Heart Failure

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 [≥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 ≥55 years of age with hypertension. Secondary outcomes were all-cause mortality and major cardiovascular disease events, including heart failure (HF). \(^1\) Compared with
Among the data collected in the HFVS were measurements of left ventricular ejection fraction (LVEF) reported in hospitalization records. Patients with reduced LVEF (REF) have primarily systolic dysfunction; those with preserved LVEF (PEF) have primarily diastolic dysfunction. Both presentations are common in hypertensive patients, and both are associated with high mortality and morbidity rates. Importantly, because HFPEF patients have generally been excluded from large clinical trials, little is known about the relative efficacy of commonly used antihypertensive medications in preventing these outcomes. The purposes of this article are to examine the incidence of HFPEF and HFREF in hospitalized HF patients by treatment assignment in ALLHAT and to determine whether differences exist in their subsequent survival.

Methods

ALLHAT 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 randomly assigned to step 1 drugs of chlorthalidone, amloidipine, lisinopril, or doxazosin in a ratio of 1.7:1:1:1. 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 clinician 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 (tales, ankle edema ≥2+, tachycardia ≥120 bpm, cardiomegaly by chest x-ray, chest x-ray characteristic of HF, S1 gallop, or jugular venous distention) 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, 1367 (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 EF 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 between 40% and 49%, 274 of 709 cases (38.6%) had LVEF <40%, and 150 of 709 cases (21.2%) had LVEF ≥40%.

Baseline characteristics of participants with hospitalized HFPEF and HFREF are shown in Table 1. Participants with HFPEF compared with those with HFREF were more likely to be women (51.5% versus 37.7%; P<0.001) and less likely to have a history of CHD (32.1% versus 39.0%; P=0.03). In addition, those with HFPEF had a higher mean body mass index (31.9 versus 29.9 kg/m²; P<0.001), had 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 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 $\geq$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>$\geq$65, n (%)</td>
<td>285 (70.5)</td>
<td>372 (73.5)</td>
<td>331 (72.4)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>259 (64.1)</td>
<td>311 (61.5)</td>
<td>247 (54.0)</td>
<td>0.91</td>
<td>0.05</td>
<td>0.13</td>
</tr>
<tr>
<td>Black</td>
<td>132 (32.7)</td>
<td>174 (34.4)</td>
<td>195 (42.7)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td>13 (3.2)</td>
<td>21 (4.2)</td>
<td>15 (3.3)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>208 (51.5)</td>
<td>191 (37.7)</td>
<td>196 (42.9)</td>
<td>$&lt;0.001$</td>
<td>0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>78 (19.3)</td>
<td>93 (18.4)</td>
<td>85 (18.6)</td>
<td>0.72</td>
<td>0.79</td>
<td>0.93</td>
</tr>
<tr>
<td>Treated (antihypertensive), n (%)</td>
<td>383 (94.8)</td>
<td>470 (92.9)</td>
<td>427 (93.4)</td>
<td>0.24</td>
<td>0.40</td>
<td>0.74</td>
</tr>
<tr>
<td>ASCVD,* n (%)</td>
<td>246 (60.9)</td>
<td>329 (65.0)</td>
<td>307 (67.2)</td>
<td>0.20</td>
<td>0.05</td>
<td>0.48</td>
</tr>
<tr>
<td>History of CHD,† n (%)</td>
<td>129 (32.1)</td>
<td>196 (39.0)</td>
<td>184 (40.8)</td>
<td>0.03</td>
<td>0.01</td>
<td>0.58</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, n (%)</td>
<td>204 (50.5)</td>
<td>255 (50.4)</td>
<td>246 (53.8)</td>
<td>0.98</td>
<td>0.33</td>
<td>0.29</td>
</tr>
<tr>
<td>LVH‡ by ECG, n (%)</td>
<td>77 (19.1)</td>
<td>102 (20.2)</td>
<td>86 (18.8)</td>
<td>0.68</td>
<td>0.93</td>
<td>0.60</td>
</tr>
<tr>
<td>LVH‡ by echocardiogram, n (%)</td>
<td>27 (6.7)</td>
<td>25 (4.9)</td>
<td>23 (5.0)</td>
<td>0.26</td>
<td>0.30</td>
<td>0.95</td>
</tr>
<tr>
<td>LVH‡ by ECG/Minnesota code, n (%)</td>
<td>33 (8.2)</td>
<td>53 (10.5)</td>
<td>52 (13.0)</td>
<td>0.24</td>
<td>0.13</td>
<td>0.72</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (SD)</td>
<td>149.6 (16.4)</td>
<td>147.8 (16.3)</td>
<td>148.8 (16.0)</td>
<td>0.09</td>
<td>0.47</td>
<td>0.32</td>
</tr>
<tr>
<td>DBP, mean (SD)</td>
<td>80.6 (10.4)</td>
<td>81.5 (11.2)</td>
<td>82.5 (10.8)</td>
<td>0.22</td>
<td>$&lt;0.01$</td>
<td>0.19</td>
</tr>
<tr>
<td>Treated</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (SD)</td>
<td>149.0 (16.4)</td>
<td>146.7 (16.1)</td>
<td>148.0 (16.0)</td>
<td>0.04</td>
<td>0.39</td>
<td>0.23</td>
</tr>
<tr>
<td>DBP, mean (SD)</td>
<td>80.5 (10.4)</td>
<td>81.1 (11.1)</td>
<td>81.8 (10.6)</td>
<td>0.44</td>
<td>0.08</td>
<td>0.32</td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (SD)</td>
<td>160.7 (12.5)</td>
<td>161.4 (12.2)</td>
<td>160.0 (10.7)</td>
<td>0.84</td>
<td>0.85</td>
<td>0.64</td>
</tr>
<tr>
<td>DBP, mean (SD)</td>
<td>82.4 (10.0)</td>
<td>86.8 (11.7)</td>
<td>91.3 (10.8)</td>
<td>0.15</td>
<td>$&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$</td>
<td>0.10</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td></td>
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</tr>
<tr>
<td>Mean (SD), mmol/L</td>
<td>7.8 (3.8)</td>
<td>8.0 (3.8)</td>
<td>8.0 (4.1)</td>
<td>0.50</td>
<td>0.50</td>
<td>0.95</td>
</tr>
<tr>
<td>$\geq$6.99 mmol/L, n (%)</td>
<td>117 (40.5)</td>
<td>188 (46.8)</td>
<td>145 (43.8)</td>
<td>0.09</td>
<td>0.38</td>
<td>0.42</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mean (SD), mL·min⁻¹·1.73 m⁻²</td>
<td>72.0 (19.6)</td>
<td>72.4 (21.7)</td>
<td>72.2 (21.7)</td>
<td>0.79</td>
<td>0.89</td>
<td>0.90</td>
</tr>
<tr>
<td>LDL, mean (SD), mmol/L</td>
<td>3.4 (1.0)</td>
<td>3.6 (1.1)</td>
<td>3.6 (1.0)</td>
<td>0.12</td>
<td>0.01</td>
<td>0.33</td>
</tr>
<tr>
<td>HDL, mean (SD), mmol/L</td>
<td>1.2 (0.4)</td>
<td>1.1 (0.3)</td>
<td>1.2 (0.4)</td>
<td>$&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 $\geq$50% documented by angiography or Doppler studies; ischemic heart disease documented by reversible or fixed ischemia on stress thallium or dipyridamole thallium, ST depression $\geq$1 mm for $\geq$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 paradoxical nocturnal dyspnea (29.0% compared with 35.4%; P=0.04), S3 gallop (9.7% versus 19.8%; P<0.001), hepatomegaly (2.2% versus 5.9%; P<0.001), 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. 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. In addition, impaired diastolic relaxation (an active energy-requiring process), increased vascular stiffness, increased intravascular volume, or volume redistribution may contribute. 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]).

