Regression of Electrocardiographic Left Ventricular Hypertrophy and Decreased Incidence of New-Onset Atrial Fibrillation in Patients With Hypertension

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ATRIAL FIBRILLATION IS THE MOST common clinically significant arrhythmia in adults and is associated with increased risks of death, heart failure, and stroke. The incidence of atrial fibrillation is increased in patients with hypertension, coronary heart disease, and heart failure. Incidence of atrial fibrillation increases with age even in the absence of these risk factors. The increasing population prevalence of atrial fibrillation and significant risks associated with antiarrhythmic and anti-thrombotic therapies aimed at preventing atrial fibrillation recurrences and decreasing the risk of embolic sequela, coupled with the increased risks associated with the development of atrial fibrillation, make prevention of atrial fibrillation a clinical priority.

Recent studies have found that therapies aimed at reducing blood pressure, and in particular blockade of the renin-angiotensin system by either angiotensin-converting enzyme (ACE) inhibitors, and decreased incidence of AF is unclear.

Objective To test the hypothesis that in-treatment regression or continued absence of electrocardiographic LVH during antihypertensive therapy is associated with a decreased incidence of AF, independent of blood pressure and treatment modality.

Design, Setting, and Participants Double-blind, randomized, parallel-group study conducted in 1995-2001 among 8831 men and women with hypertension, aged 55-80 years (median, 67 years), with electrocardiographic LVH by Cornell voltage-duration product or Sokolow-Lyon voltage, with no history of AF, without AF on the baseline electrocardiogram, and enrolled in the Losartan Intervention for Endpoint Reduction in Hypertension Study.

Interventions Losartan- or atenolol-based treatment regimens, with follow-up assessments at 6 months and then yearly until death or study end.

Main Outcome Measure New-onset AF in relation to electrocardiographic LVH determined at baseline and subsequently. Electrocardiographic LVH was measured using sex-adjusted Cornell product criteria (\(R_{at} + S_{at} [+6 \text{ mm in women}] \times \text{QRS duration})

Results After a mean (SD) follow-up of 4.7 (1.1) years, new-onset AF occurred in 290 patients with in-treatment regression or continued absence of Cornell product LVH for a rate of 14.9 per 1000 patient-years and in 411 patients with in-treatment persistence or development of LVH by Cornell product criteria for a rate of 19.0 per 1000 patient-years. In time-dependent Cox analyses adjusted for treatment effects, baseline differences in risk factors for AF, baseline and in-treatment blood pressure, and baseline severity of electrocardiographic LVH, lower in-treatment Cornell product LVH treated as a time-varying covariate was associated with a 12.4% lower rate of new-onset AF (adjusted hazard ratio [HR], 0.88; 95% CI, 0.80-0.97; \(P = .007\)) for every 1050 mm/s (per 1-SD) lower Cornell product, with persistence of the benefit of losartan vs atenolol therapy on developing AF (HR, 0.83; 95% CI, 0.71-0.97; \(P = .01\)).

Conclusions Lower Cornell product electrocardiographic LVH during antihypertensive therapy is associated with a lower likelihood of new-onset AF, independent of blood pressure lowering and treatment modality in essential hypertension. These findings suggest that antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH may reduce the incidence of new-onset AF.
METHODS

Patients
The LIFE study 17-21 enrolled 9193 hypertensive patients with electrocardiographic LVH by Cornell voltage-duration product 12,23 and/or Sokolow-Lyon voltage criteria 24 on a screening electrocardiogram in a prospective, double-blind randomized study that compared cardiovascular morbidity and mortality with use of losartan-based as opposed to atenolol-based treatment. 19 The study was approved by all individual-center ethics committees. As described in detail elsewhere, 17-21 eligible patients for the LIFE trial were men and women, aged 55 through 80 years (median, 67 years) with previously untreated or treated essential hypertension (range of mean seated systolic/diastolic blood pressure, 160-200 mm Hg/95-115 mm Hg) after 1 or 2 weeks of receiving placebo, who had not experienced a myocardial infarction or stroke within 6 months and did not require treatment with a β-blocker, ACE inhibitor, or angiotensin II receptor antagonist. All participants provided informed, written consent. A total of 362 patients with either a history of atrial fibrillation or atrial fibrillation on their baseline electrocardiogram in a prospective, double-blind randomized study that compared cardiovascular morbidity and mortality as associated with LVH regression reported in the LIFE study, 18 suggest that regression of LVH could play an important role in the prevention of atrial fibrillation. However, whether regression of electrocardiographic LVH per se is associated with a reduced incidence of atrial fibrillation is unclear.

