Heart Failure With Preserved and Reduced Left Ventricular Ejection Fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

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Background—Heart failure (HF) developing in hypertensive patients may occur with preserved or reduced left ventricular ejection fraction (PEF \(\geq 50\%\) or REF \(<50\%\)). In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 42 418 high-risk hypertensive patients were randomized to chlorthalidone, amlodipine, lisinopril, or doxazosin, providing an opportunity to compare these treatments with regard to occurrence of hospitalized HFPEF or HFREF.

Methods and Results—HF diagnostic criteria were prespecified in the ALLHAT protocol. EF estimated by contrast ventriculography, echocardiography, or radionuclide study was available in 910 of 1367 patients (66.6\%) with hospitalized events meeting ALLHAT criteria. Cox regression models adjusted for baseline characteristics were used to examine treatment differences for HF (overall and by PEF and REF). HF case fatality rates were examined. Of those with EF data, 44.4\% had HFPEF and 55.6\% had HFREF. Chlorthalidone reduced the risk of HFPEF compared with amlodipine, lisinopril, or doxazosin; the hazard ratios were 0.69 (95\% confidence interval [CI], 0.53 to 0.91; \(P=0.009\)), 0.74 (95\% CI, 0.56 to 0.97; \(P=0.032\)), and 0.53 (95\% CI, 0.38 to 0.73; \(P<0.001\)), respectively. Chlorthalidone reduced the risk of HFREF compared with amlodipine or doxazosin; the hazard ratios were 0.74 (95\% CI, 0.59 to 0.94; \(P=0.013\)) and 0.61 (95\% CI, 0.47 to 0.79; \(P<0.001\)), respectively. Chlorthalidone was similar to lisinopril with regard to incidence of HFREF (hazard ratio, 1.07; 95\% CI, 0.82 to 1.40; \(P=0.596\)). After HF onset, death occurred in 29.2\% of participants (chlorthalidone/amlodipine/lisinopril) with new-onset HFPEF versus 41.9\% in those with HFREF (\(P<0.001\); median follow-up, 1.74 years); and in the chlorthalidone/doxazosin comparison that was terminated early, 20.0\% of HFPEF and 26.0\% of HFREF patients died (\(P=0.185\); median follow-up, 1.55 years).

Conclusions—in ALLHAT, with adjudicated outcomes, chlorthalidone significantly reduced the occurrence of new-onset hospitalized HFPEF and HFREF compared with amlodipine and doxazosin. Chlorthalidone also reduced the incidence of new-onset HFREF compared with lisinopril. Among high-risk hypertensive men and women, HFPEF has a better prognosis than HFREF. (Circulation. 2008;118:2259-2267.)

Key Words: angiotensin-converting enzyme inhibitors ■ antihypertensive agents ■ calcium channel blockers ■ diuretics ■ heart failure ■ hypertension ■ ventricular ejection fraction

