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ORIGINAL RESEARCH

Implication of Different ECG Left Ventricular Hypertrophy in Patients Undergoing Transcatheter Aortic Valve Replacement

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BACKGROUND: Various ECG criteria for left ventricular hypertrophy (LVH) have been proposed, but their association with clinical outcomes in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement is unknown. We investigated the prevalence of ECG LVH according to different criteria and its prognostic impact on clinical outcomes after transcatheter aortic valve replacement.

METHODS AND RESULTS: In this prospective observational cohort, we evaluated 700 patients who underwent transcatheter aortic valve replacement between March 2010 and December 2019. Baseline preprocedural LVH was defined by 3 ECG criteria—Sokolow-Lyon, Romhilt-Estes, and Cornell voltage criteria. The primary outcome was major adverse cardiac or cerebrovascular event (MACCE; composite of death, myocardial infarction, stroke, or rehospitalization from cardiovascular cause); the key secondary outcome was all-cause and cardiovascular mortality. Among 596 eligible patients, the prevalence of LVH was determined as 56.3% by Sokolow-Lyon, 31.1% by Romhilt-Estes, and 48.1% by Cornell criteria. Regardless of the criteria, patients with ECG LVH had more severe aortic stenosis hemodynamics and higher left ventricular mass index. After multivariate adjustment, the presence of LVH by the Cornell criteria was significantly associated with lower risks of MACCE (adjusted hazard ratio [HR], 0.68; 95% CI, 0.51–0.91; *P*=0.009), all-cause mortality (adjusted HR, 0.55; 95% CI, 0.34–0.90 [*P*=0.017]), and cardiovascular mortality (adjusted HR, 0.40; 95% CI, 0.20–0.79 [*P*=0.008]). However, this association was absent with the Sokolow-Lyon and Romhilt-Estes criteria.

CONCLUSIONS: ECG LVH by Cornell criteria only was significantly associated with lower risks of MACCE and all-cause or cardiovascular mortality.

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Key Words: aortic valve stenosis ■ left ventricular hypertrophy ■ transcatheter aortic valve replacement

Aortic stenosis (AS) is one of the most common valvular heart diseases in the elderly population, and its prevalence is rapidly increasing as a result of population aging.[1] Typically, AS progressively increases left ventricular (LV) afterload, which leads to the development of LV hypertrophy (LVH) to reduce wall stress and maintain cardiac function.[2] This LVH process can be compensatory in the early stages; however, progressive LVH can become maladaptive and myocardium can progress to cell death and fibrosis, thus leading to symptom development, systolic dysfunction, and cardiac remodeling, which are associated with increased morbidity and mortality.[3,4]

LVH can be diagnosed by ECG or anatomical methods (ie, echocardiography). Although anatomic LVH diagnosed by echocardiography is currently the gold

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CLINICAL PERSPECTIVE

What Is New?

- ECG left ventricular hypertrophy (LVH) has been proposed as a risk factor for increased risks of cardiovascular events or mortality after transcatheter aortic valve replacement; however, the prognostic impact of ECG LVH by different criteria is undetermined.
- In this prospective cohort of patients treated with transcatheter aortic valve replacement for severe aortic stenosis, the prevalence of baseline ECG LVH and their prognostic impact varied greatly according to different ECG criteria.
- The presence of ECG LVH according to the Cornell voltage criteria (but not those according to the Sokolow-Lyon criteria or Romhilt-Estes score) was significantly associated with lower risks of major adverse cardiac or cerebrovascular events, all-cause mortality, and cardiovascular mortality.

What Are the Clinical Implications?

- Among patients with severe aortic stenosis undergoing transcatheter aortic valve replacement, we found that the prevalence of baseline ECG LVH and their prognostic impact varied greatly according to the different ECG criteria used.
- Further investigations are warranted to understand the underlying mechanisms and define optimal risk stratification in patients with discrepancies between electrical LVH (on ECG) and anatomic LVH (on echocardiogram).

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AV	aortic valve
EuroSCORE	European System for Cardiac Operative Risk Evaluation
MACCE	major adverse cardiac or cerebrovascular event
PARTNER	Placement of Aortic Transcatheter Valves
STS	Society of Thoracic Surgeons
TAVR	transcatheter aortic valve replacement
TVT	Transcatheter Valve Therapy
VARC-2	Valve Academic Research Consortium-2

standard,[5] ECG LVH and echocardiographic LVH are regarded to be clinically distinct entities.[6] It has also been recognized that abnormal ECG LVH changes can precede pathological echocardiographic LVH, and that electrical alterations provide additional clinical information to the imaging of the cardiac structure and function.[7]

Several studies of patients with AS undergoing surgical aortic valve (AV) replacement have shown conflicting results in terms of the association between the presence of LVH and clinical outcomes.[8–10] Also, recent studies showed mixed findings regarding the association of LVH and clinical outcomes in patients with severe AS undergoing transcatheter AV replacement (TAVR).[11–14] Several ECG criteria have been proposed to diagnose the presence of LVH,[15,16] but the prevalence of baseline LVH according to the ECG criteria and their prognostic impact on clinical outcomes and mortality after TAVR are unknown. In the present study, we thus evaluated the associations between the presence of ECG LVH as assessed by the most commonly used 3 LVH criteria (the Sokolow-Lyon criteria, the Romhilt-Estes point score, and the Cornell voltage criteria) and clinical outcomes in patients undergoing TAVR for severe AS.

METHODS

Data Sources

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population and TAVR Procedures

Patients with severe AS who had undergone successful TAVR between March 2010 and December 2019 were identified from the ASAN-TAVR registry, which is a prospective registry that includes consecutive patients with symptomatic severe AS who undergo TAVR at Asan Medical Center (Seoul, Republic of Korea).[17–19] The Society of Thoracic Surgeons (STS) score and the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) were calculated to assess the traditional surgical risk. For the current analyses, we excluded patients with unanalyzable baseline ECG (eg, complete left or right bundle branch block or ventricular paced rhythm) for a reliable assessment of LVH.

