Prognostic Value of Changes in the Electrocardiographic Strain Pattern During Antihypertensive Treatment
The Losartan Intervention for End-Point Reduction in Hypertension Study (LIFE)

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Background—The presence of the ECG strain pattern of lateral ST depression and T-wave inversion at baseline has been associated with an increased risk of cardiovascular morbidity and mortality; however, the independent predictive value for cardiovascular outcomes of regression versus persistence versus development of new ECG strain during antihypertensive therapy is unclear.

Methods and Results—ECG strain was evaluated at baseline and after 1 year of therapy in 7409 hypertensive patients in the LIFE study (Losartan Intervention For End-point reduction in hypertension) treated in a blinded manner with atenolol- or losartan-based regimens. During 3.8±0.8 years of follow-up after the year 1 ECG, cardiovascular death occurred in 236 patients (3.2%), myocardial infarction in 198 (2.7%), stroke in 313 (4.2%), the LIFE composite end point of these 3 events in 600 (8.1%), sudden death in 92 (1.2%), and death due to any cause in 486 (6.6%). Strain was absent on both baseline and year 1 ECGs in 6323 patients (85.3%), regressed from baseline to year 1 in 245 (3.3%), persisted on both ECGs in 549 (7.4%), and was absent at baseline but developed by year 1 in 292 patients (3.9%). Compared with absence of strain on both ECGs, development of new ECG strain was associated with 2.8- to 4.7-fold higher event rates; patients with regression or persistence of strain had intermediate event rates. In Cox multivariable analyses with adjustment for the known predictive value of in-treatment ECG left ventricular hypertrophy by Cornell product and Sokolow-Lyon voltage, in-treatment systolic and diastolic pressure, randomized treatment, and standard cardiovascular risk factors, development of new ECG strain was independently associated with increased risks of cardiovascular death (hazard ratio [HR] 2.42, 95% confidence interval [CI] 1.56 to 3.76), myocardial infarction (HR 1.95, 95% CI 1.11 to 3.44), stroke in 313 patients (4.2%), sudden cardiac death (HR 2.19, 95% CI 1.06 to 4.53), and all-cause mortality (HR 1.92, 95% CI 1.37 to 2.69), whereas the risk associated with regression or persistence of strain was attenuated.

Conclusions—Development of new ECG strain is associated with an increased risk of cardiovascular morbidity and mortality and of all-cause mortality in the setting of antihypertensive therapy and regression of ECG left ventricular hypertrophy. (Circulation. 2009;119:1883-1891.)

Key Words: electrocardiography ■ hypertension ■ epidemiology ■ mortality ■ hypertrophy
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Serial assessment of ECG voltage and voltage-duration product criteria for LVH has demonstrated that regression of ECG LVH appears to confer a decreased risk of cardiovascular morbidity and mortality.13–18 Among LIFE study patients,18 regression of ECG LVH by both Cornell product and Sokolow-Lyon voltage criteria was associated with a decreased risk of cardiovascular death, myocardial infarction, stroke, and the composite end point of these events, independent of treatment modality and blood pressure lowering. However, the independent predictive value of serial assessment of the ECG strain pattern has been studied less extensively,14 and whether changes in the ECG strain pattern provide additional prognostic information beyond that provided by changes in ECG LVH in the LIFE study population18 has not been examined. Therefore, the present study examines the relationship of the strain pattern on the baseline and year 1 ECGs in the LIFE study to the risk of cardiovascular morbidity and cardiovascular and all-cause mortality, independent of other risk factors and of the known effects of treatment type, blood pressure reduction, and regression of ECG LVH on outcome.

Methods

Subjects

The LIFE study19,20 enrolled hypertensive patients with ECG LVH by Cornell product21 and/or Sokolow-Lyon voltage criteria1 on a screening ECG in a prospective, double-blind study large enough (n=9193) to demonstrate an appreciable reduction in mortality and morbidity events with use of losartan as opposed to atenolol.19 Eligible patients were men and women 55 to 80 years of age with previously untreated or treated essential hypertension with mean blood pressure in the range of 160 to 200 mm Hg systolic and 95 to 115 mm Hg diastolic after 1 and 2 weeks of placebo. A total of 7409 patients had baseline and year 1 ECGs on which the strain pattern could be determined (3980 women and 3429 men, mean age 67±7 years).

