Regression of Electrocardiographic Left Ventricular Hypertrophy During Antihypertensive Treatment and the Prediction of Major Cardiovascular Events

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Context Electrocardiographic left ventricular hypertrophy (LVH) is a strong predictor of cardiovascular (CV) morbidity and mortality. However, the predictive value of changes in the magnitude of electrocardiographic LVH criteria during antihypertensive therapy remains unclear.

Objective To test the hypothesis that lesser severity of electrocardiographic LVH during antihypertensive treatment is associated with decreased CV morbidity and mortality, independent of blood pressure levels and reduction and treatment modality.

Design, Setting, and Participants Double-blind, randomized, parallel-group study conducted in 1995-2001 among 9193 men and women with hypertension aged 55 through 80 years (mean, 67 years), with electrocardiographic LVH by Cornell voltage-duration product or Sokolow-Lyon voltage criteria and enrolled in the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study.

Interventions Losartan- or atenolol-based treatment regimens, with follow-up assessments for at least 4 (mean, 4.8 [SD, 0.9]) years.

Main Outcome Measure Composite end point of CV death, myocardial infarction (MI), or stroke in relation to severity of electrocardiographic LVH determined at baseline and on subsequent electrocardiograms obtained at 1 or more annual revisits.

Results Cardiovascular death, nonfatal MI, or stroke occurred in 1096 patients (11.9%). In Cox regression models controlling for treatment type, baseline Framingham risk score, baseline and in-treatment blood pressure, and severity of baseline electrocardiographic LVH by Cornell product and Sokolow-Lyon voltage, less-severe in-treatment LVH by Cornell product and Sokolow-Lyon voltage were associated with 14% and 17% lower rates, respectively, of the composite CV end point (adjusted hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.82-0.90; P<.001 for every 1050-mm²·ms [1-SD] decrease in Cornell product; and HR, 0.83; 95% CI, 0.78-0.88; P<.001 for every 10.5-mm [1-SD] decrease in Sokolow-Lyon voltage). In parallel analyses, lower Cornell product and Sokolow-Lyon voltage were each independently associated with lower risks of CV mortality (HR, 0.78; 95% CI, 0.73-0.83; P<.001; and HR, 0.80; 95% CI, 0.73-0.87; P<.001, respectively), MI (HR, 0.90; 95% CI, 0.82-0.98; P=.01; and HR, 0.90; 95% CI, 0.81-1.00; P=.04), and stroke (HR, 0.90; 95% CI, 0.84-0.96; P=.002; and HR, 0.81; 95% CI, 0.75-0.89; P<.001).

Conclusions Less-severe electrocardiographic LVH by Cornell product and Sokolow-Lyon voltage criteria during antihypertensive therapy is associated with lower likelihoods of CV morbidity and mortality, independent of blood pressure lowering and treatment modality in persons with essential hypertension. Antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH may improve prognosis.

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See also pp 2350 and 2396 and Patient Page.
BP during antihypertensive therapy requires further evaluation.2,3,12,13

Usefulness of electrocardiographic criteria for the detection of LVH and for serial evaluation of changes in left ventricular mass has been limited by low sensitivity of standard voltage criteria for the detection of anatomic LVH.21-27 However, Cornell voltage criteria modestly improve electrocardiographic detection of LVH,22,23 and the product of Cornell voltage and QRS duration (Cornell voltage-duration product)24,25—as an approximation of the true area under the QRS complex26—further enhances sensitivity of the ECG while maintaining high specificity, with a sensitivity of 51% vs 31% for Sokolow-Lyon voltage when examined at a matched specificity of 95%.27 As a consequence, Cornell voltage-duration product criteria were used in combination with Sokolow-Lyon voltage criteria21 to identify patients with hypertension who are at increased risk of CV morbidity and mortality in the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study, a prospective trial that demonstrated a greater reduction in CV events in patients taking losartan than in those taking atenolol.28-31