TAVR was performed under general anesthesia or monitored anesthesia care using standard methods. The transfemoral route was preferred, but other approaches (eg, apical or direct aortic routes) were considered if the transfemoral route was not feasible. The type (balloon-expandable [Sapien XT and the Sapien 3; Edwards Lifesciences] or self-expandable devices [CoreValve, Evolut R and Evolut Pro; Medtronic or Lotus; Boston Scientific]) and size of devices were selected based on assessment using 3-dimensional, multidetector computed tomography scans and

transesophageal echocardiography. After TAVR, dual antiplatelet therapy with aspirin and clopidogrel or oral anticoagulants (eg, warfarin or direct oral anticoagulants) if clinically indicated were prescribed for at least 6 months. This study was approved by the institutional review board of Asan Medical Center, and all patients provided written informed consent before participation.

ECG Analysis Measurement

Baseline ECG data were obtained for all patients before TAVR during index hospitalization. ECGs were digitally recorded and stored in the MUSE Cardiology Information System (General Electric Company). The baseline ECGs of all patients were independently reviewed by 2 experienced cardiologists (Y.Y. and D.W.P.) who were blinded to the patient's echocardiographic data and outcomes, and analyzed using Cardio Calipers (On-Screen Electrocardiogram Measurement; Iconico.com). In case of disagreement, consensus was established between the 2 reviewers, or a third experienced cardiologist was consulted.

Baseline ECG LVH was defined by 3 different LVH criteria: Sokolow-Lyon criteria,[20] Romhilt-Estes score,[21] and Cornell voltage criteria.[22] In Sokolow-Lyon criteria, ECG LVH was regarded to be present if the sum of the S wave in V1 and R wave in V5/6 was >3.5 mV.[20] Romhilt-Estes score was calculated from 6 ECG features with specific points for each feature as follows: R or S wave in any limb lead of ≥2 mV, S wave in V1 or V2 of ≥3 mV, or R wave in V5 or V6 of ≥3 mV (3 points); P-terminal force (terminal negativity of P wave in V1) of ≥0.10 mV in depth and ≥0.04 ms in duration (3 points); LV strain defined as ST segment and T wave in opposite directions to QRS in V5 or V6, without digitalis (3 points); left-axis deviation defined as QRS axis ≤–30° (2 points); QRS duration of ≥0.09 ms (1 point); and intrinsicoid deflection in V5 or V6 of ≥0.05 ms (1 point). LVH was regarded to be present if the ECG score reached a total of 5 points in Romhilt-Estes score criteria.[21] In the Cornell voltage criteria, ECG was defined as an LVH if the R wave in a VL+S wave in V3 was >2.8 mV in men and >2.0 mV in women.[22]

Echocardiographic Measurement

Transthoracic echocardiography was routinely performed before TAVR, immediately after the procedure (1 day), after 30 days, 6 months, and 1 year after TAVR, and annually thereafter. Echocardiography was performed using standard views, and the chamber and valvular quantitative parameters were reported using standardized definitions.[23] LV internal dimension in diastole, LV posterior wall thickness, and interventricular septal thickness in diastole were measured from the parasternal long-axis view as recommended by the American Society of Echocardiography. Using these values, LV mass was calculated with the linear method cube formula and indexed to body surface area to calculate the LV mass index.[24] The LV ejection fraction was measured using the biplane Simpson volumetric method combining apical 4- and 2-chamber views.[25] Echocardiographic parameters included standard measures to assess the severity of AS (peak velocity, valve area, and pressure gradient) and concomitant valvular heart disease. The overall quality of the data on the echocardiographic core laboratory at Asan Medical Center was stated in previous studies.[26,27]

Study Outcomes and Follow-up

The primary outcome of this study was the major adverse cardiac or cerebrovascular event (MACCE), which was defined as a composite of death from any cause, myocardial infarction (MI), stroke, or rehospitalization from cardiovascular cause. The secondary outcomes were the individual components of the primary composite outcome: death (all-cause, cardiovascular or noncardiovascular), MI, stroke, and rehospitalization. All study outcomes were defined according to Valve Academic Research Consortium-2 (VARC-2) definitions.[28] Rehospitalization was defined as any hospitalization related to the procedure, valve, or heart failure. All events were independently reviewed and adjudicated by an independent group of clinicians blinded to the study purpose.

Clinical follow-up after TAVR procedure was routinely performed via clinical visit and/or telephone interview at 1, 6, and 12 months, and every 6 months thereafter. Referring cardiologists, general practitioners, and patients were contacted as necessary to obtain further information. Data pertaining to the patients' clinical status and occurrence of any clinical events were collected at each follow-up. All clinical, laboratory, imaging, procedural, outcomes, and other relevant data were prospectively collected using a dedicated electronic case report form by specialized personnel at each participating center.[17–19] All databases are maintained at the Clinical Research Center of Asan Medical Center.

Statistical Analysis

Patients were categorized into 2 groups based on the presence of ECG LVH by 3 different criteria (Sokolow-Lyon, Romhilt-Estes, and Cornell voltage criteria). The baseline characteristics of the study population, including demographics, risk factors, comorbidities, clinical presentation, cardiac status, and anatomic/procedural features were compared according to the presence of ECG LVH by different criteria. Continuous variables are reported as mean±SD and were compared using Student *t* test or Wilcoxon rank-sum tests. Categorical variables are expressed as counts and percentages

and were compared using chi-square or Fisher exact test as appropriate.

