

# Regression of Electrocardiographic Left Ventricular Hypertrophy Is Associated with Less Hospitalization for Heart Failure in Hypertensive Patients

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**Background:** Reduction of electrocardiographic left ventricular hypertrophy (LVH) has been associated with decreased cardiovascular death, stroke, myocardial infarction, and atrial fibrillation. However, whether reduction of electrocardiographic LVH is associated with decreased heart failure is unclear.

**Objective:** To examine the relation of reduction of electrocardiographic LVH to incident heart failure.

**Design:** Multicenter cohort study derived from a randomized, controlled trial.

**Setting:** Losartan Intervention For Endpoint reduction in hypertension study.

**Patients:** 8479 hypertensive patients without history of heart failure who were randomly assigned to losartan or atenolol treatment.

**Measurements:** Change in Cornell product electrocardiographic LVH between baseline and in-study electrocardiograms, examined as both a continuous variable and a dichotomous variable (above or below the median decrease of 236 mm · msec) to predict heart failure hospitalization occurring after the 6-month follow-up visit.

**Results:** During mean follow-up of 4.7 years (SD, 1.1 years), 214 patients were hospitalized for heart failure (2.5%): 77 patients with an in-treatment decrease of 236 mm · msec or more (4.4 per 1000 patient-years) and 137 patients with a reduction less than 236 mm · msec during treatment (6.8 per 1000 patient-years). In a univariate Cox analysis in which change in Cornell product was treated as a time-varying continuous variable, decrease in Cornell product during treatment was associated with a decreased risk for new-onset

heart failure, with a 24% lower risk for heart failure for every 817-mm · msec (1 SD of the mean) lower Cornell product (hazard ratio, 0.76 [95% CI, 0.72 to 0.80]). In a parallel analysis in which change in Cornell product was entered as a time-varying dichotomous variable, a greater-than-median in-treatment decrease in Cornell product (236 mm · msec) was associated with a 43% lower risk for heart failure (hazard ratio, 0.57 [CI, 0.44 to 0.76]). After adjustment for treatment, baseline risk factors for heart failure, baseline and in-treatment blood pressure, and baseline severity of electrocardiographic LVH, in-treatment decrease of Cornell product LVH in time-varying multivariate Cox models remained strongly associated with new heart failure hospitalization, with a 19% lower risk for every 817-mm · msec lower Cornell product treated as a continuous variable (hazard ratio, 0.81 [CI, 0.77 to 0.85]) or a 36% decreased rate of new heart failure in patients with an in-treatment reduction in Cornell product of 236 mm · msec or more (hazard ratio, 0.64 [CI, 0.47 to 0.89];  $P < 0.001$  for all comparisons).

**Limitations:** Use of electrocardiographic LVH to select patients may have increased risk compared with unselected hypertensive patients, and use of hospitalization for heart failure as the end point will underestimate the incidence of new heart failure.

**Conclusion:** Reduction in Cornell product electrocardiographic LVH during antihypertensive therapy is associated with fewer hospitalizations for heart failure, independent of blood pressure lowering, treatment method, and other risk factors for heart failure.

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**H**heart failure is an increasing public health problem—both men and women have a 20% lifetime risk for this condition (1). Because of the enormous clinical and societal impact of heart failure, current recommendations emphasize the importance of its prevention (2–4), which requires a better understanding of risk factors for it. Hypertension doubles the lifetime risk for heart failure in men and triples the risk in women (1, 5), accounting for 39% of new heart failure cases in men and 59% of incident cases in women (5). Although numerous studies have documented the efficacy of antihypertensive therapy in preventing heart failure (6–12), the mechanisms by which hypertension predisposes to heart failure or by which blood pressure reduction prevents or retards its development require further elucidation (5).

Left ventricular hypertrophy (LVH) on electrocardiography predicts incident heart failure in both hypertensive and normotensive individuals (5, 13–22), and prevention of electrocardiographic LVH appears to attenuate the risk

for new-onset heart failure in high-risk patients (22). In the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study (23–27), reduction of blood pressure by using antihypertensive therapy induced reduction of electrocardiographic LVH by both Cornell voltage-duration product and Sokolow–Lyon voltage criteria (23), which, in turn, were associated with statistically significant reductions in the risk for cardiovascular death, myocardial infarction, stroke, and the LIFE composite end point of

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**Context**

Regression of left ventricular hypertrophy (LVH) has been associated with reductions in cardiovascular death, stroke, myocardial infarction, and atrial fibrillation in patients with treated hypertension, but heart failure outcomes have not been carefully studied.

