ECG left ventricular hypertrophy as a risk predictor of sudden cardiac death

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1. Introduction

Electrocardiographic (ECG) left ventricular hypertrophy (LVH) is an established risk factor for cardiovascular events [1–6]. ECG LVH is also associated specifically with increased risk for sudden cardiac death (SCD) [7,8], which is among the leading causes of death worldwide [9]. Association between ECG LVH and SCD remains significant also after adjusting for anatomic measures of LVH (echocardiography [echo], magnetic resonance imaging) [8,10,11], indicating that adverse electrical remodelling per se conveys additional prognostic value.

ECG is widely used and a routine test, among others, in all individuals with hypertension. Because of its potential implications, searching for signs of LVH is one of the key steps in the ECG assessment. Several ECG LVH criteria have been developed, but their prognostic values have been compared in only a few studies [6,12–14] and there is even more limited data comparing the prognostic values of different LVH criteria specifically to SCD. The present study was performed to compare the relationships of three traditional and clinically useful (Sokolow–Lyon, Cornell, RaVL) and one recently proposed (Peguero–Lo Presti) ECG LVH criteria to SCD. The present study was performed to compare the relationships of three traditional and clinically useful (Sokolow–Lyon, Cornell, RaVL) and one recently proposed (Peguero–Lo Presti) ECG LVH voltage criteria, as well as their selected composites, to SCD in the general population.

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1 This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
2. Methods

2.1. Study population, electrocardiography

The Health 2000 Survey was a prospective, epidemiologic survey that was conducted in Finland between 2000 and 2001. The survey population (n = 8028) was a two-stage stratified cluster sample drawn from the population register and was representative of the Finnish urban adult (20+ years) general population. Survey procedures consisted of a structured interview, a comprehensive health examination with questionnaires, measurements, and a physician’s clinical examination. Survey was highly successful with almost 85% of the recruited subjects attending the health examination. Detailed Heale of the Health 2000 survey methodology is available online [15]. Survey was conducted according to the recommendations of the Declaration of Helsinki, and was approved by the Institutional Ethics Committee and by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. Subjects gave written informed consent.

Digital 12-lead ECGs were recorded at the Health 2000 Survey baseline with Mar- quee MAC 5000 [GE Marquette Medical Systems, Milwaukee, WI]. ECGs were read from 6305 subjects. Subject with low ECG quality, complete left/right bundle branch block, or incomplete covariate data were excluded. In addition, subjects aged >80 years at the survey baseline were excluded from adjudication of the cause of death because of the potential adjudication imprecision in this age group (due to high comorbidity rate and low autopsy rate). After exclusions, a total of 5730 Health 2000 Survey subjects were available for the present study. ECG measurements were performed on screen in a blinded fashion by a single observer with methods described previously [16].

ECG LVH voltage amplitude criteria known as Sokolow–Lyon, Cornell, RaVL, and Peguero–Lo Presti were selected for the present study. Sokolow–Lyon amplitude was calculated as $SV_3 + SV_1$ or $SV_1 + RaVL$ (whichever was greater); dichotomous cutoff for LVH was $\geq 2.5$ mV [17]. Cornell amplitude was calculated as $SV_1 + RaVL$; dichotomous cutoff for LVH was $\geq 2.0$ mV in women and $\geq 2.8$ mV in men [18]. RaVL amplitude was measured as $R_V1$; dichotomous cutoff for LVH was $\geq 1.1$ mV [19]. Peguero–Lo Presti amplitude was calculated as the deepest $S$ among all 12 leads $+ SV_1$; dichotomous cutoff for LVH was $\geq 2.3$ mV in women and $\geq 2.8$ mV in men [20].

