Effects of Losartan in Women With Hypertension and Left Ventricular Hypertrophy

Results From the Losartan Intervention For Endpoint Reduction in Hypertension Study

Ingrid Os, Veronica Franco, Sverre E. Kjeldsen, Karin Manhem, Richard B. Devereux, Eva Gerds, Darcy A. Hille, Paulette A. Lyle, Peter M. Okin, Björn Dahlof, Suzanne Oparil

Abstract—Hypertension is a risk factor for cardiovascular disease and outcomes in women. These posthoc analyses from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study evaluated losartan- versus atenolol-based therapy on the primary composite end point of cardiovascular death, stroke, and myocardial infarction and other end points in 4963 women. Fewer events occurred in women versus men. Women in the losartan group had significant reductions in the primary end point (215 [18.2 per 1000 patient-years] versus 261 [22.5 per 1000 patient-years]; hazard ratio [HR]: 0.82 [95% CI: 0.68 to 0.98]; P=0.031), stroke (109 versus 154; HR: 0.71 [95% CI: 0.55 to 0.90]; P=0.005), total mortality (HR: 0.77 [95% CI: 0.63 to 0.95]; P=0.014), and new-onset diabetes (HR: 0.75 [95% CI: 0.59 to 0.94]; P=0.015) versus the atenolol group, with no between-treatment difference for myocardial infarction (HR: 1.02 [95% CI: 0.74 to 1.39]; P=0.925), cardiovascular mortality (HR: 0.86 [95% CI: 0.64 to 1.14]; P=0.282), or hospitalization for heart failure (HR: 0.94 [95% CI: 0.68 to 1.28]; P=0.677). More women in the losartan group required hospitalization for angina (HR: 1.70 [95% CI: 1.16 to 2.51]; P=0.007). Risk reductions for the primary composite end point, stroke, total mortality, and new-onset diabetes were significantly greater with losartan- versus atenolol-based treatment in women with hypertension and left ventricular hypertrophy in the LIFE study. The risk reductions for losartan, along with the tests for the interaction of treatment and gender, indicated that the treatment effect was consistent in men and women for all of the end points tested, with the exception of hospitalization for angina. (Hypertension. 2008;51:1103-1108.)

Key Words: gender ▪ hypertension ▪ left ventricular hypertrophy ▪ outcomes

Hypertension is a major risk factor for coronary artery disease and stroke and contributes significantly to cardiovascular and renal morbidity and mortality in women.1 Prevalence and severity of hypertension increase markedly with advancing age in women, such that after age 60 years, a majority of women have stage 2 hypertension (blood pressure [BP] ≥160/100 mm Hg) or receive antihypertensive treatment.2–4 Whether the age-related decline in BP control among women is related to inadequate intensity of treatment in the practice setting, to true treatment resistance because of biological factors, or to other factors is unclear.3–5

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study compared the angiotensin II type 1 receptor blocker (ARB) losartan with the β1-adrenergic receptor blocker atenolol for reducing cardiovascular morbidity and mortality in patients with hypertension and left ventricular hypertrophy (LVH).6 This posthoc analysis from the LIFE study evaluated the effects of the study treatments in women.

Methods

Study Population

The protocol design for the LIFE study has been published.6 Patients aged 55 to 80 years with hypertension and ECG LVH were eligible. Patients with systolic BP of 160 to 200 mm Hg, diastolic BP of 95 to 115 mm Hg, or both after 1 to 2 weeks of placebo were randomly assigned to either losartan 50 mg or atenolol 50 mg. The titration of drugs and add-on therapy have been described elsewhere.6–8 BP control was defined as <140/90 mm Hg. The study was approved by all of the relevant ethics committees, and all of the patients provided written informed consent.