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, double-blind, multicenter clinical trial designed to determine whether treatment initiated with a calcium channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), or an \(\alpha\)-adrenergic blocker (doxazosin) would reduce the incidence of fatal coronary heart disease (CHD) or nonfatal myocardial infarction more than treatment with a thiazide-type diuretic (chlorthalidone) in high-risk patients \(\geq 55\) years of age with hypertension. Secondary outcomes were all-cause mortality and major cardiovascular disease events, including heart failure (HF).\(^1\) Compared with
chlorothalidone, new-onset HF occurred more frequently in patients randomized to amlodipine, lisinopril, and doxazosin-based strategies, with significant hazard ratios of 1.38, 1.19, and 1.80, respectively. To address concerns about the ALLHAT HF diagnosis, heart failure validation study (HFVS) was designed to adjudicate all hospitalized HF events in a centrally blinded manner. All patients randomized to amlodipine, Lisinopril, or doxazosin were entered into a computer adjudication system to determine if they had HF. Those adjudicated as having HF were then included in analyses of HF outcomes. The HFVS was sponsored by the National Heart, Lung, and Blood Institute. Its design and rationale have been published previously. Men and women ≥55 years of age with hypertension and 1 additional risk factor for CHD were included. Persons with a history of treated symptomatic HF or history of hospitalization for HF or known LVEF <35% were excluded. However, measurement of LVEF was not dictated by the ALLHAT protocol. Participants were randomized to step 1 drugs of chlorthalidone, amlodipine, lisinopril, or doxazosin in a ratio of 1:7:1:1. All collaborating ALLHAT clinical centers obtained institutional review board approval, and participants gave written informed consent. Follow-up visits were at 1, 3, 6, 9, and 12 months and every 4 months thereafter up to a range of possible follow-up of 3 years 8 months to 8 years 1 month. Patients were treated in a double-blind fashion to achieve a goal blood pressure (BP) of <140/90 mm Hg by titrating the step 1 randomized drug and adding step 2 (atenolol, clonidine, or reserpine) or step 3 (hydralazine) open-label agents supplied by the study as clinically indicated. The primary outcome was fatal CHD or nonfatal myocardial infarction. Major prespecified secondary outcomes were all-cause mortality, fatal and nonfatal stroke, combined CHD (primary outcome), coronary revascularization, or hospitalized angina, and combined cardiovascular disease (combined CHD; stroke; other treated angina; fatal, hospitalized, or treated nonhospitalized HF; or peripheral arterial disease). Study outcomes were assessed by the clinical centers at follow-up visits, and hospitalized or fatal outcomes were based on clinical reports supported by discharge summaries and/or death certificates.

In the HFVS, relevant hospital records were obtained for all hospitalized HF events that occurred between February 1, 1994, and March 31, 2002 (February 15, 2000, for the doxazosin/chlorthalidone comparison). The records were abstracted by cardiologists fellows blinded to treatment assignment. Six algorithmic approaches based on ALLHAT and Framingham criteria were assigned by computer. In addition, the reviewers rendered their independent clinical judgment on whether the patient had HF. This article is based on the ALLHAT definition of 1 sign (rales, ankle edema ≥2+, tachycardia ≥120 bpm, cardiomegaly by chest x-ray, chest x-ray characteristic of HF, S1 gallop, or jugular venous distension) and 1 concurrent symptom (paroxysmal nocturnal dyspnea, orthopnea, or dyspnea at rest or on ordinary exertion). Plans for analyses of outcomes by LVEF were prespecified in the HFVS protocol. HF cases were classified into those with LVEF ≥50% (HFPEF) and those with LVEF <50% (HFREF).

Among the 42,418 ALLHAT participants, 1,367 (70.6% of the 19,35 participants evaluated in the HFVS) had hospitalized HF events validated by ALLHAT criteria. Of these, LVEF assessment was available in 910 (66.6%). The source of LVEF was cardiac catheterization report in 77 (8.5%), echocardiography study in 785 (86.5%), and radionuclide study in 48 (5.3%). Actual numerical values were available for 709 events (77.9%). For the other 201 events, laboratory ranges based on the categories of normal, borderline, and impaired were available to accurately assign LVEFs of <50% or ≥50%. The analyses comparing HFPEF with HFREF presented here are based on these 910 participants with ≥1 HF events. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Analyses
Baseline characteristics were compared across 3 HF groups (HFPEF, HFREF, and no HF data) using the Z test for continuous covariates and χ² analysis for categorical data. Multivariate Cox regression models were used to examine differences in risk of the 3 HF outcomes across randomized treatment comparisons unadjusted and controlling for age, race, gender, prior treatment for hypertension, systolic BP (SBP), diastolic BP (DBP), heart rate, current smoking, type 2 diabetes mellitus, left ventricular hypertrophy (LVH) by clinic-reported ECG, evidence of CHD, estimated glomerular filtration rate, body mass index, and high-density lipoprotein cholesterol (HDL). Participants were censored at the time of death, development of another type of HF, or loss to follow-up. For example, if HF with no LVEF data was the outcome, an individual who developed HFREF first was censored at that time. In addition, multinomial multivariate logistic models were used to examine treatment differences. Cumulative event rates were calculated with the Kaplan-Meier method. Case fatality rates for HF also were examined by use of Kaplan-Meier curves and Cox regression. These mortality analyses start at the time of the HF diagnosis. Additionally, post-HF mortality risk was obtained with multivariate Cox regression with the HF event as a time-dependent variable. A value of P<0.05 was used to indicate statistical significance for the results. However, given the many analyses performed, statistical significance at this level should be interpreted with caution.