Accordingly, the present study examined whether lower in-treatment values of electrocardiographic LVH during treatment, as measured by Cornell voltage-duration product criteria, are associated with a reduced rate of atrial fibrillation—indipendent of the effects of in-treatment blood pressure change, baseline severity of electrocardiographic LVH, other risk factors for atrial fibrillation, and the previously demonstrated impact of losartan-based therapy on atrial fibrillation incidence in this population. 3

Electrocardiography
Electrocardiograms were routinely obtained according to protocol at baseline, at 6 months, and at yearly follow-up intervals until study termination or patient death. Electrocardiograms were interpreted by observers blinded to other clinical data at the core laboratory at the Sahlgrenska University Hospital/Ostra in Göteborg, Sweden, as previously reported in detail. 17-20 The product of QRS duration multiplied by the Cornell voltage combination (RaVL + Sv3, with 6 mm added in women 22,23) higher than 2440 mm × msec or Sokolow-Lyon voltage (Sv1 + RV5 or RV6) higher than 38 mm 22,23 were used to identify LVH. 17,18 New-onset atrial fibrillation was identified from the annual in-study electrocardiograms that underwent Minnesota coding for atrial fibrillation at the core laboratory or by adverse event reports from the investigators. 3

Statistical Analyses
The relationship between changing levels of the Cornell product and the risk of developing atrial fibrillation were assessed using Cox proportional hazards models, 25 with baseline and subsequent determinations of the Cornell product entered as time-varying covariates. Baseline risk factors, a treatment group indicator, and prerandomization use of digitalis drugs, antiarrhythmics, nonthiazide diuretics, aldosterone antagonists, and calcium channel blockers were included as standard covariates. Baseline and subsequent systolic and diastolic blood pressure measurements and hydrochlorothiazide use were entered as time-varying covariates. In addition, regression or continued absence of electrocardiographic
LVH by Cornell product criteria vs the development or persistence of Cornell product LVH treated as a dichotomous variable predictor of the development of atrial fibrillation was also analyzed using time-varying Cox models. The adjusted hazard ratios (HRs) for the incidence of atrial fibrillation associated with the Cornell product and treated as continuous variables were computed per 1 SD of the mean’s lower values as the antilog of the estimated coefficient multiplied by the SD. The 95% confidence interval (CI) of each HR was calculated from the estimated coefficients and their SEs.

Analyses were repeated stratifying the population by relevant subgroups with sex, age, race, treatment group, history of ischemic heart disease, myocardial infarction or congestive heart failure, prevalent diabetes, and by the presence or absence of LVH by Cornell product and Sokolow-Lyon voltage on the baseline electrocardiogram. Interaction between the time-varying Cornell product and these variables was formally tested by adding cross-product terms of the time-varying Cornell product and these variables into the models of the total population. The relationship of new atrial fibrillation over time to changing values of Cornell product LVH was illustrated by plotting atrial fibrillation rates according to the presence or absence of LVH by Cornell product using a univariate-modified Kaplan-Meier method, with assignment to LVH groups updated at the time of each new electrocardiogram based on the measurement of Cornell product at those times. For all tests, 2-tailed P<.05 was required for statistical significance.

Data analyses were primarily performed by the Clinical Biostatistics Department of Merck Research Laboratories using SAS version 8 (SAS Institute Inc, Cary, NC). Independent validation of these analyses was performed by one of the authors (P.M.O.) using SPSS version 12.0 (SPSS Inc, Chicago, Ill), on a complete set of the raw data, replicating the findings from Merck.

