Role of Diuretics in the Prevention of Heart Failure
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

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Background—Hypertension is a major cause of heart failure (HF) and is antecedent in 91% of cases. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) stipulated assessment of the relative effect of chlorthalidone, lisinopril, and amlodipine in preventing HF.

Methods and Results—ALLHAT was a double-blind, randomized, clinical trial in 33 357 high-risk hypertensive patients aged ≥55 years. Hospitalized/fatal HF outcomes were examined with proportional-hazards models. Relative risks (95% confidence intervals; P values) of amlodipine or lisinopril versus chlorthalidone were 1.35 (1.21 to 1.50; <0.001) and 1.11 (0.99 to 1.24; 0.09). The proportional hazards assumption of constant relative risk over time was not valid. A more appropriate model showed relative risks of amlodipine or lisinopril versus chlorthalidone during year 1 were 2.22 (1.69 to 2.91; <0.001) and 2.08 (1.58 to 2.74; <0.001), and after year 1, 1.22 (1.08 to 1.38; P=0.001) and 0.96 (0.85 to 1.10; 0.58). There was no significant interaction between prior medication use and treatment. Baseline blood pressures were equivalent (146/84 mm Hg) and at year 1 were 137/79, 139/79, and 140/80 mm Hg in those given chlorthalidone, amlodipine, and lisinopril. At 1 year, use of added open-label atenolol, diuretics, angiotensin-converting enzyme inhibitors, and calcium channel blockers in the treatment groups was similar.

Conclusions—HF risk decreased with chlorthalidone versus amlodipine or lisinopril use during year 1. Subsequently, risk for those individuals taking chlorthalidone versus amlodipine remained decreased but less so, whereas it was equivalent to those given lisinopril. Prior medication use, follow-up blood pressures, and concomitant medications are unlikely to explain most of the HF differences. Diuretics are superior to calcium channel blockers and, at least in the short term, angiotensin-converting enzyme inhibitors in preventing HF in hypertensive individuals. (Circulation. 2006;113:2201-2210.)

Key Words: heart failure • diuretics • hypertension

Heart failure (HF) has an annual incidence of 550 000 and a prevalence of 5 million1; it is the most frequent reason for hospital admission in individuals aged ≥65 years in the United States.2-3 The individual, community, and national burden of this disease is likely to increase in the future owing to rising levels of obesity, diabetes mellitus, and hypertension4-6 and the growing number of individuals surviving acute myocardial infarction.

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HF has a subsequent 20% to 50% 1-year mortality rate.6,7 Coronary heart disease (CHD) and hypertension account for most HF cases,8 but despite major improvements in the detection and treatment of these conditions, HF incidence, morbidity, and mortality remain high. Some antihypertensive...
agents (eg, diuretics and angiotensin-converting enzyme [ACE] inhibitors) have been shown to reduce HF incidence in patients with hypertension.9–12 The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) provided an opportunity to assess the relative benefit of these agents in the largest clinical trial in hypertension to date.13 HF rates (treated but not hospitalized, hospitalized, or fatal) were significantly higher (P<0.001) by 37% and 19% in the amldopidine and lisinopril groups, respectively, than in the chlorthalidone group. When limited to hospitalized/fatal HF, rates were significantly higher in the amldopidine group by 35% (P<0.001) and nonsignificantly higher in the lisinopril group by 11% (P=0.09).

Our purpose was to examine in depth the ALLHAT HF findings. We limited our assessment to hospitalized/fatal HF cases, making our definition comparable to that of previously reported trials.13 Hereinafter, unless otherwise specified, HF refers to hospitalized/fatal HF. We examine (1) HF outcomes by treatment group overall, within subgroups, and over time; (2) risk factors and underlying conditions associated with HF; (3) relation of antihypertensive medication use before trial entry to initial HF occurrence; (4) relation of follow-up blood pressure (BP) and additional antihypertensive drug use as modifying factors in HF occurrence; and (5) post-HF mortality, overall and by treatment group.

