Regression of Electrocardiographic Left Ventricular Hypertrophy by Losartan Versus Atenolol

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study

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Background—Electrocardiographic left ventricular hypertrophy (LVH) predicts cardiovascular morbidity and mortality, and regression of ECG LVH may predict improved prognosis in hypertensive patients. However, uncertainty persists as to how best to regress ECG LVH.

Methods and Results—Regression of ECG LVH with losartan versus atenolol therapy was assessed in 9193 hypertensive patients with ECG LVH by Sokolow-Lyon voltage or Cornell voltage-duration product criteria enrolled in the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. Patients had ECGs at study baseline and after 6 months, 1, 2, 3, 4, and 5 years of blinded losartan-based or atenolol-based therapy. After 6 months’ follow-up, adjusting for baseline ECG LVH levels, baseline and in-treatment systolic and diastolic pressures, and for diuretic therapy, losartan-based therapy was associated with greater regression of both Cornell product (adjusted means, −200 versus −69 mm·ms, \( P<0.001 \)) and Sokolow-Lyon voltage (−2.5 versus −0.7 mm, \( P<0.001 \)) than was atenolol-based therapy. Greater regression of ECG LVH persisted at each subsequent annual evaluation in the losartan-treated group, with between 140 and 164 mm·ms greater mean reductions in Cornell product and from 1.7 to 2.2 mm greater mean reductions in Sokolow-Lyon voltage (all \( P<0.001 \)). The effect of losartan was consistent across subgroups defined by gender, age, ethnicity, and diabetes.

Conclusions—After adjusting for baseline and in-treatment blood pressure and baseline severity of ECG LVH, losartan-based antihypertensive therapy resulted in greater regression of ECG LVH by Cornell voltage-duration product and Sokolow-Lyon voltage criteria than did atenolol-based therapy. These findings support the value of angiotensin receptor blockade with losartan for reversing ECG LVH. (Circulation. 2003;108:684-690.)

Key Words: angiotensin • electrocardiography • hypertension • hypertrophy

Left ventricular hypertrophy (LVH) manifested by the ECG and detected by echocardiography is a common indication of preclinical cardiovascular (CV) disease that strongly predicts CV morbidity and mortality. Antihypertensive therapy aimed at reducing blood pressure (BP) produces regression of ECG LVH, and regression of LVH appears to be associated with improved prognosis. However, despite numerous therapeutic trials, uncertainty persists as to how best to produce regression of ECG LVH. Meta-analyses examining hypertensive LVH regression suggest that therapy aimed at the renin-angiotensin system with the use of ACE inhibitors or angiotensin receptor antagonists may be more effective than traditional therapies in regressing LVH. Indeed, the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study demonstrated that losartan therapy was more effective than atenolol in preventing CV morbidity and mortality and that losartan was associated with greater reductions in Cornell voltage-duration product.
duration product and Sokolow-Lyon voltage LVH from baseline to the last available ECG. However, that report did not examine the time course of changes in ECG LVH, the independence of treatment effects from in-treatment BP changes, or the homogeneity of treatment effects on regression of LVH in subgroups of the population defined by gender, age, ethnicity, and diabetes. Therefore, the current study compared the effectiveness of losartan versus atenolol treatment for regression of ECG LVH by Cornell product and Sokolow-Lyon voltage criteria throughout the LIFE study, adjusting for possible effects of baseline severity of LVH and both baseline and in-treatment BP.

Methods

Subjects
The LIFE trial12–14 enrolled 9193 hypertensive patients with ECG LVH by Cornell voltage-duration product13 and/or Sokolow-Lyon voltage criteria16 in a prospective, double-blind, randomized study to determine whether greater reduction in mortality rates and morbidity from cardiovascular disease would occur in hypertensive patients randomized to losartan (50 mg daily) versus atenolol (50 mg daily) and matching placebo of the other agent, with a target BP of ≤140/90 mm Hg. During clinic visits at frequent intervals for the first 6 months and at 6-month intervals thereafter, study therapy could be uptitrated by adding 12.5 mg hydrochlorothiazide, followed by increased blinding losartan or atenolol to 100 mg daily. If BP was still not controlled, additional open-label upward titration of hydrochlorothiazide, and, if necessary, therapy with a calcium channel blocker or additional other medications (excluding AT1- or β-blockers or ACE inhibitors), was added to the double-blind treatment regimen.13