Independent predictors of ECG LVH according to different criteria were determined in a backward stepwise multivariable logistic regression model, and included age, sex, and clinical, anatomic, and hemodynamic variables. Cumulative event rates were estimated using the Kaplan–Meier method, and log-rank test was used for between-group comparisons. The associations between clinical outcomes and ECG LVH according to different criteria were investigated with crude and multivariable Cox proportional hazards models. The entire follow-up was used to analyze the time-to-event outcomes, and patients were censored at the time of clinical events or last available follow-up. To determine the independent association between the primary composite outcome of MACCE and ECG LVH according to different criteria, multivariable Cox proportional hazard regression model was generated using backward elimination methods with age (continuous), sex (male or female), and clinically relevant variables with *P* values <0.20 in univariate analysis: age and sex were included in the final model regardless of the statistical significance. The proportional hazards assumption was confirmed by examination of log (-log [survival]) curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found. The following variables as risk factors for mortality after TAVR were assessed in univariate analysis: baseline creatinine level, hemodialysis, New York Heart Association class, severe chronic lung disease, nonfemoral access, severe baseline LVH, and STS scores.[14,29–31] The presence of atrial fibrillation was also included as a risk factor for stroke after TAVR.[32] In these models, ECG LVH by 3 different criteria was separately included. Missing values were replaced using the Markov chain Monte Carlo method.

All reported *P* values are 2-sided and those <0.05 were considered statistically significant. No adjustments were made for multiple comparisons. All statistical analyses were performed using SPSS Statistics for Windows version 22.0 (IBM) and R software version 3.4.4. (R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics of Patients

Between March 2010 and December 2019, 700 consecutive patients with severe symptomatic AS who underwent successful TAVR were enrolled in the ASAN-TAVR registry. Among them, 105 patients were excluded for ventricular-paced rhythm (n=12), right bundle branch block (n=75), and left bundle branch block (n=18). Thus, a total of 595 patients were included in the final analysis. The mean age of the patients was 79.7±5.4 years, and 284 (47.7%) patients were men. The mean logistic EuroSCORE and STS score were 13.1±10.3 and 4.0±3.0, respectively. Most (96.1%) patients underwent TAVR by the transfemoral approach, and 77% were treated with balloon-expandable TAVR valves.

The prevalence of ECG LVH was 56.3% by Sokolow-Lyon criteria, 31.1% by Romhilt-Estes score, and 48.1% by Cornell voltage criteria. The baseline demographic and clinical characteristics of patients according to the presence of ECG LVH by different criteria are summarized in Table 1. Compared with patients without ECG LVH, those with ECG LVH by Sokolow-Lyon criteria had a lower mean body mass index and lower prevalence of atrial fibrillation and diabetes; those with ECG LVH by Romhilt-Estes criteria had a higher prevalence of men, lower mean body mass index, lower prevalence of atrial fibrillation, and a higher prevalence of chronic lung disease; those with ECG LVH by Cornell criteria had a higher prevalence of women, higher values of logistic EuroSCORE and New York Heart Association class score, and a higher prevalence of dialysis.

The procedural and baseline echocardiographic parameters according to the presence of ECG LVH by different criteria are shown in Table 2. Regardless of the criteria, patients designated to have ECG LVH had more severe AS hemodynamics (ie, smaller AV area, higher pressure gradient), higher LV mass index, and lower LV ejection fraction.

Independent Predictors of ECG LVH by Different Criteria

The results of univariate and multivariate analyses for identifying the predictors for the presence of LVH according to each criterion are shown in Tables S1 through S3. The independent predictors of ECG LVH according to the 3 criteria are summarized in Table S4. Multivariate analysis showed that higher AV peak V_{max} and higher LV mass index were independent predictors for ECG LVH by all 3 criteria.

Clinical Outcomes

The median duration of clinical follow-up was 421 days (interquartile range, 239–1113). Up to a follow-up of 3 years, there were 59 (15.7%) deaths (35 cardiac and 24 noncardiac), 25 (5.5%) MIs, 35 (6.9%) strokes, and 152 (35.1%) rehospitalizations. Overall, 203 (44.9%) patients experienced at least 1 of the composite outcomes of MACCE.

The crude and adjusted risks for primary and secondary outcomes according to the presence of ECG LVH by different criteria are summarized in Table 3. In unadjusted analysis, the observed incidences of the primary composite outcome of MACCE were significantly lower in patients with ECG LVH than in those

Table 1. Baseline Characteristics According to the Presence of LVH by 3 ECG Criteria