Methods

Study Design

The ALLHAT rationale and design have been reported previously.13,14 Participants were men and women aged ⩾55 years who had stage 1 or 2 hypertension plus an additional risk factor for CHD. Individuals with a history of hospitalized or treated symptomatic HF stage 1 or 2 hypertension plus an additional risk factor for CHD. Also, it was mandated by protocol; however, hospital discharge and death summaries were required and were reviewed by Coordinating Center staff blinded to treatment assignment.

We conducted several HF validity studies.16–17,19 The largest one, the Heart Failure Failure Study, reviewed almost all HF hospitalizations and deaths (3031 among 2091 patients) and all relevant material surrounding these events (including hospital records, death certificates, radiographic reports, and left ventricular ejection fraction measurements).19 Specially trained cardiology fellows blinded to treatment assignment reviewed each case according to both ALLHAT and Framingham Heart Study criteria20 and provided a global judgment as well. A more detailed report on this study is forthcoming.

Statistical Analyses

Data were analyzed by intention to treat. ALLHAT was designed to examine the primary CHD outcome for 3 comparisons using the Dunnett procedure, which required a critical z score of 2.37 rather than 1.96.11,14 We examined first HF event using the prespecified comparisons of amldopidine versus chlorthalidone and lisinopril versus chlorthalidone plus the post hoc comparison of amldopidine versus lisinopril. The last comparison was undertaken because it was done in the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTC),12 and because the recent Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial11 presented HF results for amldopidine versus an angiotensin receptor blocker. Cumulative event rates were calculated, and the proportional-hazards model was used to compare treatment groups or model for risk factors.22 Hazard ratios (relative risks [RRs]) and 95% confidence intervals (CIs) were obtained from the proportional-hazards model. The proportional hazards assumption was examined with log-log survival plots and tests for a treatment-by-time (time-dependent) interaction term. If the proportional hazards assumption was not met, 2 time periods (≤1 year and >1 year) were used in model treatment effects for HF in a proportional-hazards model (see Appendix in the online-only Data Supplement). Heterogeneity of effects in prespecified subgroups (men and women; participants <65 and ⩾65 years of age; black and nonblack participants; and diabetic and nondiabetic participants) was examined by testing for treatment–covariate interaction with the proportional-hazards model. Follow-up use of additional medications and follow-up BP measures were tabulated. A proportional-hazards model with time-dependent covariates was used to assess the effect of follow-up BPs on treatment differences. Mortality after first reported HF event was examined overall and by treatment group.

Given the many multivariate, subgroup, and interaction analyses performed, statistical significance at a level of P<0.05 should be interpreted with caution. Unfortunately, there is no consensus on the appropriate statistical procedure for handling multiplicity due to secondary outcomes (or multiple analyses such as subgroups and regression) in the absence (or presence) of significant findings with the primary end point.21,22 Using the more stringent method of Davis,23 the 13 listed secondary clinical outcomes in the main ALLHAT report,13 and 3 comparisons, a probability value of 0.05(3×13)=0.0013 would be needed for statistical significance. For consistency with Davis,23 a probability value of 0.0013 would be needed for statistical significance.

Results

Baseline Characteristics

Detailed baseline characteristics of ALLHAT participants have been reported previously.13 Briefly, mean age was 67
years, 53% were male, 25% had a history of CHD, and 36% had a history of diabetes mellitus.

Baseline characteristics of patients who did or did not develop HF are shown in Table 1. Also, baseline characteristics that were independently associated with HF development are presented in Table 2. After adjustment for other baseline characteristics, patients who developed HF were older; were more likely to be male, diabetic, a current smoker, or taking antihypertensive medications before trial entry; had a higher body mass index, higher systolic BP, lower diastolic BP, and higher heart rate; and were more likely to have a history of CHD and evidence of left ventricular hypertrophy. HF risk increased more than 6% for each year of age, and absolute HF risk over a mean of 4.9 years increased from 3.2% at age 55 to 5.5% at age 65 to 9.2% at age 75 years.

Prior antihypertensive medication use was associated with a 30% higher HF risk. These results were similar within each treatment group (data not shown).