2.2. Follow-up and adjudication of the cause of death

Follow-up was from the Health 2000 Survey baseline until December 31, 2013. Adjudication of the cause of death was performed blinded to ECG data as described previously [21]. Briefly, adjudication was based on national registers of drug reimbursement, hospital admission and discharge diagnoses, and causes of deaths. Extensive national registers are maintained in Finland, and data on all deaths of Finnish citizens are collected systematically. Out-of-hospital deaths and deaths within 10 days of hospitalization or those considered eligible for the SCD adjudication. Data from other registers were analyzed independently by two physicians and classified deaths as probable, possible, unlikely SCD, and unknown cause of death. Deaths in which a cardiac cause was the immediate or underlying cause of death and the death was not known to be unrelated to arrhythmia were defined as probable SCDs. Deaths in which the immediate or underlying cause of death was cardiac, but cardiac disease was present and could reasonably have contributed to arrhythmia based on mechanism (e.g., unexpected death due to aspiration in a patient with a prior myocardial infarction), or deaths that could have been arrhythmic based on circumstances (e.g., death of a driver in a motor vehicle crash, death while swimming) were defined as possible SCDs. Deaths in which there was an explained medical cause of death unrelated to cardiac disease (e.g., cancer, massive blood loss, sepsis, pulmonary embolism, stroke) or a cardiac cause of death known to be nonischemic or unrelated to lethal arrhythmia (e.g., myocardial rupture after myocardial infarction, endocarditis) were defined as unlikely SCDs. Deaths with insufficient data were defined as deaths with unknown cause. In case of disagreement on the cause of death, two additional independent physicians reviewed the case, and final decision was constituted by consensus. Autopsies were performed in 67.2% of SCDs. In the present study, probable and possible SCDs were pooled in the analyses and were classified as SCDs.

2.3. Statistical analysis

Analyses were performed with R Statistics (version 3.4.0, The R Foundation for Statis-
tical Computing, Vienna, Austria; used for Cox regression analyses and spline figures), STATA 13.0 (StataCorp, College Station, TX; used to calculate population-attributable frac-
tions), and SPSS (version 21, IBM, Armonk, NY; used for all other analyses). Values are given as mean ± SD for continuous variables, and percentages and numbers for categorical variables. Bivariate correlations between continuous LVH variables were tested with Pearson’s test. Firth’s penalized maximum likelihood bias reduction method for Cox regression (R package: coxphf) was used to obtain the hazard ratios in the survival analyses [22,23]. Concordance probability estimate was used to compare the predictive accuracy of the continuous LVH variables for SCD (R package: CPE) [24]. The validity of proportional hazards assumption was verified graphically with partial residual plots (continuous vari-
ables) and survival probability plots (dichotomous variables). LVH variables were used both as continuous and dichotomous. Selected composite LVH criteria were also used. Gender, study baseline age, body mass index, heart rate, current smoking (yes/no), arterial hypertension (yes/no), previous myocardial infarction (yes/no), and diabetes mellitus (yes/no) were used as covariates in multivariable analyses. One LVH variable was used in the multivariable models at a time. Definitions for arterial hypertension, previous myocardial infarction, and diabetes mellitus have been published [16]. Interaction term (gender × LVH criterion) was tested in the same model together with main effects (i.e., LVH criterion, gender, all covariates). Cox models with penalized splines were used to assess and plot the relationship of continuous LVH variables to SCD risk. Population-attributable fractions were calculated for dichotomous ECG LVH criteria and selected composite criteria from models including all covariates with a previously described method [25] and implemented as the STATATE module punafcc. Population-attributable fraction reflects the proportion of events that can be attributed to a given risk marker or the percentage of the cases that would be prevented if a specific exposure were to be elimi-
nated from the population. Two-tailed $P < 0.05$ was considered significant for all analyses.

3. Results

After a mean follow-up of 12.5 ± 2.2 years, 134 SCDs had occurred. Baseline characteristics are shown in Table 1. Clinical variables showed that, compared with subjects without SCD, subjects with SCD were older, more often males, had higher body mass index and heart rate, were more often smokers, had more often hypertension, previous myoc-
ardial infarction, and diabetes. ECG variables showed that, compared with subjects without SCD, subjects with SCD had longer QRS and QTC durations, higher voltages, and had more often LVH. Depending on the criterion, LVH prevalence varied markedly. Peguero–Lo Presti showed the highest prevalence, and was fulfilled in $\approx 25\%$ of all study subjects.