Electrocardiography

Hard-copy ECGs were interpreted at a core laboratory by experienced investigators blinded to clinical information, as previously reported in detail.7,11 QRS duration was measured to the nearest 4 ms in all 12 leads, and R-wave amplitudes in leads aVL, V5, and V6 and S-wave amplitudes in leads V1 and V3 were measured to the nearest 0.5 mm (0.05 mV).20,21 The product of QRS duration times the Cornell voltage combination (Rv5 + Sv1, with 6 mm [0.6 mV] added in women;21) >2440 mm⋅ms or Sokolow-Lyon voltage (Sv1 + RV5/6) >38 mm was used to identify ECG LVH.

Determination of the presence or absence of ECG strain as a dichotomous variable was assessed visually on baseline and year 1 ECGs at Helsinki University Central Hospital as described previously.7,11 Repolarization abnormalities in leads V1 or V5 were considered consistent with the presence of typical strain when a downsloping convex ST segment with an inverted asymmetrical T wave with polarity opposite to the main QRS deflection was present.7,11 Figure 1 shows an example of the strain pattern, contrasted with the typical symmetrical T-wave inversion of ischemia and classic scooping ST-segment changes associated with digitalis effect.

Echocardiography

Baseline echocardiograms were performed in 788 patients in the present study, as previously reported in detail.7 Echocardiographic left ventricular (LV) mass was calculated and indexed for body surface area and was considered consistent with LVH if LV mass index was >104 g/m² in women or >116 g/m² in men. Myocardial contractile performance was assessed by measuring LV midwall shortening, which was related to midwall circumferential end-systolic stress and expressed as a percentage of the value predicted from an equation derived in apparently normal adults.22 This variable, stress-corrected midwall shortening, was considered low if <89.2%,22

End-Point Determination

The LIFE study used a composite end point of cardiovascular death, nonfatal myocardial infarction, or stroke.11,18,19 These end points, sudden cardiac death, and all-cause mortality were ascertained and verified by an end-point committee blinded to ECG strain results when classifying possible morbid events.11,18,20 Sudden death was defined as sudden, unexpected death within 24 hours of symptom onset and included observed arrhythmic deaths and those not attributable to intractable heart failure or other identifiable cause. Only events that occurred after the year 1 ECG were included for analysis in the present study to allow determination of the relation of the pattern of ECG strain on serial ECGs to subsequent outcomes.

Statistical Analysis

Data management and analysis were performed with SPSS version 12.0 software (SPSS Inc, Chicago, Ill). Data are presented as mean±SD for continuous variables and proportions for categorical variables. Patients were classified into 4 groups according to the presence or absence of strain at baseline and year 1: No strain on either ECG (absence of strain); strain at baseline but not at year 1 (regression of strain); strain on both ECGs (persistence of strain); or no strain at baseline and strain at year 1 (development of new strain). Differences in prevalences between groups were compared with χ² analyses, and mean values of continuous variables were compared with 1-way ANOVA, with probability values given for the statistical significance of the linear trend across groups.

Event rates were calculated and plotted according to the Kaplan–Meier product limit method, and statistical significance tested for the linear trend across groups with the log-rank statistic. The relation of strain at baseline and year 1 to the risk of clinical end points was assessed with Cox proportional hazards models. Partial residuals were plotted against survival times and examined visually to check the proportional hazards assumption. To test the independence of serial assessment of ECG strain for events, the presence or absence of ECG strain at baseline and year 1 was entered into a multivariable Cox model that also included age, gender, treatment group, race, diabetes mellitus, history of ischemic heart disease, myocardial infarction, stroke, peripheral vascular disease and smoking, baseline urinary albumin/creatinine ratio, total and high-density lipoprotein (HDL) cholesterol, and body mass index as standard covariates, as well as baseline and in-treatment values of systolic and diastolic blood pressure.