	Sokolow-Lyon			Romhilt-Estes score			Cornell		
	No ECG LVH (n=260)	ECG LVH (n=335)	*P* value	No ECG LVH (n=410)	ECG LVH (n=185)	*P* value	No ECG LVH (n=309)	ECG LVH (n=286)	*P* value
Demographics									
Men	119 (45.8)	165 (49.3)	0.446	180 (43.9)	104 (56.2)	0.007	180 (58.3)	104 (36.4)	<0.001
Age, y	80.0±5.5	79.5±5.3	0.323	79.9±5.4	79.3±5.4	0.231	79.7±5.6	79.7±5.2	0.850
Body mass index, kg/m^2	24.3±3.6	23.7±3.2	0.032	24.3±3.4	23.2±3.2	<0.001	24.1±3.4	23.9±3.4	0.586
Comorbidities or risk factors									
Logistic EuroSCORE	13.5±10.8	12.7±9.9	0.322	12.9±10.2	13.4±10.6	0.564	11.8±9.6	14.4±10.9	0.003
STS score	3.8±2.6	4.1±3.2	0.302	4.1±3.2	3.7±2.5	0.134	4.0±2.8	3.9±3.1	0.708
NYHA class			0.927			0.527			0.043
1	32 (12.3)	37 (11.0)		46 (11.2)	23 (12.4)		44 (14.2)	25 (8.7)	
2	140 (53.9)	180 (53.7)		228 (55.6)	92 (49.7)		172 (55.7)	148 (51.8)	
3	75 (28.9)	103 (30.8)		116 (28.3)	62 (33.5)		81 (26.2)	97 (33.9)	
4	13 (5.0)	15 (4.5)		20 (4.9)	8 (4.3)		12 (3.9)	16 (5.6)	
Smoking			0.323			0.296			0.01
Never	196 (75.4)	234 (69.9)		304 (74.2)	126 (68.1)		207 (67.0)	223 (78.0)	
Current	21 (8.1)	32 (9.6)		35 (8.5)	18 (9.7)		31 (10.0)	22 (7.7)	
Previous	43 (16.5)	69 (20.6)		71 (17.3)	41 (22.2)		71 (23.0)	41 (14.3)	
Atrial fibrillation/flutter	43 (16.5)	26 (7.8)	0.001	58 (14.2)	11 (6.0)	0.006	41 (13.3)	28 (9.8)	0.232
Hypertension	221 (85.0)	295 (88.1)	0.332	356 (86.8)	160 (86.5)	>0.999	267 (86.4)	249 (87.1)	0.909
Diabetes	140 (53.9)	146 (43.6)	0.016	195 (47.6)	91 (49.2)	0.78	150 (48.5)	136 (47.6)	0.873
Hyperlipidemia	188 (72.3)	260 (77.61)	0.164	308 (75.1)	140 (75.7)	0.966	231 (74.8)	217 (75.9)	0.826
Peripheral artery disease	4 (1.5)	13 (3.9)	0.146	8 (2.0)	9 (4.9)	0.087	8 (2.6)	9 (3.2)	0.871
Chronic kidney disease	187 (71.9)	235 (70.2)	0.703	286 (69.8)	136 (73.5)	0.403	216 (69.9)	206 (72.0)	0.631
ESRD on dialysis	8 (3.1)	12 (3.6)	0.913	12 (2.9)	8 (4.3)	0.529	0 (0.0)	20 (7.0)	<0.001
Chronic liver disease	11 (4.2)	16 (4.8)	0.906	17 (4.2)	10 (5.4)	0.638	13 (4.2)	14 (4.9)	0.837
Chronic lung disease	36 (13.9)	45 (13.4)	0.98	47 (11.5)	34 (18.4)	0.032	46 (14.9)	35 (12.2)	0.411
Previous heart failure	47 (18.1)	52 (15.5)	0.472	60 (14.6)	39 (21.1)	0.066	47 (15.2)	52 (18.2)	0.389
Previous MI	11 (4.2)	16 (4.8)	0.906	18 (4.4)	9 (4.9)	0.964	18 (5.8)	9 (3.2)	0.17
History of PCI	72 (27.7)	97 (29.0)	0.805	122 (29.8)	47 (25.4)	0.322	94 (30.4)	75 (26.2)	0.297
History of stroke	30 (11.5)	41 (12.2)	0.893	51 (12.4)	20 (10.8)	0.667	40 (12.9)	31 (10.8)	0.506
History of CABG	15 (5.8)	12 (3.6)	0.283	19 (4.6)	8 (4.3)	>0.999	12 (3.9)	15 (5.2)	0.549
History of SAVR	8 (3.1)	6 (1.8)	0.451	11 (2.7)	3 (1.6)	0.618	5 (1.6)	9 (3.2)	0.338
Laboratory data									
Hemoglobin	11.7±1.9	11.7±1.7	0.645	11.6±1.9	11.8±1.8	0.443	11.7±1.8	11.6±1.8	0.535
Creatinine	1.2±1.1	1.2±1.3	0.853	1.18±1.2	1.22±1.2	0.727	1.0±0.4	1.4±1.6	0.001

Data are presented as mean±SD or number (percentage). CABG indicates coronary artery bypass graft; ESRD, end-stage renal disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; and STS, Society of Thoracic Surgery.

without ECG LVH according to Sokolow-Lyon criteria and Cornell criteria, but not according to Romhilt-Estes score (Figure 1). A similar pattern was observed for all-cause mortality. The observed incidences of all-cause and cardiovascular mortality were significantly lower in patients with ECG LVH by Cornell criteria, but not by Sokolow-Lyon criteria or Romhilt-Estes score (Figure 2). After multivariable adjustment, only the presence of LVH by Cornell criteria was significantly associated with a lower risk of MACCE (hazard ratio [HR], 0.68; 95% CI, 0.51–0.91 [*P*=0.009]) (Figure 3). Also, only the presence of LVH by Cornell criteria was significantly associated with an adjusted lower risk of all-cause mortality (adjusted HR, 0.55; 95% CI, 0.34–0.90 [*P*=0.017]) and cardiovascular mortality (adjusted HR, 0.40; 95% CI, 0.20–0.79 [*P*=0.008]). This significant association was absent with other criteria of Sokolow-Lyon criteria or Romhilt-Estes score.

Predictors for the primary end point of MACCE, all-cause mortality, and cardiovascular death are

Table 2. Baseline Procedural and Echocardiographic Data According to Different ECG Criteria of LVH

