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Combining Electrocardiographic Criteria for Left Ventricular Hypertrophy Improves Risk Prediction in Hypertensive Patients

Running title: *Okin et al.; Combined ECG LVH and Risk*

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ABSTRACT

Background: Hypertensive patients with ECG left ventricular hypertrophy (LVH) have higher cardiovascular (CV) morbidity and mortality, but single ECG criteria may underestimate risk. Whether continued presence or new development of ECG LVH by two criteria can further concentrate risk during blood pressure lowering is unclear.

Methods and Results: Incident stroke, myocardial infarction, CV death, the composite of these outcomes, and all-cause mortality were examined in relation to the presence of on-treatment ECG LVH by Cornell product and/or Sokolow-Lyon voltage during 4.8±0.9 years mean follow-up in 9,193 hypertensive patients randomized to losartan- or atenolol-based regimens. Patients were categorized into 4 groups according to the presence or absence of ECG LVH by each criterion at baseline and yearly during the study. At baseline, LVH by both criteria was present in 960 patients (10.4%). Compared with the absence of ECG LVH by both criteria, persistence or development of ECG LVH by both criteria entered as a time-varying covariate was associated with >3-fold increased risks of events in multivariable Cox analyses adjusting for randomized treatment, baseline risk factors and on-treatment heart rate, systolic and diastolic blood pressure; patients with ECG LVH by either Cornell product or Sokolow-Lyon voltage had 45 to 140% higher risks of all endpoints.

Conclusions: Persistence or development of ECG LVH by both Cornell product and Sokolow-Lyon voltage criteria during antihypertensive therapy is associated with markedly increased risks of CV endpoints and all-cause mortality. Further study is indicated to determine whether additional therapy in these patients can reduce their risk.

Clinical Trial Registration Information: clinicaltrials.gov. Identifier: NCT00338260.

Key words: ECG criteria; electrocardiography; hypertension; hypertrophy; prognosis

CLINICAL PERSPECTIVE

What is new?

- The combination of two different electrocardiographic (ECG) criteria for left ventricular hypertrophy (LVH) can improve risk stratification compared with either criterion alone.
- The persistence or development of ECG LVH by both Cornell product and Sokolow-Lyon voltage was associated with >3-fold increased risks of myocardial infarction, stroke, cardiovascular mortality, the composite endpoint of these three prior outcomes, and all-cause mortality after adjusting for other known or suspected predictors of risk.

What are the clinical implications?

- The use of both Cornell product and Sokolow-Lyon voltage together can aid clinicians in risk stratification of patients with hypertension.
- These findings further suggest that patients with persistence or development of new LVH by both criteria might benefit from additional therapy aimed at regressing their LVH, but further study of this issue is needed.

Left ventricular hypertrophy (LVH) detected by the 12-lead electrocardiogram (ECG) (1-3) and by echocardiography (4-8) are common manifestations of preclinical cardiovascular (CV) disease that strongly predict CV morbidity and mortality. Antihypertensive therapy aimed at reducing blood pressure (BP) can produce regression of LVH (3,4,9-15) and regression of ECG LVH and prevention of progression to LVH have been associated with a reduced risk of CV morbidity and mortality (2,3,12,13,16-20). Importantly, the improved prognosis with regression of ECG LVH is independent of reductions in BP during antihypertensive therapy (16-20). This increased risk associated with failure to regress LVH highlights the importance of better identifying patients who remain at residual risk despite aggressive BP lowering (16-20).

The well-recognized limited sensitivity of any one ECG LVH criterion as compared with imaging modalities has been put forward as a limitation of ECG-dependent approaches to LVH diagnosis (21), despite findings that imaging and ECG methods appear to similarly track prognosis (17,21,22) and may provide complimentary information (21,23-28). Based on the limited sensitivity of single ECG criteria, investigators have demonstrated that using both Sokolow-Lon voltage and Cornell voltage-duration product criteria together can increase sensitivity and population prevalence for detection of echocardiographic LVH, albeit with some loss of specificity (29,30) and that the presence of both of these criteria on an ECG was associated with higher LV mass index and a greater prevalence of echocardiographic LVH than either criterion alone or neither (31). The finding that different ECG LVH criteria identify different populations of patients at potentially increased risk (16,29-31) and the additive value of ECG and imaging-based LVH for risk stratification (21,23-28) suggests an opportunity to better track risk by combining two ECG LVH criteria with complimentary prognostic power. In this scenario, it might be predicted that the mutual absence of LVH by both criteria would be associated with the lowest risk, the presence of LVH by both criteria with the highest risk and the presence of LVH by one or the other with intermediate risk. The LIFE study recruited patients with ECG LVH by either Cornell product and/or Sokolow-Lyon voltage prior to enrollment, tracked the magnitude of ECG LVH by both criteria throughout follow-up and demonstrated that on-treatment Cornell product and Sokolow-Lyon criteria separately predicted CV risk (17-20), but did not examine whether combining the two ECG LVH criteria could improve risk stratification. Therefore, the present post-hoc analysis of data from the LIFE study was undertaken to examine whether the