Figure 1. An example of the typical strain pattern (A), contrasted with the typical symmetrical T-wave pattern associated with ischemia (B) and the classic scooping ST segment changes associated with digitalis effect (C).
pressure, Cornell product, and Sokolow-Lyon voltage as time-varying covariates.

Analyses were repeated with stratification of the population by sex, age, race, treatment group, history of ischemic heart disease, and prevalent diabetes and by the presence or absence of LVH by Cornell product and Sokolow-Lyon voltage on the baseline ECG. Interaction between the presence or absence of strain at baseline and year 1 and these variables was formally tested by the addition of cross-product terms of strain and these variables into the models of the total population. For all tests, a 2-tailed probability value <0.05 was required for statistical significance.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

#### Patient Characteristics in Relation to Presence or Absence of ECG Strain at Baseline and Year 1

Table 1. Demographic and Clinical Characteristics in Relation to the Presence of ECG Strain at Baseline and Year 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Strain−/Strain− (n=6233): No Strain</th>
<th>Strain+/Strain− (n=240): Regression of Strain</th>
<th>Strain+/Strain+ (n=549): Persistent Strain</th>
<th>Strain−/Strain+ (n=292): New Strain</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.1±7.0</td>
<td>66.9±7.1</td>
<td>68.0±6.8</td>
<td>69.2±6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>55.8</td>
<td>38.0</td>
<td>38.4</td>
<td>50.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, % black</td>
<td>4.3</td>
<td>9.8</td>
<td>15.8</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>11.6</td>
<td>15.9</td>
<td>18.6</td>
<td>17.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of IHD, %</td>
<td>11.9</td>
<td>26.9</td>
<td>33.3</td>
<td>24.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>4.3</td>
<td>9.8</td>
<td>14.8</td>
<td>11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CHF, %</td>
<td>1.1</td>
<td>2.0</td>
<td>5.1</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>3.6</td>
<td>4.5</td>
<td>7.5</td>
<td>6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of PVD, %</td>
<td>4.9</td>
<td>7.3</td>
<td>9.1</td>
<td>8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment with losartan, %</td>
<td>50.6</td>
<td>53.9</td>
<td>48.5</td>
<td>42.1</td>
<td>0.071</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.1±4.7</td>
<td>27.8±4.4</td>
<td>27.7±4.9</td>
<td>27.8±5.1</td>
<td>0.133</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.06±1.10</td>
<td>5.88±1.18</td>
<td>5.90±1.15</td>
<td>5.97±1.13</td>
<td>0.030</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.52±0.44</td>
<td>1.40±0.37</td>
<td>1.40±0.40</td>
<td>1.41±0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UACR, mg/mmol</td>
<td>5.7±28.3</td>
<td>8.9±21.3</td>
<td>13.5±35.2</td>
<td>13.9±43.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.92±2.01</td>
<td>6.30±2.42</td>
<td>6.36±2.86</td>
<td>6.31±2.46</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IHD indicates ischemic heart disease; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; and UACR, urine albumin/creatinine ratio.

* Differences in prevalences between groups were compared using χ² analyses, and mean values of continuous variables were compared with ANOVA for linear trend.

ECG strain was absent on both baseline and year 1 ECGs in 6323 patients (85.3%), regressed from baseline to year 1 in 245 (3.3%), persisted on both ECGs in 549 (7.4%), and was absent at baseline but developed by year 1 in 292 patients (3.9%). Clinical and demographic characteristics of patients in relationship to the presence or absence of ECG strain at baseline and year 1 are shown in Table 1. Patients without strain on either ECG were younger; more likely to be female; less likely to be black or to have diabetes, a history of myocardial infarction, heart failure, stroke, or peripheral vascular disease; and had higher total and HDL cholesterol levels, less albuminuria, and lower serum glucose levels.