Results
Characteristics of Participants With HFPEF and HFREF
Among 910 HF cases with LVEF assessment, HFPEF was present in 404 cases (44%), and HFREF was present in the remaining 506 cases (56%). One-hundred forty-eight of 709 cases (20.9%) had LVEF ≥50% (HFREF). Additional, those with HFPEF had a higher mean body mass index (31.9 versus 29.9 kg/m²; P<0.001) and a higher mean HDL cholesterol (1.2 versus 1.1 mmol/L [45.2 versus 42.5 mg/dL]; P<0.01), and tended to have a higher mean SBP.
In the general ALLHAT population, 46.8% of participants were women, and 25.6% had a history of CHD; mean body mass index was 29.7 kg/m²; mean HDL cholesterol was 1.2 mmol/L; and mean SBP was 146.3 mm Hg. No statistically significant differences were found between these LVEF groups in terms of age, race, diabetic status, LVH by clinic-reported or centrally Minnesota-coded ECG, lipid values, potassium, glucose, estimated glomerular filtration rate, or assignment to statins. When these characteristics were examined by assigned therapy (data not shown), the patterns noted above were essentially similar.

### Table 1. Baseline Characteristics by EF

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>PEF (EF ≥50%) (n=404)</th>
<th>REF (EF &lt;50%) (n=506)</th>
<th>No EF Data (n=457)</th>
<th>PEF vs REF</th>
<th>PEF vs No EF</th>
<th>REF vs No EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>69.6 (8.1)</td>
<td>69.7 (7.8)</td>
<td>69.8 (7.8)</td>
<td>0.90</td>
<td>0.78</td>
<td>0.87</td>
</tr>
<tr>
<td>55–64, n (%)</td>
<td>119 (29.5)</td>
<td>134 (26.5)</td>
<td>126 (27.6)</td>
<td>0.32</td>
<td>0.54</td>
<td>0.70</td>
</tr>
<tr>
<td>≥65, n (%)</td>
<td>285 (70.5)</td>
<td>372 (73.5)</td>
<td>331 (72.4)</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>259 (64.1)</td>
<td>311 (61.5)</td>
<td>247 (54.0)</td>
<td>0.91</td>
<td>0.05</td>
<td>0.13</td>
</tr>
<tr>
<td>Black</td>
<td>132 (32.7)</td>
<td>174 (34.4)</td>
<td>195 (42.7)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td>13 (3.2)</td>
<td>21 (4.2)</td>
<td>15 (3.3)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>208 (51.5)</td>
<td>191 (37.7)</td>
<td>196 (42.9)</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>78 (19.3)</td>
<td>93 (18.4)</td>
<td>85 (18.6)</td>
<td>0.72</td>
<td>0.79</td>
<td>0.93</td>
</tr>
<tr>
<td>Treated (antihypertensive), n (%)</td>
<td>383 (94.8)</td>
<td>470 (92.9)</td>
<td>427 (93.4)</td>
<td>0.24</td>
<td>0.40</td>
<td>0.74</td>
</tr>
<tr>
<td>ASCVD,* n (%)</td>
<td>246 (60.9)</td>
<td>329 (65.0)</td>
<td>307 (67.2)</td>
<td>0.20</td>
<td>0.05</td>
<td>0.48</td>
</tr>
<tr>
<td>History of CHD,† n (%)</td>
<td>129 (32.1)</td>
<td>196 (39.0)</td>
<td>184 (40.8)</td>
<td>0.03</td>
<td>0.01</td>
<td>0.58</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, n (%)</td>
<td>204 (50.5)</td>
<td>255 (50.4)</td>
<td>246 (53.8)</td>
<td>0.98</td>
<td>0.33</td>