## RESULTS

### Regression of Electrocardiographic LVH and New-Onset Atrial Fibrillation

After a mean (SD) follow-up of 4.7 (1.1) years, new-onset atrial fibrillation occurred in 701 patients (7.9%). New atrial fibrillation was detected solely on the annual electrocardiogram in 129 patients (1.5%), only as an adverse clinical event in 296 patients (3.4%), and by both annual electrocardiogram and adverse event in 276 patients (3.1%).

New-onset atrial fibrillation occurred in 290 patients with in-treatment regression or continued absence of Cornell product LVH for a rate of 14.9 per 1000 patient-years and in 411 patients with in-treatment persistence or development of LVH by Cornell product criteria for a rate of 19.0 per 1000 patient-years. The relationship of changing Cornell product LVH to the development of new-onset atrial fibrillation is examined in Table 1 and in the Figure.

In univariate Cox analyses in which time-varying Cornell product was treated as a continuous variable, lower in-treatment values of Cornell product were strongly associated with a decreased risk of developing atrial fibrillation—a 1050 mm/sec decrease (1 SD of the baseline mean in the overall LIFE study population) lower Cornell product was associated with a 14.5% lower risk of new-onset atrial fibrillation. In parallel analyses in which Cornell product LVH was treated as present or absent on each electrocardiogram based on the threshold value of 2440 mm/sec, in-treatment regression or absence of LVH by Cornell product was associated with a 30% lower incidence of atrial fibrillation compared with in-treatment persistence or development of electrocardiographic LVH by Cornell product criteria. Modified Kaplan-Meier curves comparing the rate of new-onset atrial fibrillation according to the presence or absence of Cornell product LVH on electrocardiograms over the course of the study (Figure) demonstrate that regression or continued absence of LVH was associated with lower risk of developing atrial fibrillation compared with persistence or development of Cornell product LVH. Regression or continued absence of Cornell product LVH was associated with an estimated 1.5% lower absolute incidence of atrial fibrillation after 4 years of follow-up. Of note, the predictive value of the time-varying Cornell product for new-onset atrial fibrillation was not dependent on whether it was determined by annual electrocardiogram or by an adverse clinical event. Lower in-treatment Cornell product was simi-
larly predictive of decreased incidence of atrial fibrillation defined by annual electrocardiograms (n = 405; HR, 0.85 [95% CI, 0.77-0.92]) or by adverse event reports (n = 572; HR, 0.88 [95% CI, 0.83-0.94]).

We examined the independent relationship of new-onset atrial fibrillation to in-treatment Cornell product after adjusting for the possible effects of treatment, age, sex, race, prevalent diabetes, history of ischemic heart disease, myocardial infarction, congestive heart failure (defined by patient or enrolling physician report), stroke, peripheral vascular disease and smoking, baseline ratio of urinary albumin to creatinine, total cholesterol and high-density lipoprotein cholesterol, serum creatinine, body mass index, in-treatment systolic and diastolic blood pressure, and baseline Cornell product and Sokolow-Lyon voltage (Table 1). After adjusting for these factors, a 1050 mm × msec lower Cornell product remained associated with a 12% lower risk of new-onset atrial fibrillation; in a parallel analysis, in-treatment regression or absence of LVH by Cornell product criteria was associated with a 17% lower incidence of atrial fibrillation after controlling for these covariates. In-treatment Cornell product remained a significant predictor of incident atrial fibrillation after further adjustment for pre-randomization therapy with digitalis drugs, antiarrhythmics, nonthiazide diuretics, aldosterone antagonists, calcium channel blockers, and in-treatment use of hydrochlorothiazide (Table 1). Of note, losartan-based therapy remained a significant predictor of decreased atrial fibrillation incidence in these multivariable models (HR, 0.83 [95% CI, 0.71-0.97]; P = .01 in model 1 and HR, 0.85 [95% CI, 0.73-0.98]; P = .03 in model 2).