Early Divergence of HF Curves
HF occurred in 1773 patients (724, 578, and 471 in the chlorthalidone, amlodipine, and lisinopril groups, respectively) over a mean follow-up of 4.9 years. These patients experienced 2577 HF events (1064, 836, and 677 in the chlorthalidone, amlodipine, and lisinopril groups, respectively) during the trial. Kaplan-Meier plots of HF incidence by treatment group showed the chlorthalidone group had a lower HF rate than either the amlodipine or lisinopril groups (Figure 1). RRs were 1.35 (95% CI 1.21 to 1.50, P<0.001) for amlodipine versus chlorthalidone, 1.11 (95% CI 0.99 to 1.24, P=0.09) for lisinopril versus chlorthalidone, and 1.22 (95% CI 1.08 to 1.38, P=0.001) for amlodipine versus lisinopril. HF validation study data showed that percentages of agreement with site physician diagnosis were 71%, 80%, and 84% for ALLHAT, Framingham Heart Study, and reviewers’ judgment criteria, respectively. In addition, treatment-group differences using confirmed cases were, if agreement with site physician diagnosis were 71%, 80%, and 84% for ALLHAT, Framingham Heart Study, and reviewers’ judgment criteria, respectively. In addition, treatment-group differences using confirmed cases were, if

![Figure 1. Cumulative event rates for hospitalized/fatal HF by treatment group. All comparisons are unadjusted. The amlodipine group had a 35% higher risk of hospitalized and fatal HF vs chlorthalidone (RR 1.35, 95% CI 1.21 to 1.50, P<0.001). No significant difference was observed for lisinopril vs chlorthalidone (RR 1.10, 95% CI 0.98 to 1.23, P<0.11). The amlodipine group had a 23% higher risk of hospitalized and fatal HF than lisinopril (RR 1.23, 95% CI 1.09 to 1.38, P<0.001).](image)
anything, larger than previously published, eg, based
on Framingham criteria, RR 1.42 (95% CI 1.25 to 1.62,
P<0.001) for amlodipine versus chlorthalidone and RR 1.13 (95% CI 0.99 to 1.30, P=0.07) for lisinopril versus chlorthalidone.13,19

Observed HF differences were larger earlier in the follow-up. The lisinopril group had a lower HF rate than the amlodipine group, but event curves did not separate until later. A test of the proportional hazards assumption for Cox regression revealed that RRs were not constant over time. A Cox regression that used a time-dependent indicator variable (>1 year versus ≤1 year) was utilized.

Figure 2 shows RRs for the first year and beyond. The RR for amlodipine versus chlorthalidone was 2.22 (95% CI 1.69 to 2.91; P<0.001) for year 1 and 1.22 (95% CI 1.08 to 1.38; P=0.001) beyond year 1; for lisinopril versus chlorthalidone, it was 2.08 (95% CI 1.58 to 2.74; P<0.001) for year 1 and 0.96 (95% CI 0.85 to 1.10; P=0.58) beyond year 1. The RR for amlodipine versus lisinopril was 1.07 (95% CI 0.82 to 1.38; P=0.63) for year 1 and 1.27 (95% CI 1.10 to 1.46; P=0.001) beyond year 1. Relative benefits of chlorthalidone versus amlodipine or lisinopril in reducing these HF outcomes were consistent across major relevant subgroups (Figure 3), ie, there were no significant interactions.

HF Development and Relation to Other Outcomes
HF development was associated with a 6.6-fold (95% CI 6.1 to 7.1) increase in death rate (P<0.0001) and an 11.7-fold (95% CI 10.6 to 12.4) increase in cardiovascular death rate (P<0.0001). HF occurred in 372 patients (20.6%) with and 1401 (4.4%) without an interim myocardial infarction, which resulted in a 5.7-fold (95% CI 4.8 to 6.8) increased HF risk if a myocardial infarction occurred (P<0.0001). Hospitalization for HF occurred in 1594 patients (2353 HF hospitalizations). Of patients hospitalized with HF, 72.0% were hospitalized once, 23.3% on 2 to 3 occasions, and 4.7% on 4 or more occasions.