In the prespecified echocardiographic substudy of the LIFE study, the presence of electrocardiographic LVH by Cornell product and/or Sokolow-Lyon voltage criteria identified patients with hypertension having a greater than 70% likelihood of having echocardiographic LVH as well as those not fulfilling the strict cutoff criteria for echocardiographic LVH but with high-normal values of indexed left ventricular mass.32 Moreover, regression of electrocardiographic LVH by Cornell product criteria was associated with greater 1-year reductions in left ventricular mass and a higher likelihood of regression of echocardiographic LVH in the LIFE study,13 suggesting that lower values of electrocardiographic LVH criteria during serial evaluation over time may predict improved outcome during antihypertensive therapy. Accordingly, the present study examined whether lower in-treatment values of electrocardiographic LVH as measured by Cornell product and Sokolow-Lyon voltage criteria are associated with a reduced rate of major CV events in the LIFE study, independent of the effects of BP change, treatment type, and severity of baseline electrocardiographic LVH.28-31

METHODS

Participants

The LIFE study28-31 enrolled patients with hypertension having electrocardiographic LVH by Cornell voltage-duration product24,25 and/or Sokolow-Lyon voltage criteria21 on a screening ECG in a prospective, double-blind, randomized study large enough (n=9193) to have sufficient power (80%) to detect a difference of at least 15% in the incidence of combined CV morbidity and mortality with use of losartan as opposed to atenolol.28 As described in detail elsewhere,28-31 patients eligible for the LIFE study were men and women aged 55 to 80 years with previously untreated essential hypertension. LIFE participants were assigned to treatment based on sex and systolic blood pressure at baseline: 660 mm Hg systolic, 65 to 80 mm Hg diastolic, or both, after 1 and 2 weeks of receiving placebo who had not experienced a myocardial infarction (MI) or stroke within 6 months and did not require treatment with a β-blocker, angiotensin-converting enzyme inhibitor, or AT1-receptor antagonist. The study was approved by all ethics committees concerned. All participants gave written informed consent.

Treatment Regimens

Blinded treatment was begun with losartan, 50 mg, or atenolol, 50 mg, daily and matching placebo of the other agent, with a target BP of 140/90 mm Hg or lower. During clinic visits at frequent intervals for the first 6 months and at 6-month intervals thereafter, study therapy could be up-titrated by addition of hydrochlorothiazide, 12.5 mg, followed by increase in blinded losartan or atenolol to 100 mg/d. In patients whose BP was still not controlled, additional open-label upward titration of hydrochlorothiazide and, if necessary, institution of therapy with a calcium channel blocker or additional other medications (excluding β-blockers, angiotensin-converting enzyme inhibitors, or AT1-receptor antagonists) was added to the double-blind treatment regimen.28

Electrocardiography

Electrocardiograms were obtained at study baseline, at 6 months, and at yearly follow-up intervals until study termination or patient death. Electrocardiograms were interpreted at the core laboratory at Sahlgrenska University Hospital/Ostra, Göteborg, Sweden, by experienced readers blinded to clinical information. QRS duration was measured to the nearest 4 ms and the QRS amplitudes to the nearest 0.5 mm (0.05 mV). The product of QRS duration × the Cornell voltage combination (R1+SV3, with 8 mm added in women24,25) was used with a threshold value of 2440 mm ms to identify LVH. After the LIFE trial was designed, studies were published suggesting a smaller sex adjustment,33,34 and feedback from LIFE investigators showed that otherwise-eligible patients had electrocardiographic LVH by highly specific but insensitive Sokolow-Lyon voltage21 but not by Cornell product criteria. Accordingly, changes were made in electrocardiographic entry criteria for patients recruited after April 30, 1996 (n=7708): the sex adjustment of Cornell voltage was reduced from 8 to 6 mm and Sokolow-Lyon voltage (R1+SV3) greater than 38 mm was accepted for electrocardiographic eligibility.20

End Point Determination

The LIFE trial used a composite end point of CV death, nonfatal MI, or nonfatal stroke, according to previously defined criteria.28 Potential end points were ascertained and then verified by an expert end point committee who were blinded to ECG results when classifying possible morbid events, as previously described.28,31