**Contribution**

This analysis of data from the LIFE (Losartan Intervention For Endpoint reduction in hypertension) trial found an association between reduction of LVH by Cornell product electrocardiographic criteria and hospitalization for new-onset heart failure. This relationship appeared to be unrelated to blood pressure reduction and type of therapy.

**Caution**

Without clinical trials that directly address the issue, it remains uncertain whether clinicians should adjust antihypertensive therapy on the basis of electrocardiographic findings of LVH.

—The Editors

these 3 outcomes, independent of treatment method and blood pressure reduction (24). These findings suggest that reduction of LVH could play an important mechanistic role in decreasing incident heart failure among treated hypertensive patients (5–12). However, whether reduction of electrocardiographic LVH itself is associated with a decreased incidence of new-onset heart failure during antihypertensive therapy is unclear (19). Accordingly, we examined whether in-treatment reduction of electrocardiographic LVH, as measured by change in Cornell voltage-duration product criteria, is associated with a reduced incidence of heart failure in the LIFE study sample, independent of the effects of blood pressure, baseline severity of electrocardiographic LVH, and other risk factors for heart failure.

**METHODS****Patients**

The LIFE trial (23–27) enrolled 9193 hypertensive patients with electrocardiographic LVH by Cornell voltage-duration product (28, 29) or Sokolow–Lyon voltage criteria (30) on a screening electrocardiogram. The trial was a double-blind, randomized study that compared cardiovascular morbidity and mortality with use of losartan-based as opposed to atenolol-based treatment (25, 27). It was approved by all ethics committees concerned. As described in detail elsewhere (23–27), patients eligible for the LIFE study were men and women age 55 to 80 years who 1) had previously untreated or treated essential hypertension with a mean seated blood pressure of 160 to 200 mm Hg/95 to 115 mm Hg after 1 and 2 weeks of receiving placebo; 2) had not had myocardial infarction or stroke within 6 months; and 3) did not require treatment with a

$\beta$ -blocker, angiotensin-converting enzyme inhibitor, or angiotensin-1-antagonist. All participants gave written informed consent. Patients with a history of heart failure ( $n = 166$ ), incident heart failure before the 6-month electrocardiogram ( $n = 58$ ), follow-up less than 6 months ( $n = 101$ ), or no 6-month electrocardiogram ( $n = 389$ ) were excluded from analyses, leaving 8479 patients in our study.

**Treatment Regimens**

Blinded treatment was begun with losartan, 50 mg/d, or atenolol, 50 mg/d, and matching placebo of the other agent, with a target blood pressure of 140/90 mm Hg or lower. During clinic visits, dose of the study drug could be titrated upward by addition of hydrochlorothiazide, 12.5 mg, followed by an increase in the dose of blinded losartan or atenolol to 100 mg/d. In patients whose blood pressure was still not controlled, additional open-label upward titration of the hydrochlorothiazide dose and, if necessary, therapy with a calcium-channel blocker or other medications (excluding angiotensin-1-blockers,  $\beta$ -blockers, or angiotensin-converting enzyme inhibitors) was added to the double-blind treatment regimen (25).

**Electrocardiography**

Electrocardiograms were obtained at 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/Östra in Göteborg, Sweden, as reported elsewhere (23–26). The product of QRS duration times the Cornell voltage combination ( $R_{aVL} + S_{V3}$ , with 6 mm added in women [28, 29]) greater than 2440 mm · msec or Sokolow–Lyon voltage ( $S_{V1} + RV_{5/6}$ ) greater than 38 mm (30) was used to identify LVH (23, 24). Because patients were selected for the study on the basis of electrocardiographic LVH above these threshold levels on a screening electrocardiogram obtained before baseline (23–27), a proportion of patients at baseline would be expected to no longer meet threshold criteria for LVH as a result of regression to the mean (23, 24). As a consequence, despite this selection process, 1934 patients (22.8%) did not meet threshold criteria for electrocardiographic LVH by either Cornell product or Sokolow–Lyon voltage on their baseline electrocardiogram.

**End Point Determination**

Hospitalization for heart failure was a prespecified secondary end point in the LIFE study (25); the diagnosis of heart failure was based on clinical and diagnostic findings. Each case was reviewed and verified by the Endpoint Committee, which was blinded to study electrocardiographic LVH findings when classifying possible morbid events (25–27).

