Imaging and Diagnostic Testing

Prognostic value of electrocardiographic criteria for left ventricular hypertrophy

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Background Many electrocardiographic (ECG) criteria for left ventricular hypertrophy (LVH) exist, but few studies have compared their relative prognostic value for predicting cardiovascular (CV) mortality.

Methods We analyzed the first ECG on 46 950 consecutive veterans. We targeted male outpatients with a body mass index >20 to avoid confounding by complicating catabolic illnesses and further excluded those with conduction abnormalities. Using Cox regression models adjusted for age, heart rate, and body mass index, we compared the hazard ratios (HRs) for CV mortality obtained from seventeen commonly used ECG criteria for LVH.

Results During a mean follow-up of 7 ± 4 years, in a total population of 19 434 patients (mean age 54 ± 14 years), 1254 (6%) patients died of CV causes. The adjusted HR for CV mortality ranged from 1.4 (95% CI 1.2-1.6) to 3.7 (95% CI 2.7-5.0) among the various criteria. Left ventricular hypertrophy defined by composite criteria was generally associated with higher adjusted HRs compared with voltage-only criteria. Among patients with ECG-LVH, the presence of a left ventricular strain pattern or increased negative P-terminal force were most predictive of CV mortality (HR 3.9 and 3.5, 95% CI 3.3-4.6 and 2.8-4.2).

Conclusions Compared with voltage-only criteria for detecting LVH, composite ECG criteria are more strongly predictive of CV mortality. By applying these ECG criteria into routine clinical practice, individuals with LVH who are at higher risk for CV mortality can be identified and appropriately treated. (Am Heart J 2005;150:161-7.)

Left ventricular hypertrophy (LVH) has consistently been shown to be a strong independent risk factor for cardiovascular (CV) mortality.[1] Despite the existence of multiple modalities for identifying LVH, the electrocardiogram (ECG) remains a simple, low-cost, and widely available modality. Multiple studies have consistently demonstrated an association between ECG evidence of LVH and CV mortality.[2-4] However, the magnitude of this association has varied widely among existing studies.[5] Aside from differences in patient population and adjustment for confounding factors, the use of different ECG criteria in these studies may account for at least part of the variability in risk prediction. The variable risk association among different ECG patterns for LVH has long been recognized. For example, LVH defined by the presence of a left ventricular strain pattern on the ECG confers a worse prognosis than LVH by an increased voltage pattern alone.[6] However, because few studies have comprehensively compared the prognostic value of various ECG criteria for LVH, the optimal criteria for assessing CV risk have not yet been defined. We therefore sought to evaluate the relative prognostic value of a broad range of ECG criteria for LVH to identify the optimal ECG criteria for predicting CV mortality.

Methods

Sample

Beginning in March 1987, the ECGs obtained within the Palo Alto VA Health Care System have been digitally recorded and stored in the Marquette MUSE system. The ECGs were obtained as part of a screening or diagnostic evaluation performed on inpatients and outpatients selected by their physicians for unknown reasons. As of December 1999, a database of 12-lead ECG measurements and interpretation from 46 950 veterans has been gathered. If a patient had more than one ECG in the database, only the first study was included. All computerized interpretations were overread by a cardiologist before being recorded into the database.

Because of the proportionally small female population among the veterans, females (n = 4616) were excluded from the study. To avoid confounding by catabolic complicating illness, we excluded ECG recordings from hospitalized patients (n = 12 368), from patients with a body mass index (BMI) ≤20 kg/m^2 (n = 21 437), and from patients in whom

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doi:10.1016/j.ahj.2004.08.041