continued presence or new development of ECG LVH by both Cornell product and Sokolow-Lyon voltage was associated with increased risk of CV events, CV and all-cause mortality compared with continued absence or regression of ECG LVH by both these criteria, and whether the presence or development of LVH by either Cornell product or Sokolow-Lyon voltage is associated with intermediate elevation of risk.

METHODS

Subjects

The LIFE study (17-20,32) enrolled 9,193 hypertensive patients with ECG LVH by Cornell voltage-duration product (33) and/or Sokolow-Lyon voltage criteria (34) on a screening ECG in a prospective, double-blind randomized study that compared cardiovascular morbidity and mortality with use of losartan- as opposed to atenolol-based treatment. The study was approved by all ethics committees concerned. As described in detail elsewhere (17-20,32), eligible patients for LIFE were men and women aged 55 to 80 with previously untreated or treated essential hypertension with mean seated BP in the range 160-200/95-115 mm Hg after one and two weeks on placebo who had not suffered a myocardial infarction or stroke within 6 months and did not require treatment with a beta-blocker, angiotensin converting enzyme-(ACE)-inhibitor or angiotensin receptor-(AT1)-antagonist. IRB approval was obtained and all participants gave informed written 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 daily. 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 AT1- or beta-blockers or ACE-inhibitors) was added to the double-blind treatment regimen (17-20,32).

Electrocardiography

ECGs were obtained at study baseline, at 6-months and at yearly follow-up intervals until study termination or patient death. ECGs were interpreted at the Core Laboratory at Sahlgrenska University Hospital/Östra in Göteborg Sweden by experienced readers blinded to clinical information. QRS duration was measured to the nearest 4 msec and the QRS amplitudes to the nearest 0.5 mm (0.05 mV). The product of QRS duration times the Cornell voltage combination (R_{aVL} + S_{V3}, with 6 mm added in women [32,33]) >2,440 mm·msec or Sokolow-Lyon voltage (S_{V1} + $RV_{5/6}$) >38 mm were used to identify LVH (17-20,32-34). A sex adjustment of 6 mm as opposed to the originally proposed 8 mm (17), was employed based on studies published as the LIFE study was getting started suggesting that a higher threshold in women was necessary to maintain specificity (new 35,36).

Endpoint Determination

The LIFE study used a composite endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke, according to previously defined criteria (32). These endpoints and the secondary endpoint of all-cause mortality were ascertained and then verified by an expert Endpoint Committee who were blinded to ECG results when classifying possible morbid events (17-20,32).

Statistical Analyses

Data management and analysis were performed with SPSS version 22 software. Data are presented as mean±SD for continuous variables and proportions for categorical variables. Patients were classified into four groups according to the presence or absence of ECG LVH by both Cornell product and Sokolow-Lyon voltage. Differences in prevalence between groups were compared using χ^2 analyses and mean values of continuous variables were compared using one-way analysis of variance (ANOVA).

Event rates in relation to the presence or absence of LVH by Cornell product and Sokolow-Lyon voltage at baseline were calculated from Kaplan-Meier survival estimates. The relation of the presence or absence of LVH by Cornell product and/or Sokolow-Lyon voltage to the risk of events was assessed using Cox proportional hazards models, with baseline and subsequent determinations of the presence or absence of LVH by Cornell product and Sokolow-Lyon voltage entered as time-varying covariates (17-20). Initial analyses were performed with Cornell product and Sokolow-Lyon voltage LVH as separate variables in univariate and multivariate Cox models and then with LVH classified by these variables into four

groups with the group with no LVH by either criterion serving as the reference group. Baseline risk factors and a treatment group indicator were included as standard covariates, and baseline and subsequent systolic and diastolic blood pressure and heart rate measurements were entered as time-varying covariates. The 95% CI of each hazard ratio was calculated from the estimated coefficients and their standard errors. The relationship of the combination of Cornell product and Sokolow-Lyon voltage LVH to the composite endpoint was further examined in relevant subgroups of the study population using the same multivariable Cox analysis as noted above and differences in the predictive value between subgroups tested by examining the interaction between the combined LVH variable and each subgroup variable in the overall population. For all tests, a two-tailed $p < 0.05$ was required for statistical significance.

