Regression of Hypertensive Left Ventricular Hypertrophy by Losartan Compared With Atenolol

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Trial

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Background—An echocardiographic substudy of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial was designed to test the ability of losartan to reduce left ventricular (LV) mass more than atenolol.

Methods and Results—A total of 960 patients with essential hypertension and LV hypertrophy (LVH) on screening ECG were enrolled at centers in 7 countries and studied by echocardiography at baseline and after 1, 2, 3, 4, and 5 years’ randomized therapy. Clinical examination and blinded readings of echocardiograms in 457 losartan-treated and 459 atenolol-treated participants with ≥1 follow-up measurement of LV mass index (LVMI) were used in an intention-to-treat analysis. Losartan-based therapy induced greater reduction in LVMI from baseline to the last available study than atenolol with adjustment for baseline LVMI and blood pressure and in-treatment pressure (−21.7±21.8 versus −17.7±19.6 g/m²; P=0.021). Greater LVMI reduction with losartan was observed in women and men, participants >65 or <65 years of age, and with mild or more severe baseline hypertrophy. The difference between treatment arms in LVH regression was due mainly to reduced concentricity of LV geometry in both groups and lesser increase in LV internal diameter in losartan-treated patients.

Conclusions—Antihypertensive treatment with losartan, plus hydrochlorothiazide and other medications when needed for pressure control, resulted in greater LVH regression in patients with ECG LVH than conventional atenolol-based treatment. Thus, angiotensin receptor antagonism by losartan has superior efficacy for reversing LVH, a cardinal manifestation of hypertensive target organ damage.

Key Words: angiotensin II controlled clinical trials echocardiography hypertension hypotrophy, left ventricular

Left ventricular hypertrophy (LVH) is a cardinal manifestation of preclinical cardiovascular disease that strongly predicts myocardial infarction, stroke, and cardiovascular death in hypertensive patients and the general population. Cardiovascular event rates are 2- to 4-fold higher in the presence of LVH independent of standard risk factors. Several studies suggest that regression of hypertensive LVH is associated with improved prognosis. As a result, prevention or reversal of LVH is widely accepted as a desirable treatment goal despite the lack of definitive confirmation. However, despite numerous therapeutic trials, uncertainty persists as to how best to regress hypertensive LVH. Most studies have been relatively small and have had additional limitations, including short duration, lack of comparative agents, nonblinded echocardiogram readings, and performance in populations without gender and ethnic diversity. Available large-scale trials have been confounded by effects of concomitant nutritional-hygienic therapy, high subject dropout, or absence of LVH before therapy.

Meta-analyses of available studies have suggested that interruption of renin-angiotensin system activity with ACE inhibitors or angiotensin II receptor antagonists may regress hypertensive LVH most effectively, but this has not been established in a large, definitive trial. Recently, the main results of the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial demonstrated both prevention of the prespecified clinical end point and greater reduction in indirect ECG measures of LVH with losartan than atenolol. The present study was undertaken to examine the relative effectiveness of losartan versus atenolol for regression of hypertensive LVH in the large LIFE echocardiographic substudy.
Methods

Study Design
The LIFE study enrolled hypertensive patients with ECG LVH in a prospective, double-blind, randomized study large enough to determine whether losartan-based as opposed to atenolol-based treatment yielded greater reductions in cardiovascular events and ECG LVH. As part of LIFE, >10% of study participants were enrolled in a substudy in which echocardiograms were performed at study baseline and yearly thereafter. The present report uses data from this substudy to determine the comparative effects of losartan versus atenolol treatment on regression of LVH. Patients 55 to 80 years of age with mean seated blood pressure (BP) of 160 to 200/95 to 115 mm Hg and ECG LVH were recruited into the LIFE substudy. LIFE Echocardiography Substudy participants enrolled at 47 sites in Denmark, Finland, Iceland, Norway, Sweden, the United Kingdom, and the United States. They closely resembled the entire study population with regard to BP, age, cardiovascular risk factors, and prevalent diseases but were more commonly male (59% versus 46%) and nonwhite (16% versus 7%).