**Statistical Analysis**

Data were managed and analyzed by using SPSS, version 12.0 (SPSS, Chicago, Illinois). Data are presented as

means (SDs) for continuous variables and as proportions for categorical variables. Differences in mean values between patients with and without new-onset heart failure were compared by using unpaired *t* tests; proportions were compared between groups by using chi-square tests. Differences in mean Cornell product between baseline and subsequent in-treatment electrocardiograms were compared with repeated-measures analysis of variance, and differences in changes in Cornell product between baseline and each in-treatment electrocardiogram were compared between patients with and without heart failure by using analysis of variance.

The relation of an in-treatment reduction in Cornell product to the risk for heart failure was assessed by using Cox proportional hazards models (31), with the change in Cornell product between baseline and subsequent in-treatment electrocardiograms entered as a time-varying covariate (24). Baseline risk factors and a treatment group indicator were included as standard covariates; baseline and subsequent systolic and diastolic blood pressure and in-treatment changes in Sokolow–Lyon voltage measurements were entered as time-varying covariates. In addition, we also analyzed the relation of a reduction in Cornell product of 236 mm · msec or more versus a reduction less than 236 mm · msec (the median decrease between baseline and last in-study measurement) treated as a dichotomous time-varying variable to the development of heart failure. The adjusted hazard ratios for the incidence of heart failure associated with in-treatment reduction of Cornell product treated as a continuous variable were computed per

817–mm · msec lower Cornell product (1 SD of the mean change in Cornell product between baseline and last in-study measurement) as the anti-log of the estimated coefficient times the SD (32). The 95% CI of each hazard ratio was calculated from the estimated coefficients and their SEs. Analyses were repeated by stratifying the population by sex, age, race, treatment group, whether the patient was 65 years of age or older, history of atrial fibrillation, ischemic heart disease, myocardial infarction, prevalent diabetes, and the presence or absence of LVH by Cornell product or Sokolow–Lyon voltage on the baseline electrocardiogram. Interaction between time-varying change in Cornell product and these variables was formally tested by adding cross-product terms of time-varying reduction of Cornell product with these variables into the models of the total population. The relationship of new-onset heart failure over time to in-treatment reduction of Cornell product LVH was illustrated by plotting heart failure rates according to the presence or absence of reduction in Cornell product of 236 mm · msec by using a modified Kaplan–Meier method (33); assignment to groups was adjusted at the time that each electrocardiogram was obtained, on the basis of the change in Cornell product between baseline and those times. For all tests, a 2-tailed *P* value less than 0.05 was required for statistical significance.

### Role of the Funding Source

Merck & Co. provided the study authors with free access to all of the data; the authors were free to interpret data and write the paper. The sponsor agreed to support

**Table 1. Patient Characteristics and Development of Heart Failure**

Variables	Patients without Heart Failure (n = 8265)	Patients with New-Onset Heart Failure (n = 214)	P Value
Mean age (SD), y	66.7 (7.0)	70.7 (6.6)	<0.001
Men, %	45.5	47.2	0.671
African-American patients, %	5.2	9.3	0.011
Diabetes, %	12.3	27.6	<0.001
History of ischemic heart disease, %	14.2	34.1	<0.001
History of myocardial infarction, %	5.1	16.8	<0.001
History of stroke, %	4.1	7.0	0.051
History of peripheral vascular disease, %	5.2	14.0	<0.001
History of atrial fibrillation, %	3.3	12.6	<0.001
Treatment with losartan, %	50.1	49.5	0.924
Current smoker, %	15.6	27.6	<0.001
Mean body mass index (SD), kg/m <sup>2</sup>	28.0 (4.7)	29.0 (5.8)	0.002
Mean serum glucose level (SD)			<0.001
mmol/L	5.98 (2.13)	6.96 (3.42)	
mg/dL	108 (38)	125 (62)	
Mean serum creatinine level (SD)			<0.001
μmol/L	86.2 (19.6)	91.3 (23.1)	
mg/dL	0.98 (0.22)	1.04 (0.26)	
Mean total cholesterol level (SD)			0.052
mmol/L	6.06 (1.11)	5.90 (1.17)	
mg/dL	235 (43)	228 (45)	
Mean high-density lipoprotein cholesterol level (SD)			0.003
mmol/L	1.50 (0.43)	1.41 (0.45)	
mg/dL	58 (17)	55 (17)	
Mean urine albumin–creatinine ratio (SD), mg/mmol per L	6.5 (27.6)	15.9 (34.7)	<0.001