<td>0.29</td>
</tr>
<tr>
<td>LVH‡ by ECG, n (%)</td>
<td>77 (19.1)</td>
<td>102 (20.2)</td>
<td>86 (18.8)</td>
<td>0.68</td>
<td>0.93</td>
<td>0.60</td>
</tr>
<tr>
<td>LVH‡ by echocardiogram, n (%)</td>
<td>27 (6.7)</td>
<td>25 (4.9)</td>
<td>23 (5.0)</td>
<td>0.26</td>
<td>0.30</td>
<td>0.95</td>
</tr>
<tr>
<td>LVH‡ by ECG/Minnesota code, n (%)</td>
<td>33 (8.2)</td>
<td>53 (10.5)</td>
<td>52 (13.0)</td>
<td>0.24</td>
<td>0.13</td>
<td>0.72</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (SD)</td>
<td>149.6 (16.4)</td>
<td>147.8 (16.3)</td>
<td>148.8 (16.0)</td>
<td>0.09</td>
<td>0.47</td>
<td>0.32</td>
</tr>
<tr>
<td>DBP, mean (SD)</td>
<td>80.6 (10.4)</td>
<td>81.5 (11.2)</td>
<td>82.5 (10.8)</td>
<td>0.22</td>
<td>&lt;0.01</td>
<td>0.19</td>
</tr>
<tr>
<td>Treated</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SBP, mean (SD)</td>
<td>149.0 (16.4)</td>
<td>146.7 (16.1)</td>
<td>148.0 (16.0)</td>
<td>0.04</td>
<td>0.39</td>
<td>0.23</td>
</tr>
<tr>
<td>DBP, mean (SD)</td>
<td>80.5 (10.4)</td>
<td>81.1 (11.1)</td>
<td>81.8 (10.6)</td>
<td>0.44</td>
<td>0.08</td>
<td>0.32</td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SBP, mean (SD)</td>
<td>160.7 (12.5)</td>
<td>161.4 (12.2)</td>
<td>160.0 (10.7)</td>
<td>0.84</td>
<td>0.85</td>
<td>0.64</td>
</tr>
<tr>
<td>DBP, mean (SD)</td>
<td>82.4 (10.0)</td>
<td>86.8 (11.7)</td>
<td>91.3 (10.8)</td>
<td>0.15</td>
<td>&lt;0.01</td>
<td>0.11</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>31.9 (7.5)</td>
<td>29.9 (6.4)</td>
<td>30.6 (7.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
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<tr>
<td>Mean (SD), mmol/L</td>
<td>7.8 (3.8)</td>
<td>8.0 (3.8)</td>
<td>8.0 (4.1)</td>
<td>0.50</td>
<td>0.50</td>
<td>0.95</td>
</tr>
<tr>
<td>≥6.993 mmol/L, n (%)</td>
<td>117 (40.5)</td>
<td>188 (46.8)</td>
<td>145 (43.8)</td>
<td>0.09</td>
<td>0.38</td>
<td>0.42</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mean (SD), mL/min−1·1.73 m²²</td>
<td>72.0 (19.6)</td>
<td>72.4 (21.7)</td>
<td>72.2 (21.7)</td>
<td>0.79</td>
<td>0.89</td>
<td>0.90</td>
</tr>
<tr>
<td>LDL, mean (SD), mmol/L</td>
<td>3.4 (1.0)</td>
<td>3.6 (1.1)</td>
<td>3.6 (1.0)</td>
<td>0.12</td>
<td>0.01</td>
<td>0.33</td>
</tr>
<tr>
<td>HDL, mean (SD), mmol/L</td>
<td>1.2 (0.4)</td>
<td>1.1 (0.3)</td>
<td>1.2 (0.4)</td>
<td>&lt;0.01</td>
<td>0.87</td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;0.9065 mmol/L, n (%)</td>
<td>86 (22.8)</td>
<td>136 (28.2)</td>
<td>105 (24.5)</td>
<td>0.07</td>
<td>0.57</td>
<td>0.21</td>
</tr>
<tr>
<td>Triglycerides, mean (SD), mmol/L</td>
<td>2.1 (1.5)</td>
<td>2.1 (1.6)</td>
<td>2.1 (1.5)</td>
<td>0.63</td>
<td>0.61</td>
<td>0.97</td>
</tr>
<tr>
<td>Assigned to pravastatin (LLT), n (%)</td>
<td>40 (9.9)</td>
<td>61 (12.1)</td>
<td>45 (9.8)</td>
<td>0.33</td>
<td>0.96</td>
<td>0.34</td>
</tr>
</tbody>
</table>

