Effects of Losartan on Cardiovascular Morbidity and Mortality in Patients With Isolated Systolic Hypertension and Left Ventricular Hypertrophy
A Losartan Intervention For Endpoint Reduction (LIFE) Substudy

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Context Drug intervention in placebo-controlled trials has been beneficial in isolated systolic hypertension.

Objective To test the hypothesis that losartan improves outcome better than atenolol in patients with isolated systolic hypertension and electrocardiographically documented left ventricular hypertrophy (ECG-LVH).


Setting and Participants A total of 1326 men and women aged 55 through 80 years (mean, 70 years) with systolic blood pressure of 160 to 200 mm Hg and diastolic blood pressure of less than 90 mm Hg (mean, 174/83 mm Hg) and ECG-LVH, recruited from 945 outpatient settings in the Nordic countries, the United Kingdom, and the United States.

Interventions Patients were randomly assigned to receive once-daily losartan (n=660) or atenolol (n=666) with hydrochlorothiazide as the second agent in both arms, for a mean of 4.7 years.

Main Outcome Measure Composite end point of cardiovascular death, stroke, or myocardial infarction.

Results Blood pressure was reduced by 28/9 and 28/9 mm Hg in the losartan and atenolol arms. The main outcome was reduced by 25% with losartan compared with atenolol, 25.1 vs 35.4 events per 1000 patient-years (relative risk [RR], 0.75; 95% confidence interval [CI], 0.56-1.01; P=.06, adjusted for risk and degree of ECG-LVH; unadjusted RR, 0.71; 95% CI, 0.53-0.95; P=.02). Patients receiving losartan had reductions in the following without a difference in the incidence of myocardial infarction: cardiovascular mortality (8.7 vs 16.9 events per 1000 patient-years; RR, 0.54; 95% CI, 0.34-0.87; P=.01), nonfatal and fatal stroke (10.6 vs 18.9 events per 1000 patient-years; RR, 0.60; 95% CI, 0.38-0.92; P=.02), new-onset diabetes (12.6 vs 20.1 events per 1000 patient-years; RR, 0.62; 95% CI, 0.40-0.97; P=.04), and total mortality (21.2 vs 30.2 events per 1000 patient-years; RR, 0.72; 95% CI, 0.53-1.00; P=.046). Losartan decreased ECG-LVH more than atenolol (P<.001) and was better tolerated.

Conclusion These data suggest that losartan is superior to atenolol for treatment of patients with isolated systolic hypertension and ECG-LVH.
especially effective in reversing LVH and could confer protective benefits over and above blood pressure lowering.8

Losartan was the first available selective AT1-receptor antagonist.9 Atenolol was chosen as a comparative agent to losartan in the LIFE study1 because it has similar antihypertensive effectiveness as losartan10 and because β-blockers have been recognized as a first-line therapy for cardiovascular protection in hypertension.11,12 Isolated systolic hypertension (ISH) carries higher risk than isolated diastolic blood pressure elevation.13,14 The outcome of drug intervention in placebo-controlled trials has been highly beneficial in patients with ISH.15-17 In a pre-defined substudy of LIFE,18 we tested the hypothesis that losartan has preventive effects beyond blood pressure control in patients with ISH and LVH. This is the first comparative drug trial to report CV outcomes in ISH.

METHODS

Study Design and Organization

The LIFE study was an investigator-initiated, prospective multinational, multicenter, double-blind, double-dummy, randomized, active-controlled, parallel group study. The primary objective was to evaluate the long-term effects of once daily losartan-based vs atenolol-based antihypertensive therapy in patients with hypertension and electrocardiographically (ECG) documented LVH on the incidence of CV morbidity and mortality. The complete study protocol with study design, organization, clinical measures, end point definitions, basis for choice of comparative agent, and statistical considerations, as well as recruitment details, baseline characteristics, and outcome for the entire LIFE population have been published.1,18,21 The trial protocol was approved by the ethics committees of all participating institutions and was conducted in accordance with the Declaration of Helsinki and was overseen by an independent data and safety monitoring board.1