**Table 2. Blood Pressure and Electrocardiographic Left Ventricular Hypertrophy and Development of Heart Failure\***

Variable	Patients without Heart Failure (n = 8265)	Patients with New-Onset Heart Failure (n = 214)	P Value
<b>Baseline measurements</b>			
Systolic blood pressure, mm Hg	174 (14)	175 (14)	0.411
Diastolic blood pressure, mm Hg	98 (9)	95 (9)	<0.001
Cornell voltage-duration product, mm · msec	2805 (1022)	3085 (1165)	<0.001
Sokolow–Lyon voltage, mm	29.8 (10.4)	33.4 (11.4)	<0.001
<b>Change from baseline to last measurement</b>			
Systolic blood pressure, mm Hg	−30 (19)	−36 (22)	<0.001
Diastolic blood pressure, mm Hg	−17 (10)	−18 (12)	0.326
Cornell voltage-duration product, mm · msec	−228 (795)	111 (1389)	<0.001
Sokolow–Lyon voltage, mm	−5.0 (7.0)	−4.0 (9.7)	0.042

\* Values are expressed as the mean (SD).

performance of the study, at which time it was agreed that the findings would be published by the investigators regardless of the results. The decision to publish the paper, the choice of analyses to include, and the drafting of the manuscript were wholly controlled by all authors.

## RESULTS

### Patient Characteristics and New-Onset Heart Failure

During mean follow-up of 4.7 years (SD, 1.1), new-onset heart failure occurred in 214 patients (2.5%). Table 1 shows clinical and demographic characteristics of patients and development of heart failure. Compared with patients who did not develop heart failure, hypertensive patients who developed heart failure were older; were more likely to be African American, have diabetes, and have histories of myocardial infarction, ischemic heart disease, stroke, peripheral vascular disease, or atrial fibrillation; were more likely to be current smokers; had higher body mass index, glucose levels, and creatinine levels; had lower total and high-density lipoprotein cholesterol levels and greater albuminuria; and were equally likely to have been treated with losartan or atenolol.

Table 2 shows blood pressure and electrocardiographic LVH measurements at baseline, changes in these measurements between baseline and the last in-study determination, and development of heart failure. Patients who developed heart failure had similar baseline systolic pressure, lower baseline diastolic pressure, and greater reductions in systolic pressure but similar changes in diastolic pressure. Development of heart failure was associated with greater baseline severity of Cornell product and Sokolow–Lyon voltage LVH and with higher baseline prevalences of electrocardiographic LVH according to both Cornell product (71.2% vs. 66.7%;  $P = 0.018$ ) and Sokolow–Lyon voltage (27.4% vs. 20.5%;  $P < 0.001$ ) criteria. Despite similar reductions in diastolic pressure and a greater decrease in systolic pressure, there were modest progression of Cornell product LVH and less regression of Sokolow–Lyon voltage

LVH between baseline and last in-study measurement over the course of treatment in patients who developed heart failure.

Table 3 further examines in-treatment Cornell product LVH, changes in Cornell product LVH between baseline and each in-treatment annual electrocardiogram, and development of heart failure. Among patients who did not develop heart failure, Cornell product LVH decreased significantly between baseline and year 1, with a further decrease by the year 2 electrocardiogram; in-treatment Cornell product and the change between baseline and these electrocardiograms leveled out over subsequent years. In contrast, among patients who developed heart failure, Cornell product LVH did not change significantly between baseline and any of the in-treatment annual electrocardiograms, with small mean decreases in Cornell product between baseline and years 1 and 2 and subsequent mean increases in Cornell product over the remainder of the study. All these changes were statistically significantly different from the changes in Cornell product among patients without heart failure.