Prior Use of Antihypertensive Agents
Approximately 10% of participants entered ALLHAT with no history of taking antihypertensive drugs. Prior medication use was associated with increased HF risk, especially in the first year (RR 1.42, 95% CI 1.18 to 1.71; P<0.001). However, there was no significant interaction between prior use and treatment group for HF (P for interaction=0.15) during the first year, ie, the relative benefits of chlorthalidone were consistent regardless of prior antihypertensive agent use.

Data on the type of prior antihypertensive medication used were not collected within ALLHAT but were collected for a subset (n=1115) of HF cases (n=1773). Among HF cases, ≈47% were taking calcium channel blockers (CCBs), 37% were taking ACE inhibitors, and 39% were taking diuretics. Patients could be taking >1 medication. By case-only analysis,26 there was no evidence for any statistically significant interaction between prior drug type (eg, diuretic) and treatment group for the outcome of HF overall or during the first year.25 A more detailed report on this component is in preparation.

**Figure 2.** Cumulative event rates for hospitalized (Hosp)/fatal HF by treatment group. All comparisons are unadjusted. A, Year 1: both the amlodipine and lisinopril groups had a significantly higher risk of hospitalized/fatal HF than the chlorthalidone group (RR 2.22, 95% CI 1.69 to 2.91, P<0.001 and RR 2.08, 95% CI 1.58 to 2.74, P<0.001, respectively). No significant difference was observed for amlodipine vs lisinopril (RR 1.07, 95% CI 0.82 to 1.38, P=0.63). B, >Year 1: the amlodipine group had a 22% higher risk of hospitalized/fatal HF than the chlorthalidone group (RR 1.22, 95% CI 1.08 to 1.38, P=0.001). No significant difference was observed for lisinopril vs chlorthalidone (RR 0.96, 95% CI 0.85 to 1.10, P=0.58). The amlodipine group had a 27% higher risk of hospitalized/fatal HF than the lisinopril group (RR 1.27, 95% CI 1.10 to 1.45, P=0.001).
Use of Step-Up Antihypertensive Agents

The addition of step 2 and step 3 drugs could have been a possible contributor to the lessening or cessation of the divergence of the HF curves after 1 year. Table 3 shows open-label medication use by treatment group at selected time points. Given the large sample sizes, differences of $\pm 0.5\%$ between treatment groups are significant at $P<0.05$. At 1 year, percentages of patients to whom open-label step-up drugs were given in addition to chlorthalidone, amlodipine, and lisinopril were, respectively, atenolol (a protocol-specified step-up drug), 17.3%, 16.6%, and 19.7%; diuretic, 6.0%, 9.5%, and 9.3%; ACE inhibitors, 4.8%, 5.2%, and 5.9%; and CCBs, 4.7%, 4.7%, and 7.3%. Table 4 shows use of any of the 3 types of open-label medication (diuretics, ACE inhibitors, or atenolol) that could be considered protective with respect to HF. By year 1, the percentages of all participants given such medication were 91.4%, 27.7%, and 88.9% for the chlorthalidone, amlodipine, and lisinopril groups, respectively, and by year 3, these percentages were 89.3%, 41.7%, and 86.7%. Table 4 also shows that a greater proportion of the chlorthalidone group remained on the assigned treatment or same class throughout follow-up than in the other groups.

BP Differences

BPs were equal at baseline (146/84 mm Hg). At 3 months, mean systolic/diastolic BP levels were 140/81, 142/81, and 143/82 mm Hg in the chlorthalidone, amlodipine, and lisinopril groups, respectively. At 6 months, they were 138/80, 140/80, and 141/81 mm Hg; and at 1 year, they were 137/79, 138/79, and 140/80 mm Hg, respectively. Mean follow-up systolic BP was $\approx 1$ mm Hg higher overall in the amlodipine group versus the chlorthalidone group and $\approx 2$ mm Hg higher (4 mm Hg higher in black participants) overall in the lisinopril group versus the chlorthalidone group. For more detail on race differences, see Wright et al.\textsuperscript{27} RRs remained statistically significant after adjustment for follow-up systolic BP as a time-dependent covariate in Cox regression models. Adjustment only slightly modified the HF RRs for amlodipine versus chlorthalidone for all participants in the first year (2.22 to 2.16) and after the first year (1.22 to 1.18), as well as for lisinopril versus chlorthalidone for all participants in the first year (2.08 to 2.01), and after the first year (0.96 to 0.93).