Target Population and Treatment Schedule

This study included patients aged 55 through 80 years with previously treated or untreated hypertension and ECG evidence of LVH and who were not excluded.1,18,21 Patients randomized to receive losartan- or atenolol-based regimens after 1 to 2 weeks of placebo were selected to be included in this analysis if trough sitting blood pressures were between 160 and 200 mm Hg systolic with diastolic pressure less than 90 mm Hg (FIGURE 1). There was no stratification as part of the randomization process. From July 6, 1995, through May 2, 1997, a total of 1326 patients with ISH were randomly assigned: 164 in Denmark, 164 in Finland, 15 in Iceland, 194 in Norway, 323 in Sweden, 90 in the United Kingdom, and 376 in the United States. Patients were followed up for 4 or more years with regular visits and upward titration of medication to reach a goal systolic blood pressure of less than 140 mm Hg (Figure 1). Sitting blood pressure was recorded 24 hours after dose (range, 22-26 hours). Only 2 patients (0.2%) with ISH were lost to follow-up (FIGURE 2).

ECG Coding and LVH Criteria

All ECGs were evaluated at a central core reading center for LVH criteria and Minnesota code. The product of QRS duration times Cornell voltage (with adjustment of 6 mm in women and a partition value of >2440 mm × ms) and Sokolow-Lyon voltage greater than 38 mm were chosen to define LVH.1,22-26

Outcome Measures

The primary end point was a composite of CV death, stroke, and myocardial infarction. Other prespecified outcome measures were components of the primary end point (CV death, all stroke, and all myocardial infarction), total mortality, angina pectoris, or heart failure requiring hospitalization, coronary or peripheral revascularization procedures, resuscitated cardiac arrest, and new-

<table>
<thead>
<tr>
<th>Figure 1. Titration Schedule and Electrocardiograph (ECG) Criteria</th>
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</thead>
</table>

**Drug Treatment and Upward Titration Schedule**

- **Losartan, 50 mg** or Atenolol, 50 mg
- **Losartan, 100 mg** or Atenolol, 100 mg

**Other Antihypertensive Medication**

- Hydrochlorothiazide, 12.5 mg
- Hydrochlorothiazide, 12.5 to 25 mg

**Randomization**

- **Placebo**

**Titration Upward if Sitting Systolic Pressure Was 140 mm Hg or Higher**

- **Day –14**
- **Day 1**
- **Month 2**
- **Month 4**
- **Month 6**

*Titration upward encouraged if sitting systolic pressure was 140 mm Hg or higher, but mandatory if it was 160 mm Hg or higher. Addition of angiotensin-converting enzyme inhibitors, other angiotensin II AT1-antagonists, or other β-blockers prohibited.*
onset diabetes mellitus.\textsuperscript{1,18-21} Routine laboratory tests were performed in 2 central laboratories. New-onset diabetes, defined according to 1985 World Health Organization criteria,\textsuperscript{22} was evaluated by a subcommittee of the steering committee. Adverse experiences were monitored throughout the study. The study ran its full course and end point follow-up was stopped on September 16, 2001, at midnight local time.\textsuperscript{19}

\textbf{Statistical Methods}

The prespecified data analysis plan for the LIFE study highlighted ISH as being of particular interest and indicated that all end point analyses were to be performed in this subgroup. All CV end points and blood pressures were analyzed using the intention-to-treat approach. The findings in the analysis of the primary efficacy variable were confirmed with an on-treatment approach that censored end points from patients 14 days after permanent discontinuation of study drug. Patients with multiple end points were counted as having had an event in all relevant end point analyses; however, only the first event in a specific category counted in any individual analysis. Safety analyses included all randomized patients from the time of randomization through September 16, 2001, or permanent discontinuation of blinded study medication, whichever came first.

There were 6193 patient-years of follow-up. Treatment effects were measured by hazard ratios (relative risks [RRs]) and their 95\% confidence intervals (CIs) based on Cox regression models, with degree of ECG-LVH and the Framingham risk score (sex, cholesterol, high-density lipoprotein cholesterol, smoking status, presence of diabetes and LVH, systolic blood pressure, and body mass index)\textsuperscript{28} at baseline as a priori determined covariates. Secondary unadjusted analyses were also performed to validate the adjusted results. The risk reduction for losartan vs atenolol was calculated as 100 × (1−RR). Numbers needed to treat were calculated as 1/absolute risk reduction (1/ARR). Event rates over time are presented as Kaplan-Meier curves: the numbers below curves represent the numbers of event-free patients remaining in follow-up at the corresponding time point. Adjustment for blood pressure was based on Cox regression models with blood pressure values throughout the trial as time-varying covariates. Differences between groups in changes in ECG-LVH were analyzed with the Wilcoxon rank-sum test and frequencies of adverse experiences were analyzed with the Fisher exact test. All tests were performed at 2-sided 5\% significance levels using the statistical package SAS version 8.0 (SAS Inc, Cary, NC).