Statistical Analyses

Data are presented as mean (SD) for continuous variables and as propor-
tions for categorical variables. Analyses of changes in mean values over time were performed using repeated-measures analysis of variance. To test the hypothesis that lower values of Cornell product and Sokolow-Lyon voltage during antihypertensive therapy are associated with a reduction of clinical events, independent of treatment type and magnitude of BP lowering, the relations of electrocardiographic LVH criteria to the risk of developing the LIFE composite clinical end point and its individual components were analyzed based on the intention-to-treat principle; ie, all randomized patients were assessed for end points for the duration of the study, regardless of protocol violations or adherence to study medication. All patients enrolled in the LIFE trial with a valid baseline ECG were included in the statistical analyses. According to a prespecified statistical analysis plan, the relations of changing levels of Cornell product and Sokolow-Lyon voltage to the risk of clinical end points were assessed using Cox proportional hazards models, with baseline and subsequent determinations of Cornell product and Sokolow-Lyon voltage entered as time-varying covariates. Baseline Framingham risk score and a treatment group indicator were included as standard covariates, and baseline and subsequent systolic and diastolic BP measurements were entered as time-varying covariates. The adjusted hazard ratios (HRs) for the incidence of the composite end point for Cornell product and Sokolow-Lyon voltage treated as continuous variables were computed per 1-SD-of-the-mean lower values of the electrocardiographic criteria as the antilogarithm of the estimated coefficient multiplied by the SD. The 95% confidence interval (CI) of each relative risk was calculated from the estimated coefficients and their standard errors, and Wald $\chi^2$ statistics and probability values were calculated.

The relationship of event rates over time to changing values of each LVH criterion was illustrated by plotting event rates as functions of grouped ranges of Cornell product and Sokolow-Lyon voltage using a modified Kaplan-Meier method, with assignment to groups adjusted at the time of each ECG performed based on the measurement of Cornell product and Sokolow-Lyon voltage at those times. These modified Kaplan-Meier curves are intended to illustrate the results of the time-varying covariate analyses.

For all tests, a 2-tailed $P<.05$ was required for statistical significance. Data management and analyses were primarily performed by the Clinical Bio-statistics Department of Merck Research Laboratories using SAS version 8 (SAS Institute Inc, Cary, NC), with independent validation performed by 1 of the investigators (P.M.O.). All study data currently reside in the Merck & Co Inc database.

**RESULTS**

After mean follow-up of 4.8 (SD, 0.9) years, 1096 of the 9193 patients (11.9%) had documented LIFE primary end points of cardiovascular death, nonfatal MI, or stroke. As previously reported, LIFE patients were a mean age of 67 years, and 54% were women; 72% were previously treated for hypertension and previous coronary, cerebral, or peripheral vascular disease, and diabetes occurred in 16%, 8%, 6%, and 13% of these patients, respectively, without difference between treatments.

**Serial Assessment of BP and Electrocardiographic LVH**

Baseline and serial assessments of mean systolic and diastolic BP, Cornell product, and Sokolow-Lyon voltage are shown in Table 1. As expected based on the entry criteria for the LIFE study, the mean systolic and diastolic BP, Cornell voltage-duration product, and Sokolow-Lyon voltage were elevated at baseline and decreased substantially during the first year in the LIFE study, concomitant with the institution of protocol-based antihypertensive therapy. In subsequent years, BP continued to decrease only slightly, whereas there were continued significant further decreases in Cornell product and Sokolow-Lyon voltage between 12- and 24-month ECGs, with small further decreases through the 60-month ECGs.

**Regression of Electrocardiographic LVH and CV Events**

Lower in-treatment values of both Cornell voltage-duration product and Sokolow-Lyon voltage during antihypertensive therapy were strongly associated with decreased risk of CV morbidity and mortality (Table 2, Figure 1, and Figure 2). In Cox analyses adjusting only for possible treatment effect (Table 2), a 1050-mm X ms (1 SD of the