Post-HF Mortality

Post-HF mortality curves are displayed in Figure 4. Mortality rates after hospitalized HF occurrence were high relative to...
Diuretics and ACE inhibitors have been shown to prevent HF in patients with hypertension compared to placebo in major trials that included patients with hypertension. Findings with CCB-based treatment have been less conclusive. Most of these trials utilized diuretics and/or β-blockers as active therapeutic regimens.

Other more recent trials have compared the relative benefits of these agents on HF events. The Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) study randomized >16,000 patients to a CCB or diuretic/β-blocker–based regimen. BP was reduced similarly between the 2 groups. HF occurred 30% more often in patients receiving the CCB.

The BPLTTC meta-analysis included data from 29 trials and 162,341 patients. This analysis demonstrated that treatment with CCB-based therapies resulted in a nonsignificant 21% increase in HF incidence compared with placebo despite a significant (3/0–4 mm Hg) BP reduction and 33% higher risk (95% CI 21% to 47%) than with the diuretic/β-blocker regimen (with only a 1/0-mm Hg BP difference). Because the analysis was restricted to hospitalized/fatal HF, minor side effects of CCBs, such as peripheral edema, were unlikely to be responsible for this finding. Treatment based on ACE inhibitors resulted in 18% fewer HF events than with CCBs (95% CI –27% to 8%) despite a minimal BP difference (1/1 mm Hg). These data indicate that CCBs are less effective in preventing HF than other treatment regimens, and they support the ALLHAT findings.

BPLTTC analyses showed that ACE inhibitor–based therapies resulted in a significant 18% decrease in HF incidence compared with placebo, with a significant (−5/−2 mm Hg) BP reduction and a 7% nonsignificant higher risk than with diuretic/β-blocker regimens (95% CI −4% to 19%) and minimal BP difference (2/0 mm Hg). These data indicate that ACE inhibitors are no more effective in preventing HF than diuretics/β-blockers and are consistent with ALLHAT findings. BPLTTC analyses that compared CCBs or ACE inhibitor use with diuretics/β-blockers had a large contribution of data from ALLHAT (on the order of 33% for ACE inhibitors and 50% for CCBs); however, when ALLHAT was removed from these analyses, the conclusions remained the same.

The validity of the HF outcome has been verified. Traditional risk factors for HF were in agreement with previous studies (eg, Framingham). Several analyses,
including postevent medication use and postevent mortal-
ity, have demonstrated this. In addition, the Heart Failure
Validation Study clearly confirmed the original observed
treatment differences, on the basis of an independent
central review that used both ALLHAT and Framingham
criteria.\textsuperscript{19}

ALLHAT HF results appear to differ by time periods
(\leq 1 year and > 1 year). At 1 year, HF incidence for
lisinopril was double that of chlorthalidone, but this
increased incidence diminished by year 6 to result in an
overall 0.4% absolute difference throughout follow-up.
Several possible explanations for this phenomenon were
explored. One possibility examined was that participants
who had previously been taking diuretics had “subclinical
HF” that had been well treated. According to this hypo-
thesis, on entry into ALLHAT, those patients who were
assigned to chlorthalidone would do well, but those given
amlodipine or lisinopril would not. Our analyses indicate
that prior use of any antihypertensive medication increases
subsequent HF risk but that there was no significant
influence on treatment effects during the first year. Post
hoc power calculations show that for the study parameters,
we would have \( \approx 80\% \) power to detect a significant
interaction of a 4-fold difference or more.