Table I. ECG criteria for LVH

Name	Criteria	Cut-point for LVH	Prevalence
Voltage-only criteria			
Minnesota code 3.1	RV5/V6 > 26 mm, RI/II/III/aVF > 20 mm, or RaVL > 12 mm	NA	6.9
Lewis index	(RI + SIII) − (RIII + SI)	>1.7 mV	7.8
Sokolow-Lyon voltage	SV1 + RV5 ≥ 3.5 mV, RV5/6 ≥ 2.6 mV, RaVL ≥ 1.1 mV, or RaVF ≥ 2 mV	NA	13.2
Cornell voltage	RaVL + SV3	≥2.8 mV (men), ≥2.0 mV (women)	2.4
Framingham adjusted Cornell voltage	Men: RaVL + SV3 + 0.0174 × (age − 49) + 0.191 × (BMI − 26.5) Women: RaVL + SV3 + 0.0387 × (age − 50) + 0.212 × (BMI − 24.9)	≥2.8 mV (men), ≥2.0 mV (women)	17.2
Gubner and Ungerleider	RI + SIII	≥22 mm	4.1
Sum of 12 leads	Sum of Max (R, S) amplitude in each of the 12 leads	179 mm	3.8
QRS voltage and duration product			
12-lead product	12-lead sum voltage × QRS duration	17472 mm × ms	4.3
Cornell product	(RaVL + SV3) × QRS duration	2436 mm × ms	5.9
Scores			
Framingham score	RI + SIII > 2.5 mV, SV1/2 + RV5/6 > 3.5 mV, SV1/2/3 > 2.5 mV + RV4/5/6 > 2.5 mV plus Left ventricular strain pattern*	NA	0.6
Perugia score	Positivity of at least one of the following: (1) SV3 + RaVL > 2.4 mV (2) Left ventricular strain pattern* (3) Romhilt-Estes point score ≥ 5	NA	7.6
Romhilt-Estes point score	• Any limb-lead R or S ≥ 2.0 mV or SV1/2 ≥ 3.0 mV or RV5/6 ≥ 3.0 mV (3 points)	≥5 points—definite LVH	2.4
	• Left ventricular strain pattern* without digitalis (3 points) or with digitalis (1 point)	≥4 points—probable LVH	5.8
	• LAE† (3 points)		
	• LAD ≥ −30‡ (2 points)		
	• QRS duration ≥ 90 ms (1 point)		
	• Intrinsicoid QRS deflection of ≥50 ms in V5/6 (1 point)		
Regression models			
Rautaharju LV mass index equation	White and black men: LVMI (g/m^2) = 36.4 + 0.01 × RV5 + 0.02 × SV1 + 0.028 × max(SIII, QIII) + 0.182 × Tneg(V6) − 0.148 × Tpos(aVR) + 1.049 × QRS duration		10.9
	White women: LVMI (g/m^2) = 88.5 + 0.018 × RV5 + 0.053 × max(SV5, QV5) − 0.112 × max(SI, QI) + 0.108 × Tpos(V1) + 1.7 × Tneg(aVF) − 0.094 × Tpos(V6)	≥131 g/m^2 (Men)	
	Black women: LVMI (g/m^2) = −22.3 + 0.022 × RaVL + 0.018 RV6 + SV2 − 0.014 × RV2 − 0.069 × max(SV5, QV5) + 0.199 × Tneg(aVL) + 0.746 × QRS duration	≥110 g/m^2 (Women)	
de Vries LV mass equation	LV mass (g) = 1.1 × age + 101.4 × BSA + 0.43 × PT V1 + 28.7 × SV1 + 26.5 × SV4 − 137.5 − 13.1 × sex§	≥131 g/m^2 (Men), ≥110 g/m^2 (Women)	0.2
Wolf logistic regression	Men: exponent = 0.0016 × RaVL + 0.00069 × SV1 + 0.00638 × TnegV6 − 3.0314 Women: exponent = 0.0021 × RaVL − 0.00877 × SI + 0.01047 × TnegV6 − 1.5	Risk‖ > 0.8 for LVMI ≥ 131 g/m^2 in men, ≥110 g/m^2 in women	0.7
Casale-Devereux logistic regression	Exponent = 4.558 − 0.092 × (RaVL +SV3) − 0.306 × TV1 − 0.212 × QRS dur − 0.278 × PT V1 − 0.859 × sex¶	Risk‖ > 0.8 (for LVMI ≥ 125 g/m^2)	3.5