Treatment Regimens
Blinded treatment started with 50 mg losartan or 50 mg atenolol daily and matching placebo of the other agent, with a target BP of ≤140/90 mm Hg. During clinic visits at frequent intervals for the first 6 months and at 6-month intervals thereafter, study therapy could be uptitrated by adding 12.5 mg hydrochlorothiazide, followed by increasing blinded losartan or atenolol to 100 mg daily. If BP was still not controlled, additional open-label upward titration of hydrochlorothiazide, and, if necessary, therapy with a calcium channel blocker or additional other medications (excluding AT1- or β-blockers or ACE inhibitors), was added to the double-blind treatment regimen.13

Electrocardiography
ECGs were obtained at baseline, 6 months, and at 1-year follow-up intervals thereafter until study termination or patient death. QRS duration was measured to the nearest 4 ms, and R-wave and S-wave amplitudes were measured to the nearest 0.5 mm (0.05 mV) at the LIFE ECG Core Laboratory.12–14 The product of QRS duration times the Cornell voltage combination (RvL+SvS), with 8 mm added in women13 (>) >2440 mm/ms was used to identify LVH. After design of LIFE, studies were published suggesting a smaller gender adjustment.17,18 and LIFE investigators indicated that otherwise eligible patients had ECG LVH by highly specific but insensitive Sokolow-Lyon voltage16 but not by Cornell product criteria. Accordingly, ECG entry criteria were changed to reduce the gender adjustment of Cornell voltage from 8 to 6 mm and add Sokolow-Lyon voltage (SvS + RvS) >38 mm.14

Statistical Analyses
Data management and analysis were performed by the Clinical Biostatistics department of Merck Research Laboratories. Differences in prevalences were compared by χ2 analyses. Mean changes in Sokolow-Lyon voltage and Cornell product ECG LVH between baseline and subsequent measurements were compared between losartan and atenolol by Wilcoxon rank sum tests. Mixed models with repeated measures over time as time-varying covariates were used to assess if treatment effect was independent of possible treatment group differences in baseline Cornell product or Sokolow-Lyon voltage, baseline and in-treatment systolic and diastolic BP, change in systolic BP, and diuretic use. Treatment effects on changes in ECG LVH were assessed in prespecified subsets of the study population divided according to gender, presence or absence of diabetes at baseline, age dichotomized at 65 years, and race. For all tests, a 2-tailed value of P<0.05 was required for statistical significance.

Results
Baseline characteristics in the 4605 patients randomly assigned to losartan and the 4588 patients randomly assigned to atenolol were well matched, as previously reported in detail.12 At study baseline, there were no differences between losartan- and atenolol-treated groups in mean Cornell product (2834±1065 versus 2824±1033 mm · ms), Sokolow-Lyon voltage (30.0±10.6 versus 30.1±10.4 mm), systolic pressure (174.3±14.2 versus 174.5±14.4 mm Hg), or diastolic pressure (97.9±8.8 versus 97.7±9.0 mm Hg) (all P>0.20).17 Baseline prevalences of ECG LVH were similar in losartan- and atenolol-treated groups for Cornell product (65.8% versus 65.5%) and Sokolow-Lyon voltage (21.5% versus 21.9%). Concomitant with the period of ECG observation during treatment, systolic pressure remained slightly lower in the losartan-treated group beginning at 6 months (149.2±16.3 versus 150.8±17.4 mm Hg, P<0.001) and extending out through 5 years of follow-up (144.2±16.0 versus 145.3±16.7 mm Hg, P=0.011). In contrast, diastolic pressure was slightly higher in losartan-treated patients at the 6-month visit (85.3±9.1 versus 84.1±9.2 mm Hg, P<0.001) but had nearly equalized in the treatment arms by the 5-year follow-up (81.0±8.8 versus 80.6±9.2 mm Hg, P=0.115).