\textbf{TABLE 4. Use of Antihypertensive Medication With and Without HF Prevention Activity by Treatment by Year*}

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<thead>
<tr>
<th>Sample size for which treatment information is available</th>
<th>6 Months</th>
<th>1 Year</th>
<th>3 Years</th>
<th>5 Years</th>
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<tbody>
<tr>
<td>Chlorthalidone</td>
<td>12 918</td>
<td>13 853</td>
<td>12 330</td>
<td>11 172</td>
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<td>8157</td>
<td>7179</td>
<td>6454</td>
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Assigned medication or same class only but not taking
open-label HFPA drugs, %†

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<th>6 Months</th>
<th>1 Year</th>
<th>3 Years</th>
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<tr>
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<tr>
<td>Lisinopril</td>
<td>68.8</td>
<td>58.4</td>
<td>43.5</td>
<td>38.1</td>
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Assigned medication or same class plus HFPA drugs, %

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<th>1 Year</th>
<th>3 Years</th>
<th>5 Years</th>
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<td>18.7</td>
<td>24.0</td>
<td>33.6</td>
<td>36.6</td>
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Not taking assigned or same class of medication but taking
HFPA drugs, %

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<th>1 Year</th>
<th>3 Years</th>
<th>5 Years</th>
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<td>9.6</td>
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Not taking assigned or same class of medication or
HFPA drugs, %

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<th>1 Year</th>
<th>3 Years</th>
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<td>11.1</td>
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Any HFPA drug, %

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<th>1 Year</th>
<th>3 Years</th>
<th>5 Years</th>
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<td>88.8</td>
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<td>Lisinopril</td>
<td>91.7</td>
<td>88.9</td>
<td>86.7</td>
<td>85.0</td>
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HFPA indicates HF prevention activity.

*Antihypertensive drugs with HF prevention activity include diuretics, ACE inhibitors, and atenolol.
†HFPA drugs for the chlorthalidone group do not include open-label diuretics, and for the lisinopril group, they do
not include open-label ACE inhibitors, because they appear in the category “same class.”

\textbf{Figure 4. Years from hospitalized HF to death.}
Data on BP medication type taken before ALLHAT initiation were collected on approximately two thirds (1418/2091) of HF patients. There was no significant impact of prior medication type used (diuretics, CCBs, ACE inhibitors, or β-blockers) on treatment-group differences for HF occurrence in the first year.

Another possibility is that chlorthalidone was initially superior in lowering BP, but the higher percentage use of step 2 medication, specifically atenolol, and the add-on, open-label use of diuretics and ACE inhibitors in the amlodipine and lisinopril groups caused subsequent diminution in HF differences. A related explanation is that the BP difference itself was higher between groups shortly after baseline than later, and subsequent use of additional medication equalized the BPs, thus reducing HF differences between treatment groups.

In an analysis limited to events after the first year, HF RR for amlodipine versus chlorthalidone was 1.40 for those undergoing monotherapy at year 1. The RR was 1.22 for those undergoing either monotherapy or combined therapy at year 1. A similar analysis for lisinopril versus chlorthalidone yielded RRs of 1.10 and 1.04, respectively. This suggests that concomitant medications might account for some but not all of the observed HF differences between treatment groups during the trial. It is difficult to see how BP differences could explain most or all of the treatment differences. Using data from the Prospective Studies Collaboration, a 2- to 3-mm Hg increase in systolic BP would increase the 5-year HF risk by approximately 4% to 5%. On the basis of the data from the Framingham Study, a 2- to 3-mm Hg increase would result in a 1% to 2% increase in 4-year HF risk for men and approximately a 1% increase for women. Because the increase in HF risk was 35% for amlodipine versus chlorthalidone and 10% for lisinopril versus chlorthalidone, data from these epidemiological studies would not support this hypothesis. In addition, accounting for follow-up BP in statistical analyses within ALLHAT did not substantially ameliorate the increased risk.

Another possible explanation for the differential findings by time is that diuretics have a more immediate effect on HF prevention than ACE inhibitors. Diuretics have been shown to have a preventive effect for HF that begins at trial onset. ACE inhibitors prevent HF compared with placebo, but several studies show that the effect is not immediate. We note that the recent VALUE trial has also shown differing results for different time periods. In VALUE, high-risk hypertensive patients were randomized to valsartan- or amlodipine-based regimens. HF events were similar between groups for the first 2 years of the study, and thereafter, a strong trend emerged toward fewer events in patients receiving valsartan.