BSA indicates body surface area; *LAD*, left axis deviation; *LAE*, left atrial enlargement; *LVMI*, left ventricular mass index; *NA*, not applicable; *PT*, P-terminal force duration (ms).
*Defined as 1-mm ST-J point depression ≥1 mm + inverted T wave in lead V5.
†Defined as P-terminal force in V1 >4 mV ms.
‡Defined as an R wave axis less than −45° and greater than −90°.
§Male = 0, female = 1.
‖Risk = 1/(1 + e$^{-\text{exponent}}$).
¶Male = 1, female = 2.

Table II. Characteristics of patients with and without ECG evidence of LVH

	No LVH (n = 12743)	LVH (n = 6691)	*P*
Age (y)	53 ± 13	55 ± 14	<.05
Height (m)	1.76 ± 0.08	1.75 ± 0.09	<.05
Weight (kg)	82.6 ± 13.0	92.4 ± 21.2	<.05
BMI (kg/m^2)	26.5 ± 3.5	30.2 ± 6.7	<.05
Heart rate (beats/min)	72 ± 14	72 ± 15	.7
Ethnicity			
Caucasian (%)	79.1	66.6	<.05
African American (%)	10.4	23.1	<.05
Other races (%)	10.5	10.3	.7

BMI could not be determined (n = 4360). We chose to exclude patients with a low BMI because we found that a BMI ≤20 in our study population is associated with increased mortality, whereas there was no significant relationship between BMI and mortality in patients with a BMI >20 (unpublished data). To allow comparison between different ethnic groups, we also excluded patients in whom information on ethnicity was not available (n = 402). Finally, we excluded ECGs containing conduction abnormalities that obscure true characterization of LVH. These include atrial fibrillation (n = 536), left or right bundle branch blocks (n = 247 and 705, respectively), ventricular preexcitation (n = 23), or paced rhythms (n = 126).

ECG criteria

Sixteen ECG methods, including various voltage criteria, point score systems, and regression equations for estimating left ventricular mass, were used to identify LVH in our cohort (Table I). These include the Minnesota code 3.1,[7] Lewis Index,[8] Sokolow-Lyon,[9] Gubner-Ungerleider,[10] sum of 12 leads,[11] Framingham adjusted[12] and unadjusted Cornell voltages,[13] Cornell[14] and 12-lead voltage products,[11] Perugia score,[15] Framingham score criteria,[16] Romhilt-Estes point score,[17] de Vries left ventricular mass[18] and Rautaharju left ventricular mass index equations,[19] and Wolf[20] and Casale-Devereux logistic regression equations.[21] Because these methods result in nominal measures of LVH, ordinal point scores, and continuous estimates of left ventricular mass, we used conventional cut-points to dichotomize the identification of LVH as either present or absent. Because LVH can be defined by a score of more than 4 points (probable) or 5 points (definite) using the Romhilt-Estes method, both cutoffs were used for our analysis, yielding a total of 17 criteria.

Follow-up

Vital status was ascertained for each patient as of February 2003 using the Social Security Death Index, and cause of death was identified by searching the California Department of Health Services' Death Statistical Master File. We defined our primary end point as death from CV causes, defined according to the Ninth International Statistical Classification of Diseases (ICD-9) code numbers 390-459.[22] We were unable to identify the cause of death in 26 patients because they emigrated to other states, and these patients were excluded from our analyses.