**Subset Analyses**

The predictive value of time-varying Cornell product for new-onset atrial fibrillation in relevant subsets of the population is presented in Table 2. The association between in-treatment Cornell product and new-onset atrial fibrillation was similar in men and women, in both treatment groups of the study, in patients older and younger than 65 years, among patients with and without diabetes or a history of ischemic heart disease or myocardial infarction, and among patients with and without LVH on their baseline electrocardiogram by either Cornell product or Sokolow-Lyon voltage criteria, with nonsignificant interaction terms for these variables. In contrast, lower in-treatment Cornell product was associated with a greater decrease in risk of developing atrial fibrillation in patients with than without a history of congestive heart failure and in patients without black race. Although in-treatment Cornell product significantly stratified atrial fibrillation risk in patients with and without a history of heart failure, patients with heart failure had a higher incidence of atrial fibrillation (17.1% vs 7.8%) and a 1050 mm × msec lower Cornell product was associated with a 31% lower risk of atrial fibrillation in patients with a history of heart failure as opposed to a 13% decreased risk in patients with no history of heart failure at baseline. In-treatment Cornell product was a strong predictor of new-onset atrial fibrillation among the large subset of the population that was not black but did not significantly stratify risk among hypertensive patients with black race, perhaps in part reflecting the lower incidence of new-onset atrial fibrillation among black patients (4.8% vs 8.1%; P = .007).

**COMMENT**

These findings demonstrate that regression of electrocardiographic LVH during antihypertensive therapy is associated with a lower likelihood of new-onset atrial fibrillation, independent of blood pressure lowering and of the beneficial effect of losartan-based therapy on the development of fibrillation. In contrast, persistence or development of high values of Cornell product during treatment are associated with higher rates of new-onset atrial fibrillation. These findings support the value of serial measurement of Cornell product LVH criteria for assessing the risk of developing atrial fibrillation in hypertensive patients and suggest that antihypertensive therapy targeted at regression or prevention of Cornell product LVH may reduce the incidence of atrial fibrillation.
Atrial Fibrillation and LVH

The relationship of LVH to the risk of developing atrial fibrillation has been demonstrated in population-based studies\(^5\) and among hypertensive patients,\(^3,7\) using both electrocardiographic measures of LVH\(^3,5,7,8\) and echocardiographic left ventricular mass.\(^7,9\) An earlier report from the LIFE study\(^3\) found that the baseline presence of electrocardiographic LVH and a decreased incidence of atrial fibrillation. After controlling for other risk factors for atrial fibrillation and for the effect of losartan on atrial fibrillation incidence,\(^3\) regression or continued absence of Cornell product LVH on serial assessment of electrocardiograms in the LIFE study was associated with a 17% lower incidence of atrial fibrillation. Importantly, the predictive value of in-treatment Cornell product was not dependent on the use of the 2440 mm × msec threshold for defining LVH and was not dependent on whether new-onset atrial fibrillation was determined by centrally read annual electrocardiograms or by physician reports of atrial fibrillation as an adverse clinical event with associated atrial fibrillation. Moreover, losartan therapy remained independently associated with reduced atrial fibrillation incidence in the current multivariable models, supporting the independent value of losartan therapy\(^3\) and of the renin-angiotensin system blockade by either ACE-inhibition or angiotensin II receptor blockade for reducing atrial fibrillation incidence.\(^14,16\)

The strong association of increased left atrial size with atrial fibrillation\(^9,28\) and with echocardiographic LVH and concentric left ventricular geometry in the echocardiographic substudy of the LIFE study,\(^28\) and the relationship of left atrial dilation to electrophysiological and structural abnormalities of the atria that are also associated with atrial fibrillation\(^29-31\) provide a potential mechanistic link between regression of LVH and a decrease in atrial fibrillation incidence. Increased atrial dilatation in isolated Langendorff-perfused canine heart preparations has been linked to increased dispersion of atrial relative refractory periods and increased percentage of slow conduction in the atria, both of which are highly correlated with atrial fibrillation inducibility.\(^29\) Further study of the relationship of changes in left atrial size to changing values of electrocardiographic LVH during antihypertensive therapy will hopefully provide greater insight into this potential mechanistic link between electrocardiographic LVH regression and the development of atrial fibrillation.