	Sokolow-Lyon			Romhilt-Estes score			Cornell		
	No ECG LVH (n=260)	ECG LVH (n=335)	*P* value	No ECG LVH LVH (n=410)	ECG LVH (n=185)	*P* value	No ECG LVH LVH (n=309)	ECG LVH (n=286)	*P* value
Procedure-related factors									
Type of valve deployment			0.935			0.543			0.078
Balloon-expandable	202 (77.7)	256 (7.6)		312 (76.1)	146 (79.4)		247 (80.2)	211 (73.8)	
Self-expandable	57 (21.9)	77 (23.1)		97 (23.7)	37 (20.1)		61 (19.8)	73 (25.5)	
Others	1 (0.4)	1 (0.3)		1 (0.2)	1 (0.5)		0 (0.0)	2 (0.7)	
Access site			0.138			0.832			0.488
Transfemoral	252 (96.9)	320 (95.5)		395 (96.3)	177 (95.7)		297 (96.1)	275 (96.2)	
Transapical	5 (1.9)	14 (4.2)		12 (2.9)	7 (3.8)		11 (3.6)	8 (2.8)	
Transaortic	3 (1.2)	1 (0.3)		3 (0.7)	1 (0.5)		1 (0.3)	3 (1.1)	
Type of anesthesia			0.043			0.144			0.01
General	80 (30.8)	131 (39.1)		137 (33.4)	74 (40.0)		94 (30.4)	117 (40.9)	
Monitored care	180 (69.2)	204 (60.9)		273 (66.6)	111 (60.0)		215 (69.6)	169 (59.1)	
Baseline echocardiographic findings									
AV V_{max} , m/sec	4.6±0.7	5.1±0.8	<0.001	4.8±0.7	5.1±0.9	<0.001	4.7±0.7	5.1±0.9	<0.001
Peak PG, mm Hg	87.0±26.0	105.5±34.4	<0.001	92.4±28.4	108.4±37.4	<0.001	88.8±24.5	106.7±36.8	<0.001
Mean PG mm Hg	51.8±17.7	64.0±22.4	<0.001	55.3±19.2	66.0±23.7	<0.001	52.9±16.7	64.8±23.9	<0.001
AV area, cm^2	0.64±0.16	0.59±0.15	<0.001	0.64±0.2	0.56±0.1	<0.001	0.65±0.2	0.57±0.2	<0.001
Significant AR*	47 (18.1)	75 (22.4)	0.234	83 (20.2)	39 (21.1)	0.901	60 (19.4)	62 (21.7)	0.561
Significant MR*	31 (11.9)	49 (14.6)	0.402	50 (12.2)	30 (16.2)	0.23	39 (12.6)	41 (14.3)	0.623
LVEDD, mm	47.2±6.6	49.3±6.5	<0.001	47.3±6.3	50.8±6.9	<0.001	47.6±6.7	49.3±6.5	0.002
LVPWT, mm	10.8±1.6	11.4±1.4	0.011	10.9±1.4	11.6±1.6	0.001	10.9±1.3	11.4±1.6	0.019
LV mass, g	189.9±52.1	225.7±55.5	<0.001	195.8±51.9	241.6±54.8	<0.001	194.8±53.5	226.5±55.9	<0.001
LV mass index	119.4±32.3	143.2±34.6	<0.001	123.6±30.9	153.2±37.0	<0.001	121.3±32.5	145.2±34.7	<0.001
Ejection ECG	59.7±10.3	58.0±10.7	0.051	60.6±8.7	54.6±13.0	<0.001	60.3±9.6	57.2±11.3	<0.001

Data are presented as mean±SD or number (percentage). AR indicates aortic regurgitation; AV, aortic valve; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVH, left ventricular hypertrophy; LVPWT, left ventricular posterior wall thickness MR, mitral regurgitation; PG, pressure gradient.

*"Significant" refers to grade 3 (moderate) or grade 4 (severe) regurgitation.

summarized in Table 4, Table S5, and Table S6, respectively. Only the presence or absence of LVH by Cornell criteria (but not by Sokolow-Lyon criteria or Romhilt-Estes score) was found as an independent correlate for MACCE, all-cause mortality, and cardiovascular mortality.

DISCUSSION

In this study, we used a prospective, real-world cohort of consecutive patients with severe AS undergoing TAVR to evaluate the association between clinical outcomes after TAVR and the presence of baseline ECG LVH as determined by 3 of the most commonly used criteria—Sokolow-Lyon criteria, Romhilt-Estes score, and Cornell voltage criteria. The main findings were as follows: (1) regardless of the criteria used, the presence of ECG LVH was associated with smaller AV area, higher AV gradient, and higher LV mass index; (2) higher AV peak V_{max} and higher LV mass index were identified as common independent predictors for ECG LVH regardless of the criteria; and (3) after adjusting for clinically relevant covariates, only the presence of LVH by the Cornell criteria was significantly associated with lower risks of the primary composite of MACCE and mortality (mainly driven by cardiovascular death). Such significant association was not observed with the presence of LVH by Sokolow Lyon criteria and Romhilt-Estes score.

ECG LVH has been widely studied and known as a traditional risk factor. Prior imaging studies demonstrated a significant correlation between various ECG criteria and LV mass index by cardiac magnetic resonance.[33] Although a previous small study showed poor correlation between ECG LVH by 3 criteria and LV mass by echocardiography in patients who underwent TAVR,[34] our study showed that ECG LVH was independently associated with a higher LV mass index, which was consistently observed across 3 different ECG criteria. ECG LVH is not only associated with an