Blood pressure and ECG LVH measurements at baseline and changes in these measurements between baseline and last in-study determination in relation to the presence or absence of ECG strain on baseline and year 1 ECGs are shown in Table 2. The absence of strain on both ECGs was associated with lower baseline systolic pressures, Cornell product, and Sokolow-Lyon voltage and with smaller reductions in systolic and diastolic pressure. Regression of strain between baseline and year 1 was associated with the greatest reductions in Cornell product and Sokolow-Lyon voltage, whereas development of new strain was associated with the smallest reductions in ECG LVH during the course of the study.

Baseline LV findings in relation to the presence or absence of ECG strain at baseline and year 1 in the subset of the population who underwent echocardiography are shown in Table 3. Persistence or development of new ECG strain was associated with greater echocardiographic LV mass index and a higher prevalence of LVH. Development of new ECG strain was associated with depressed LV systolic function, with the lowest midwall shortening and stress-corrected midwall shortening and the greatest likelihood of having subnormal midwall performance for the level of end-systolic stress.

**ECG Strain and Prediction of Outcome**

During 3.8±0.8 years of follow-up after the year 1 ECG, cardiovascular death occurred in 236 patients (3.2%), myocardial infarction in 198 (2.7%), stroke in 313 (4.2%), the LIFE composite end point of the first occurrence of these 3 events in 600 (8.1%), sudden cardiac death in 92 (1.2%), and death of any cause in 486 (6.6%). The relationship of serial evaluation of ECG strain at baseline and year 1 to outcomes is shown in Table 4 and Figure 2. Compared with absence of strain on both ECGs, development of new ECG strain was associated with higher event rates; patients with regression or persistence of ECG strain had intermediate event rates. In
univariate Cox analyses, development of new ECG strain pattern was associated with the highest risk of all end points, with nearly 3- to 5-fold increased risks compared with the absence of strain on both ECGs. In contrast, regression of strain between baseline and year 1 was associated with a nonsignificant or marginally significant increased risk of events, and persistence of ECG strain on both baseline and year 1 ECGs was associated with ≈2-fold higher risks of these end points.

Because patients who developed strain differed significantly from those who did not with respect to demographic and clinical variables that could affect outcome (Tables 1 and 2), the independent relation of outcomes to the presence or absence of strain at baseline and year 1 was examined after adjustment for the possible effects of treatment, age, gender, race, prevalent diabetes, history of ischemic heart disease, myocardial infarction, stroke, peripheral vascular disease and smoking, baseline urinary albumin/creatinine ratio, total and HDL cholesterol, and body mass index and for the possible effects of baseline and in-treatment systolic and diastolic blood pressure, Cornell product, and Sokolow-Lyon voltage, which were treated as time-dependent covariates (Table 4). After adjustment for these factors, development of new ECG strain remained associated with an approximately 2- to 2.4-fold increased risk of all end points, whereas the risk associated with regression or persistence of ECG strain was attenuated and no longer statistically significant. Importantly, in-treatment ECG LVH by Cornell product or Sokolow-Lyon voltage, treated as a time-varying covariate in these Cox models, remained a significant predictor of all end points in these multivariable Cox models (data not shown).

The predictive value of the presence or absence of ECG strain at baseline and year 1 for the LIFE composite end point in relevant subsets of the population is examined in Table 5. The association between baseline and year 1 ECG strain and the composite end point was similar in men and women, in blacks and other ethnicities, in both treatment arms of the study, in patients above and below 65 years of age, among patients with and without a history of ischemic heart disease and with or without prevalent diabetes, and among patients with and without LVH on their baseline ECG by either Cornell product or Sokolow-Lyon voltage criteria, with nonsignificant interaction terms for these variables. The association of ECG strain at baseline and year 1 with cardiovascular mortality, nonfatal myocardial infarction, stroke, sudden death, and all-cause mortality was also similar across all subgroups of the population examined, with nonsignificant interaction terms (data not shown).