Table III. Risk of CV death according to various ECG criteria for LVH

	Hazard ratios		
ECG criteria	Unadjusted	Adjusted*	95% CI*
Voltage only			
Minnesota code 3.1	1.8	1.8	1.5-2.2
Lewis index	1.9	1.4	1.2-1.7
Sokolow-Lyon voltage	1.7	1.9	1.6-2.2
Gubner-Ungerleider voltage	2.2	1.7	1.4-2.1
Sum of 12 leads	NS	2.0	1.5-2.6
Cornell voltage	3.8	3.1	2.5-3.8
Framingham adjusted Cornell voltage	1.8	1.4	1.2-1.6
Product of QRS voltage and duration			
Sum of 12-lead product	1.9	2.6	2.1-3.2
Cornell product	3.3	2.7	2.3-3.1
Score system			
Perugia	3.6	2.9	2.5-3.3
Framingham score	5.8	3.4	2.4-4.9
Romhilt-Estes point score ≥ 4	3.3	2.9	2.5-3.4
Romhilt-Estes point score ≥ 5	4.8	3.7	3.0-4.4
Regression models			
Rautaharju LV mass index equation	3.2	2.6	2.0-3.0
de Vries LV mass equation	4.8	2.5	1.5-4.4
Wolf logistic equation	5.3	3.7	2.7-5.0
Casale-Devereux logistic regression	4.1	3.3	2.8-3.9

NS indicates nonsignificant.
*Adjusted for age, heart rate, and BMI.

Statistical methods

Differences in characteristics between patients with ECG-LVH and those without were compared using the Student *t* test for continuous variables and χ^2 test for categorical variables. We determined the unadjusted risk of CV death for each of the 17 ECG criteria for LVH using Cox proportional hazards models. We then performed multivariate analyses adjusting for age, heart rate, and BMI. All continuous variables are expressed as mean ± SD. All analyses were performed using the Number Cruncher Statistical System (Kaysville, Utah).

Results

Baseline characteristics and prevalence of LVH

The overall cohort consisted of 19434 male patients with a mean age of 54 ± 14 years. There were 6691 patients (34.4%) who met one or more ECG criteria for LVH. Patients with ECG evidence of LVH had higher BMIs and were more likely to be African American

compared to those without ECG-LVH (Table II). The prevalence of LVH varied widely between the 17 criteria and was highest when using the Framingham adjusted Cornell voltage (17.2%), the Sokolow-Lyon voltage (13.2%), and the Rautaharju LV mass index equation (10.9%). The de Vries equation (0.2%), Framingham score (0.6%), and Wolf logistic equation (0.7%) yielded the lowest prevalence of LVH (Table I). Voltage-only criteria as a group yielded a higher median prevalence (6.9%) compared with criteria incorporating repolarization abnormalities (3%).

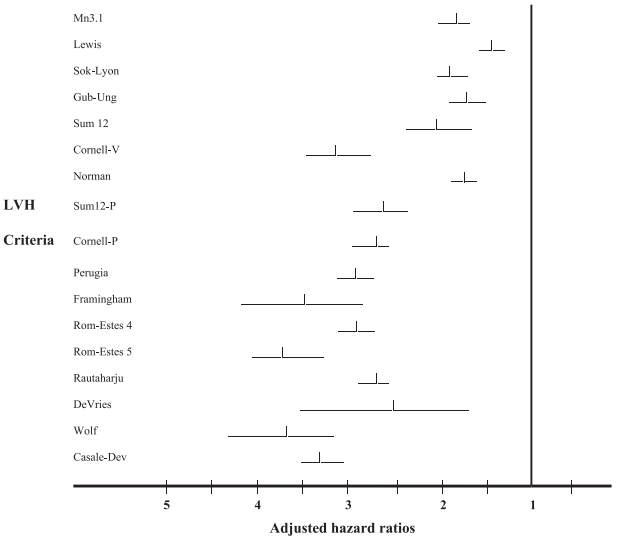
Cardiovascular mortality

During a mean follow-up of 7 ± 4 years, there were a total of 3251 (17%) deaths and 1254 deaths (6%) due to CV causes, resulting in an annual CV mortality of 0.9% per year. Patients with ECG-LVH had a higher average annual mortality compared with those without ECG-LVH (1.4% per year vs 0.7% per year, $P < .05$).