Table 3. Clinical Outcomes at 3 Years in Patients With or Without ECG-LVH*

			Unadjusted analysis			Adjusted analysis		
	No ECG LVH	ECG LVH	HR	95% CI	*P* value	HR*	95% CI	*P* value
Sokolow-Lyon criteria	**n=260**	**n=335**						
Primary outcome								
MACCE*	99 (51.3)	104 (40.3)	0.76	0.58–0.99	0.042	0.87	0.66–1.15	0.331
Secondary outcome								
All death	35 (22.7)	24 (10.9)	0.67	0.43–1.05	0.080	0.77	0.49–1.22	0.268
Cardiovascular death	19 (13.7)	16 (7.2)	0.65	0.36–1.16	0.141	0.59	0.32–1.08	0.088
Noncardiovascular death	16 (10.4)	8 (4.0)	0.71	0.35–1.42	0.335	0.69	0.34–1.42	0.317
MI	16 (9.0)	9 (3.2)	0.40	0.18–0.89	0.026	0.40	0.18–0.91	0.029
Stroke	15 (7.5)	20 (6.6)	1.06	0.54–2.05	0.869	1.17	0.60–2.29	0.641
Rehospitalization	86 (39.2)	66 (31.1)	0.68	0.50–0.92	0.013	0.75	0.54–1.05	0.091
Romhilt-Estes score	**n=410**	**n=185**						
Primary outcome								
MACCE*	143 (48.2)	60 (38.3)	0.93	0.70–1.24	0.631	0.95	0.70–1.28	0.719
Secondary outcome								
All death	39 (16.4)	20 (14.4)	1.37	0.87–2.17	0.177	1.26	0.78–2.04	0.348
Cardiovascular death	21 (9.2)	14 (10.9)	1.56	0.87–2.81	0.137	1.20	0.63–2.28	0.573
Noncardiovasculardeath	18 (7.9)	6 (4.0)	1.13	0.54–2.35	0.747	0.99	0.45–2.21	0.988
MI	17 (6.0)	8 (4.7)	0.96	0.42–2.21	0.927	0.87	0.37–2.02	0.745
Stroke	23 (6.9)	12 (7.0)	1.25	0.63–2.47	0.522	1.22	0.61–2.44	0.567
Rehospitalization	109 (37.8)	43 (29.4)	0.88	0.63–1.22	0.437	0.93	0.66–1.33	0.705
Cornell criteria	**n=309**	**n=286**						
Primary outcome								
MACCE*	117 (50.7)	86 (39.3)	0.74	0.56–0.96	0.024	0.68	0.51–0.91	0.009
Secondary outcome								
All death	39 (21.1)	20 (10.6)	0.54	0.34–0.86	0.010	0.55	0.34–0.90	0.017
Cardiovascular death	21 (11.5)	14 (8.0)	0.57	0.31–1.04	0.065	0.40	0.20–0.79	0.008
Noncardiovascular death	18 (10.8)	6 (2.9)	0.51	0.24–1.06	0.071	0.42	0.18–0.99	0.047
MI	15 (7.1)	10 (4.1)	0.64	0.29–1.42	0.276	0.67	0.30–1.48	0.320
Stroke	22 (8.7)	13 (5.1)	0.65	0.33–1.27	0.206	0.58	0.29–1.14	0.115
Rehospitalization	86 (39.2)	66 (31.1)	0.82	0.61–1.12	0.209	0.82	0.59–1.13	0.229

LVH indicates left ventricular hypertrophy.
*Cumulative event rates (percentages) were derived from the Kaplan–Meier method and compared by the log-rank test.
†Hazard ratios (HRs) were adjusted for age (continuous), sex (male or female), and statistically significant variables with *P* values <0.20 in univariate analysis.
‡Major adverse cardiac or cerebrovascular event (MACCE) was defined as a composite of death from cardiovascular cause, myocardial infarction (MI), stroke, or rehospitalization from cardiovascular causes.

increase in myocardium mass but also electrogenesis.[35] In addition, because ECG LVH is a marker for both anatomic LVH and electrical conduction delay, ECG LVH can have its own prognostic value independent from anatomic LVH.[6,36] In our study, despite the significant association between ECG LVH and LV mass index, the absence of ECG LVH was identified as an independent predictor for adverse clinical outcomes, whereas LV mass index was not; this suggests that electrical conduction delay may be a more important factor than anatomical LVH for predicting poorer outcomes after TAVR. Especially, among the 3 different ECG criteria, the Cornell voltage criteria may most closely reflect electrical conduction delay and was identified as the only criteria that predicts for MACCE and all-cause or cardiovascular mortality.

There have been conflicting results regarding the association between LVH and clinical outcomes in patients with AS undergoing AV replacement.[8–14] An analysis of the PARTNER (Placement of Aortic Transcatheter Valves) trials and registries showed that compared with patients without LVH, those with severe baseline LVH measured by echocardiographic LV mass index had higher 5-year rates of death and rehospitalization after

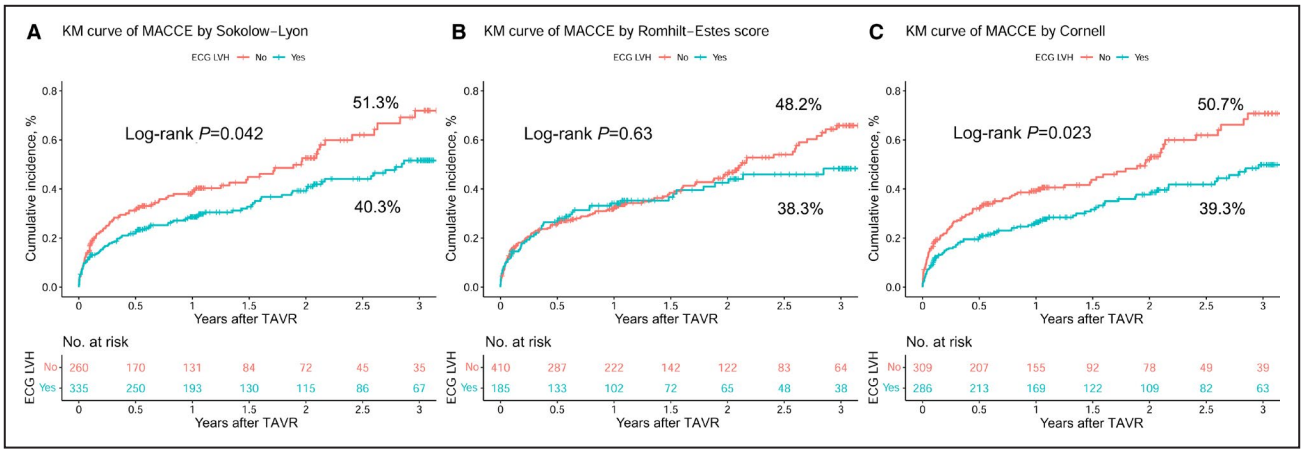

Figure 1. Time-to-event curves for the primary composite outcome according to the presence of ECG left ventricular hypertrophy (LVH) by Sokolow-Lyon criteria (A), Romhilt-Estes score (B), and Cornell criteria (C).
Kaplan–Meier (KM) estimates of the rate of the primary composite outcome of major adverse cardiac or cerebrovascular events (MACCE), which was a composite of all-cause death, myocardial infarction, stroke, and rehospitalization from cardiovascular causes. TAVR indicates transaortic valvular replacement.