### Reduction in Electrocardiographic LVH and New-Onset Heart Failure

Table 4 and the Figure examine the relationship of in-treatment reduction of Cornell product LVH to hospitalization for new-onset heart failure. Heart failure developed in 77 patients who had an in-treatment decrease in Cornell product of 236 mm · msec or more (4.4 per 1000 patient-years) and in 137 patients with a reduction less than 236 mm · msec in Cornell product during treatment (6.8 per 1000 patient-years). In a univariate Cox analysis in which change in Cornell product was treated as a time-varying continuous variable, a decrease in Cornell product during treatment was associated with a decreased risk for new-onset heart failure, with a 24% lower risk for heart failure for every 817–mm · msec (1 SD of the mean) lower Cornell product. In a parallel analysis in which change in Cornell product was entered as a time-varying dichoto-

mous variable, an in-treatment decrease in Cornell product of 236 mm · msec or more was associated with a 43% lower risk for heart failure than was an in-treatment reduction less than 236 mm · msec. Modified Kaplan–Meier curves (33) comparing the rate of new-onset heart failure according to the reduction of Cornell product LVH between baseline and in-study electrocardiograms over the duration of the study (Figure) demonstrate that reduction of Cornell product LVH of 236 mm · msec or more was associated with lower risk for heart failure compared with lesser reductions of Cornell product LVH; reduction of Cornell product LVH was associated with an estimated 1.0% lower absolute incidence of heart failure after 4 years of follow-up.

Because patients who developed heart failure differed from those who did not develop heart failure with respect to demographic and clinical variables that could affect outcome (Tables 1 and 2), the independent relation of new-onset heart failure to in-treatment reduction of Cornell product LVH was examined after adjustment for the possible effects of these variables, in-treatment systolic and diastolic blood pressure, in-treatment change in Sokolow–Lyon voltage, and baseline Cornell product and Sokolow–Lyon voltage (Table 4). After adjustment for these factors, every 817–mm · msec decrease in Cornell product treated as a continuous variable remained associated with a 19% lower risk for new-onset heart failure; in a parallel analysis, in-treatment reduction of Cornell product of 236 mm · msec or more was associated with a 36% lower incidence of heart failure after controlling for these covariates. Of note, the predictive value of in-treatment change in Cornell product for new-onset heart failure remained highly statistically significant and nearly identical to outcomes in the overall study sample when analyses were restricted to the subset of the sample ( $n = 5585$ ) who had Cornell products on their baseline electrocardiograms that met study criteria for LVH ( $>2440$  mm · msec), whether change in Cornell product was treated as a time-varying continuous variable (hazard ratio, 0.80 [95% CI, 0.70 to 0.90]) or as a time-varying dichotomous variable (hazard

ratio for reduction  $\geq 236$  mm · msec, 0.57 [CI, 0.40 to 0.81]) in multivariable Cox analyses. In addition, in-treatment change in Cornell product remained predictive of new-onset heart failure after further adjustment for the presence or absence of the electrocardiographic strain pattern (34) in the subset of the sample in which electrocardiographic strain was determined ( $n = 8219$ ).

Table 5 examines the predictive value of a reduction of Cornell product for new-onset heart failure in relevant subsets of the sample. The association between in-treatment decrease of Cornell product and less new-onset heart failure was similar when the sample was stratified by sex, ethnicity, age, study treatment group, history of atrial fibrillation, ischemic heart disease or myocardial infarction, and the presence or absence of Cornell product LVH or Sokolow–Lyon voltage LVH on the baseline electrocardiogram. In contrast, reduction of Cornell product LVH was associated with statistically significant greater decreased risk for heart failure in patients without prevalent diabetes at baseline.

## DISCUSSION

These findings demonstrate that reduction of electrocardiographic LVH during antihypertensive therapy is associated with a lower likelihood of new-onset heart failure, independent of blood pressure lowering and the predictive value of other risk factors for heart failure. In contrast, the absence of a reduction in Cornell product LVH during treatment is associated with a higher rate of new-onset heart failure. These findings support the value of serial measurement of Cornell product criteria for assessing the risk for heart failure in hypertensive patients.

### Heart Failure and LVH

The relationship of electrocardiographic LVH at baseline to the risk for heart failure has been well documented in population-based studies and among hypertensive patients (13–22). Relevant studies were identified from a MEDLINE search of English-language articles, published through January 2007, of clinical trials of hypertrophy,