To confirm that randomization was successfully achieved in the ISH subset, we compared baseline characteristics between treatment groups using the Wilcoxon rank-sum, the Fisher exact, and $\chi^2$ tests as appropriate. Second, we performed a logistic regression analysis\textsuperscript{29} in which treatment assignment was the dependent variable and used the $c$ statistic (equivalent of area under a receiver operating characteristic curve) to assess whether there was a systematic difference of distributions between the 2 groups. Third, we used the model to generate a propensity score for drug assignment\textsuperscript{30} and added that score to the Cox regression analyses.

\textbf{RESULTS}

\textbf{Follow-up and Blood Pressure Control}

Patients assigned to receive either losartan- or atenolol-based treatment were similar in characteristics (Table 1). Mean follow-up time (from randomization through death, loss to follow-up, or end of study) was 4.7 years. Patients continued study therapy 83.7\% and 74.9\% of entire follow-up time in the losartan and atenolol groups, respectively. The distribution of blinded study treatments for patients at the end of follow-up or at occurrence of the first primary end point, if earlier, and the distribution of additional therapy on top of blinded study drug or hydrochlorothiazide were not substantially different in the 2 groups (Table 2). The mean final losartan dose was 79 mg and the mean final atenolol dose was 76 mg. Patients taking losartan were more likely to continue study therapy, and the likelihood of receiving hydrochlorothiazide was the same in both groups.

The mean sitting blood pressures at end of follow-up or at the last visit preceding a primary end point, if one occurred, were reduced by 28/9 in the losartan and 28/9 mm Hg in the atenolol groups (Figure 3). The mean blood pressure levels at the last visit were 146/75 in the losartan and 146/74 mm Hg in the atenolol groups ($P = .67$, systolic; $P = .04$, diastolic blood pressure). The mean pulse pressure in the losartan group was 71 vs 73 mm Hg in the atenolol group ($P = .07$), and the mean arterial pressures were 98 and 98 mm Hg ($P = .28$), respectively.

A blood pressure of less than 140/90 mm Hg was achieved for 44.4\% of those taking losartan and 42.9\% of those taking atenolol. As expected, heart rate decreased by −6.6/min in patients taking
Table 1. Characteristics of Patients Treated With Losartan and Atenolol* 

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Losartan (n = 660)</th>
<th>Atenolol (n = 666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.2 (6.4)</td>
<td>70.4 (6.2)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>388 (58.8)</td>
<td>409 (61.4)</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>606 (91.8)</td>
<td>616 (92.5)</td>
</tr>
<tr>
<td>Black</td>
<td>44 (6.7)</td>
<td>38 (5.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (0.8)</td>
<td>9 (1.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (0.6)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>174 (11)</td>
<td>174 (11)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 (5)</td>
<td>82 (6)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71.5 (10.3)</td>
<td>71.6 (11.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.2 (4.6)</td>
<td>27.7 (5.2)</td>
</tr>
<tr>
<td>Cornell voltage-duration product, mm × ms</td>
<td>2771.1 (1077.8)</td>
<td>2820.6 (1157.9)</td>
</tr>
<tr>
<td>Sokolow-Lyon, mm</td>
<td>30.8 (10.5)</td>
<td>31.4 (10.6)</td>
</tr>
<tr>
<td>Framingham risk score, arbitrary units</td>
<td>0.230 (0.103)</td>
<td>0.234 (0.098)</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>96 (14.4)</td>
<td>101 (15.3)</td>
</tr>
<tr>
<td>Medical history, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously untreated isolated systolic hypertension</td>
<td>230 (34.8)</td>
<td>211 (31.7)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>156 (23.9)</td>
<td>140 (21.0)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>70 (10.8)</td>
<td>86 (12.9)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>57 (8.6)</td>
<td>55 (8.3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>28 (4.2)</td>
<td>39 (5.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>103 (15.6)</td>
<td>132 (19.8)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated.