RESULTS

At baseline, LVH by both criteria was present in 960 patients (10.4%). Baseline clinical and demographic characteristics of patients in relationship to the presence or absence of ECG LVH by Cornell product and Sokolow-Lyon voltage at study baseline are shown in Table 1. Patients across ECG LVH groups differed significantly with respect to age, sex, race, prevalent diabetes, history of ischemic heart disease, arrhythmia, stroke, peripheral vascular disease, smoking, prior antihypertensive treatment, body mass index, serum glucose, creatinine, and total and HDL cholesterol levels and urine albumin/creatinine ratio. Compared with patients without LVH by either criterion, patients with ECG LVH by both criteria tended to be older, less likely to be female, diabetic and have received prior antihypertensive therapy, more likely to be black and a current smoker, have a history of ischemic heart disease, arrhythmia, stroke and peripheral vascular disease, had lower body mass index and serum glucose levels, and higher serum creatinine and urine albumin/creatinine ratios.

Blood pressure and ECG LVH measurements at baseline and changes in these measurements between baseline and last in-study determination in relation to the presence or absence of ECG LVH by Cornell product and Sokolow-Lyon voltage at study baseline are shown in Table 2. Patients across ECG LVH groups differed significantly with respect to all baseline BP and ECG measurements and for all changes in these measurements with the exception of change in heart rate. Baseline levels of QRS duration, Cornell product and Sokolow-Lyon voltage varied as

would be predicted by group definition. Changes in SBP and DBP were greatest in patients with ECG LVH by both criteria, while regression of ECG LVH during treatment was higher in groups defined by the presence of LVH by that criterion at baseline, and greatest among patients with ECG LVH by both criteria at study baseline.

During mean follow-up of 4.6±1.2 years, myocardial infarction occurred in 386 patients (4.2%), stroke in 541 patients (5.9%), CV death in 438 patients (4.8%), the LIFE composite endpoint of CV death, myocardial infarction or stroke in 1,096 patients (11.9%) and all-cause mortality in 814 patients (8.9%). Univariate and multivariable Cox analyses for the prediction of these endpoints by Cornell product or Sokolow-Lyon LVH separately are shown in Table 3. Compared with the absence of LVH by each criterion, the presence of LVH by either Sokolow-Lyon voltage or Cornell product was associated with 39 and 128% increased unadjusted risks of these outcomes and from 14 to 69% increased adjusted risk of all outcomes in multivariable Cox models that adjusted for other risk factors.

Compared with each LVH criterion alone (Table 3), the combination of Cornell product and Sokolow-Lyon voltage further concentrates the risk of all endpoints (Figure 1 and 2). Rates of each outcome in relation to the presence or absence of LVH by Cornell product and Sokolow-Lyon voltage at study baseline are shown in Figure 1. For all outcomes, event rates varied significantly across groups and were lowest in patients who did not have LVH, intermediate in patients with LVH by either Cornell product or Sokolow-Lyon voltage and highest in patients with LVH by both criteria, with from 2.5- to 3.5-fold higher event rates among patients with LVH by both criteria than in in those without ECG LVH by either.

The risk of CV morbidity, CV and all-cause mortality in relationship to the on-treatment presence or absence of ECG LVH by both Cornell voltage-duration product and Sokolow-Lyon voltage treated as time-varying covariates is shown in Figure 2. In univariate Cox analyses, the persistence or development of new ECG LVH was associated with significantly higher risks of all events: compared with the absence of LVH by both criteria, the presence of LVH by both Cornell product and Sokolow-Lyon voltage was associated with between 4.71- and 5.80-fold increased risks of CV events, CV mortality and all-cause mortality and the presence of LVH by one or the other criteria with intermediate increased risks of events. After controlling for randomized treatment with losartan or atenolol, age, sex, prevalent diabetes, history of stroke, myocardial

infarction, ischemic heart disease, heart failure, peripheral vascular disease or prior antihypertensive treatment, baseline serum cholesterol, HDL cholesterol, glucose and creatinine, and urine albumin/creatinine ratio treated as standard covariates, and on-treatment heart rate and diastolic and systolic blood pressure treated as time-varying covariates, on-treatment presence of ECG LVH by either criterion remained associated with between at 45 and 140% increased risk of events and the presence of ECG LVH by both criteria was associated with a >3-fold adjusted risk of all outcomes. There were no significant differences in the predictive value of the combination of Cornell product and Sokolow-Lyon voltage for the composite endpoint in subgroups of the LIFE study population stratified by sex, race, age, history of ischemic heart disease, diabetes or randomized treatment allocation to losartan vs atenolol (Table 4).