The association between in-treatment Cornell product and new-onset atrial fibrillation was robust across most subsets of the population, including similar effects in patients taking losartan or atenolol, suggesting that the impact of LVH regression on atrial fibrillation incidence may be independent of the treatment modality used to achieve regression despite the greater level of regression with losartan-based therapy in the LIFE study\(^17\) and the independent effect of losartan on atrial fibrillation incidence.\(^3\)

Table 2. Predictive Value of Time-Varying Cornell Voltage-Duration Product in the Development of New-Onset Atrial Fibrillation in Prespecified Subgroups

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>HR (95% CI)*</th>
<th>P Value for Interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male (n = 4022)</td>
<td>356</td>
<td>0.84 (0.77-0.91)</td>
</tr>
<tr>
<td>Female (n = 4809)</td>
<td>345</td>
<td>0.85 (0.78-0.92)</td>
</tr>
<tr>
<td>Race/ethnicity White or other (n = 8313;‡)</td>
<td>676</td>
<td>0.85 (0.80-0.91)</td>
</tr>
<tr>
<td>Black (n = 518)</td>
<td>25</td>
<td>1.01 (0.71-1.43)</td>
</tr>
<tr>
<td>Type of treatment Atenolol (n = 4392)</td>
<td>377</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td>Losartan (n = 4439)</td>
<td>324</td>
<td>0.88 (0.80-0.98)</td>
</tr>
<tr>
<td>Age, y &lt;65 (n = 3412)</td>
<td>155</td>
<td>0.84 (0.72-0.97)</td>
</tr>
<tr>
<td>≥65 (n = 5419)</td>
<td>546</td>
<td>0.89 (0.84-0.95)</td>
</tr>
<tr>
<td>History of congestive heart failure No (n = 8702)</td>
<td>679</td>
<td>0.87 (0.82-0.93)</td>
</tr>
<tr>
<td>Yes (n = 129)</td>
<td>22</td>
<td>0.69 (0.54-0.88)</td>
</tr>
<tr>
<td>History of ischemic heart disease No (n = 7474)</td>
<td>543</td>
<td>0.85 (0.80-0.91)</td>
</tr>
<tr>
<td>Yes (n = 1357)</td>
<td>158</td>
<td>0.92 (0.83-1.02)</td>
</tr>
<tr>
<td>History of myocardial infarction No (n = 8304)</td>
<td>642</td>
<td>0.85 (0.80-0.91)</td>
</tr>
<tr>
<td>Yes (n = 527)</td>
<td>59</td>
<td>0.90 (0.75-1.08)</td>
</tr>
<tr>
<td>Diabetes No (n = 7725)</td>
<td>599</td>
<td>0.85 (0.79-0.90)</td>
</tr>
<tr>
<td>Yes (n = 1100)</td>
<td>102</td>
<td>0.92 (0.78-1.08)</td>
</tr>
<tr>
<td>Cornell product LVH on baseline ECG No (n = 2907)</td>
<td>202</td>
<td>0.93 (0.77-1.12)</td>
</tr>
<tr>
<td>Yes (n = 5924)</td>
<td>499</td>
<td>0.85 (0.80-0.90)</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage LVH on baseline ECG No (n = 6976)</td>
<td>509</td>
<td>0.83 (0.76-0.90)</td>
</tr>
<tr>
<td>Yes (n = 1855)</td>
<td>192</td>
<td>0.86 (0.79-0.96)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; LVH, left ventricular hypertrophy.
*Values for HR are per 1 SD of the mean (1050 mm × msec) decrease in Cornell product.
†Between time-varying Cornell product and the subgroup variable.
‡Excludes blacks.
However, quantitative differences in the association between changing levels of Cornell product did not appear to stratify equally the risk of developing atrial fibrillation between black patients and patients of other races and in patients with vs without a history of congestive heart failure. Lack of an association between in-treatment Cornell product and new-onset atrial fibrillation in black patients with hypertension could in part reflect the lower incidence of atrial fibrillation among black patients with hypertension in the LIFE study or the higher prevalence of other risk factors for atrial fibrillation in black patients with hypertension in the current population. Indeed, the interaction term between race and time-varying Cornell product was no longer significant (P = .15) after further adjustment for these variables. Of note, the lower incidence of atrial fibrillation among black patients with hypertension in the LIFE study is consistent with the lower prevalence of atrial fibrillation among black patients in the Anticoagulation and Risk Factors in Atrial Fibrillation Study (1.5% vs 2.2%; P < .001). Although regression of Cornell product LVH significantly stratified atrial fibrillation risk in patients with and without a history of heart failure, LVH regression was associated with a greater than 2-fold risk reduction of atrial fibrillation incidence in patients with a history of heart failure than in those without such a history (Table 2). This finding, taken together with the more than 2-fold higher incidence of atrial fibrillation among hypertensive patients in the LIFE study with a history of heart failure (17.1% vs 7.8%), the increased mortality associated with development of atrial fibrillation in patients with pre-existing heart failure, and the apparently greater impact of angiotensin II receptor blockers and ACE inhibitors on atrial fibrillation incidence among heart failure patients, suggest that therapy with these agents aimed at regressing LVH to prevent atrial fibrillation should in particular be targeted to patients with heart failure. Further study of the impact of LVH regression on atrial fibrillation incidence and the risks associated with atrial fibrillation is necessary to clearly delineate the potential prognostic benefit in this population.