Mean values at baseline, subsequent in-study measurements, and changes between baseline and follow-up measurements for Cornell product and Sokolow-Lyon voltage are compared between losartan- and atenolol-treated patients in Table 1. Because treatment differences in changes in Cornell product and Sokolow-Lyon voltage could be related to baseline levels of Cornell product and Sokolow-Lyon voltage and could be affected by in-treatment differences in systolic and diastolic pressures, change in systolic pressure or diuretic use, treatment differences in ECG LVH were assessed, adjusting for these differences. As expected, based on LIFE entry criteria, mean Cornell product and Sokolow-Lyon voltage were elevated at baseline in both treatment groups and decreased substantially during the first 6 months of treatment, concomitant with the institution of protocol-based antihypertensive therapy. Greater regression of ECG LVH by both Cornell product and Sokolow-Lyon voltage criteria in losartan- than atenolol-treated patients became apparent and highly significant after only 6 months of blinded therapy (−200 versus −69 mm · ms and −2.5 versus −0.7 mm, both P<0.001). ECG LVH decreased further and to a similar degree in losartan- and atenolol-treated patients between 6 months and 2 years, with maintenance of mean treatment differences in regression at subsequent annual evaluations of 140 to 149 mm · ms (P<0.001) for Cornell product and 1.7 to 1.8 mm (P<0.001) for Sokolow-Lyon voltage. The additional decreases in ECG LVH from the 1-year tracing to the last available measurement did not differ between treatment
groups for Cornell product ($P=0.352$) or Sokolow-Lyon voltage ($P=0.871$).

Prevalences of ECG LVH by Cornell product and Sokolow-Lyon voltage criteria at study baseline and subsequent in-study measurements are compared between treatment groups in Figure 1. Prevalences of ECG LVH by both criteria were highest at study baseline and declined in both study groups in a pattern similar to the decreases in mean values shown in Table 1. The prevalences of ECG LVH by Cornell product and Sokolow-Lyon voltage were significantly lower in losartan- than in atenolol-treated patients by 6 months and remained lower to the end of study. Reductions in prevalence of ECG LVH from study baseline to the final available in-study ECG were greater in losartan-treated than in atenolol-treated patients for Cornell product LVH ($-20.5\%$ versus $-12.8\%, P<0.001$) and Sokolow-Lyon voltage LVH ($-11.7\%$ versus $-8.5\%, P<0.001$).

The greater benefit of losartan for ECG LVH reduction by both Cornell product and Sokolow-Lyon voltage criteria persisted across population subsets (Tables 2 and 3). Greater reduction of ECG LVH by losartan therapy was seen for both ECG criteria in men and women, in patients with and without diabetes at study baseline, among patients younger and older than 65 years of age, and in whites as well as in nonwhites.

### Discussion

The LIFE study is the first study to compare regression of ECG LVH between two active treatment arms in a population large enough to provide adequate power. LIFE demonstrates that treatment with a losartan-based regimen reduced both Cornell voltage-duration product and Sokolow-Lyon voltage measures of ECG LVH during up to 5 years of treatment significantly more than antihypertensive therapy based on the $\beta$-blocker atenolol. These greater reductions in ECG LVH with losartan occurred by 6 months of treatment and in all examined subsets of the LIFE study population and were independent of baseline severity of ECG LVH and of baseline and in-treatment BP and diuretic use in the study groups, suggesting that the greater treatment effect of losartan on regression of ECG LVH is independent of the BP-lowering effect of the drug.

Previous studies of regression of ECG LVH during anti-hypertensive therapy have been limited by failure to directly compare two active treatment arms and by not taking into account the impact of treatment differences in BP changes on observed changes in ECG LVH.\textsuperscript{3,8,9,19} In the Hypertension Detection and Follow-Up Program of 10,940 hypertensive adults,\textsuperscript{9} the incidence of new ECG LVH by Minnesota Code Criteria was slightly lower in subjects who were randomly assigned to stepped-care (SC) therapy than to the community-based referred-care (RC) group (5.6\% versus 6.6\%, $P<0.05$). Moreover, when patients with tall R waves and ECG LVH were combined, regression of these findings was more common in SC than in RC patients (54.3\% versus 42.9\%, $P<0.01$). However, the lower mean BPs in the SC group were not taken into account when comparing differences in ECG LVH. In the Multiple Risk Factor Intervention Trial (MRFIT),\textsuperscript{19} the incidence of new ECG LVH by Minnesota Code Criteria among hypertensive men was significantly lower in the special intervention than in the usual care arm of the study (4.2\% versus 5.4\%, $P<0.01$). However, the risk of incident ECG LVH in the treatment groups became nearly identical after adjusting for baseline differences in race and systolic BP and change in systolic pressure (risk ratio, 0.98;
In the Treatment of Mild Hypertension Study (TOMHS),\(^8\) nutritional therapy alone was compared with a combination of nutritional therapy and 5 active treatment groups in patients without ECG LVH by Minnesota Code. Active therapy was associated with greater reductions in systolic and diastolic BP, with lower incidences of Minnesota Code LVH, and with greater decreases in continuous measures of ECG LVH, including Cornell voltage.\(^8\) However, these analyses did not adjust for greater BP reduction in medicated patients, were not powered to allow accurate comparisons between the different active treatments, included only patients with mild hypertension, and excluded patients with ECG LVH at baseline. More recently, the Heart Outcomes Prevention Evaluation (HOPE) study\(^3\) demonstrated that compared with placebo, a ramipril-based regimen was associated with lower likelihood of development or persistence of ECG LVH by Sokolow-Lyon voltage and with greater likelihood of prevention or regression of ECG LVH, even after adjusting for the greater decrease in BP with ramipril therapy. However, the HOPE study did not compare ramipril with another active treatment, did not follow BP as closely as in the LIFE study, had a very low (8.2\%) prevalence of ECG LVH at study baseline, did not adjust for the severity of baseline ECG LVH, and did not take into account the magnitude of change in Sokolow-Lyon voltage in their analyses, only whether ECG LVH by the standard threshold of 3.5 mV was present or absent.\(^3\)