Table 2. Study Drug at End Point or Termination of Follow-up* 

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Losartan (n = 660)</th>
<th>Atenolol (n = 666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg only</td>
<td>65 (9.9)</td>
<td>56 (8.7)</td>
</tr>
<tr>
<td>50 mg plus other therapy with HCTZ</td>
<td>136 (20.6)</td>
<td>148 (22.2)</td>
</tr>
<tr>
<td>100 mg with or without HCTZ</td>
<td>290 (44.1)</td>
<td>246 (36.8)</td>
</tr>
<tr>
<td>Therapy alone</td>
<td>14 (2.3)</td>
<td>10 (1.4)</td>
</tr>
<tr>
<td>With HCTZ only</td>
<td>107 (16.1)</td>
<td>91 (13.5)</td>
</tr>
<tr>
<td>With other therapy only</td>
<td>23 (3.6)</td>
<td>16 (2.6)</td>
</tr>
<tr>
<td>With HCTZ and other drugs</td>
<td>146 (22.1)</td>
<td>129 (19.4)</td>
</tr>
<tr>
<td>Discontinued therapy</td>
<td>169 (25.5)</td>
<td>216 (32.3)</td>
</tr>
</tbody>
</table>

*HCTZ indicates hydrochlorothiazide.

Atenolol vs −0.3/min in those taking losartan (P<.001).

Occurrence of End Points

For the primary end point, there was an overall 25% relative risk reduction on losartan (TABLE 3 and FIGURE 4). The Kaplan-Meier curves for CV mortality and for stroke all separated early (FIGURE 5) in favor of losartan. There was no significant difference for myocardial infarction. Adjustment for blood pressure, as a time-varying covariate, did not change the outcome. Among other prespecified end points (Table 3), there was a lower incidence of new-onset diabetes and a lower total mortality rate among those in the losartan group (Figure 4). Non-CV mortality was almost identical in the 2 groups (39 vs 41 deaths).

Outcome data (primary, components of primary and secondary) in patients without ISH are presented in TABLE 4. The interaction between treatment and ISH status was not statistically significant (P = .21 for the adjusted analysis and P = .18 for the unadjusted analysis of primary outcomes). The interactions were also nonsignificant for the components and secondary end points, with the exception of CV death (adjusted, P = .02; unadjusted, P = .01).

Twenty-three patients with ISH were needed to treat with losartan vs β-blocker atenolol to prevent 1 primary outcome event during the 4.7-year course of the LIFE study, 25 were need to prevent death; 28, stroke; and 31, new-onset diabetes.

The primary composite end point occurred less often with losartan in patients with diabetes (RR, 0.71; 95% CI, 0.40-1.24; P = .22) and in those without diabetes (RR, 0.80; 95% CI, 0.56-1.14; P = .22). Risks for events in patients with and without ISH are provided in Table 3 and Table 4. The event rates were generally higher with ISH than without ISH.

Adverse Events and Safety Profile

Losartan was better tolerated with fewer overall and drug-related discontinuations (TABLE 5). Descriptive laboratory values are reported at baseline and end of study in TABLE 6.

Change in ECG-LVH

At end of study, mean Cornell voltage-duration product was reduced by 211 × ms in the losartan and 63 mm × ms in the atenolol groups (P < .001) and Sokolow-Lyon voltage was reduced by 3.9 and 2.3 mm, respectively (P < .001).

Confirmation of Randomized Assignments

In supplementary analyses, we constructed a logistic regression model in which treatment assignment was the dependent variable and the baseline characteristics listed in Table 1 were the independent variables. The c statistic for the model was only 0.579, suggesting that there was little if any association between the baseline characteristics and treatment assignment. Furthermore, a log-likelihood test showed that a model for treatment assignment with the 16 covariates was no better than a model with no covariates (P = .14). We also created a propensity score by summing for each patient the products of baseline characteristics and their coefficients from this logistic regression model. When we added the propensity score into the Cox regression models for analyses of the study end points, there were no material changes in the results.
COMMENT
This substudy showed that losartan treatment resulted in a 25% reduction in the main outcome, the predefined primary composite end point of CV morbidity and mortality (CV death, stroke, and myocardial infarction) vs atenolol, in 1326 LIFE patients with ISH. Interaction analysis (treatment and ISH status) suggested that losartan prevented CV death particularly well in ISH patients. Baseline blood pressure and pulse pressure reductions were similar with both therapies. Adjustment for changes in blood pressures had no appreciable effect on the outcome.