Hazard ratios of SCD for continuous LVH criteria are shown in Table 2. In multivariable adjusted models, all criteria except for $R_AVL$ remained significantly associated with SCD. As an example, one millimeter increase in Cornell was associated with a 1.04-fold (95% confidence interval [CI] 1.01–1.07, $P = 0.008$) risk of SCD. Concordance probability estimate was highest, 0.63 (95% CI 0.60–0.66), for Cornell, while it was 0.56 (95% CI 0.52–0.60) for Sokolow–Lyon, 0.60 (95% CI 0.57–0.63) for Peguero–Lo Presti, and 0.59 (95% CI 0.56–0.62) for $R_AVL$.

When continuous ECG LVH variables were used to test gender-LVH in-
teraction terms in multivariable Cox models, interactions were not found ($P > 0.114$ for all gender-LVH interaction terms). Adjusted, con-
secutive associations between SCD risk and the three voltage criteria that were significantly associated with SCD in adjusted models are shown in Supplementary Fig. 1 (Panels A–C). Compared to Sokolow– Lyon and Peguero–Lo Presti, increase in Cornell was associated with a more pronounced SCD risk increase.

Hazard ratios of SCD for dichotomous LVH criteria are shown in Table 3. Of the single criteria, only Cornell remained significant after adjustments. Of the composite criteria, only composite of Sokolow–Lyon and Cornell remained significant after adjustments. Overlap of dichotomatic Sokolow–Lyon, Cornell, and Peguero–Lo Presti criteria is shown in Fig. 1. Overlap between Sokolow–Lyon and Cornell was relatively small. By contrast, Cornell became mostly embedded by Peguero–Lo Presti. Bivariate correlation between continuous Cornell and Peguero–Lo Presti criteria was high ($r = 0.71$, $P < 0.001$), whereas other correlations were lower (Sokolow–Lyon vs. Cornell, $r = 0.20$, $P < 0.001$; Sokolow–Lyon vs. Peguero–Lo Presti, $r = 0.21$, $P < 0.001$). When population-attributable fractions were calculated for dichoto-
mous ECG LVH criteria and selected composite criteria, population-attributable fraction was 4.8% (95% CI –1.9–11.2%, $P = 0.158$) for Sokolow–Lyon, 6.1% (95% CI –0.2–12.1%, $P = 0.059$) for Cornell, 9.5% (95% CI –2.3–20.0%, $P = 0.111$) for Peguero–Lo Presti, 2.0% (95% CI –3.1–6.8%, $P = 0.442$) for $R_AVL$, 11.0% (95% CI 1.9–19.2%, $P = 0.019$) for composite of Sokolow–Lyon and Cornell, 11.5% (95% CI –2.1–23.3%, $P = 0.095$) for composite of Sokolow–Lyon and Peguero–Lo Presti, and 8.3% (95% CI –3.7–18.9%, $P = 0.168$) for composite of Corn-
ell and Peguero–Lo Presti. Thus, only composite of Sokolow–Lyon and Cornell was statistically significant.

4. Discussion

4.1. Main findings

Our study in white general population showed that Sokolow–Lyon, Cornell, and Peguero–Lo Presti ECG voltage LVH criteria provided prognos-
tic information on SCD risk as continuous variables even after adjusting for
estimated to account for 4.2. LVH as a modi-
after adjustments and was the only LVH measure that showed statistically

evidence of SCD, with a proportion of 10

Values are given as mean ± SD for continuous variables, and percentages and numbers for
categorical variables.

LVH indicates left ventricular hypertrophy; SCD, sudden cardiac death.

Table 1

Baseline characteristics of the study subjects.