ASCVD indicates atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; and LLT, lipid-lowering therapy.

*History of MI or stroke, history of coronary revascularization, major ST-segment depression or T-wave inversion on any ECG in the past 2 years, other ASCVD (history of angina pectoris; history of intermittent claudication, gangrene, or ischemic ulcers; history of transient ischemic attack; coronary, peripheral vascular, or carotid stenosis ≥50% documented by angiography or Doppler studies; ischemic heart disease documented by reversible or fixed ischemia on stress thallium or dipyridamole thallium, ST depression ≥1 mm for ≥1 minute on exercise testing, or Holter monitoring; reversible wall motion abnormality on stress echocardiogram; ankle-arm index <0.9; abdominal aortic aneurysm detected by ultrasonography, computed tomography scan, or radiograph; or carotid or femoral bruits).

†Six subjects are missing CHD data (PEF, n=2; REF, n=4).

‡LVH ascertained from ECG or echocardiography by check box on enrollment form or Minnesota code as measured by ALLHAT on baseline ECG.
Symptoms and Signs in Participants With HFPEF and HFREF

The symptoms and signs of HF were similar in the 2 groups of participants. However, participants with HFPEF compared with those with HFREF were more likely to have bilateral ankle edema (66.6% versus 54.2%; P<0.001) or ankle edema of 2+ (38.1% versus 26.1%; P<0.001). They were less likely to have paroxysmal nocturnal dyspnea (29.0% compared with 35.4%; P<0.001), S3 gallop (9.7% versus 19.8%; P<0.001), hepatomegaly (2.2% versus 5.9%; P=0.006), and pulmonary vascular redistribution (16.1% versus 22.3%; P=0.02).

Treatment Effects in Participants With HFPEF and HFREF

Cox regression models were used to examine relative treatment effects for patients with HFPEF, HFREF, or HF with no EF data available versus patients with no HF (Table 2 and Figure 1) unadjusted and adjusted for baseline characteristics of age, race, gender, prior hypertension treatment, SBP, DBP, heart rate, smoking, diabetes mellitus, LVH by reported ECG, history of CHD, estimated glomerular filtration rate, body mass index, and HDL. Those with no EF data available showed results similar to those with HFPEF. Chlorthalidone significantly reduced the risk of overall hospitalized HF, HFPEF, and HF in patients with no EF data available compared with amlodipine, lisinopril, and doxazosin. Chlorthalidone also significantly reduced HFREF risk compared with amlodipine and doxazosin but had an effect similar to lisinopril. Multinomial logistic regression analyses also were performed and showed similar results (data not shown).