Treatment Regimens
Blinded treatment was begun with losartan 50 mg or atenolol 50 mg and matching placebo of the other agent. During clinic visits at 1, 2, 4, and 6 months and semianually thereafter, study therapy could be uptitrated by adding hydrochlorothiazide 12.5 mg and then increasing blinded losartan or atenolol to 100 mg and thereafter if needed to reduce BP to ≤140/90 mmHg, increasing hydrochlorothiazide to 25 mg, and instituting calcium channel blockade or other medications (excluding angiotensin II receptor antagonists, β-blockers, or ACE inhibitors).

Echocardiographic Methods
Centers for the present LIFE substudy had established expertise in quantitative echocardiography. To standardize echocardiogram performance in multiple sites, physician or technician sonographers from each center underwent training with written materials, didactic presentations, and practical demonstrations of the performance protocol.

Echocardiograms were performed between October 5, 1995, and September 30, 2001, with phased-array echocardiographs. Recordings were made by a standardized protocol under which ≥10 consecutive beats of 2D and M-mode recordings of LV internal diameter and wall thicknesses at or just below the tips of the mitral leaflets were recorded in parasternal long- and short-axis views. Apical 2- and 4-chamber images were used to assess LV wall motion. Studies were read at Cornell Medical Center by investigators blinded to clinical information.

Echocardiographic Measurements
Correct orientation of imaging planes was verified as described previously. Measurements were made by investigators blinded to treatment allocation and temporal sequence using a computerized review station; measurements were verified, and commonly corrected, or made by experienced investigators (R.B.D. in 89%). End-diastolic and end-systolic LV internal dimension and wall thicknesses were measured by American Society of Echocardiography (ASE) recommendations on up to 3 cardiac cycles.

Calculation of Derived Variables
End-diastolic ASE LV dimensions were used to calculate LV mass by a formula validated by necropsy comparison (r=0.90, P<0.001). The ability to substitute 2D LV dimensions when M-mode beam orientation was suboptimal increased the yield of LV mass values to 91% to 98% in previous large studies. The resultant LV mass values showed excellent reproducibility (r=0.93, P<0.001); ±17 g had an 80% likelihood of being a true change without significant regression to the mean in 183 hypertensive patients studied twice by echocardiography. To account for the impact of body size, LV mass was indexed for body surface area [LV mass index (LVMI)].

Statistical Analyses
Data are expressed as mean±SD. Differences between groups were assessed by independent-samples t tests for continuous variables and χ² statistics for categorical variables. After verification readings to determine the accuracy of extreme values, data were exported electronically to the Clinical Biostatistics Department at Merck Research Laboratories for statistical analyses.

Analysis Plan
The study was considered positive if losartan was more effective than atenolol for LVMI reduction at the P<0.05 level. Analysis of clinical end-point data in the LIFE study was based on the intention-to-treat principle. All randomized patients were followed up for end-point determination for the entire duration of the study, regardless of protocol violations or adherence to study medication. All randomized patients in the echocardiography substudy were included in statistical analyses if they had a valid, readable baseline echocardiogram and ≥1 readable follow-up echocardiogram. The main hypothesis was addressed by comparing change in echocardiographic LVMI between treatment groups from the baseline measurement to the patients’ last measurement during the trial; the time course of LV mass change in the 2 groups was also compared. The distribution of change in LV mass was nearly normal; therefore, comparison between treatment groups used a parametric model. To investigate the overall effect of treatments on LVMI over time, mixed models with repeated measures over time were used. The primary model used annual changes in LVMI as the dependent variables and baseline LVMI and BP as covariates. To determine the treatment effect independent of BP control, annual BP values were added to the mixed model as time-varying covariates. Further analyses adjusted for on-treatment heart rate reduction, a manifestation of the biological effect of β-blockade and a stimulus to increase in stroke volume.

Study Power
The planned sample of 1000 patients was based on a projected between-study SD of 25 g/m². Given the observed SD of 20 g/m² over the first year of blinded therapy in LIFE, the study had >90% power to detect a between-group difference of 10 g/m².