<table>
<thead>
<tr>
<th></th>
<th>No SCD (n = 5596)</th>
<th>SCD (n = 134)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
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</tr>
<tr>
<td>Age, years</td>
<td>51 ± 13</td>
<td>62 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender, (%)(n)</td>
<td>46 (2547)</td>
<td>78 (104)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 ± 5</td>
<td>28 ± 5</td>
<td>0.008</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>62 ± 11</td>
<td>68 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking, (%)(n)</td>
<td>22 (1248)</td>
<td>43 (58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial hypertension, (%)(n)</td>
<td>45 (2503)</td>
<td>75 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous myocardial infarction, (%)(n)</td>
<td>2 (103)</td>
<td>19 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, (%)(n)</td>
<td>5 (290)</td>
<td>15 (20)</td>
<td>&lt;0.001</td>
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</table>

**ECC variables**

QRS duration, ms | 93 ± 9 | 98 ± 14 | <0.001 |
| QTC duration, ms | 409 ± 25 | 423 ± 29 | <0.001 |
| Sokolow–Lyon voltage, mVa | 2.5 ± 0.7 | 2.7 ± 0.9 | 0.002 |
| Cornell voltage, mVb | 1.5 ± 0.6 | 1.8 ± 0.7 | <0.001 |
| Peguero–Lo Presti voltage, mVc | 2.1 ± 0.7 | 2.5 ± 1.0 | <0.001 |
| RaVL voltage, mV | 0.4 ± 0.3 | 0.6 ± 0.3 | <0.001 |

**EGC LVH by voltage criteria**

| Sokolow–Lyon, \(\%\)(n) | 9 (482) | 14 (19) | 0.030 |
| Cornell, \(\%\)(n) | 7 (386) | 13 (17) | 0.016 |
| Peguero–Lo Presti, \(\%\)(n) | 25 (1392) | 34 (45) | 0.026 |
| Rpv0, \(\%\)(n) | 4 (215) | 8 (11) | 0.023 |

Values are given as mean ± SD for continuous variables, and percentages and numbers for
categorical variables.

Several risk factors, whereas RaVL was not associated with SCD after adjustments.
When single LVH criteria were used as dichotomous variables, only Cornell was significant after adjustments. The dichotomous composite of Sokolow–Lyon and Cornell was also significantly associated with SCD after adjustments and was the only LVH measure that showed statistically significant population-attributable fraction.

**4.2. LVH as a modifier of SCD risk**

Myocardial ischemia is central in SCD, and coronary disease has been estimated to account for >80% all SCDs [26]. The second most common etiology of SCD, with a proportion of 10–15%, is (hypertrophic and dilated) cardiomyopathy [28]. Hypertrophied myocardium predisposes to malignant arrhythmias by various mechanisms. These include, among others, reduced coronary blood flow predisposing to ischemia; cardiomyocyte loss and increased fibrosis creating a substrate for electric reentry and increased dispersion of repolarization [27]; arrhythmogenic alterations in cardiomyocyte ion channel expression and function predisposing to afterdepolarizations [28]. In hypertrophic cardiomyopathy, SCD risk has been reported to increase with the maximum left ventricular (LV) wall thickness [29]. Importantly, even in the absence of coronary disease or cardiomyopathy, increase in echo LV mass already within normal to mildly elevated range is linearly associated with adverse changes in ECG repolarization measures [30]. Thus, in the presence of ischemia, SCD risk may be assumed to be modified, in addition to other factors (e.g., electrolyte disturbances, genetic factors), by the degree of pathological myocardial hypertrophy.