Table 3. Cornell Voltage-Duration Product and Development of Heart Failure\*

Visit Year	Patients without Heart Failure ( $n = 8265$ )					Patients with New-Onset Heart Failure ( $n = 214$ )					P Value†
	Patients, $n$	Baseline Cornell Product, mm · ms	Visit Cornell Product, mm · ms	Change in Cornell Product, mm · ms	P Value	Patients, $n$	Baseline Cornell Product, mm · ms	Visit Cornell Product, mm · ms	Change in Cornell Product, mm · ms	P Value	
1	7680	2800 (1011)	2610 (1010)	–189 (616)	<0.001	193	3109 (1195)	3096 (1409)	–13 (1067)	0.870	<0.001
2	7347	2797 (1010)	2547 (1009)	–250 (685)	<0.001	166	3029 (1032)	2995 (1134)	–35 (871)	0.608	<0.001
3	7016	2788 (996)	2536 (1018)	–252 (701)	<0.001	154	3060 (992)	3069 (1164)	9 (923)	0.908	<0.001
4	6835	2787 (991)	2548 (1052)	–239 (743)	<0.001	129	3036 (1051)	3119 (1370)	83 (1175)	0.422	<0.001
5	4993	2805 (980)	2549 (1001)	–255 (753)	<0.001	85	3041 (911)	3077 (1336)	35 (1361)	0.811	0.001
Last	8265	2805 (1022)	2578 (1082)	–228 (795)	<0.001	214	3085 (1165)	3195 (1539)	111 (1389)	0.246	<0.001

\* Unless otherwise noted, values are the mean (SD).

† Comparison between patients with heart failure and those without heart failure.

**Table 4. Predictive Value of the In-Treatment Decrease in Cornell Product Left Ventricular Hypertrophy for Heart Failure\***

Predictor Variable	Hazard Ratio (95% CI)	P Value
<b>Univariate†</b>		
Change in Cornell product LVH (per 817-mm · msec decrease)	0.76 (0.68–0.85)	<0.001
Decrease in Cornell product LVH ≥ 236 mm · msec	0.57 (0.44–0.76)	<0.001
<b>Multivariate‡</b>		
Change in Cornell product LVH (per 817-mm · msec decrease)	0.81 (0.74–0.89)	<0.001
Decrease in Cornell product LVH ≥ 236 mm · msec	0.64 (0.47–0.89)	<0.001

\* LVH = left ventricular hypertrophy.  
 † New-onset heart failure occurred in 77 patients with an in-treatment decrease in Cornell product  $\geq 236$  mm · msec (a rate of 4.4 per 1000 patient-years) and in 137 patients with a lesser in-treatment decrease or an increase in Cornell product LVH (a rate of 6.8 per 1000 patient-years).  
 ‡ Adjusted for possible effects of treatment with losartan versus atenolol, age, sex, race, prevalent diabetes, history of ischemic heart disease, myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation or smoking, baseline albumin-creatinine ratio, serum glucose and creatinine levels, total and high-density lipoprotein cholesterol levels, body mass index, and Cornell product; baseline and in-treatment systolic and diastolic blood pressures; and baseline and changes in Sokolow–Lyon voltage.

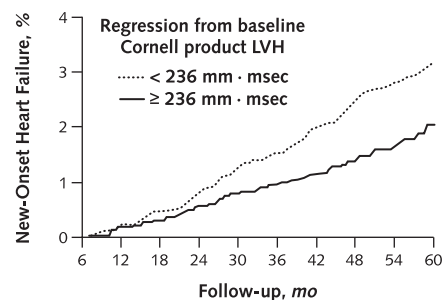
hypertension, and heart failure and from the authors' experience. A recent report (21) found that baseline severity of Cornell product LVH remained a statistically significant predictor of the development of new-onset heart failure in diabetic patients in the LIFE and RENAAL (Reduction of Endpoints in NIDDM [non-insulin-dependent diabetes mellitus] with the Angiotensin II Antagonist Losartan) studies after controlling for other risk factors and the effect of losartan treatment on heart failure incidence. In addition, we recently demonstrated that the electrocardiographic strain pattern of ST-segment depression and T-wave inversion in the lateral precordial leads, which is strongly associated with increased left ventricular mass and depressed left ventricular function (35) and with adverse cardiovascular outcomes in the LIFE study (36), is a strong predictor of incident heart failure in the large subset of the LIFE sample with electrocardiographic strain determinations (34). However, whether a decrease in electrocardiographic LVH is associated with a reduced incidence of heart failure has not been clearly demonstrated.