In contrast, the current study demonstrates that losartan-based antihypertensive therapy achieved greater reductions in ECG LVH by both Cornell voltage-duration product and Sokolow-Lyon voltage criteria that were manifest by 6 months of therapy and were independent of baseline severity of ECG LVH and hypertension and of any therapy-related differences in changes in BP. Of note, regression lines of Sokolow-Lyon voltage and Cornell product reduction versus systolic BP changes in losartan- and atenolol-treated groups
demonstrated greater reductions in ECG LVH with losartan treatment for any level of change in systolic BP, further supporting the independence of treatment differences in ECG LVH regression from changes in BP (Figure 2). At all time points through 5 years of study treatment, losartan therapy was associated with significantly lower prevalences of ECG LVH by both Cornell product and Sokolow-Lyon voltage and with greater decreases in the prevalence of ECG LVH by these criteria from study baseline (Figure 1). Importantly, greater regression of ECG LVH with losartan as compared with atenolol was observed in women and men, younger and older patients, those with and without diabetes, and in whites and nonwhites.

The greater reduction in ECG LVH with losartan in the setting of similar reductions in BP with both therapies suggests a potential antihypertrophic effect of losartan, possibly mediated by direct blockade of myocardial effects of angiotensin II.20 Previous studies demonstrating that increased regression of echocardiographic LVH with ACE inhibition was in part independent of BP reductions7 further suggest a possible nonhemodynamic contribution of the renin-angiotensin system to hypertrophy. Studies in the neonatal renin transgenic rat21 provide more direct support for a blood pressure–independent role of the angiotensin II receptor in hypertrophy. Single administration of retroviral vector containing angiotensin II type I receptor antisense resulted in long-term expression of the antisense transgene in the heart and other cardiovascular tissues, and this expression was associated with significant attenuation of cardiac hypertrophy compared with viral vector–treated rats, despite its failure to normalize the elevated BP in these rats.21 Of note, the greater impact of losartan than atenolol on ECG measures of LVH was fully apparent by 6 months of treatment, consistent with the direct effects of losartan on relatively rapid myocyte