Results
Patients
The total of 960 participants at LIFE echocardiography substudy centers (see Appendix) included 271 (28%) in Denmark, 145 (15%) in Finland, 12 (1%) in Iceland, 198 (21%) in Norway, 89 (9%) in Sweden, 7 (1%) in the United Kingdom, and 243 (25%) in the United States, paralleling the distribution of the 9193 participants in LIFE. Baseline clinical and echocardiographic characteristics of losartan or atenolol groups were virtually identical (the Table). Prior antihypertensive therapies were similar in the losartan and atenolol arms, including angiotensin receptor blockers (3.3 or 3.1%), β-blockers (26.6 or 24.2%), diuretics (26.8 or 27.9%), ACE inhibitors (22.0 or 25.0%), calcium channel blockers (31.8 or 33.3%), α-blockers (4.0 or 3.1%), and vasodilators (4.2 or 3.9%).

Among patients with baseline LV mass, 438 of 457 randomized to losartan and 440 of 459 (both 96%) randomized to atenolol had ≥1 follow-up LV mass determination. Echocardiograms were scheduled annually for all patients whether or not they remained on blinded study medication.
Baseline and 1-year echocardiographic data could be compared in 414 losartan-treated and 411 atenolol-treated patients (both 91%) with baseline LV mass; 24 and 29 additional losartan- and atenolol-treated patients without 1-year LVMI measurements provided LVMI comparisons with baseline at subsequent follow-up times.

Hemodynamic Effects of Study Treatment
Systolic and diastolic BPs were controlled similarly during the course of LIFE by losartan and atenolol (Figure 1). Target BP in the LIFE study (<140/90 mmHg) was attained in 37% and 33% in the losartan and atenolol treatment arms, respectively, at the last evaluation (P=0.139). By the end of the study, 8% and 9% of losartan- and atenolol-treated patients were on 50 mg test drug monotherapy, 15% and 19% took 50 mg of study drug with hydrochlorothiazide and/or other antihypertensive medications, and 53% and 45% took 100 mg of test drug, usually with other antihypertensive therapy (P=NS). At study end, 23% and 27% of losartan and atenolol patients were no longer receiving study therapy. Mean daily study therapy dose was 80 and 84 mg in the losartan and atenolol groups.

On average, heart rate fell from baseline by 1 to 2 and 7 to 9 bpm in the losartan- and atenolol-treated groups, respectively, at each annual visit (all P<0.001), whereas body weight showed no significant change.

Characteristics of Patients Randomized to Losartan or Atenolol Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Losartan (n=479)</th>
<th>Atenolol (n=481)</th>
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<tbody>
<tr>
<td>Demographic and clinical</td>
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<tr>
<td>Age, y (65.9±7.1)</td>
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<tr>
<td>Female, n (%)</td>
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<td>Ethnicity, n (%)</td>
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<tr>
<td>White (84.6%)</td>
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<td>Black (14.2)</td>
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<td>Hispanic (0.4)</td>
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<td>Asian (1.3)</td>
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<td>Other (0.3)</td>
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<tr>
<td>BP, mm Hg</td>
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<tr>
<td>173.4±98.5/14.0±8.8</td>
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<td>Heart rate, bpm</td>
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<td>72.6±11.1</td>
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<td>Weight, kg</td>
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<td>79.5±14.3</td>
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<td>Height, cm</td>
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<td>169.5±9.3</td>
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<td>BMI, kg/m²</td>
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<td>27.4±4.3</td>
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<td>LVMI, g/m²</td>
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<td>Framingham risk score</td>
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<td>0.229±0.094</td>
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<td>Current smokers, n (%)</td>
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<td>Regular alcohol use,* n (%)</td>
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<td>105 (21.9)</td>
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<tr>
<td>Regular exercise,† n (%)</td>
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<td>250 (52.2)</td>
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<td>Medical history, n (%)</td>
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<tr>
<td>Coronary heart disease</td>
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<tr>
<td>Diabetes</td>
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<td>55 (11.4)</td>
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BMI indicates body mass index. Data are mean (SD) when appropriate.