In the HOPE (Heart Outcomes Prevention Evaluation) study (22), 8281 patients with high-risk vascular disease or diabetes had Sokolow–Lyon voltage LVH determined at baseline and at study end. Electrocardiographic LVH was present in 672 patients (8.2%) at baseline and in 742 patients (9.0%) after a 4.5-year mean follow-up. Using a simple chi-square analysis, the investigators found that persistence or development of electrocardiographic LVH was associated with a higher heart failure incidence than prevention or regression of LVH (15.4% vs. 9.3%). However, this analysis did not consider time to develop-

ment of heart failure, which may have preceded the end-study electrocardiogram; did not assess baseline or subsequent severity of LVH; and did not adjust for baseline or in-study blood pressures or for other heart failure risk factors that differed between the groups with and without persistent LVH (22). In addition, this analysis primarily examined the relationship of persistent LVH over time to the development of heart failure (22), since the prevalence of LVH was only 8.2% at baseline and increased minimally over follow-up. In a study evaluating the prognostic value of serial electrocardiographic voltage in 4159 patients with systolic hypertension (19), Fagard and colleagues found a strong association between baseline electrocardiographic left ventricular mass defined as the sum of 3 voltages (RaVL + SV1 + RV5) and new-onset heart failure, but change in the sum of voltage during follow-up was not a statistically significant predictor of the development of heart failure in these patients in multivariable Cox models.

In contrast, to our knowledge, our study is the first to demonstrate a clear association between a reduction in electrocardiographic LVH and decreased incidence of heart failure. After controlling for other risk factors for heart failure, in-treatment blood pressures, and treatment effects, greater-than-median reduction of electrocardiographic LVH by Cornell product on serial assessment of electrocardiograms in the LIFE study was associated with a 36% lower incidence of heart failure (Table 4). When the analysis was restricted to patients with LVH on their baseline electrocardiograms, greater-than-median reduction of Cornell product was associated with a 43% lower rate of new heart failure. Of note, the predictive value of a decrease in Cornell product did not depend on use of the median values for the change between baseline and last in-study measure-

**Figure. Rate of new-onset heart failure according to presence or absence of a 236-mm · msec reduction in Cornell product left ventricular hypertrophy (LVH).**



Cornell product LVH regression < 236 mm · msec						
Cumulative events, n	0	12	39	68	106	128
Patients at risk, n	5331	4632	4094	3905	3868	1439
Cornell product LVH regression ≥ 236 mm · msec						
Cumulative events, n	0	6	20	37	53	73
Patients at risk, n	3012	3671	4033	4025	3887	1649

Patient group assignment was adjusted at the time of each electrocardiogram on the basis of the Cornell product at that time (33).

**Table 5. Association of Decreases in Cornell Voltage-Duration Product with New-Onset Heart Failure: Univariate Analyses\***

Subgroup	New-Onset Heart Failure, <i>n</i>	Hazard Ratio (95% CI)†	<i>P</i> Value for Interaction‡
<b>Sex</b>			
Male ( <i>n</i> = 3861)	101	0.46 (0.31–0.70)	0.194
Female ( <i>n</i> = 4618)	113	0.67 (0.46–0.98)	
<b>Ethnicity</b>			
White or other ( <i>n</i> = 8033)	194	0.53 (0.39–0.71)	0.104
Black ( <i>n</i> = 446)	20	1.12 (0.46–2.68)	
<b>Treatment</b>			
Atenolol ( <i>n</i> = 4232)	108	0.63 (0.42–0.93)	0.482
Losartan ( <i>n</i> = 4247)	106	0.51 (0.36–0.76)	
<b>Age</b>			
<65 y ( <i>n</i> = 3282)	46	0.87 (0.49–1.56)	0.113
≥65 y ( <i>n</i> = 5197)	168	0.51 (0.33–0.70)	
<b>History of atrial fibrillation</b>			
No ( <i>n</i> = 8178)	185	0.52 (0.39–0.71)	0.179
Yes ( <i>n</i> = 301)	29	0.88 (0.42–1.83)	
<b>History of ischemic heart disease</b>			
No ( <i>n</i> = 7229)	141	0.51 (0.36–0.72)	0.150
Yes ( <i>n</i> = 1250)	73	0.78 (0.49–1.25)	
<b>History of myocardial infarction</b>			
No ( <i>n</i> = 8018)	178	0.51 (0.38–0.70)	0.161
Yes ( <i>n</i> = 461)	36	0.88 (0.46–1.69)	
<b>Diabetes</b>			
No ( <i>n</i> = 7406)	155	0.43 (0.31–0.60)	0.001
Yes ( <i>n</i> = 1073)	59	1.20 (0.72–2.00)	
<b>Cornell product LVH on baseline ECG</b>			
No ( <i>n</i> = 2894)	56	0.44 (0.23–0.86)	0.578
Yes ( <i>n</i> = 5585)	156	0.54 (0.40–0.75)	
<b>Sokolow–Lyon voltage LVH on baseline ECG</b>			
No ( <i>n</i> = 6666)	152	0.60 (0.43–0.84)	0.423
Yes ( <i>n</i> = 1813)	62	0.46 (0.27–0.78)	

\* ECG = electrocardiogram; LVH = left ventricular hypertrophy.