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**Table 1. Baseline and Follow-up Blood Pressure and Electrocardiographic Left Ventricular Hypertrophy, by Cornell Voltage-Duration Product and Sokolow-Lyon Voltage During Treatment in the LIFE Study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>6 Months</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>174.3 (14.5)</td>
<td>150.0 (16.9)</td>
<td>150.4 (16.9)</td>
<td>148.4 (16.4)</td>
<td>147.0 (16.7)</td>
<td>145.6 (16.1)</td>
<td>144.8 (16.4)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>97.7 (6.0)</td>
<td>84.7 (9.2)</td>
<td>85.0 (9.2)</td>
<td>83.8 (8.9)</td>
<td>82.8 (8.2)</td>
<td>81.6 (9.1)</td>
<td>80.8 (9.0)</td>
</tr>
<tr>
<td>Cornell product, mm X ms</td>
<td>2829 (1049)</td>
<td>2690 (1042)</td>
<td>2646 (1061)</td>
<td>2579 (1040)</td>
<td>2571 (1059)</td>
<td>2579 (1077)</td>
<td>2576 (1038)</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage, mm</td>
<td>30.0 (10.5)</td>
<td>28.4 (9.9)</td>
<td>27.8 (9.8)</td>
<td>26.9 (9.7)</td>
<td>26.5 (9.7)</td>
<td>26.0 (9.5)</td>
<td>25.9 (9.6)</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; LIFE, Losartan Intervention For End Point Reduction in Hypertension.

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Multivariate-Adjusted†
basevel mean) lower Cornell product was associated with a 15.4% lower risk of the composite CV end point, and was a significant predictor of reduced risk of CV mortality, MI, and stroke. In similar fashion, a 10.5-mm (1 SD of the baseline mean) lower Sokolow-Lyon voltage during treatment was associated with a 20.4% lower risk of the composite end point and was a significant predictor of decreased CV mortality, MI, and stroke. Survival curves for Cornell product (Figure 1) and Sokolow-Lyon voltage criteria (Figure 2) depicting outcomes in varying quartiles of these measures over the time-course of the study illustrate that higher in-treatment levels of electrocardiographic LVH were associated with greater risks of CV morbidity and mortality, whereas lower in-treatment levels of electrocardiographic LVH were associated with lower rates of the composite end point, CV mortality, MI, and stroke. After controlling for treatment with losartan or atenolol, for baseline Framingham risk score, Cornell product, and Sokolow-Lyon voltage, and for baseline and in-treatment systolic and diastolic BP, both lower in-treatment Cornell product and Sokolow-Lyon voltage remained in the Cox analyses as significant predictors of CV morbidity and mortality (Table 2). In these Cox models, a 1050-mm (1 SD of the baseline mean) lower Sokolow-Lyon voltage was associated with a 14.5% decrease in the composite end point, a 22.0% lower risk of CV death, and 10% decreases in the rates of MI and stroke. A 10.5-mm lower Sokolow-Lyon voltage was associated with a 16.6% decrease in the composite end point, a 20.4% lower risk of CV mortality, a 10% decrease in MI, and an 18.8% lower rate of stroke over the pe-

### Table 2. Cox Proportional Hazards Models for Prediction of Primary Cardiovascular End Points, Examining Electrocardiographic Left Ventricular Hypertrophy by Cornell Voltage-Duration Product and Sokolow-Lyon Voltage Criteria as Time-Dependent Covariates

<table>
<thead>
<tr>
<th>End Points</th>
<th>Treatment Effect-Adjusted*</th>
<th>Multivariate-Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)‡</td>
<td>P Value</td>
</tr>
<tr>
<td>Composite (n = 1096, rate = 11.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornell product</td>
<td>0.85 (0.81-0.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage</td>
<td>0.80 (0.75-0.85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiovascular mortality (n = 438, rate = 4.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornell product</td>
<td>0.76 (0.71-0.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage</td>
<td>0.76 (0.70-0.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myocardial infarction, fatal/nonfatal (n = 386, rate = 4.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornell product</td>
<td>0.88 (0.81-0.97)</td>
<td>.005</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage</td>
<td>0.85 (0.76-0.94)</td>
<td>.002</td>
</tr>
<tr>
<td>Stroke, fatal/nonfatal (n = 541, rate = 5.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornell product</td>
<td>0.88 (0.82-0.95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage</td>
<td>0.78 (0.72-0.85)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Adjusted for treatment effect only.
†Adjusted for treatment effect, baseline Framingham risk score, and systolic and diastolic blood pressures at baseline and during treatment.
‡Hazard ratios calculated for a 1-SD decrease in Cornell product (1050 mm × ms) and Sokolow-Lyon voltage (10.5 mm).