Statistical Analysis

This is a posthoc analysis. The following end points were assessed by intention-to-treat analysis: primary composite end point of car-

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Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women Overall (N=4963)</th>
<th>Losartan (N=2487)</th>
<th>Atenolol (N=2476)</th>
<th>Men Overall (N=4230)</th>
<th>Losartan (N=2118)</th>
<th>Atenolol (N=2112)</th>
<th>P (Women vs Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.7 (7.0)</td>
<td>67.7 (7.0)</td>
<td>67.7 (7.0)</td>
<td>66.1 (6.9)</td>
<td>66.1 (7.0)</td>
<td>66.1 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4641 (93.5)</td>
<td>2331 (93.7)</td>
<td>2310 (93.3)</td>
<td>3862 (91.3)</td>
<td>1927 (91.0)</td>
<td>1935 (91.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>247 (5.0)</td>
<td>115 (4.6)</td>
<td>132 (5.3)</td>
<td>286 (6.6)</td>
<td>155 (7.3)</td>
<td>131 (6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>43 (0.9)</td>
<td>22 (0.9)</td>
<td>21 (0.8)</td>
<td>57 (1.3)</td>
<td>25 (1.2)</td>
<td>32 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>26 (0.5)</td>
<td>16 (0.6)</td>
<td>10 (0.4)</td>
<td>17 (0.4)</td>
<td>9 (0.4)</td>
<td>8 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (0.1)</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>8 (0.2)</td>
<td>2 (0.1)</td>
<td>6 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>175.3 (14.1)</td>
<td>175.2 (14.1)</td>
<td>175.5 (14.1)</td>
<td>173.3 (14.5)</td>
<td>173.3 (14.3)</td>
<td>173.4 (14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>97.1 (8.9)</td>
<td>97.3 (8.7)</td>
<td>97.0 (9.0)</td>
<td>98.6 (8.8)</td>
<td>98.7 (8.8)</td>
<td>98.5 (8.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75.5 (11.0)</td>
<td>75.6 (10.8)</td>
<td>75.4 (11.1)</td>
<td>71.8 (10.9)</td>
<td>71.9 (11.0)</td>
<td>71.8 (10.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.3 (5.3)</td>
<td>28.2 (5.4)</td>
<td>28.4 (5.3)</td>
<td>27.6 (4.0)</td>
<td>27.7 (3.9)</td>
<td>27.6 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Framingham risk score</td>
<td>17.1 (6.8)</td>
<td>17.0 (6.6)</td>
<td>17.3 (6.8)</td>
<td>28.6 (8.5)</td>
<td>28.5 (8.3)</td>
<td>28.6 (8.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cornell product, mm-ms</td>
<td>2925 (1027)</td>
<td>2925 (1015)</td>
<td>2908 (1009)</td>
<td>2716 (1065)</td>
<td>2714 (1075)</td>
<td>2710 (1002)</td>
<td>-0.001</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage, mV</td>
<td>28.2 (9.8)</td>
<td>28.2 (9.8)</td>
<td>28.2 (9.6)</td>
<td>32.2 (10.9)</td>
<td>32.0 (10.8)</td>
<td>32.2 (10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>666 (13.4)</td>
<td>321 (12.9)</td>
<td>345 (13.9)</td>
<td>833 (19.7)</td>
<td>408 (19.3)</td>
<td>425 (20.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated systolic hypertension*</td>
<td>797 (16.1)</td>
<td>388 (15.6)</td>
<td>409 (16.5)</td>
<td>529 (12.5)</td>
<td>272 (12.8)</td>
<td>257 (13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>634 (12.8)</td>
<td>302 (12.1)</td>
<td>332 (13.4)</td>
<td>561 (13.3)</td>
<td>284 (13.4)</td>
<td>277 (13.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>350 (7.1)</td>
<td>184 (7.4)</td>
<td>166 (6.7)</td>
<td>378 (8.9)</td>
<td>185 (8.7)</td>
<td>193 (9.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>646 (13.0)</td>
<td>346 (13.9)</td>
<td>300 (12.1)</td>
<td>823 (19.5)</td>
<td>425 (20.1)</td>
<td>398 (18.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>271 (5.5)</td>
<td>148 (6.0)</td>
<td>123 (5.0)</td>
<td>249 (5.9)</td>
<td>128 (6.0)</td>
<td>121 (5.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data reported are mean (SD) or percentage. NS indicates not significant.

