is the use of additional medications added during the study. Nonetheless, hospitalized HF risk decreased with chlorthalidone vs amlodipine during the first year and subsequently, and the hospitalized HF risk was decreased for chlorthalidone vs lisinopril during the first year. It is unlikely that these differences can be attributed in large measure to prior BP medication use, concomitant medications, or follow-up BP. Rather, they point to the likely superiority of diuretics vs other classes, at least in the short term in comparison with ACE inhibitors, in preventing HF in hypertensive patients.[7] A third point is that approximately one third of the data for type of drug at entry was missing; however, an analysis (with imputation) of the entire group yielded similar results. If all the data were available, case-only analysis is as valid as full data set analysis (as demonstrated in Table III). The width of the 95% CIs reflects the limitations of the sample size. Given the available data and the use of case-only analysis, we were able to reasonably address the question.

In addition to providing important data relevant to the HF treatment effects, this study represents an application of a case-only analysis. This can be a valuable method in situations where important questions are posed that can only be addressed by retrieving data not collected at baseline.

Thus, although not designed to determine why such large differences in HF outcomes were observed in ALLHAT, but, rather, if pre-study medications might be related, this ALLHAT substudy based on case-only analysis produced no support for the hypothesis that pre-randomization treatment with a particular class of drugs, especially diuretics, modified the differences between the randomized groups regarding HF risk.

Acknowledgments and disclosures: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was supported by a contract with the National Heart, Lung, and Blood Institute. 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. The following disclosures are made: Richard Grimm, MD, PhD: Research grants from Pfizer, Merck, Novartis; speakers' bureau, Pfizer. Barry R. Davis, MD, PhD; Linda B. Piller, MD, MPH; Jeffrey A. Cutler, MD, MPH; Richard Dart, MD; Richard Graumlich, MD; Otelio Randall, MD: No disclosures. Karen L. Margolis, MD, MPH: Consultant, King Pharmaceuticals. Joshua Barzilay, MD: Research grant, Boehringer Ingelheim. Robert Murden, MD: Expert witness.

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