Table 2. Baseline and Change From Baseline to Last In-Study Measurement of Blood Pressure and ECG LVH in Relation to the Presence of ECG Strain at Baseline and Year 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Strain+/Strain− (n=623): Regression of Strain</th>
<th>Strain+/Strain− (n=549): Persistent Strain</th>
<th>Strain+/Strain+ (n=292): New Strain</th>
<th>P for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>173.9±14.4</td>
<td>176.6±14.2</td>
<td>176.8±14.8</td>
<td>177.3±13.6</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>98.1±8.6</td>
<td>97.6±9.9</td>
<td>97.4±9.4</td>
<td>97.6±9.5</td>
</tr>
<tr>
<td>Cornell product, mm · ms</td>
<td>2624±724</td>
<td>2953±966</td>
<td>2931±907</td>
<td>2855±927</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage, mm</td>
<td>28.9±9.9</td>
<td>34.9±10.5</td>
<td>37.9±11.0</td>
<td>33.3±10.9</td>
</tr>
<tr>
<td>Change from baseline to last measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>−29.8±19.3</td>
<td>−32.1±19.9</td>
<td>−32.0±18.9</td>
<td>−32.1±21.3</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>−17.3±10.0</td>
<td>−17.9±10.8</td>
<td>−18.7±10.3</td>
<td>−18.0±11.5</td>
</tr>
<tr>
<td>Cornell product, mm · ms</td>
<td>−207±700</td>
<td>−384±861</td>
<td>−181±926</td>
<td>−102±960</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage, mm</td>
<td>−3.8±6.8</td>
<td>−7.6±8.9</td>
<td>−4.9±10.0</td>
<td>−3.5±9.2</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

Table 3. Baseline Echocardiographic Measurements in Relation to the Presence of ECG Strain at Baseline and Year 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Strain+/Strain− (n=647): Regression of Strain</th>
<th>Strain+/Strain− (n=33): Persistent Strain</th>
<th>Strain+/Strain+ (n=83): New Strain</th>
<th>P for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index, g/m²</td>
<td>119.2±21.8</td>
<td>133.2±26.5</td>
<td>145.6±34.5</td>
<td>139.3±28.1</td>
</tr>
<tr>
<td>LVH, %</td>
<td>66.0</td>
<td>78.8</td>
<td>90.1</td>
<td>83.3</td>
</tr>
<tr>
<td>LV midwall shortening, %</td>
<td>15.8±2.0</td>
<td>15.5±1.8</td>
<td>14.3±2.3</td>
<td>14.0±1.6</td>
</tr>
<tr>
<td>Stress-corrected LV midwall shortening, %</td>
<td>98.5±12.3</td>
<td>97.3±10.7</td>
<td>91.6±16.0</td>
<td>88.0±10.3</td>
</tr>
<tr>
<td>Stress-corrected LV midwall shortening &lt;89.2%, %</td>
<td>21.4</td>
<td>18.8</td>
<td>41.3</td>
<td>70.0</td>
</tr>
</tbody>
</table>
ECG Strain and the Prediction of Outcomes

The relationship of cardiovascular risk to ECG strain pattern on a single ECG has been demonstrated in population-based studies and in patients with hypertension\(^9\)-\(^{14}\); however, the relationship of the presence or absence of ECG strain over time to cardiovascular outcomes has been evaluated less extensively.\(^6\) In a serial analysis of 274 men and 250 women from the Framingham Study with ECG LVH by Framingham criteria,\(^13\) development of worsening repolarization abnormalities was associated with statistically significant 1.9- to 2-fold increased risks of incident cardiovascular disease in men and women, respectively. In contrast, improvement in repolarization findings was associated with only a marginally significant reduction in cardiovascular risk in men but not in women.\(^13\) Although these findings remained similar when additionally adjusted for serial change in systolic pressure, the further impact of serial changes in Cornell voltage on outcome was not evaluated.\(^13\) Among 496 hypertensive patients with ECG LVH by the Perugia score at baseline in the Hypertrophy at ECG And its Regression during Treatment (HEART) Survey,\(^14\) in-treatment persistence or development of ECG strain was associated with a 2-fold increased risk of cardiovascular events, independent of the predictive value of age, sex, diabetes, and in-treatment levels of Cornell voltage LVH; however, patients in that study had a high prevalence of ECG strain at baseline (35%) because of the inclusion of strain in the selection criteria for the study, and the predictive value of new strain was not examined separately from persistence of strain, the multivariate analyses did not adjust for treatment modalities or blood pressure levels over time, and the numbers of patients and events in the study were modest.