In multivariate models adjusted for age, heart rate, and BMI, LVH identified by each of the 17 ECG criteria predicted an increased risk of CV death, with adjusted hazard ratios (HRs) ranging from 1.4 to 3.7 (Table III, Figure 1). The average risk of CV death was highest in patients with a Romhilt-Estes point score ≥5 (adjusted HR 3.7, 95% CI 3.0-4.4) and in patients with LVH identified by the Wolf logistic equation (adjusted HR 3.7, 95% CI 2.7-5.0). Cornell voltage (adjusted HR 3.1, 95% CI 2.5-3.8) and Casale-Devereux logistic equation (adjusted HR 3.3, 95% CI 2.8-3.9) were also associated with relatively high CV mortality. However, the HR CIs for these 4 criteria significantly overlap with those of other criteria (Figure 1). No single criterion is significantly superior for predicting CV mortality. In general, with the exception of the Cornell voltage criteria, composite criteria for LVH were associated with higher adjusted HRs compared with the voltage-only criteria.

When further investigating the 10 composite criteria, defined as criteria incorporating more than one ECG pattern, we identified 5 general patterns commonly included. These include increased negative P-terminal forces (defined as the product of the amplitude and duration of any terminal negative P wave in lead V1 greater than 4 mV × ms), increased QRS duration (QRS width > 100 ms), left axis deviation (QRS axis < −30°), typical left ventricular strain pattern (defined as the combination of ST depression of greater than 1 mm and asymmetric T-wave inversions in any of the leads in V4-6), and isolated T-wave inversions in lead V4-6 without any concomitant ST-segment depression or strain pattern. By performing univariate analyses on each of the 5 ECG patterns in a subgroup of patients in whom ECG-LVH was detected by any of the 17 criteria, we found that left ventricular strain pattern and increased P-terminal force were associated with the highest HRs for CV mortality (HR 3.9 and 3.5, 95% CI 3.3-4.6 and 2.8-4.2), followed by isolated T-wave inversions (Table IV, Figure 2).

Figure 1



Adjusted HRs of CV mortality according to various ECG criteria for LVH. Adjusted for age, heart rate, and BMI. *Mn3.1* indicates Minnesota code 3.1; *Lewis* I, Lewis Index; Sok Lyo, Sokolow-Lyon voltage; *Gub-Ung*, Gubner-Ungerleider voltage; *Sum 12*, sum of 12 lead voltage; *Cornell-V*, Cornell voltage; *Norman*, Framingham adjusted Cornell voltage; *Sum12P*, sum of 12 lead × QRS product; *Cornell-P*, Cornell voltage × QRS product; *Perugia*, Perugia score; *Fram*, Framingham score; *Rom 4/5*, Romhilt-Estes point score ≥4/5; *Raut*, Rautaharju LV mass index equation; *de Vries*, de Vries LV mass equation; *Wolf*, Wolf logistic regression; *Cas-Dev* = Casale-Devereux logistic regression.

Discussion

In a cohort of ambulatory male patients, we found that the prevalence of LVH as detected by ECG ranges from 0.6% to 17% depending upon the criteria used. During a mean follow-up of 7 ± 4 years, patients who had ECG evidence of LVH had higher rates of CV mortality. Although no single ECG criteria appeared to be clearly superior in predicting CV mortality, we found that among 17 available ECG criteria for detecting LVH, composite criteria incorporating various ECG-LVH patterns were associated with higher adjusted HRs compared with voltage-only criteria.