DISCUSSION

Previous work provides a conceptual framework for combining ECG LVH criteria to concentrate risk. A number of studies, including in the LIFE population, have demonstrated that serial assessment of either Sokolow-Lyon voltage or Cornell product can stratify risk of CV outcomes, CV and all-cause mortality (16-20). However, none of these earlier studies analyzed whether combining these two criteria could further concentrate risk. Based on the limited sensitivity of single ECG LVH criteria which utilize QRS voltage or voltage-duration product measurements, several studies have demonstrated that defining ECG LVH by the presence of either increased Cornell product or Sokolow-Lyon voltage increased ECG sensitivity and population prevalence of LVH, but at the cost of lower specificity (29,30). In analyses of baseline echocardiographic data from the LIFE study (31), persistence of ECG LVH by both Cornell product and Sokolow-Lyon voltage on ECGs performed at study baseline was associated with increased LV chamber volume and wall thickness, higher LV mass, and with increased prevalences of echocardiographic LVH and abnormal LV geometry compared with the absence of ECG LVH by both criteria. Indeed, after adjusting for the possible effects of age, sex, race, baseline SBP and body mass index on LV mass, the presence of ECG LVH by both Cornell product and Sokolow-Lyon voltage was associated with a >4-fold increased odds of echocardiographic LVH (31). Paralleling outcome findings in the current study, the presence of ECG LVH by either Cornell product or Sokolow-Lyon voltage alone were associated with smaller

increases in LV mass, abnormal LV geometry and echocardiographic LVH (31).

Further supporting the construct of using two different ECG LVH criteria together, combinations of ECG LVH with imaging-derived LV mass determinations (21,28) or QT prolongation (37) carry higher risk than either finding alone. In an analysis of 4,748 participants in the MESA study (21), only the presence of LVH on both ECG (by either Cornell or Sokolow-Lyon voltage) and on cardiac MRI remained significantly associated with an increased risk of a composite endpoint of CV disease events after adjusting for other risk factors (HR1.77, 95% CI 1.03-3.04), whereas neither LVH by ECG alone (HR 1..20, 95% CI 0.69-2.09) or on MRI alone (HR 1.38, 95% CI 0.98-1.96) were significantly associated with increased risk in their fully adjusted Cox model. Similarly, in hypertensive patients in the echocardiographic sub-study of LIFE (28), the incidence of hospitalization for new-onset heart failure was markedly higher in patients with LVH on both echocardiography and ECG (by either Cornell product or Sokolow-Lyon voltage) (4.9%) compared to patients with echocardiographic LVH only (2.2%), ECG LVH only (0.6%) or LVH on neither test (0%, $p<0.01$). After controlling for other heart failure risk factors in this population, the presence of LVH on both ECG and echocardiogram remained associated with a >3-fold increased risk of new heart failure (HR 3.60, 95% CI 1.24-10.49). Lastly, among 7,506 participants in the US Third National Health and Nutrition Examination Survey (NHANES-III), Soliman et al (37) found that after adjusting for other risk factors, risk of all-cause mortality was highest in the group with concomitant ECG LVH by Cornell voltage and a prolonged heart rate-adjusted QT interval (HR 1.63, 95% CI 1.12-2.36) with intermediate adjusted mortality risks in those with isolated ECG LVH (HR 1.48, 95% CI 1.24-1.77) and those with an isolated long QT interval (HR 1.27, 95% CI 1.12-1.46).

The current study builds upon the above findings and concepts and on the well-established prognostic value of serial assessment of ECG LVH (2,3,12,13,16-20) to demonstrate that the combination of two different ECG LVH criteria can dramatically concentrate risk in hypertensive patients undergoing treatment compared with either criterion alone. Taking advantage of the complimentary information provided by Sokolow-Lyon voltage and Cornell voltage-duration product criteria, these findings suggest that the persistence or development of ECG LVH by both criteria in the face of substantial BP lowering can identify patients who remain at >3-fold increased adjusted risk of CV morbidity, CV or all-cause mortality. In contrast, regression or