No. at Risk
Chlorthalidone 15255 14953 13325 11624 6586 3212
Amlodipine 9048 8597 8266 7904 6889 3912
Lisinopril 9054 8548 8181 7790 6811 3909
No. at Risk
Chlorthalidone 15255 14953 13325 11624 6586 3212
Amlodipine 9048 8597 8266 7904 6889 3912
Lisinopril 9054 8548 8181 7790 6811 3909
No. at Risk
Doxazosin 9061 8063 6796 3870 1884
No. at Risk
Doxazosin 9061 8063 6796 3870 1884
this picture. 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. 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.

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 efficacy of these agents in preventing the occurrence of HF overall and in patients with either HFPEF or HFREF.

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 observations of many HF trials that renin-angiotensin system inhibition effects go beyond BP lowering in preventing HF in the pathophysiology of these presentations and confirm the similar to lisinopril. These data suggest that differences exist in the pathophysiology of these presentations and confirm 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 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 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 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 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 occurrence of HF relative to doxazosin and amlodipine, it was similar to lisinopril.
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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A complete list of members of the ALLHAT Collaborative Research Group has been published previously.3

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Disclosures
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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]).
Cushman has consulted for Bristol-Myers Squibb, Calpis, Forest Pharmaceuticals, King, Myogen, Novartis, Pfizer, Roche, Sankyo, Sanofi-Aventis, Sanofi-Synthelabo, and Takeda; has received honoraria from AstraZeneca, Boehringer Ingelheim, Forest Pharmaceuticals, Novartis, Pfizer, Roche, and Sankyo; and has received research grants from Abbott Laboratories, AstraZeneca, and Novartis. Dr Davis has consulted for BioMarin, GlaxoSmithKline, Merck, Proctor and Gamble, and Takeda. Dr Farber has ownership interest in Pfizer. Dr Ford has consulted for BioMarin. Dr Kostis has consulted for Pfizer and Schering Plough; has received research grants from Boehringer Ingelheim, KOS, and Pfizer; and has received honoraria from Lilly/ICOS, Pfizer, Sanofi-Aventis, and Schering Plough. Dr Massie has consulted for AstraZeneca, Bayer Corp, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Novacardia, Novartis, Sanofi-Synthelabo, and Scios; has received research grants from Bristol-Myers Squibb, Novacardia, and Sanofi-Synthelabo; and has received honoraria from Sanofi-Synthelabo. The other authors report no conflicts.

References


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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