**4.3. ECG LVH and anatomic LVH in relation to SCD risk**

Increase in risk-factor adjusted hazard ratio for SCD has been reported in the general population both for ECG LVH [7,8,31] and echo LVH [32–35]. Of note, LVH diagnosed by ECG vs. echo or magnetic resonance imaging contains distinct prognostic value for SCD risk [8,10,11], showing that ECG LVH is a marker of adverse electric remodelling even in the absence of anatomic hypertrophy. Simulation studies indicate that electric properties of the heart, especially slowed electric conduc-
tion velocity (fibrosis), may also increase ECG QRS voltages and may thus explain why many subjects with ECG LVH do not present with anatomic LVH (and vice versa), and why both ECG LVH and anatomic LVH convey prognostic value independent of each other [36]. Highlighting the importance of LVH, echo LVH has been reported as at least equiva-
lent to severely decreased LV ejection fraction as a predictor of mortality or SCD [37]. Recently, in an epidemiologic case-control study, the Oregon Sudden Unexpected Death Study (Oregon SUDS), an ECG risk score which included ECG LVH (composite of Sokolow–Lyon and Cor-
nel voltages) as a score component resulted in significant additive improvement above LV ejection fraction in SCD risk estimation [38].

Despite the confirmed link between LVH and SCD, little has been known about the prognostic values of different ECG LVH criteria specifically to SCD. The prognostic values of different LVH criteria for incident cardiovascular events vary [14], suggesting that some criteria may out-
perform others in stratifying specifically SCD risk. Previous studies showing the relationship between ECG LVH and SCD have mainly reported one single LVH measure. In one of the earliest studies, Minnesota code 3–1 was used [31], whereas in another report from the 1970’s the definition for ECG LVH was not specified [7]. In the Oregon SUDS, Sokolow–Lyon voltage was used as a dichotomous ECG LVH variable and was associated with sudden cardiac arrest also after adjusting for other risk factors, including echo LVH [8]. More recently in the Oregon SUDS, Romhilt–Estes score ≥5 (“definite LVH”) was associated with sudden cardiac arrest in the adjusted model [39].

Our present study may be the first comprehensive comparison on the performance of several LVH criteria as risk predictors of SCD. Three traditional and clinically useful and one recently proposed LVH criteria were analyzed both as continuous and dichotomous. Data were collected prospectively. First, as expected, significant associations between traditional risk factors and SCD was observed. Second, LVH prevalence varied markedly between criteria, which is not surprising as similar has been reported previously [6,14]. Prevalence of Peguero–Lo Presti showed a relatively high prevalence (~25% of all subjects). Our study may be the first reporting the prevalence of this new criterion in the general population. In their work including mainly hypertensive hospital patients, Peguero et al. reported that, compared to Sokolow–Lyon, Cornell, and Rpv0, Peguero–Lo Presti criterion had markedly higher sensitivity and lower specificity for detecting echo LVH [20]. Thus, our results showing higher LVH prevalence rates for Peguero–Lo Presti compared to other criteria are in line with the previous report [20].

**Table 2**

<table>
<thead>
<tr>
<th>Modela</th>
<th>LVH voltage criteria</th>
<th>HR (95% CI)b</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
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</tr>
<tr>
<td>Sokolow–Lyon</td>
<td>1.03 (1.01–1.06)</td>
<td>0.003</td>
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</tr>
<tr>
<td>Cornellc</td>
<td>1.09 (1.06–1.12)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Peguero–Lo Presticiel</td>
<td>1.05 (1.03–1.07)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td><strong>Multivariable adjusted</strong></td>
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</tr>
<tr>
<td>Sokolow–Lyon</td>
<td>1.12 (1.07–1.16)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cornell</td>
<td>1.04 (1.01–1.07)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Peguero–Lo Presti</td>
<td>1.03 (1.01–1.05)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Rpv0</td>
<td>1.03 (0.98–1.09)</td>
<td>0.262</td>
<td></td>
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</tbody>
</table>

CI indicates confidence interval; otherwise, abbreviations as in Table 1.

a Covariates in the multivariate analyses: gender, age at the study baseline, body mass index, heart rate, current smoking (yes/no), arterial hypertension (yes/no), diabetes mellitus (yes/no), previous myocardial infarction (yes/no).

b Hazard ratio per 100 μV (1 mm with the 10 mm/mV calibration) increase in the ECG LVH measure value.

c Sokolow voltage, mV.
d Cornell voltage, mV.
e Peguero–Lo Presti voltage, mV.
f Peguero–Lo Presti.
g RaVL.
h Lo Presti.
i Lyon.
j Sokolow.
k Cornell.