### Figure 1. Rate of the Composite End Point, Cardiovascular Mortality, Stroke, and Myocardial Infarction by Time-Varying Categories of Cornell Voltage-Duration Product

Patient group assignment is adjusted at the time of each electrocardiogram, based on the value of Cornell product at each time.
period of the study. Of note, the predictive values of changing levels of both Cornell product and Sokolow-Lyon voltage remained significant when examined separately in each treatment group. Moreover, inclusion in the multivariate Cox models of baseline QRS and QT interval duration and changing levels of uric acid as a time-varying covariate—variables previously demonstrated to stratify risk in the LIFE study40,41—did not impact the relation of changing levels of Cornell product or Sokolow-Lyon voltage to CV morbidity and mortality. These findings support the value of electrocardiographic LVH and prevention of progression to LVH are associated with a reduced risk of CV morbidity.2,3,12,13 An observational study of 524 participants in the Framingham Heart Study with electrocardiographic LVH by various criteria at a qualifying examination found that a significant decline in Cornell voltage was associated with lower rate of CV disease, whereas a significant increase in Cornell voltage identified individuals at increased risk of CV disease. Prineas et al13 demonstrated that increases in electrocardiographic LVH by Cornell product and Novacode criteria and incidence electrocardiographic LVH by these criteria were associated with increased risk of mortality in men in the usual-care arm of the Multiple Risk Factor Intervention Trial (MRFIT). In contrast, increases in Sokolow-Lyon voltage were associated with decreased risk in this study.11 However, these investigators averaged changes in electrocardiographic LVH criteria over 6 years of follow-up, which could underesti-

Figure 2. Rate of the Composite End Point, Cardiovascular Mortality, Stroke, and Myocardial Infarction by Time-Varying Categories of Sokolow-Lyon Voltage

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Sokolow-Lyon Voltage, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤20</td>
<td>1573 20 1573 20 1573 20</td>
</tr>
<tr>
<td>20.5-25</td>
<td>20 1573 20 1573 20 1573 20</td>
</tr>
<tr>
<td>25.5-30</td>
<td>20 1573 20 1573 20 1573 20</td>
</tr>
<tr>
<td>&gt;30</td>
<td>20 1573 20 1573 20 1573 20</td>
</tr>
</tbody>
</table>

Patient group assignment is adjusted at the time of each electrocardiogram, based on the value of Cornell product at each time.

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Regression of Electrocardiographic LVH and Prognosis

A number of previous studies have demonstrated that regression of electrocardiographic LVH and prevention of progression to LVH are associated with a reduced risk of CV morbidity.2,3,12,13
mate the predictive value of serial increases or decreases in electrocardiographic measures over this time period, and their findings were limited to men. In contrast, recent data from the Heart Outcomes Prevention Evaluation (HOPE) trial provided perhaps the strongest previous evidence supporting the hypothesis that regression of electrocardiographic LVH improves prognosis, demonstrating that the combined end point of either regression of electrocardiographic LVH or prevention of progression to electrocardiographic LVH in response to ramipril-based therapy was associated with reduced risk of death, MI, stroke, and congestive heart failure. However, the usefulness of these findings is limited by the low prevalence of electrocardiographic LVH in the HOPE trial, the absence of adjustment for other clinical variables in outcome analyses, and by the absence of specific data addressing the value of changes in Sokolow-Lyon voltage for predicting outcome.

The present study supports the importance of serial measurement of electrocardiographic LVH during antihypertensive treatment for risk stratification. We found that significantly lower values of both Cornell product and Sokolow-Lyon voltage were associated with 14.5% to 16.6% reductions in the incidence of major CV morbidity and mortality over 4.8 years of follow-up, independent of primary study assignment to losartan or atenolol, baseline Framingham risk score, and of baseline and treatment levels of BP. Intriguingly, serial measures of both Cornell product and Sokolow-Lyon voltage remained in the adjusted Cox models for all end points, such that the combination of lower in-treatment values of both electrocardiographic LVH criteria was associated with a greater than 29% reduction in the composite end point of CV morbidity and mortality.