The results of the main LIFE study contrast with recent hypertension studies comparing angiotensin-converting enzyme inhibitors, calcium-antagonists, and β-blockers to β-blocker or diuretic therapy, in which there have been no differences in primary outcome between treatment groups. In this article we extend the main study findings to patients with ISH. This is the first demonstration in patients with ISH that a treatment modality better reduces CV morbidity and mortality than another proven antihypertensive therapy without a meaningful difference in pressure reduction. It appears that in non-

Table 3. End Points in Patients With Isolated Systolic Hypertension

<table>
<thead>
<tr>
<th>End Point</th>
<th>Losartan (n = 660)</th>
<th>Atenolol (n = 666)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Primary Composite</td>
<td>25.1</td>
<td>75 (11.4)</td>
</tr>
<tr>
<td>Components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>8.7</td>
<td>27 (4.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>10.6</td>
<td>32 (4.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10.2</td>
<td>31 (4.7)</td>
</tr>
<tr>
<td>Other prespecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>21.2</td>
<td>66 (10.0)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>11.3</td>
<td>34 (5.2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8.5</td>
<td>26 (3.9)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>16.4</td>
<td>49 (7.4)</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>0.3</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>New onset of diabetes‡</td>
<td>12.6</td>
<td>32 (5.8)</td>
</tr>
</tbody>
</table>

* Rates are based on 1000 patient-years of follow-up. RR indicates relative risk; CI, confidence interval.
† For degree of left ventricular hypertrophy and Framingham risk score at randomization.
‡ Among patients without diabetes at randomization (losartan, n = 557; atenolol, n = 535).

Figure 3. Systolic, Diastolic, and Mean Arterial Blood Pressure During Study Follow-up in Intention-to-Treat Analysis

Figure 4. Kaplan-Meier Curves for Rates of Primary Composite End Point for Patients in Each Treatment Group

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ISH patients, the main findings are reduced stroke and new-onset diabetes while in ISH patients losartan also lowers CV death and all-cause death. Previous intervention studies in ISH with diuretic or β-blocker or calcium-antagonist or angiotensin-converting enzyme inhibitors have shown 36%,15 42%,16 and 38%17 reductions in stroke vs placebo. A further 40% reduction in stroke with losartan-based therapy, as demonstrated in this study, is an important finding because stroke is a major cause of death and disability and more common than myocardial infarction in the LIFE study as in all other hypertension trials during the last decade.31 It was recently emphasized that LVH (both on ECG and echocardiography) is, independent of blood pressure, a strong predictor of cerebrovascular events.32 This might be even more pronounced in patients with ISH.

The effect of incident myocardial infarction was comparable between losartan and atenolol. Reduction of heart rate, and hence myocardial oxygen demand, is generally thought to contribute to the cardioprotective properties of β-blockers11,12,33 and might have outweighed additional and potentially beneficial coronary vascular effects of losartan with regard to incident of myocardial infarction. Potentially, the vascular effects of losartan34 may be more pronounced in stroke protection.

The reduction in CV events by losartan-based therapy in LIFE was further accompanied by better tolerability and fewer drug withdrawals. As a result, more patients in the losartan than in the atenolol groups remained blinded to their therapy until the end of the study. This favorable combination of better prevention and higher tolerability may facilitate the choice of losartan as the first-line antihypertensive medication in patients with ISH.

A major hypothesis of the LIFE study, that losartan would be more effective than atenolol in reversing LVH,35 was confirmed both in the overall study36 and among patients with ISH, by greater reduction during the trial of both ECG indices of LVH in losartan.

Figure 5. Kaplan-Meier Curves of Cardiovascular Mortality, Stroke, and Myocardial Infarction