We presented an explanation for why differences in HF incidence would not have affected differences in total mortality during the trial’s duration. This phenomenon was noted in BPLTTC analyses by Steffen et al and was explained by the absolute HF risk being low and the increase in RR being outweighed by even a small reduction in the higher absolute risks for stroke and CHD. Also, differences in the number of HF events during the trial would result in only very small differences in the number of deaths. Planned post-trial mortality surveillance will examine whether a mortality difference emerges.

This study provides evidence for the superiority of diuretics over CCBs and ACE inhibitors in HF prevention. Although achieving optimal BP control is important in HF prevention and control, the type of antihypertensive agent used also plays a role. Guidelines from the 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for HF prevention and treatment recommend use of ACE inhibitors, diuretics, and β-blockers, alone and in combination, especially because a significant proportion of patients with hypertension require >1 medication. The ALLHAT results are consistent with many other studies. Diuretics are superior to CCBs and, at least in the short-term, ACE inhibitors in preventing HF in high-risk patients with hypertension.

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Disclosures
Dr Davis has worked as a consultant for Takeda, Merck, and Glaxo Smith Kline. Dr Franklin has served on speakers’ bureaus for Boehringer Ingelheim, Merck, and Bristol-Myers Squibb; as an expert witness for La Follette, Johnson, De Haas, Fesler & Ames, Los Angeles, Calif, and Gordon, Thomas, Honeywell, Malanca, Peterson, & Dalheim LLP, Seattle, Wash; and as a consultant for AtCor Medical, Inc. Dr Leenen has received honoraria from Pfizer; has ownership interest in Bristol-Myers Squibb, Merck, Johnson and Johnson, and Schering Plough; and has worked as a consultant for Pfizer. Dr Mohiuddin has worked on research grants funded by Health Future Foundation, Nebraska Tobacco Settlement Biomedical Research Development Grants, and AstraZeneca; has served on the speakers’ bureau for AstraZeneca; has received honoraria from the American College of Cardiology and AstraZeneca; has ownership interest in Pfizer, Johnson and Johnson, and Abbot Laboratories; and has served as a consultant for Pfizer and AstraZeneca. Dr Papademetriou has received research grants from AstraZeneca; has worked on the speakers’ bureau for AstraZeneca; and has received honoraria from AstraZeneca. The other authors report no conflicts.

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Heart failure is the most frequent reason for hospital admission among people ≥65 years of age in the United States, and its 5-year mortality rate is approximately 40% to 50%. The societal and individual burden of this disease may increase in the coming years owing to rising levels of obesity, diabetes mellitus, and hypertension and growing numbers of acute myocardial infarction survivors. Because hypertension is antecedent in >90% of heart failure cases, the type of antihypertensive treatment used could influence heart failure risk. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) of 33,357 high-risk hypertensive participants 55 years or older randomly assigned to either a diuretic (chlorthalidone), a calcium channel blocker (amlodipine), or an angiotensin-converting enzyme inhibitor (lisinopril) provided an opportunity to examine this question for hospitalized and fatal heart failure outcomes. In the first year of ALLHAT, both the amlodipine and lisinopril groups showed increased heart failure risk compared with the chlorthalidone group, with relative risks of 2.22 (P<0.001) and 2.08 (P<0.001), respectively. After the first year, the amlodipine group continued to show significantly increased heart failure risk compared with the chlorthalidone group (relative risk 1.22, P=0.001), but the lisinopril group had heart failure risk equivalent to that of the chlorthalidone group (relative risk 0.96 [95% confidence interval 0.85 to 1.10], P=0.58). Further analyses failed to show that antihypertensive medication taken before randomization, blood pressure differences, or concomitant medications were major contributors to these treatment differences. For hypertensive patients, diuretics are superior to calcium channel blockers and, at least in the short term, superior to angiotensin-converting enzyme inhibitors in preventing heart failure.