Results

Patient Characteristics

Baseline characteristics are given in Table 1. Women were significantly older, had higher systolic but lower diastolic BP, and had higher heart rate than men. Isolated systolic hypertension (BP ≥160/<90 mm Hg) was more prevalent in women. Women had a lower mean Framingham risk score and less coronary heart disease and cerebrovascular disease than men, whereas the proportions of patients with peripheral arterial disease and diabetes did not differ between the sexes. LVH based on Cornell product criteria (corrected for sex) was higher in women; LVH based on Sokolow-Lyon voltage criteria was lower in women. Fewer women were smokers, but women had a higher mean body mass index than men. There were no significant treatment-by-gender differences in any of the baseline characteristics.

Study Drugs

Distribution of antihypertensive drugs added to study drug and hydrochlorothiazide did not differ between treatments or genders; however, there were trends for fewer women to be on monotherapy, more women to be on 2 drugs (including a diuretic), and fewer women to be on 3 drugs (Table S1, please see http://hyper.ahajournals.org).

Blood Pressure

BPs were reduced substantially in both treatment groups and in both genders within 1 month, and reductions were sustained throughout the trial (Figure 1). At year 5, mean systolic BP changes in women were −30.3 mm Hg in the losartan group and −29.4 mm Hg in the atenolol group. Mean diastolic BP changes in women were −16.7 mm Hg in the losartan group and −17.1 mm Hg in the atenolol group. Similar results were observed in men. Mean systolic BPs at year 5 in women were 145.3 mm Hg in the losartan group and 146.8 mm Hg in the atenolol group; mean diastolic BPs were 81.0 and 80.7 mm Hg, respectively. Systolic BPs were 2 to
3 mm Hg higher in women than in men, whereas diastolic BPs were ~1 mm Hg lower in women than in men at year 5, paralleling differences in baseline BP. In the study as a whole, BP control (<140/90 mm Hg) was achieved in 36.6% and 34.7% of losartan- and atenolol-treated participants, respectively, and in 35.9% and 32.3% of losartan- and atenolol-treated women, respectively.

Outcomes

End points by gender and treatment are summarized in Table 2. Fewer women in the losartan group compared with the atenolol group had a primary end point (215 [18.2 per 1000 patient-years] versus 261 [22.5 per 1000 patient-years]; HR: 0.82 [95% CI: 0.68 to 0.98]; P=0.031). Stroke occurred in 109 women treated with losartan versus 154 treated with atenolol (HR 0.71 [95% CI: 0.55 to 0.90]; P=0.005). Total mortality was reduced more in losartan-treated than atenolol-treated women (HR: 0.77 [95% CI: 0.63 to 0.95]; P=0.014).

New-onset diabetes was less frequent in the losartan group (HR: 0.75 [95% CI: 0.59 to 0.94]; P=0.015). No between-treatment differences were observed for women in myocardial infarction (HR: 1.02 [95% CI: 0.74 to 1.39]; P=0.925), cardiovascular mortality (HR: 0.86 [95% CI: 0.64 to 1.14]; P=0.282), or hospitalization for heart failure (HR: 0.94 [95% CI: 0.68 to 1.28]; P=0.677). More women required hospitalization for angina in the losartan group compared with the atenolol group (HR: 1.70 [95% CI: 1.16 to 2.51]; P=0.007). The P value of the treatment-gender interaction test for hospitalization for angina was 0.012 and for total mortality was 0.051. All of the other treatment-gender interaction P values were ≥0.4.