### Table 4. Five-Year Event Rates and Univariate and Multivariable Cox Regression Analyses to Assess the Relation of Outcomes to ECG Strain at Baseline and Year 1

<table>
<thead>
<tr>
<th>Event</th>
<th>Strain−/Strain− (n=6323)</th>
<th>Strain+/Strain− (n=245)</th>
<th>Strain+/Strain+ (n=549)</th>
<th>Strain−/Strain+ (n=292)</th>
<th>P for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIFE composite end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate hazard ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE composite point</td>
<td>1.63 (1.11–2.41)</td>
<td>2.13 (1.67–2.71)</td>
<td>3.23 (2.45–4.24)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.82 (0.99–3.35)</td>
<td>2.58 (1.78–3.73)</td>
<td>4.74 (3.24–6.93)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.05 (1.11–3.78)</td>
<td>2.19 (1.44–3.33)</td>
<td>2.83 (1.71–4.68)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.70 (1.01–2.86)</td>
<td>1.88 (1.32–2.67)</td>
<td>3.03 (2.07–4.43)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sudden death</td>
<td>2.02 (0.82–2.23)</td>
<td>2.21 (1.20–4.10)</td>
<td>3.54 (1.82–6.90)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.40 (0.88–2.23)</td>
<td>2.10 (1.60–2.75)</td>
<td>3.27 (2.43–4.40)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate hazard ratio (95% CI)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE composite end point</td>
<td>1.35 (0.91–2.01)</td>
<td>1.24 (0.94–1.64)</td>
<td>2.05 (1.51–2.78)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.43 (0.76–2.66)</td>
<td>1.40 (0.92–2.15)</td>
<td>2.42 (1.56–3.76)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.72 (0.92–3.24)</td>
<td>1.30 (0.79–2.12)</td>
<td>1.95 (1.13–3.44)</td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.49 (0.87–2.54)</td>
<td>1.20 (0.81–1.79)</td>
<td>1.98 (1.30–3.01)</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1.31 (0.47–3.68)</td>
<td>1.18 (0.57–2.44)</td>
<td>2.19 (1.06–4.53)</td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.13 (0.70–1.82)</td>
<td>1.21 (0.88–1.65)</td>
<td>1.92 (1.37–2.69)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for possible effects of treatment with losartan vs atenolol, age, sex, race, prevalent diabetes mellitus, history of ischemic heart disease, myocardial infarction, stroke, heart failure or peripheral vascular disease, baseline albumin/creatinine ratio, total and HDL cholesterol, glucose, body mass index, baseline and in-treatment systolic and diastolic blood pressure, and baseline and in-treatment Sokolow-Lyon voltage and Cornell voltage-duration product.