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. While the present findings may not be representative of hypertensive populations with less severe disease, it has been estimated that 7.8 million patients would have met eligibility criteria for the LIFE study in the first 15 member-nations of the European Union, with similar numbers in the rest of Europe and in the United States. Second, although both annual electrocardiograms and adverse event reports were used by the LIFE study investigators to detect atrial fibrillation, the true incidence of atrial fibrillation may have been underestimated, particularly asymptomatic atrial fibrillation, potentially reducing precision of the effect estimates of LVH regression on atrial fibrillation incidence, particularly if most of the undetected cases of atrial fibrillation were associated with high levels of in-treatment Cornell product. Unfortunately, regular ambulatory electrocardiographic monitoring was not feasible in a study the size of the LIFE trial (> 43 000 patient-years of follow-up). In addition, although the statistical phenomenon of regression to the mean unlikely, mitigating the impact of any overestimations.

Implications
These findings potentially have important implications for the management of patients with hypertension and LVH. Given the increasing incidence and prevalence of atrial fibrillation in the population and the increased risk of death, stroke, and heart failure associated with atrial fibrillation in the LIFE study and in other studies, these data support the use of serial evaluation of Cornell product criteria during treatment to monitor the risk of developing atrial fibrillation. These observations and the previous finding that regression of Cornell product LVH is associated with decreased cardiovascular morbidity and mortality in the LIFE study provide preliminary evidence suggesting that antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH may be an additional goal of therapy, beyond blood pressure lowering, to reduce the incidence of atrial fibrillation and its associated morbidity and mortality. However, further study will be required to determine whether therapy aimed specifically at regression of LVH above and beyond attainment of a target blood pressure will further reduce the incidence of new-onset atrial fibrillation in hypertensive patients with electrocardiographic LVH.

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Author Contributions: Dr Okin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Okin, Wachtell, Devereux, Kjeldsen, Julius, Edelman, Dahlof. Acquisition of data: Wachtell, Devereux, Kjeldsen, Julius, Nieminen, Hille. Analysis and interpretation of data: Okin, Wachtell, Devereux, Harris, Jern, Kjeldsen, Lindholm, Edelman, Dahlof.
ELECTROCARDIOGRAPHIC LVH AND ATRIAL FIBRILLATION


Study supervision: Edelman, Dahlof.

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REFERENCES