absence of ECG by both criteria was associated with the lowest event rates over time, whereas persistence or development of LVH by either Cornell product or Sokolow-Lyon voltage, but not the other, was associated with intermediate risks of adverse outcomes (Figure 2). The high residual risk associated with persistence or development of ECG LVH by both criteria despite attaining similar levels of on-treatment BP (Table 2) suggests that persistence of LVH by both criteria may identify a subgroup of hypertensive patients in whom more aggressive BP lowering could possibly improve their prognosis. However, the significantly increased risks of CV death, stroke and the LIFE study composite endpoint in patients with persistent LVH by Cornell product criteria despite having average on-treatment SBP≤130 mm Hg (3 8) raises the possibility that additional BP lowering in patients who do not adequately regress LVH may not improve prognosis. In contrast, Soliman et al (39,40) demonstrated that more intensive blood pressure reduction was associated with greater LVH regression and lower rates of developing new LVH among hypertensive diabetic patients in ACCORD (39) and non-diabetic patients in SPRINT (40), but that the greater LVH regression in SPRINT did not appear to explain most the reduction in CV events. Further study will be required to evaluate whether specifically targeting patients with persistent LVH to further reduce BP and produce regression of LVH can improve prognosis in this high-risk subgroup of hypertensive patients.

There are several limitations of the current study which warrant mention. First, this is a post-hoc analysis of data from a randomized treatment trial that compared two different treatment approaches to blood pressure reduction. Although determining the relationship of ECG LVH changes with treatment to outcome was a planned secondary analysis of the LIFE study (17), evaluation of the combination of Sokolow-Lyon voltage and Cornell product criteria was not a pre-specified analysis. Because use of ECG LVH criteria to select patients for LIFE (32) increased the baseline risk of the population, caution should be used in generalizing these findings to hypertensive patients at lower risk or younger than 55 years old. However, ECG LVH have demonstrated significant risk stratification in populations that have quite varied degrees of baseline risk and baseline prevalence of ECG LVH (1-3,12,13, 21,23-27), suggesting that these findings are likely to apply in other, lower-risk hypertensive populations.

In summary, these findings have important implications for the management of patients with hypertension. First, these observations suggest that serial assessment of both Cornell

product and Sokolow-Lyon voltage can improve risk stratification in hypertensive patients during treatment. More intriguingly, the residual high risk associated with persistence or development of ECG LVH by both criteria suggest that these patients might benefit from additional therapy aimed at further lowering their BP and reducing their ECG LVH to reduce risk. Further study is clearly warranted to determine whether combining ECG LVH criteria similarly concentrates risk in other patient populations and under other treatment conditions and whether therapy targeted at regression of ECG LVH in patients with persistence of ECG LVH by both criteria can reduce risk or whether this risk marker identifies a subset of hypertensive patients whose prognosis is less likely to improve despite adequate BP reduction.

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Table 1. Study Baseline Demographic and Clinical Characteristics in Relation to the Presence or Absence of Electrocardiographic Left Ventricular Hypertrophy by Both Cornell Product and Sokolow-Lyon Voltage at Baseline

Variables	CP-/SL- (n=2023)	CP+/SL- (n=5220)	CP-/SL+ (n=990)	CP+/SL+ (n=960)	p value
Age (years)	66.1±7.1	67.2±7.0	66.5±7.0	67.7±6.8	<0.001
Sex (% female)	56.7	58.4	32.5	46.0	<0.001
Race (% Black)	5.3	4.0	13.6	8.5	<0.001
Diabetes (%)	11.6	14.5	10.1	10.4	<0.001
History of ischemic heart disease (%)	13.0	16.4	18.0	17.9	<0.001
History of myocardial infarction (%)	5.2	6.6	6.3	6.1	0.214
History of arrhythmia (%)	5.2	7.0	8.0	9.8	<0.001
History of Stroke (%)	3.6	4.3	5.7	5.2	0.031
History of heart failure (%)	0.8	2.1	1.1	3.1	<0.001
History of peripheral vascular disease (%)	5.7	5.3	5.7	7.6	0.043
Current smoker (%)	17.4	13.8	23.1	20.7	<0.001

Prior antihypertensive treatment (%)	71.8	73.4	67.9	70.9	0.003
Randomized Treatment (% Losartan)	50.5	50.0	49.2	50.8	0.870
Body mass index (kg/m^2)	27.9±4.7	28.7±4.8	25.5±3.8	26.8±4.6	<0.001
Serum glucose (mM)	5.90±2.03	6.14±2.31	5.80±1.99	5.87±2.02	<0.001
Total cholesterol (mM)	6.03±1.12	6.08±1.13	5.85±1.08	6.05±1.15	<0.001
HDL cholesterol (mM)	1.50±0.43	1.48±0.43	1.54±0.45	1.51±0.44	<0.001
Creatinine (mg/mM)	85.4±19.7	85.8±19.4	92.3±23.0	90.7±21.0	<0.001
UACR (mg/mM)	4.7±16.1	8.0±38.8	9.7±38.7	9.2±28.6	<0.001