TAVR.[14] In contrast, in the large TVT (Transcatheter Valve Therapy) registry, baseline LVH determined by echocardiographic LV mass index and relative wall thickness was not significantly associated with adverse outcomes at 1 year.[12] Until recently, there have been limited data on the relationship between ECG LVH and outcomes

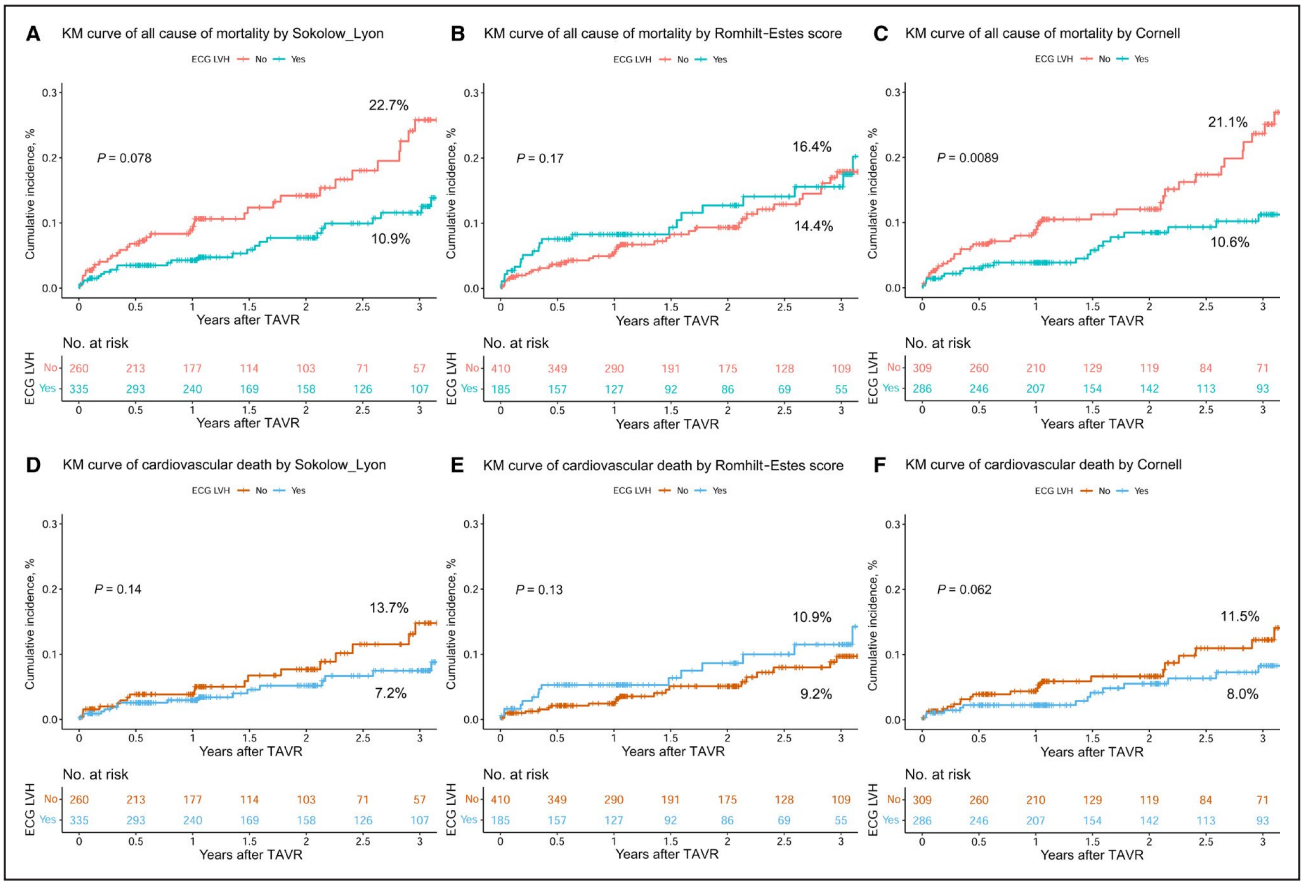

Figure 2. Time-to-event curves for all-cause and cardiovascular death according to the presence of ECG left ventricular hypertrophy (LVH) by Sokolow-Lyon criteria (A and D), Romhilt-Estes score (B and E), and Cornell criteria (C and F).
Kaplan–Meier (KM) estimates of the rates of all-cause death and cardiovascular death. TAVR indicates transaortic valvular replacement.

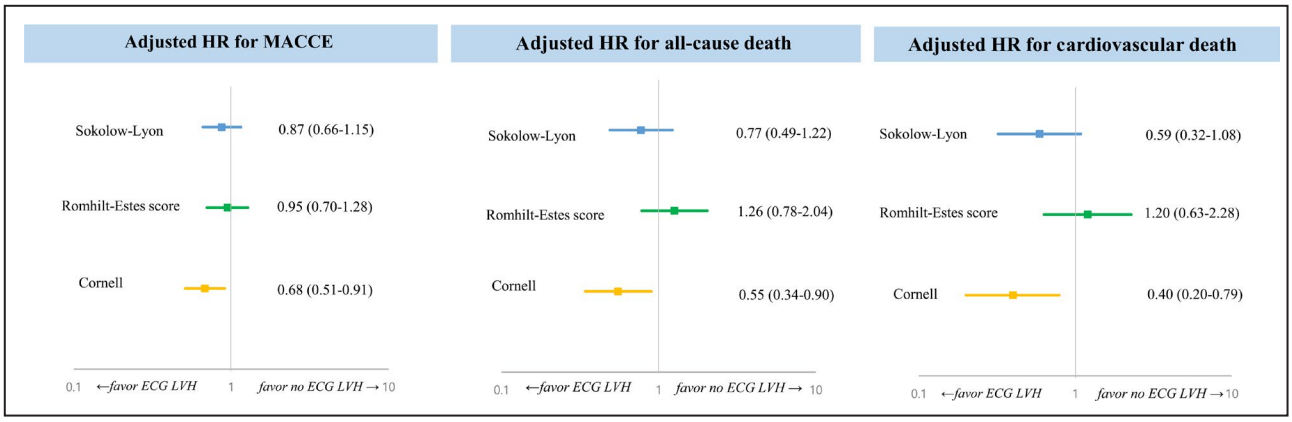

Figure 3. Adjusted hazard ratios for (HRs; A) primary composite outcome, (B) all-cause death, and (C) cardiovascular death according to the presence of ECG left ventricular hypertrophy (LVH) by Sokolow-Lyon criteria, Romhilt-Estes score, and Cornell criteria.