Table 4. End Points in Patients Without Isolated Systolic Hypertension

<table>
<thead>
<tr>
<th>End Point</th>
<th>Losartan (n = 3945)</th>
<th>Atenolol (n = 3922)</th>
<th>Unadjusted RR (95% CI)</th>
<th>P Value</th>
<th>Adjusted RR (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>23.6 (11.0)</td>
<td>26.7 (12.3)</td>
<td>0.88 (0.78-1.01)</td>
<td>.06</td>
<td>0.90 (0.79-1.02)</td>
<td>.11</td>
</tr>
<tr>
<td>Components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>9.3 (4.5)</td>
<td>9.6 (4.6)</td>
<td>0.97 (0.79-1.19)</td>
<td>.77</td>
<td>0.99 (0.80-1.22)</td>
<td>.90</td>
</tr>
<tr>
<td>Stroke</td>
<td>10.8 (5.1)</td>
<td>13.8 (6.5)</td>
<td>0.78 (0.65-0.94)</td>
<td>.01</td>
<td>0.79 (0.66-0.96)</td>
<td>.01</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9.0 (4.2)</td>
<td>8.2 (3.9)</td>
<td>1.10 (0.88-1.36)</td>
<td>.41</td>
<td>1.12 (0.90-1.40)</td>
<td>.30</td>
</tr>
<tr>
<td>Other prespecified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>16.7 (8.0)</td>
<td>17.9 (8.6)</td>
<td>0.93 (0.80-1.09)</td>
<td>.38</td>
<td>0.95 (0.82-1.11)</td>
<td>.51</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>6.8 (3.2)</td>
<td>6.5 (3.0)</td>
<td>1.06 (0.83-1.37)</td>
<td>.62</td>
<td>1.08 (0.84-1.39)</td>
<td>.54</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>6.8 (3.2)</td>
<td>6.5 (3.1)</td>
<td>1.05 (0.82-1.34)</td>
<td>.72</td>
<td>1.06 (0.83-1.36)</td>
<td>.65</td>
</tr>
<tr>
<td>Heart failure</td>
<td>11.5 (5.4)</td>
<td>13.2 (6.1)</td>
<td>0.87 (0.73-1.05)</td>
<td>.15</td>
<td>0.89 (0.74-1.08)</td>
<td>.23</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.4 (0.2)</td>
<td>0.3 (0.1)</td>
<td>1.60 (0.52-4.88)</td>
<td>.41</td>
<td>1.65 (0.54-5.07)</td>
<td>.38</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>13.1 (6.1)</td>
<td>17.0 (7.9)</td>
<td>0.77 (0.64-0.92)</td>
<td>.004</td>
<td>0.77 (0.64-0.92)</td>
<td>.005</td>
</tr>
</tbody>
</table>

* Rates are based on 1000 patient-years of follow-up. RR indicates relative risk; CI, confidence interval.
† For degree of left ventricular hypertrophy and Framingham risk score at randomization.
‡ Among patients without diabetes at randomization (losartan, n = 3462; atenolol, n = 3446).
treated vs patients treated with atenolol. It is possible that the CV protective effect of losartan vs atenolol is due to a more complete blockade of the detrimental effects of angiotensin II effects that extend the benefits beyond blood pressure reduction alone. The more complete protection against angiotensin II with losartan at the AT₁-receptor, whether generated by the circulating renin-angiotensin-system or alternative mechanisms, is a likely contributor, especially in the light of alternative mechanisms, is a likely contributor, especially in the light of an- gloeic fibrinogen II as an independent risk fac-

ator, especially in the light of an-

culating renin-angiotensin-system or
receptor, whether generated by the cir-

cling characteristics noted in Table 1, all

eels, along with the similarity of base-

as the dependent variable. The low

regression with treatment assignment
confirm this, we performed a logistic

and atenolol in these patients would in

pated that the comparison of losartan

tion blood pressure values, we antici-

able at the time of randomization. Since

defined based on information avail-

comparisons, provided the subsets are

sions of the treatment groups within any

sons of the treatment groups within any

 randomized clinical trial, compar-

ishments of the treatment groups within any

subset are fully randomized

procedures, either in the main study or in

ISH subset of patients. However, in

any randomized clinical trial, compar-

isons of the treatment groups within any

subset are fully randomized comparisons, provided the subsets are defined based on information available at the time of randomization. Since ISH was defined using prerrandomization blood pressure values, we anticipated that the comparison of losartan and atenolol in these patients would in fact be a randomized comparison. To confirm this, we performed a logistic regression with treatment assignment as the dependent variable. The low c statistic of only 0.579 and the lack of any change of findings when adding a prop-

ensity score to Cox regression mod-

els, along with the similarity of baseline characteristics noted in Table 1, all

argue that randomization was successful-

fully achieved in the ISH subset.

Conclusion

Losartan-based antihypertensive therapy was more effective than an atenolol-based treatment in preventing CV morbidity and mortality, especially stroke and CV death, in a large prespecified subset of LIFE participants with ECG-LVH and ISH. In addition, losartan was associated with a lower incidence of new-onset diabetes and lower total mor-

tity. It is currently not known whether losartan is superior to diuretics or cal-

cium channel blockers as a first-

line treatment of isolated systolic hy-

perension.

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