Overall, fewer events occurred in women than in men (Table 2). A gender difference in the primary composite end point was observed even after adjustment for baseline characteristics: 476 women (9.6%) and 620 men (14.7%; P<0.001) experienced a primary end point. Furthermore, all of the secondary end points tended to occur less frequently in women. HRs on treatment and tests for interaction of treatment and gender indicated that the treatment effect was consistent in men and women for all of the end points tested, with the exception of hospitalization for angina. Kaplan–Meier curves (Figure 2) illustrate the reduction in risk for the primary composite end point and stroke in both women and men treated with losartan compared with atenolol. Curves of the primary end point appeared to diverge within the first year of the study.

Adverse Events

Women had more adverse events (AEs) but fewer serious drug-related AEs than men (Table S2). AEs did not differ between treatments. However, drug-related AEs were more frequent in the atenolol group than in the losartan group, both in women (43.8% versus 37.3%) and in men (46.8% versus 37.2%). Serious AEs (ie, events causing hospitalization, prolongation of hospitalization, or death) did not differ

Table 2. End Points by Gender and Treatment

<table>
<thead>
<tr>
<th>End Point</th>
<th>Losartan</th>
<th>Atenolol</th>
<th>Adjusted HR Losartan vs Atenolol*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate†</td>
<td>Events n (%)</td>
<td>Rate†</td>
<td>Events n (%)</td>
</tr>
<tr>
<td>Primary composite†</td>
<td>18.23</td>
<td>215 (8.6)</td>
<td>30.75</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>7.26</td>
<td>88 (3.5)</td>
<td>11.60</td>
</tr>
<tr>
<td>Stroke</td>
<td>9.21</td>
<td>109 (4.4)</td>
<td>12.72</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6.54</td>
<td>78 (3.1)</td>
<td>12.37</td>
</tr>
<tr>
<td>Total mortality</td>
<td>13.11</td>
<td>159 (6.4)</td>
<td>22.37</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>5.81</td>
<td>69 (2.8)</td>
<td>9.38</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>6.22</td>
<td>74 (3.0)</td>
<td>8.09</td>
</tr>
<tr>
<td>New-onset diabetes§</td>
<td>11.94</td>
<td>123 (5.6)</td>
<td>14.36</td>
</tr>
</tbody>
</table>

The P value on the treatment-gender interaction test for hospitalization for angina was 0.012 and for total mortality was 0.051. The other treatment-gender interaction P values were ≥0.4.

*For degree of LVM and Framingham risk score at random assignment.
†Per 1000 patient-years of follow-up.
§Among patients without diabetes at random assignment (losartan, N=2185; atenolol, N=2144).
between treatments: 36.3% in women in the losartan group and 35.9% in women in the atenolol group, and in 38.3% in men in the losartan group and 36.5% in men in the atenolol group; <10% of these were described as drug related. Significantly fewer women and men in the losartan group than in the atenolol group stopped taking the study drug because of AEs or drug-related AEs (both $P<0.001$).

**Discussion**

The main finding in this posthoc analysis is that, compared with atenolol-based treatment, losartan-based treatment resulted in fewer overall cardiovascular events and strokes, reduced total mortality, and less new-onset diabetes in women with hypertension and LVH. These treatment effects occurred in the absence of major differences in BP control and appear to be related to mechanisms other than BP lowering.

Losartan-based antihypertensive therapy resulted in a greater regression of ECG LVH than did atenolol-based therapy in the LIFE study, and this was consistent for gender subgroups. Regression of ECG LVH was independent of the severity of baseline ECG LVH. Furthermore, regression of ECG LVH predicted lower cardiovascular morbidity and mortality. This is also a likely explanation for the greater reduction in cardiovascular events, strokes, and total mortality in the losartan-treated women than in the atenolol-treated women. Okin et al reported that women had less regression of ECG LVH than men, independent of baseline gender differences in severity of LVH and after taking into account treatment effects. These findings suggest that gender differences in ECG LVH may need to be taken into account when assessing the relation of changes in Cornell product and Sokolow-Lyon voltage duration measurements to outcome. However, analyses examining the relationship of in-treatment levels of Cornell product and Sokolow-Lyon voltage LVH to cardiovascular morbidity and mortality and to the risk of development of new atrial fibrillation did not demonstrate significant interactions between gender and changing levels of in-treatment LVH. These findings suggest that gender does not need to be taken into account when examining these ECG LVH criteria in relationship to those outcomes.