| TABLE 2. Baseline, Last, and Changes in Cornell Voltage-Duration Product in Relation to Treatment With Losartan Versus Atenolol in Subgroups According to Gender, Presence of Diabetes, Age, and Race |
|---------------------------------|---------------------------------|-----------------------------|
|                                | Losartan (n=4591)               | Atenolol (n=4561)           |
|                                | n Baseline Last Visit Change    | N Baseline Last Visit Change |
| Gender                         |                                |                            |
| Female                         | 2322 2937 2688 294 249         | 2320 2910 2843 292 66      |
| Male                           | 1963 2719 2381 233 338         | 1938 2719 2527 292 192     |
| Diabetes                       |                                |                            |
| Yes                             | 535 2905 2659 293 245          | 555 2933 2916 217 17       |
| No                              | 3750 2827 2531 276 296         | 3703 2807 2667 278 140     |
| Age <65                         | 1651 2719 2406 233 313         | 1646 2717 2522 233 195     |
| Age ≥65                         | 2634 2911 2636 276 275         | 2612 2890 2811 233 78      |
| Race                           |                                |                            |
| White                           | 3984 2856 2560 296 296         | 3968 2838 2711 256 126     |
| Other                           | 301 2585 2372 213 301          | 290 2625 2542 213 82      |
| Table 2. Baseline, Last, and Changes in Sokolow-Lyon Voltage in Relation to Treatment With Losartan Versus Atenolol in Subgroups According to Gender, Presence of Diabetes, Age, and Race |
|---------------------------------|---------------------------------|-----------------------------|
|                                | Losartan (n=4591)               | Atenolol (n=4561)           |
|                                | n Baseline Last Visit Change    | N Baseline Last Visit Change |
| Gender                         |                                |                            |
| Female                         | 2340 28.2 24.3 286 286         | 2341 28.1 26.1 286 261     |
| Male                           | 2007 32.0 26.5 286 286         | 1957 32.2 28.7 261 286     |
| Diabetes                       |                                |                            |
| Yes                             | 539 28.6 24.7 286 286         | 562 28.1 26.5 286 261     |
| No                              | 3778 30.1 25.4 286 286         | 3736 30.3 27.4 286 261   |
| Age <65                         | 1662 29.8 24.9 286 286         | 1651 30.0 26.7 286 261   |
| Age ≥65                         | 2655 30.0 25.6 286 286         | 2647 29.9 27.6 286 261   |
| Race                           |                                |                            |
| White                           | 4015 29.6 25.1 286 286         | 4005 29.7 27.0 286 261   |
| Other                           | 302 34.4 28.7 286 286         | 297 33.6 29.9 286 261   |

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remodeling, whereas the full effect on BP lowering was not apparent for 2 years, possibly reflecting slower effects on myocardial connective tissue and on systemic arterial remodeling.

Several potential limitations of the current study should be noted. Because patients in the LIFE study were selected on the basis of elevated Cornell product and Sokolow-Lyon voltage and moderate-to-severe hypertension, the current findings cannot necessarily be extrapolated to less-selected patients with milder hypertension and less evidence of end-organ damage at initiation of treatment. In addition, because patients were selected on the basis of elevated ECG LVH measures, some degree of the decreases in these values, particularly over the initial 6 months, could in part reflect regression to the mean. However, changes caused by regression to the mean would not interfere with interpretation of the observed treatment differences, since there were no differences in baseline ECG findings between groups and because these effects should be randomly distributed across the population independent of treatment group. Importantly, previous anterior or lateral myocardial infarction does not appear to significantly impact on the diagnostic accuracy of Cornell product criteria for LVH. Analyses performed in 2194 American Indian participants in the second phase of the Strong Heart Study found no difference in sensitivity of Cornell product criteria for ECG LVH between participants with and without Minnesota Code evidence of anterior or lateral myocardial infarction (33.2% versus 35.6%, P=NS) (Okin, unpublished observation). The loss of anteriorly directed QRS vector forces as the result of anterior infarction

Figure 2. Regression lines comparing changes in Cornell voltage-duration product (top) and Sokolow-Lyon voltage (bottom) in relation to change in systolic blood pressure in losartan- vs atenolol-treated patients. For any given change in systolic blood pressure, losartan therapy was associated with greater decreases in ECG LVH, illustrating the independence of treatment differences in regression of ECG LVH from changes in blood pressure.
may not significantly affect S-wave amplitude in lead V3, which predominantly reflects posteriorly directed forces of LV depolarization. Furthermore, loss of lateral forces in the frontal plane with concomitant loss of R-wave amplitude in lead aVL is typically offset by greater posteriorly directed forces and increases in V5, S-wave amplitude, preserving Cornell voltage amplitudes in the setting of these myocardial infarctions.

Thus, the LIFE Study demonstrated significantly greater regression of ECG LVH by Sokolow-Lyon voltage and Cornell product criteria on losartan versus atenolol therapy in the presence of comparable BP lowering in both treatment arms, supporting the hypothesis that losartan has additional cardiac effects beyond those obtained by BP lowering. These findings and the observation that regression of ECG LVH by Cornell product and Sokolow-Lyon voltage criteria predict lower CV morbidity and mortality rates in LIFE23 support the use of losartan for greater reductions in ECG LVH in hypertensive patients with ECG LVH.

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References
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