Our present study may be the first comprehensive comparison on the performance of several LVH criteria as risk predictors of SCD. Three traditional and clinically useful and one recently proposed LVH criteria were analyzed both as continuous and dichotomous. Data were collected prospectively. First, as expected, significant associations between traditional risk factors and SCD was observed. Second, LVH prevalence varied markedly between criteria, which is not surprising as similar has been reported previously [6,14]. Prevalence of Peguero–Lo Presti showed a relatively high prevalence (~25% of all subjects). Our study may be the first reporting the prevalence of this new criterion in the general population. In their work including mainly hypertensive hospital patients, Peguero et al. reported that, compared to Sokolow–Lyon, Cornell, and Rpv0, Peguero–Lo Presti criterion had markedly higher sensitivity and lower specificity for detecting echo LVH [20]. Thus, our results showing higher LVH prevalence rates for Peguero–Lo Presti compared to other criteria are in line with the previous report [20].
It has been postulated that, compared to S waves, R waves represent the depolarization of the ventricular free wall and myocardium, whereas S waves are believed to represent depolarization of the interventricular septum, conduction system, and LV endomyocardium, whereas S waves are believed to represent depolarization of the interventricular septum, conduction system, and LV endomyocardium. Special attention with SCD. ECG Q, R, and S waves are believed to represent different parts of the depolarizing areas in the heart. Specifically, Q and R waves represent depolarization of the interventricular septum, conduction system, and LV endomyocardium, whereas S waves are believed to represent the depolarization of the ventricular free wall and myocardium. It has been postulated that, compared to S waves, R waves are less sensitive in detecting mild to moderate anatomic LVH. In contrast to this, $R_{AVL}$ has also been reported to perform as good or even better in echo LVH detection compared to Sokolow–Lyon and Cornell [5]. Risk-factor-adjusted association between $R_{AVL}$ and cardiovascular outcomes has been reported [5,14], but also conflicting results have been published [6]. We report here as a new finding that $R_{AVL}$ acts as a sole criterion does not seem to capture the malignant arrhythmogenic risk of LVH in the general population.

Fourth, when LVH criteria were used in the present study as dichotomous variables, relationships of Sokolow–Lyon and Peguero–Lo Presti to SCD were nonsignificant in multivariable adjusted models although they were significant when used as continuous variables. One explanation for this may be diminished statistical power related to dichotomization. The composite of Sokolow–Lyon and Cornell was the only composite criterion that remained significantly associated with SCD after adjustments. In addition, composite of Sokolow–Lyon and Cornell was the only criterion that showed statistically significant population-attributable fraction. Use of composite LVH criteria is generally supported because of expected enhanced sensitivity in LVH detection. When criteria are selected, a logical step is to combine criteria that are supported because of expected enhanced sensitivity in LVH detection. According to expected enhanced sensitivity in LVH detection, when criteria are combined, a logical step is to combine criteria that are supported because of expected enhanced sensitivity in LVH detection.

4.4. Limitations

Our study was performed in white general population. Future studies may evaluate whether our findings are reproducible also in multiracial populations as well as in populations with a more elevated SCD risk, such as in coronary heart disease and/or previous myocardial infarction.

4.5. Conclusions

Sokolow–Lyon, Cornell, and Peguero–Lo Presti ECG, but not $R_{AVL}$ voltage, are associated with SCD risk as continuous ECG voltage LVH variables. When SCD risk assessment/adjustment is performed using a dichotomous ECG LVH measure, composite of Sokolow–Lyon and Cornell voltages is the preferred option.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.104.
Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Disclosures

Veikko Salomaa has participated in a conference trip sponsored by Novo Nordisk. Other authors have nothing to disclose.

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