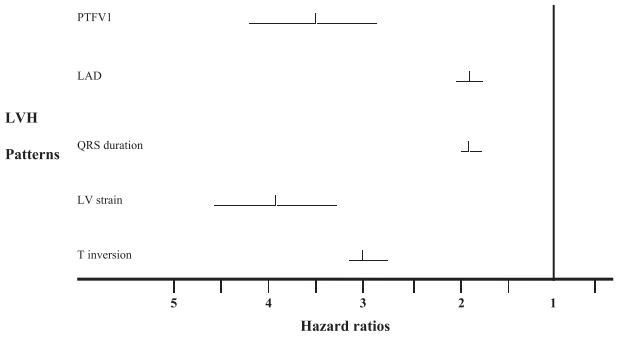
LVH and CV mortality

When using conventional cut-points to define LVH, we have demonstrated that the presence of ECG-LVH significantly confers an increased risk of CV mortality

Table IV. Incremental risk of CV mortality for nonvoltage ECG-LVH patterns

ECG patterns in LVH	Hazard ratios	95% CI	Prevalence of patterns (%)
Increased P-terminal force in V1	3.5	2.8-4.2	1.4
Left axis deviation	1.9	1.7-2.1	13.0
Increased QRS duration	1.9	1.7-2.0	43.8
Left ventricular strain	3.9	3.3-4.6	2.1
Isolated T-wave inversion	3.0	2.7-3.2	10.6

Figure 2



Incremental HRs of CV mortality according to various nonvoltage ECG-LVH patterns. *PFT-V1* indicates increased P-terminal force in V1; QRS dur, increased *QRS duration*; *Strain*, left ventricular strain; *T inversion*, isolated T-wave inversion; *LAD*, left axis deviation.

irrespective of the criteria used. However, the increased risk of CV mortality observed in voltage-only criteria has not been consistently demonstrated in the literature. For example, Rautaharju et al[19] compared the relative risks of 4 ECG criteria, including both voltage-only criteria (Sokolow-Lyon and Cornell voltage) and criteria incorporating repolarization abnormalities (Minnesota code 3.1 to 3.3 plus 5.1 to 5.3 and the Rautaharju LV mass index regression equation). When adjusted for age, they found that LVH by the Sokolow-Lyon criterion was an insignificant predictor of CV mortality. Larsen et al[6] studied the relative prognostic values of different combinations of Minnesota code pertaining to LVH. Specifically, they compared codes that identified LVH by voltage only with codes incorporating voltage and various repolarization changes, including ST depression, T inversions, and left ventricular strain pattern. After adjustment for clinical covariates, including age, blood pressure, heart rate, BMI, cholesterol levels, physical exercise, history of smoking, diabetes, alcohol, and family history of ischemic heart disease, voltage-only LVH was the only pattern of LVH that was not found to be significantly associated with CV mortality. Similarly, the Framingham study investigators found that the excess CV risk associated with voltage-only LVH was virtually eliminated when adjustment was made for coexistent hypertension.[23] It therefore appears that not all LVH identified by voltage-only criteria are predictive of CV mortality when certain risk factors are taken into consideration.

In contrast to voltage-only LVH, LVH defined by a combination of voltage and repolarization abnormalities has been consistently shown to predict CV mortality irrespective of adjustment for clinical covariates, suggesting stronger risk associations with the repolarization-inclusive criteria.[6] The criteria incorporating repolarization abnormalities examined in our study include the Framingham, Perugia, Romhilt-Estes scores, Rautaharju, Wolf, and Casale-Devereux regression equations, all of which demonstrated significantly higher average adjusted HRs, ranging from 2.6 to 3.7 when compared with the range of 1.4 to 2.0 observed with most of the voltage-only criteria. The Cornell criterion was the only voltage-only criteria in our study that conferred a moderately high risk for CV mortality. This association was not observed by Verdecchia et al,[24] who reported a lower adjusted HR for CV mortality for the Cornell criterion when compared with criteria incorporating strain patterns (Romhilt-Estes, Framingham, and Perugia scores).[24] It is not clear why the Cornell voltage criterion outperformed other voltage criteria for risk prediction in our cohort of patients.

Left ventricular hypertrophy identified by the 2 voltage × QRS duration product criteria in our study, the Cornell product, and the 12-lead product criteria were also stronger predictors of CV mortality compared with voltage-only criteria.