In contrast to the LIFE study, the prespecified subgroup analysis from the Valsartan Antihypertensive Long-Term Use Evaluation Trial found a relative excess of the primary composite end point of cardiac mortality and morbidity with valsartan-based treatment compared with amlodipine-based treatment in women but not in men. There was a greater unintended BP difference in favor of women in the amlodipine arm than in the valsartan arm (2.8 versus 1.8 mm Hg), which could explain the difference in outcome. BP differential of this magnitude could have had an important impact on outcomes. However, the authors discuss whether there was a genuine gender difference in the cardiac protection afforded by the amlodipine-based and valsartan-based treatments, because the trend toward less heart failure in valsartan-treated patients was significant only in men.

The Australian National Blood Pressure-2 Trial showed that the benefit of angiotensin-converting enzyme inhibitor enalapril-based treatment compared with a diuretic-based treatment was only observed in men. Only 524 events were observed in women in the Australian National Blood Pressure-2 Trial compared with 2002 events in the LIFE study, suggesting that the Australian National Blood Pressure-2 Trial was underpowered to detect a beneficial effect in hypertensive women. The results may also reflect differences in baseline characteristics of the populations included in the 2 studies.

It is difficult to compare the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial with those of the LIFE study because of differences in study populations (eg, only 16% had ECG LVH) and study designs. There was a slightly greater BP response to amlodipine compared with lisinopril in women, and this finding was associated with a more pronounced reduction in stroke in women taking amlodipine.

The Study on Cognition and Prognosis in the Elderly is the only other outcome trial that compared an ARB (candesartan) with other antihypertensive treatment. The prespecified subgroup analysis found no significant outcome benefit of...
ARB treatment in women and no treatment-gender interaction. However, interpretation of this finding is limited by design issues and the small number of events (n=273) experienced by these women.

In the LIFE study, more women required hospitalization for angina in the losartan group than in the atenolol group, whereas no such difference appeared among the men. This is in spite of fewer myocardial infarctions and other cardiac events in women. The explanation for this observation is not apparent to us except that this could be related to the higher Cornell product LVH in women or to other differences that we did not measure. Women used aspirin less than men, and each had similar statin use. However, we cannot rule out that this could be a chance finding in this subgroup analyses with few women hospitalized for angina.

Women in the LIFE study had more AEs but fewer serious drug-related AEs than men. Similar results have been seen previously, and it has been suggested that some antihypertensive drugs have gender-specific adverse profiles. For example, in the Treatment of Mild Hypertension Study, in which 902 women and men received nonpharmacologic treatment plus treatment with a drug chosen at random from each class of antihypertensive agent then available, women reported twice as many adverse effects as men. Biochemical responses to drugs may be gender dependent. Although men are more likely to develop gout, women are more likely to develop hyperuricemia and hypokalemia associated with diuretic therapy. Women develop cough related to angiotensin-converting enzyme inhibitor therapy 3 times more often than men. Furthermore, there is evidence that sexual dysfunction related to antihypertensive therapy may be a problem in women, as well as in men. This effect is most often associated with centrally acting agents, β-blockers, and thiazide diuretics, whereas ARB therapy may improve these symptoms.

Perspectives
The LIFE study provides evidence that treatment based on the ARB losartan with addition of a thiazide diuretic is superior to the β-blocker atenolol plus thiazide diuretic in preventing cardiovascular disease outcomes in women with LVH. The risk reductions with losartan, along with the tests for the interaction of treatment and gender, indicated that the treatment effect was consistent in men and women for all of the end points tested, with the exception of hospitalization for angina. The more favorable AE profile of losartan-based treatment in hypertensive women at high cardiovascular risk makes it a particularly attractive choice for this population.

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References


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