Prognosis of Participants With HFPEF and HFREF

Lower mortality was associated with HFPEF compared with HFREF during the remainder of the ALLHAT follow-up, with median times of 1.74 years (chlorthalidone/amlodipine/lisinopril) and 1.55 years (chlorthalidone/doxazosin). After the first HF hospitalization with HFPEF in the chlorthalidone/amlodipine/lisinopril comparison, 29.2% of participants died compared with 41.9% of those with HFREF (P<0.001). In the chlorthalidone/doxazosin comparison, these rates were 20.0% (HFPEF) and 26.0% (HFREF) (P=0.185; Table 3 and Figure 2). Among those with data available on the visit after HF, 51.6% of HFPEF patients (174 of 337), 59.7% of HFREF patients (249 of 417), and 47.9% of HF patients with no EF data (167 of 349) were on an angiotensin-converting enzyme inhibitor or β-blocker. In addition, at the post-HF visit, statin use was lower in the HFREF group (64.5%) than in the other HF groups (PEF, 75.4%; no EF data, 73.6%). The patterns of occurrence of death among participants with either HFREF or HFPEF by randomized drug treatment were similar, and no differences in the occurrence of death after HF by randomized drug treatment were seen (Figure 2). With time-dependent Cox regression, the hazard ratios for mortality for participants who developed HFPEF, HFREF, and HF with no EF data versus those who did not develop HF were 4.17, 5.76, and 6.04 (all P<0.001), respectively.

Discussion

Patients presenting with HF and PEF are heterogeneous.8,14,15,23,24 It is assumed that in most cases they have elevated left atrial pressures resulting in pulmonary congestion and dyspnea, but this may occur only transiently. The underlying pathophysiology usually includes loss of LV diastolic compliance resulting from LVH, interstitial abnormalities, or both.25–33 In addition, impaired diastolic relaxation (an active energy-requiring process), increased vascular stiffness, increased intravascular volume, or volume redistribution may contribute.12,28,34–36 Chronic hypertension and cardiovascular changes associated with aging, often associated with renal impairment, are the most common causes. Valvular abnormalities, myocardial ischemia, restrictive cardiomyopathy, and pericardial disease also may present with
Figure 1. Validated hospitalized HF, Validated HF by PEF, REF, and no EF data categories by treatment group (A through D, chlorthalidone [solid line]/amlodipine [dashed and dotted line]/lisinopril [dotted line]; E through H, chlorthalidone [solid line]/doxazosin [dashed and dotted line]).
in clinical practice, the focus is on the accurate diagnosis of HF, measurement of LVEF, and exclusion of alternative and reversible causes of this condition.\textsuperscript{39,40} At present, no proven therapy is available for this condition, and treatment is largely empirical, focusing on BP control and treating or avoiding intravascular volume overload.\textsuperscript{27,41}

As a result of its large number of patients and their prolonged prospective follow-up, the ALLHAT HFVS has provided an unrivaled opportunity to observe and characterize the occurrence of this condition. Furthermore, because ALLHAT compared 4 different classes of initial antihypertensive drugs, it provides unique information on the relative inhibition effects go beyond BP lowering in preventing HF in the pathophysiology of these presentations and confirm the occurrence of HF relative to doxazosin and amlodipine, it was statistically significant versus all 3 comparators. In the group with HFREF, however, although chlorthalidone reduced the risk of HF presenting with REF compared with amlodipine, lisinopril, or doxazosin. It also reduced the overall risk of HF and HF presenting with PEF compared with amlodipine, lisinopril, or doxazosin.