From a pathophysiologic standpoint, the high prevalence of voltage-only LVH and its associated lower CV mortality risk suggests that voltage-only LVH is nonspecific for pathological LVH. Larsen et al[6] postulated that voltage-only LVH in younger subjects is associated with good prognosis and therefore represents good physical fitness. Moreover, the elimination of excess risk associated with this pattern of LVH after adjustment for blood pressure led to a conclusion by the Framingham study investigators that voltage-only LVH in hypertensive individuals reflects chiefly the severity and duration of the associated hypertension, and therefore signifies ventricular muscle hypertrophy without myocardial damage.[3]

Left ventricular hypertrophy defined by the presence of more than one ECG pattern, on the other hand, was less prevalent and conferred higher risks of CV death independent of coexisting clinical factors. In our study, the presence of left ventricular strain pattern and increased P-terminal force were particularly ominous findings among patients with any ECG evidence of LVH.

On a pathological level, these ECG changes may be partially explained by the development of myocardial fibrosis, a feared consequence of LV remodeling after longstanding afterload strain. There is some evidence to suggests that myocardial fibrosis may impair microvascular coronary reserve, leading to ischemia.[25] For example, Pringle et al[26] have shown that patients with left ventricular strain experienced more episodes of exercise-induced ECG abnormalities and more reversible thallium perfusion abnormalities. In addition, a negative P-terminal force of greater than 0.04 mV × ms in lead V1, the most sensitive index for left atrial enlargement, has been found to correlate with impaired LV diastolic function on echocardiogram.[27] Recke et al[28] have also shown that the negative P-terminal force in V1 is greater in patients with left ventricular systolic dysfunction on echocardiogram.

Study limitations

The findings from our male cohort may not generalize to women. Few studies have specifically addressed the differential prognostic value of LVH in men and women. In their prospective follow-up of 436 African American patients, Liao et al[29] found a significantly higher relative risk of cardiac deaths among women with echocardiographic LVH compared to men. In contrast, the Framingham study found that both ECG-LVH and echocardiographic LVH were associated with comparable HRs for all-cause and CV mortality in men and women.[1,30]

Other clinical factors such as concurrent heart disease and traditional risk factors for CV disease, which were not accounted for in the present study, might also potentially attenuate the effect of ECG-LVH on CV mortality. Finally, the ECGs in our study cohort represent a broad outpatient sample, but the specific reasons why the ECGs were obtained are not available. This limitation may actually be a strength when evaluating scores that are applied to a general population. We do not have results of diagnostic testing such as echocardiogram or cardiac catheterization and are therefore unable to evaluate prognostication for such events as myocardial infarction, heart failure, and coronary heart disease. However, using test results as surrogate end points would bias our results because tests are usually performed for specific clinical indications.

Clinical implications

In summary, we found that among the 17 commonly used ECG criteria for LVH, voltage-only criteria carried lower HRs for CV mortality compared with composite criteria. In addition, ECG-LVH criteria incorporating left ventricular strain pattern, increased negative P-terminal force, and T wave inversions are most strongly predictive of CV mortality.

Because of their relative simplicity, voltage-only criteria are frequently used by clinicians to identify LVH on the ECG. However, LVH identified by these criteria are associated with a relatively low risk of CV mortality. Reliance on these criteria alone may overlook the presence of more ominous ECG patterns. The use of composite criteria, on the other hand, is impractical because of the cumbersome calculations involved. The use of computer interpretation algorithms that incorporate composite ECG diagnostic criteria may be useful in identifying patients with ECG-LVH who are at higher risk for CV mortality and who may benefit from more aggressive therapy. For example, ACE inhibitors and angiotensin receptor blockers have been shown to be superior to other classes of agents in regressing LVH and reducing CV mortality.[31-33] Physicians may consider use of these agents or multiple agents when treating patients with ECG-LVH at higher risk for CV mortality. Furthermore, more frequent blood pressure (BP) surveillance, including ambulatory BP techniques, may be considered in these patients. Further studies are needed to evaluate the effectiveness of such strategies.

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