† Hazard ratio for in-treatment decrease in Cornell product LVH  $\geq 236$  mm · msec.

‡ *P* values for interaction term in Cox models between time-varying Cornell product and the subgroup variable coded as absent or present.

ment for defining regression, but remained statistically significant when change in Cornell product was examined as a continuous variable as well.

The strong associations of left ventricular mass with echocardiographic measures of systolic and diastolic function (37, 38) and of changes in left ventricular mass with changes in systolic performance (39), and the established predictive value of left ventricular mass and left ventricular systolic and diastolic dysfunction for incident heart failure (40–42), provide potential mechanistic links between reductions of Cornell product LVH and a decrease in heart failure incidence. In the echocardiographic substudy of the LIFE study, increased baseline left ventricular mass was the strongest independent correlate of impaired endocardial and midwall shortening (37) and correlated with prolonged isovolumetric relaxation time (38). Moreover, in 679 LIFE patients with serial echocardiograms obtained at baseline and yearly during 3 years of blinded therapy (39),

multivariable analyses showed that reduction of left ventricular mass was associated with improvement in midwall shortening and contractility. Taken together, these findings suggest that the relationship between reduction of electrocardiographic LVH and decreased incidence of heart failure in the LIFE sample may reflect reduction-mediated improvements in left ventricular systolic and diastolic function. Further study of the relationship of changes in variables of left ventricular systolic and diastolic function to changing values of electrocardiographic LVH during antihypertensive therapy may provide greater insight into this potential mechanistic link between electrocardiographic LVH reduction and development of heart failure.

### Limitations

Several limitations of our study warrant review. First, use of Cornell product and Sokolow–Lyon voltage criteria to select patients for the LIFE study increased the baseline

risk for the study sample, and as a consequence, our findings may not be representative of hypertensive populations with less severe disease. Second, use of hospitalization for heart failure to define new-onset heart failure most certainly underestimates the true incidence of heart failure, potentially reducing precision of the estimates of effect of reduction of LVH on heart failure incidence. In addition, the statistical phenomenon of regression to the mean may affect the current findings, particularly in light of the use 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 electrocardiograms (24, 25). As a consequence of this selection process and the intrinsic variability of electrocardiographic measurements, both the degree of electrocardiographic LVH at baseline and the subsequent decrease in electrocardiographic LVH during therapy were probably overestimated in some patients. However, decreased heart failure hospitalization was associated with reduction of Cornell product considered as a continuous measure, which would bias against our findings because overestimations due to statistical fluctuations would lead to a more conservative estimate of the effect of electrocardiographic LVH on outcome. Moreover, assessment of risk based on Cornell product LVH criteria considered as time-dependent continuous covariates adjusts for both baseline and subsequent levels of these variables, mitigating the impact of any overestimations. Finally, examination of the 5585 patients who met Cornell product criteria for LVH at baseline did not affect our results, further arguing against a substantial impact of regression to the mean on these findings.

### Implications and Future Directions

Taken together with the increasing incidence and prevalence of heart failure in the U.S. population (1) and the strong associations of both preexisting hypertension and LVH with the development of heart failure (1, 5, 13–22), these data support the use of serial evaluation of Cornell product criteria during antihypertensive treatment to monitor the risk for heart failure. These observations and the previous finding that lower in-treatment values of Cornell product and Sokolow–Lyon voltage LVH are associated with decreased cardiovascular morbidity and mortality in the LIFE study (24) suggest that antihypertensive therapy targeted at reduction of electrocardiographic LVH may be an additional goal of therapy, beyond blood pressure lowering, to reduce the incidence of heart failure and its associated morbidity and mortality. However, further study is required to determine whether therapy aimed specifically at reduction of LVH above and beyond attainment of a target blood pressure will reduce the incidence of new-onset heart failure in hypertensive patients with electrocardiographic LVH.

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