CP=Cornell product; SL=Sokolow-Lyon voltage, GFR= glomerular filtration rate; UACR=urine albumin/creatinine ratio**Table 2.** Study Baseline and Change From Study Baseline to Last In-Study Measurement of Blood Pressure, Electrocardiographic Left Ventricular Hypertrophy, QRS Duration and Heart Rate in Relation to the Presence or Absence of Electrocardiographic Left Ventricular Hypertrophy by Both Cornell Product and Sokolow-Lyon Voltage at Baseline

Variables	**CP-/SL-** **(n=2023)**	**CP+/SL-** **(n=5220)**	**CP-/SL+** **(n=990)**	**CP+/SL+** **(n=960)**	**p value**
			Baseline Measurements		

Systolic BP (mm Hg)	172±14	174±14	176±14	176±143	<0.001
Diastolic BP (mm Hg)	98±8	98±9	97±9	98±9	<0.001
Cornell product (mm•msec)	2065±393	3212±897	1715±518	3454±1239	<0.001
Sokolow-Lyon voltage (mm)	26.4±7.3	25.7±6.8	44.9±5.9	45.3±6.4	<0.001
QRS duration (ms)	92.8±11.5	105.7±19.5	96.6±9.4	103.8±18.5	<0.001
Heart rate (bpm)	74.1±11.2	74.2±11.1	72.2±10.7	73.0±11.3	<0.001
		Change From Baseline to Last Measurement			
Systolic BP (mm Hg)	-27.7±18.6	-29.4±19.4	-30.8±20.2	-31.3±21.4	<0.001
Diastolic BP (mm Hg)	-16.8±10.1	-17.2±10.2	-16.8±10.6	-17.8±11.0	<0.001
Cornell product (mm•msec)	13±659	-270±852	-13±790	-428±1140	<0.001
Sokolow-Lyon voltage (mm)	-2.5±6.0	-2.8±6.5	-7.6±8.4	-8.6±9.1	<0.001
QRS duration (ms)	2.7±11.5	1.5±12.3	1.4±13.1	1.4±13.2	<0.001
Heart rate (bpm)	-4.8±12.7	-5.3±13.0	-5.1±12.6	-4.2±12.7	0.091

BP=blood pressure

Table 3. Univariate and Mulitvariable Cox Models for the Prediction of Outcomes According to On-Treatment Left Ventricular Hypertrophy by Either Cornell Product or Sokolow-Lyon Voltage Treated as Time-Dependent Covariates

Outcomes	Cornell Product LVH			Sokolow-Lyon Voltage LVH		
	Hazard Ratio	95% CI	p value	Hazard Ratio	95% CI	p value
			Univariate			
Myocardial Infarction	1.53	1.25-1.88	<0.001	1.62	1.25-2.10	<0.001
Stroke	1.44	1.21-1.71	<0.001	2.28	1.87-2.10	<0.001
Cardiovascular Death	1.80	1.48-2.19	<0.001	2.11	1.69-2.64	<0.001
Composite Endpoint	1.52	1.34-1.71	<0.001	2.00	1.73-2.31	<0.001
All-Cause Mortality	1.39	1.21-1.60	<0.001	2.05	1.74-2.43	<0.001
			Multivariable*			
						<0.001
Myocardial Infarction	1.28	1.05-1.49	0.014	1.33	1.14-1.55	0.009
Stroke	1.21	1.07-1.34	0.010	1.69	1.35-2.11	<0.001
Cardiovascular Death	1.37	1.11-1.70	0.004	1.53	1.19-1.98	0.001

Composite Endpoint	1.17	1.03-1.34	0.021	1.50	1.27-1.76	<0.001
All-Cause Mortality	1.14	1.04-1.33	0.017	1.57	1.30-1.89	<0.001

CI=confidence interval; LVH=left ventricular hypertrophy

* adjusted for randomized treatment, age, sex, prevalent diabetes, history of stroke, myocardial infarction, ischemic heart disease, heart failure, peripheral vascular disease or prior antihypertensive treatment, baseline serum cholesterol, HDL cholesterol, glucose and creatinine, and urine albumin/creatinine ratio treated as standard covariates, and on-treatment heart rate and diastolic and systolic blood pressure treated as time-varying covariates.