The strong, independent relation between lower values of electrocardiographic LVH and reduced rates of CV events in the current study are paralleled by findings from the echocardiographic substudy of LIFE, which provided evidence of a similarly powerful association of changing left ventricular mass with CV morbidity and mortality. As reported by Devereux and colleagues in this issue of JAMA, 1-SD (25.3) lower values of indexed left ventricular mass were associated with a 22% lower rate of the LIFE composite end point, a 38% reduction in CV mortality, a 24% reduction in stroke, and a 15% lower rate of MI. Taken together, these electrocardiographic and echocardiographic findings demonstrate that the strong association between serial assessments of LVH and CV outcomes is independent of the method used to serially assess the degree of hypertrophy.

Methodological Issues
Several limitations of the present study warrant review. Use of Cornell product and Sokolow-Lyon voltage criteria to select patients for the LIFE study increased the baseline risk of the study population and, as a consequence, the present findings may not be representative of those for hypertensive populations with less-severe disease. In this context, it is important to note that the prevalence of electrocardiographic LVH in 1746 ambulatory patients with hypertension was 9.8% in men and 5.7% in women for Sokolow-Lyon voltage and 14.9% and 18.8%, respectively, by Cornell product criteria. In addition, the statistical phenomenon of regression to the mean may impact the current findings, particularly in light of the use of values of Cornell product and Sokolow-Lyon voltage above threshold levels to select patients for the LIFE study, despite our attempt to minimize this problem by using separate screening and baseline ECGs. As a consequence of this selection process and the intrinsic variability of electrocardiographic measurements, it is likely that both the degree of ECG LVH at baseline and the subsequent decrease in electrocardiographic LVH during therapy were overestimated in some patients. However, improved outcome was associated with regression of electrocardiographic LVH despite these limitations, which would actually bias against our findings, because these overestimations due to statistical fluctuations would lead to a more conservative estimate of the impact of electrocardiographic LVH on outcome. Moreover, assessment of risk based on electrocardiographic LVH criteria considered as time-dependent covariates adjusts for both baseline and subsequent levels of these variables, mitigating the impact of any overestimations.

Implications
These findings have important implications for the management of patients with hypertension, beyond the demonstrated beneficial effect of losartan on outcomes in the LIFE study. These data support the use of Cornell product and Sokolow-Lyon voltage criteria to identify patients with hypertension who are most likely to benefit from aggressive antihypertensive therapy and suggest that serial evaluation of these criteria during treatment can be used to monitor risk. These observations further suggest that antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH may become an additional goal of therapy beyond that of lowering BP, in order to further decrease the risk of CV morbidity and mortality.

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Author Contributions: Dr Okin had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: Okin, Devereux, Julius, Nieminen, Snapinn, Aurup, Edelman, Wedel, Dahlöf. Acquisition of data: Jern, Kjeldsen, Julius, Nieminen, Snapinn, Harris, Aurup, Edelman, Wedel, Dahlöf. Analysis and interpretation of data: Okin, Julius, Snapinn, Harris, Aurup, Edelman, Wedel, Lindholm, Dahlöf. Drafting of the manuscript: Okin, Julius, Aurup, Wedel.
Critical revision of the manuscript for important intellectual content: Okin, Devereux, Jern, Kjeldsen, Julius, Nieminen, Snappin, Harris, Aurup, Edelman, Wedel, Lindholm, Dahlof. Statistical analysis: Okin, Julius, Snappin, Harris, Wedel. Obtained funding: Devereux, Kjeldsen, Julius, Aurup, Edelman, Wedel, Dahlof. Administrative, technical, or material support: Devereux, Julius, Nieminen, Aurup, Edelman, Wedel. Study supervision: Julius, Edelman, Wedel, Lindholm, Dahlof.

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