### Discussion

This study demonstrates that development of new ECG strain between baseline and year 1 during the LIFE study identifies patients at increased risk of cardiovascular morbidity and mortality and all-cause mortality in the setting of antihypertensive therapy associated with substantial decreases in both systolic and diastolic pressure. The increased risk associated with new ECG strain was independent of the improved prognosis with losartan therapy\(^9\) and with regression of ECG LVH in LIFE,\(^18,23\) and it persisted after adjustment for the greater baseline severity and prevalence of ECG LVH and the higher prevalence of other cardiovascular disorders associated with ECG strain. These findings suggest that more aggressive therapy may be warranted in hypertensive patients who develop new ECG strain to reduce the risk of cardiovascular morbidity, cardiovascular and all-cause mortality, and sudden death.
In contrast, the present study demonstrates that development of new ECG strain between baseline and year 1 ECGs for the development of the LIFE composite end point of cardiovascular mortality, myocardial infarction, or stroke (A), cardiovascular mortality (B), myocardial infarction (C), stroke (D), sudden death (E), and all-cause mortality (F), n=number of patients. Strain-/Strain- indicates absence of strain on baseline and year 1 ECG; Strain-/Strain-, presence of strain on baseline ECG and absence of strain on year 1 ECG, regression of strain; Strain-/Strain-, presence of strain on baseline and year 1 ECG, persistence of strain; and Strain-/Strain-, absence of strain on baseline ECG and presence of strain on year 1 ECG, development of new strain.

Figure 2. Kaplan–Meier curves comparing event rates between patients according to the presence or absence or ECG strain on their baseline and year 1 ECGs for the development of the LIFE composite end point of cardiovascular mortality, myocardial infarction, or stroke (A), cardiovascular mortality (B), myocardial infarction (C), stroke (D), sudden death (E), and all-cause mortality (F). n=number of patients. Strain-/Strain- indicates absence of strain on baseline and year 1 ECG; Strain-/Strain-, presence of strain on baseline ECG and absence of strain on year 1 ECG, regression of strain; Strain+/Strain-, presence of strain on baseline and year 1 ECG, persistence of strain; and Strain+/Strain+, absence of strain on baseline ECG and presence of strain on year 1 ECG, development of new strain.

In contrast, the present study demonstrates that development of new ECG strain between baseline and year 1 was a significant predictor of cardiovascular mortality, myocardial infarction, stroke, the LIFE composite end point of these events, sudden cardiac death, and all-cause mortality in a large population of hypertensive patients with ECG LVH by Cornell product or Sokolow-Lyon voltage at baseline. The predictive value of new ECG strain was independent of the possible impact of standard cardiovascular risk factors, baseline and in-treatment diastolic and systolic blood pressure, and the known impact of treatment with losartan versus atenolol on these outcomes in the LIFE study. Most importantly, the predictive value of new ECG strain was independent of the previously demonstrated prognostic value of regression of Cornell product and Sokolow-Lyon voltage in this population. Furthermore, in contrast to the HEART Survey, regression of ECG LVH by Cornell product and
cardiographic or autopsy measures of LV mass,4 ECG strain
of these factors. In a population of 161 patients with echo-
in the present study after adjustment for the possible impact
However, new ECG strain remained predictive of outcomes
ECG LVH by Cornell product and Sokolow-Lyon voltage.
who developed new ECG strain had the least regression of
and vascular disease, and had evidence of greater end-organ
prevalences of diabetes and history of various forms of heart
adverse prognosis associated with strain. In the present study,
cardiovascular structure and function may explain in part the
known, the strong association of strain with abnormalities of
ECG strain to increased cardiovascular morbidity, sudden
death, and cardiovascular and all-cause mortality are not
known, the strong association of strain with abnormalities of
vascular disease, and had evidence of greater end-organ
damage as manifested by albuminuria. In addition, patients
who developed new ECG strain had the least regression of
ECG LVH by Cornell product and Sokolow-Lyon voltage.
However, new ECG strain remained predictive of outcomes
in the present study after adjustment for the possible impact
of these factors. In a population of 161 patients with eco-
cardiographic or autopsy measures of LV mass,4 ECG strain
was associated with increased LV mass and with a reduced
Sokolow-Lyon voltage retained predictive value for all out-
comes in the present study when serial assessment of ECG
strain was taken into account, which emphasizes the need
for serial assessment of both standard ECG LVH criteria
and lateral repolarization abnormalities to accurately
assess changing risk over time in the hypertensive
population.
Although the precise mechanisms linking development of
ECG strain to increased cardiovascular morbidity, sudden
death, and cardiovascular and all-cause mortality are not
known, the strong association of strain with abnormalities of
vascular disease, and had evidence of greater end-organ
damage as manifested by albuminuria. In addition, patients
who developed new ECG strain had the least regression of
ECG LVH by Cornell product and Sokolow-Lyon voltage.
contribute to the increased risk of sudden death in these patients.