Table 4. Multivariable Cox Analyses to Assess the Predictive Value of the Combination of On-Treatment Cornell Product and Sokolow-Lyon Voltage for the LIFE Study Composite Endpoint in Relevant Subgroups of the Study Population

Subgroup	**Composite Endpoint (n)**	**Hazard Ratio**	**95% CI**	**p value for interaction**
Sex				0.190

Female (n=4963)	476			
Cornell product+/Sokolow-Lyon voltage-		1.44	1.12-1.84	
Cornell product-/Sokolow-Lyon voltage+		1.62	1.02-2.57	
Cornell product+/Sokolow-Lyon voltage+		3.02	2.18-4.18	
Male (n=4230)	620			
Cornell product+/Sokolow-Lyon voltage-		1.44	1.17-1.78	
Cornell product-/Sokolow-Lyon voltage+		1.99	1.49-2.66	
Cornell product+/Sokolow-Lyon voltage+		3.13	2.41-4.06	
Race				0.154
White/Other (n=8660)	1021			
Cornell product+/Sokolow-Lyon voltage-		1.44	1.22-1.70	
Cornell product-/Sokolow-Lyon voltage+		1.82	1.40-2.37	
Cornell product+/Sokolow-Lyon voltage+		3.20	2.60-3.95	
Black (n=533)	75			

Cornell product+/Sokolow-Lyon voltage-		1.69	0.84-3.40	
Cornell product-/Sokolow-Lyon voltage+		1.80	0.81-3.95	
Cornell product+/Sokolow-Lyon voltage+		1.87	0.79-4.42	
Age				0.481
<65 years (n=3489)	250			
Cornell product+/Sokolow-Lyon voltage-		1.52	1.11-2.08	
Cornell product-/Sokolow-Lyon voltage+		1.90	1.15-3.14	
Cornell product+/Sokolow-Lyon voltage+		4.60	3.08-6.88	
≥65 years (n=5704)	846			
Cornell product+/Sokolow-Lyon voltage-		1.52	1.26-1.82	
Cornell product-/Sokolow-Lyon voltage+		2.03	1.53-2.69	
Cornell product+/Sokolow-Lyon voltage+		2.98	2.36-3.77	
History of Ischemic Heart Disease				0.969
No (n=7724)	802			

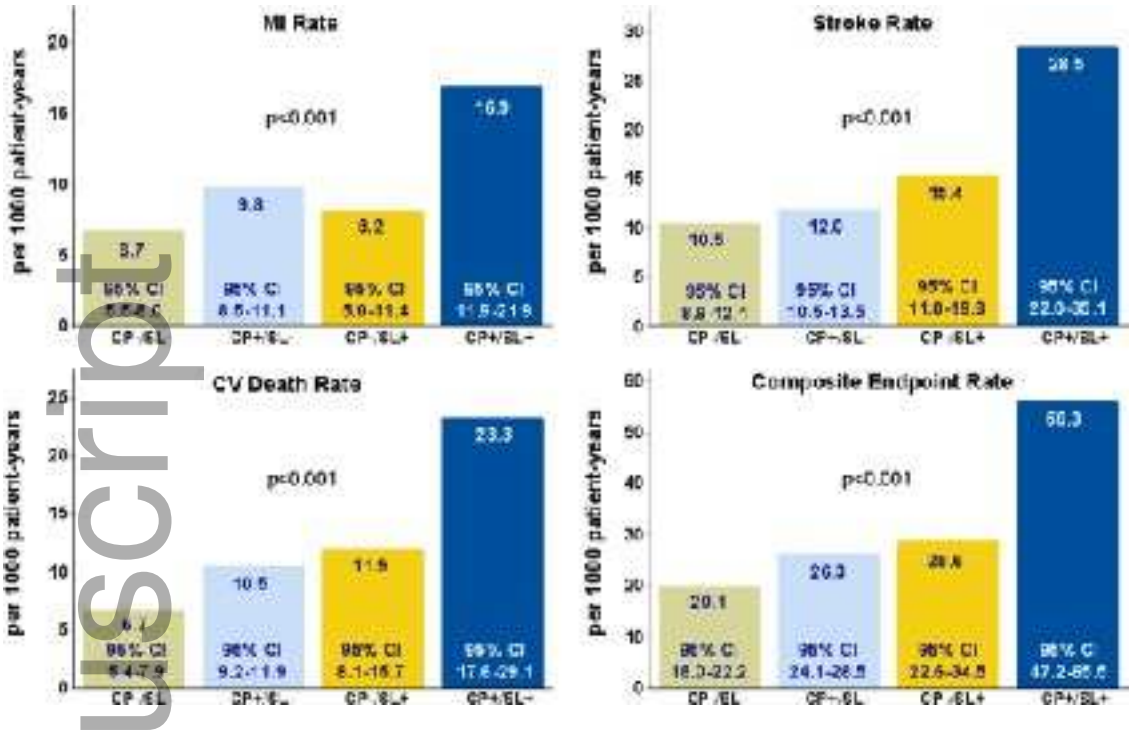
Cornell product+/Sokolow-Lyon voltage-		1.46	1.22-1.75	
Cornell product-/Sokolow-Lyon voltage+		1.76	1.32-2.35	
Cornell product+/Sokolow-Lyon voltage+		3.06	2.42-3.87	
Yes (n=1469)	294			
Cornell product+/Sokolow-Lyon voltage-		1.48	1.04-2.10	
Cornell product-/Sokolow-Lyon voltage+		2.45	1.52-3.96	
Cornell product+/Sokolow-Lyon voltage+		3.50	2.32-5.27	
Diabetes				0.140
No (n=7998)	854			
Cornell product+/Sokolow-Lyon voltage-		1.45	1.21-1.73	
Cornell product-/Sokolow-Lyon voltage+		1.64	1.24-2.17	
Cornell product+/Sokolow-Lyon voltage+		3.02	2.40-3.79	
Yes (n=1195)	242			
Cornell product+/Sokolow-Lyon voltage-		1.53	1.05-2.21	