The findings from ALLHAT demonstrate what has previously been observed in registries and observational studies of patients with decompensated HF: In high-risk older treated hypertensive patients, HFPEF (when defined by an LVEF cut point of 50%) is somewhat less common than HFREF, occurs more frequently in women, has lower initial mortality than HFREF, and has a long-term outcome that is still poor. The low prevalence of ECG LVH by Minnesota code (11.7% overall) in those with HF outcomes seems at odds with other reports. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trials,\textsuperscript{42} the prevalence was 15.7%; in the Framingham Heart Study, it was 14% of those with REF and 22% of those with PEF;\textsuperscript{10} and in a study by Thomas et al.,\textsuperscript{19} it was 42% in those with REF and 22% in those with PEF. Measures of LVH at the time of HF in ALLHAT were not obtained, so the actual prevalence of LVH at the time of HF diagnosis is unknown.

The most important findings of this study relate to the observed differences in the occurrence of HF among the randomized treatment groups and their relationship to the associated LVEF presentation. EF data have not been available for patients developing HF in most previous hypertension treatment trials, although it is likely, given the generally older age of these patients, that many had HFPEF. Trials that have demonstrated a reduction in HF with antihypertensive therapy have, for the most part, used diuretic-based therapies or inhibitors of the renin-angiotensin system.\textsuperscript{41,43–45} In ALLHAT, chlorthalidone treatment was associated with a lower incidence of new-onset validated hospitalized HF than doxazosin, amlodipine, or lisinopril treatment. In patients with HFPEF, this difference was statistically significant versus all 3 comparators. In the group with HFREF, however, although chlorthalidone reduced the occurrence of HF relative to doxazosin and amlodipine, it was similar to lisinopril. These data suggest that differences exist in the pathophysiology of these presentations and confirm the observations of many HF trials that renin-angiotensin system inhibition effects go beyond BP lowering in preventing HF in patients with REF.\textsuperscript{41,45} However, in ALLHAT, a thiazide-type diuretic prevented HFREF as well as a renin-angiotensin system inhibitor.

Limitations of this analysis of ALLHAT data include the following: The evaluation of ventricular function was not dictated by the protocol; only hospitalized HF events were evaluated; assessment of LVEF was not available in a significant proportion of the patients; complete information on post-HF medication use was lacking; and post-HF mortality analyses were based on postrandomization data. However, the large number of HF events analyzed and the double-blind analyses lend credence to the results.

**Conclusions**

Compared with HFREF, HFPEF is common in treated patients with hypertension and is associated with lower case fatality, but the case fatality rate is still high. Using validated outcomes, we found that chlorthalidone significantly reduced the overall risk of HF and HF presenting with PEF compared with amlodipine, lisinopril, or doxazosin. It also reduced the risk of HF presenting with REF compared with amlodipine and doxazosin. Chlorthalidone was similar to lisinopril in...
reducing HF presenting with REF. On the basis of the data
from many HF trials, a combination of the last 2 agents would
be expected to be particularly effective in preventing HF in
this group.

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Figure 2. Mortality after occurrence of validated HF with PEF and REF in ALLHAT (A through C, chlorthalidone [solid line]/amlodipine
[dashed and dotted line]/lisinopril [dotted line]; D through F, chlorthalidone [solid line]/doxazosin [dashed and dotted line]).
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References


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**CLINICAL PERSPECTIVE**

Hypertension remains the greatest population-attributable risk for developing heart failure. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) of 42,418 high-risk hypertensive patients, 1,367 developed heart failure during follow-up. Of 910 with an estimate of left ventricular ejection fraction, 44% and 56% had preserved (ejection fraction ≥50%) and reduced ejection fraction, respectively. Mortality risk after heart failure onset was greatly increased in both the preserved and reduced ejection fraction groups compared with those who did not manifest heart failure, and heart failure patients with preserved ejection fraction had a lower case fatality rate than those with reduced ejection fraction. Compared with amlodipine and doxazosin, chlorthalidone reduced the incidence of heart failure with reduced and preserved ejection fraction; compared with lisinopril, chlorthalidone reduced the incidence of heart failure with preserved ejection fraction.
Heart Failure With Preserved and Reduced Left Ventricular Ejection Fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

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