*<1 drink per day.
†≥30 minutes at least twice weekly. No difference between treatment groups is statistically significant.
Change in LV Dimensions and Mass During Blinded Treatment

Septal and posterior wall thickness decreased progressively in both treatment groups during blinded treatment with significantly greater increase in LV internal diameter in atenolol-treated patients ($P=0.004$; Figure 2). As a result of changes in primary LV dimensions, LV relative wall thickness decreased similarly with both treatments (Figure 3).

A greater decrease in mean LV mass in losartan-than atenolol-treated patients was present after 1 year of blinded treatment and persisted to the last available echocardiogram ($P=0.009$; Figure 4). The change from baseline to the final available in-study echocardiogram in the primary predesignated end point of LVMI was greater ($-21.7 \pm 21.8 \text{ g/m}^2$) in losartan- than atenolol-treated patients ($-17.7 \pm 19.6 \text{ g/m}^2$; $P=0.011$ adjusted for baseline LVMI and BP, $P=0.027$ with additional adjustment for in-treatment BPs; Figure 5). Additional analysis comparing all in-study echocardiograms on patients randomized to losartan or atenolol, adjusting for in-study BPs, confirmed the greater reduction in LVMI with losartan ($-21.1 \pm 21.0$ versus $-17.5 \pm 18.8 \text{ g/m}^2$; $P=0.016$). Most of the reduction in LV mass occurred by month 24 of study treatment (Figure 4). LVMI was significantly affected by in-treatment systolic BP ($P=0.009$) and marginally by on-treatment heart rate ($P=0.055$) but not diastolic BP. Addition of baseline and on-treatment heart rate to the model evaluating the effect of treatment on LVMI reduced the statistical significance of the between-treatment difference in change in LVMI from baseline to the last available measurement (from $P=0.027$ to 0.062) and from baseline to all available in-trial measurements (from $P=0.016$ to $P=0.070$).

Figure 2. Top, Posterior wall thickness (PWT; vertical axis) was reduced similarly in patients randomized to losartan (solid bars) and atenolol (open bars) at each annual follow-up and at last in-study echocardiogram. Bottom; LV diameter (LVD; y axis, bottom) showed little change early during treatment but increased progressively more in atenolol-treated patients beginning at year 3.

Figure 3. Relative wall thickness (RWT; y axis) was reduced similarly in both losartan- and atenolol-treated patients.

Figure 4. LV mass (y axis) was reduced more in patients randomized to losartan than atenolol.

Figure 5. LVMI (y axis) was reduced more in patients randomized to losartan than atenolol.
LV Mass Change in Population Subsets

The greater benefit of losartan in LVMI reduction was seen in women (−20.0 versus −15.2 g/m²) and men (−22.9 versus −19.4 g/m²; \( P = \text{NS} \)) and patients younger (−22.8 versus −18.2 g/m²) and older (−20.8 versus −17.4 g/m²) than 65 years of age. LV mass decreased more on losartan than atenolol in whites (−22.1 versus −17.7 g/m²) but not in the smaller group of other races (−16.7 versus −17.8 g/m²). Patients without diabetes at baseline benefited more from losartan than atenolol (−23.0 versus −17.6 g/m²), whereas the 103 with diabetes had slightly greater benefit with atenolol (−11.4 versus −18.4 g/m²). LVMI decreased more on losartan than atenolol in patients with baseline Cornell voltage-duration products in the lowest tertile (<2491 mV×ms in women and <2380 mV×ms in men) (−20.9 versus −16.2 g/m²) and in the highest tertile (>2970 and >2912 mV×ms, respectively) (−24.4 versus −19.2 g/m²), with a parallel trend in the group with intermediate ECG LV hypertrophy (−19.4 versus −18.6 g/m²). LVMI decreased more with losartan than atenolol in patients who exercised or consumed alcohol regularly at enrollment in LIFE (−21.8±21.8 versus −17.9±18.8, \( P = 0.027 \); and −23.1±22.2 versus −19.3±18.0, \( P = 0.096 \), respectively).