Cornell product-/Sokolow-Lyon voltage+		3.40	2.03-5.68	
Cornell product+/Sokolow-Lyon voltage+		3.44	2.17-5.45	
Randomized Treatment				0.209
Atenolol (n=4558)	588			
Cornell product+/Sokolow-Lyon voltage-		1.36	1.09-1.70	
Cornell product-/Sokolow-Lyon voltage+		1.45	1.01-2.07	
Cornell product+/Sokolow-Lyon voltage+		2.62	1.98-3.47	
Losartan (n=4605)				
Cornell product+/Sokolow-Lyon voltage-		1.55	1.23-1.96	
Cornell product-/Sokolow-Lyon voltage+		2.44	1.74-3.41	
Cornell product+/Sokolow-Lyon voltage+		3.78	2.82-5.08	

Figure Legends:

Figure 1. Rates of myocardial infarction, stroke, cardiovascular death, the composite endpoint and all-cause mortality in relationship to the presence or absence of electrocardiographic left ventricular hypertrophy by both Cornell Product and Sokolow-Lyon voltage at study baseline. (CP=Cornell product; SL=Sokolow-Lyon voltage).

Figure 2. Risk of myocardial infarction, stroke, cardiovascular death, the composite endpoint and all-cause mortality in relationship to the on-treatment presence or absence of electrocardiographic left ventricular hypertrophy by both Cornell Product and Sokolow-Lyon voltage treated as time-varying covariates in Cox analyses. (*adjusted for randomized treatment, age, sex, prevalent diabetes, history of stroke, myocardial infarction, ischemic heart disease, heart failure, peripheral vascular disease or prior antihypertensive treatment, baseline serum cholesterol, HDL cholesterol, glucose and creatinine, and urine albumin/creatinine ratio treated as standard covariates, and on-treatment heart rate and diastolic and systolic blood pressure treated as time-varying covariates. CP=Cornell product; SL=Sokolow-Lyon voltage).



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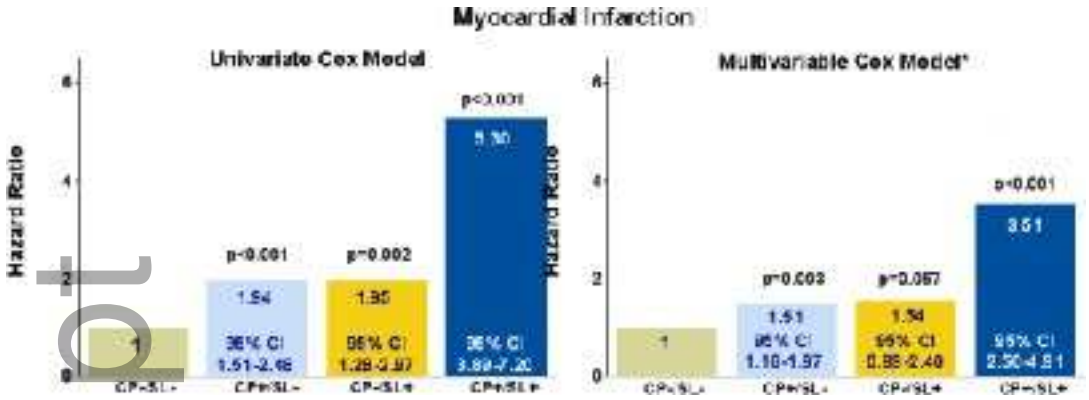

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