Study Limitations and Perspectives

The independent relation of new ECG strain to increased risk in the LIFE study despite aggressive blood pressure reduction suggests that the development of new strain on the ECG may be used to identify hypertensive patients with ECG LVH who require more aggressive antihypertensive therapy aimed at further risk reduction in these patients. However, the inferences that may be drawn from the present study are potentially limited by the lack of ECG strain data on ECGs obtained after year 1 and by the absence of quantitative data assessing the degree of ST depression in this population. Previous observations that the magnitude of ST depression in the lateral leads is strongly related to the presence and severity of LVH\(^6\) and that measured ST depression and echocardiographic LV mass provide complementary prognostic information\(^29\) suggest that serial assessment of the magnitude of lateral repolarization abnormality may provide additional prognostic benefit in hypertensive patients. Further study will be necessary to address this important question.

Sources of Funding

This study was supported in part by grant COZ-368 and an investigator-initiated study proposal grant from Merck & Co, Inc, West Point, Pa.

Disclosures

Drs Okin and Okinari receive grant support from Merck & Co, Inc. Dr Kjeldsen receives honoraria from Merck & Co, Inc, AstraZeneca, Abbott, Bayer, Boehringer-Ingelheim, Bristol-Meyer-Squibb, Novartis, Pfizer, Sanofi, Sankyo, and Menarini. Dr Edelman is employed by and owns stock in Merck & Co, Inc. Dr Dahlof receives grant support from Boehringer-Ingelheim, Novartis, and Pfizer; receives honoraria from Merck & Co, Inc, Novartis, Boehringer-Ingelheim, and Pfizer; and serves as a consultant for Merck & Co, Inc, Novartis, and Boehringer-Ingelheim. Dr Devereux receives grant support and serves on advisory boards for Merck & Co, Inc and Novartis. The remaining authors report no conflicts.

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**CLINICAL PERSPECTIVE**

This study demonstrates that development of a new ECG strain pattern of lateral ST depression and T-wave inversion in lead V5 or V6 between baseline and year 1 during the LIFE study (Losartan Intervention For End-point reduction in hypertension) identifies patients at increased risk of cardiovascular morbidity and mortality, sudden cardiac death, and all-cause mortality in the setting of antihypertensive therapy associated with substantial decreases in both systolic and diastolic pressure. The increased risk associated with new ECG strain was independent of the improved prognosis with losartan therapy and with regression of ECG left ventricular hypertrophy in the LIFE study and persisted after adjustment for the greater baseline severity and prevalence of ECG left ventricular hypertrophy and the higher prevalence of other cardiovascular disorders associated with ECG strain. The independent relation of new ECG strain to increased risk in the LIFE study despite aggressive blood pressure reduction suggests that the development of new strain on the ECG may be used to identify hypertensive patients with ECG left ventricular hypertrophy who require more aggressive antihypertensive therapy aimed at further risk reduction. Further research will be required to determine whether additional treatment in patients with new ECG strain will improve prognosis in this high-risk group of hypertensive patients.
Prognostic Value of Changes in the Electrocardiographic Strain Pattern During Antihypertensive Treatment: The Losartan Intervention for End-Point Reduction in Hypertension Study (LIFE)

Peter M. Okin, Lasse Oikarinen, Matti Viitasalo, Lauri Toivonen, Sverre E. Kjeldsen, Markku S. Nieminen, Jonathan M. Edelman, Björn Dahlöf and Richard B. Devereux for the LIFE Study Investigators

_Circulation_. 2009;119:1883-1891; originally published online March 30, 2009; doi: 10.1161/CIRCULATIONAHA.108.812313

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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