Discussion

The LIFE trial provides the largest prospective, randomized, double-blind study to date comparing cardiac effects of angiotensin II AT1 receptor antagonism and conventional antihypertensive treatment in hypertensive patients with ECG LVH and the largest study to date of regression of hypertensive LVH in terms of the number of echocardiograms providing LV mass data. The most important result of the study is that treatment based on once-daily administration of losartan reduced LVMI during up to 5 years of treatment significantly more than conventional atenolol-based treatment. The primary outcome measure of LVMI was reduced modestly more by losartan- than atenolol-based treatment in the primary analysis that included all available data, regardless of adherence to the study medication, in patients treated per protocol (data not shown) and in most population subsets.

Comparison With Previous Studies

In an early meta-analysis, Dahlöf et al reported that ACE inhibitors reduced LV mass the most with more modest benefit from other treatments when induced BP reduction and baseline LV mass were taken into account. More recent analyses of randomized, controlled parallel-group trials found a significant difference between LV effects of ACE inhibitors and \( \beta \)-blockers and suggested similar benefits for AT1 receptor antagonists. The present study provides definitive evidence of a greater reduction in LV mass by losartan than by atenolol, confirming previous suggestions of superior regression of hypertensive LVH by AT1 receptor antagonism. In the Treatment of Mild Hypertension Study (TOMHS), no difference was observed between the ACE inhibitor and \( \beta \)-blocker arms. The Veterans’ Administration Study provided suggestive evidence of greater LVH regression by a diuretic or ACE inhibitor but was partially confounded by high participant dropout (61%). The greater regression of LVH with losartan than with atenolol, which itself decreases renal renin release, may be related to the ability of selective AT1 angiotensin receptor antagonism to block angiotensin II effects more completely than usual doses of ACE inhibitors or indirect effects of \( \beta \)-blockade.

Hemodynamic Correlates of LV Mass Change

As expected, LV mass change was related to BP reduction in the LIFE echocardiography substudy population. Previous studies have revealed that on-treatment LV mass change is more closely related to change in 24-hour BP than in clinic BP. Thus, the impact of intrapatient variability in BP reduction on LVMI change may be underestimated in the present study. The greater reduction in LVMI with losartan was partially attenuated when on-treatment heart rate was considered, but whether this reflects biological effects of \( \beta \)-blockade or an increase in stroke volume with slower heart rate cannot be determined.

Time Course of LV Geometric Changes

In contrast to earlier trials in which regression of LVH was often assessed over months, LIFE performed annual echocardiograms over 5 years of blinded treatment. Beyond the substantial decrease in LV mass during the first year, especially in losartan-treated patients, there were smaller further decreases in LV wall thicknesses, relative wall thickness, and LVMI during years 2 and 3 in both treatment arms. These results suggest that the benefit of antihypertensive treatment on LV remodeling cannot be fully appreciated unless treatment trials last ≥3 years.

Study Limitations

Because it was considered unethical to include a placebo arm in the LIFE study, which enrolled patients with hypertension and LVH, the study could overestimate or underestimate beneficial cardiac effects of study treatments. However, precautions were taken to minimize measurement bias. Echocardiograms from at least 2 and usually 3 different study years were read concurrently; and final measurements on 89% of studies, including 100% of baseline recordings and 96% of those after 4 and 5 years, were made by a highly experienced investigator. In addition, primary intention-to-treat results reflect LV effects of losartan- and atenolol-based regimens rather than pure monotherapy. However, in view of the known difficulty of controlling BP in moderate hypertension complicated by target organ damage, this closely emulates actual clinical practice.

Clinical Implications

LIFE revealed significantly greater regression of LVMI in hypertensive patients with ECG LVH on losartan- than atenolol-based therapy despite comparable BP lowering, thereby supporting the hypothesis that losartan has direct cardiac benefits.

Appendix

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