Primary composite outcome of major adverse cardiac or cerebrovascular event (MACCE) was defined as a composite of all-cause, myocardial infarction, stroke, and rehospitalization from cardiovascular causes.

after TAVR. Several observational studies and a meta-analysis showed that the absence of ECG LVH was associated with poor outcomes in patients undergoing TAVR.[11,13,37,38] Similarly, we also found that the presence of ECG LVH had a protective effect on post-TAVR clinical outcomes, which was statistically significant with the Cornell criteria and not with the other 2 criteria.

There might be some explanations for the discrepant findings regarding echocardiographic LVH or ECG LVH and its association with adverse outcomes. First, the high amplitude of voltage in the left ventricle may indicate myocardial viability, which is useful in determining LV recovery or reverse cardiac remodeling after TAVR. Thus, the presence of preprocedural ECG LVH may be a proxy for a greater reverse remodeling after TAVR. Second, the absence of ECG LVH in AS might be attributed to myocardial apoptosis and fibrosis, which are associated with increased morbidity and mortality.[38] Chronic pressure overload in AS causes myocyte hypertrophy and low-grade inflammation, which result in myocyte degeneration and replacement of fibrosis.[39] Low QRS voltage can reflect altered electrical conduction by replacement of fibrosis in the myocardium. Third, there is a possibility of underdiagnosis of cardiac amyloidosis in patients with AS. Cardiac amyloid has been reported in a subset of patients with AS undergoing TAVR, in whom conduction abnormality and low voltage in ECG could be reflective of cardiac amyloidosis.[40] Last, although a large proportion of patients had both electrical LVH on 12-lead ECG and anatomic LVH on echocardiogram, there were subgroups that had isolated electrical LVH or isolated anatomic LVH.[6] Although there is an overlap between these 2 conditions, patients with isolated ECG LVH or echocardiographic LVH should be separated from a clinical standpoint.

Prior studies showed that the absence ECG LVH by Cornell and Sokolow-Lyon criteria was associated with poorer outcomes and increased mortality.[11,13,37,38] In our study, only the Cornell criteria showed a significant association with all-cause and cardiovascular mortality. Although an exact physiological explanation for such discrepancy should be further elucidated, the clinical ECG LVH indices, Cornell criteria and Sokolow-Lyon index, were affected differently by LV mass and by anatomic changes and/ or conduction velocity slowing (Cornell voltage was more affected by conduction velocity than Sokolow-Lyon criteria).[36] Also, among 3 ECG LVH criteria, Cornell index is the only negative predictor for myocardium fibrosis in patients with hypertrophic cardiomyopathy.[41] Considering these characteristics of Cornell criteria, the absence of ECG LVH by Cornell criteria in patients with severe AS may have advanced myocardium fibrosis and altered conduction, which resulted in poor prognosis after TAVR.

Our study has several limitations. First, as our study is an analysis of nonrandomized, observational data, unaccounted confounding variables may have influenced the observed findings. Therefore, our findings should be considered hypothesis generating only. Second, although ECG measurements were performed by 2 experienced cardiologists, the ECG data were not adjudicated by an independent core laboratory. However, our results showed consistency in that the patients determined to have ECG LVH had severe AS hemodynamics and higher LV mass index regardless of the criteria used. Third, ECG LVH was categorized simply as present or absent according to a cutoff value of the criteria score. Also, ECG measurements provide a less accurate assessment of LVH than echocardiographic or other imaging measurements. Nevertheless, ECG

Table 4. Univariate and Multivariate Analyses for the Primary Outcome of MACCE*

	Univariate			Multivariable Model 1			Multivariable Model 2			Multivariable Model 3		
Parameter	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
ECG LVH by Sokolow-Lyon	0.76	0.58–0.99	0.042	0.87	0.66–1.15	0.331						
ECG LVH by Romhilt-Estes score	0.93	0.70–1.24	0.631				0.95	0.70–1.28	0.719			
ECG LVH by Cornell	0.74	0.56–0.96	0.024							0.68	0.51–0.91	0.009
Age	1.00	0.97–1.02	0.820	1.00	0.98–1.03	0.998	1.00	0.98–1.03	0.957	1.00	0.97–1.02	0.751
Male sex	0.81	0.62–1.05	0.121	0.72	0.5–50.96	0.023	0.72	0.540.95	0.021	0.67	0.50–0.88	0.005
Body mass index, kg/m^2	1.00	0.96–1.04	0.880									
Logistic EuroSCORE	1.02	1.01–1.03	0.001	1.01	1.00–1.03	0.023	1.01	1.00–1.03	0.024	1.02	1.00–1.03	0.008
STS score	0.98	0.94–1.02	0.409									
NYHA class												
1	1.00			1.00			1.00			1.00		
2	0.60	0.41–0.88	0.009	0.57	0.39–0.84	0.005	0.56	0.38–0.83	0.004	0.56	0.38–0.83	0.004
3	0.70	0.46–1.04	0.083	0.60	0.39–0.91	0.018	0.60	0.39–0.91	0.016	0.60	0.39–0.92	0.018
4	0.81	0.41–1.56	0.529	0.59	0.30–1.17	0.130	0.59	0.30–1.16	0.125	0.61	0.31–1.21	0.159
Atrial fibrillation/flutter	1.33	0.89–1.98	0.157									
Hypertension	1.25	0.83–1.88	0.286									
Diabetes	1.53	1.16–1.99	0.002	1.54	1.17–2.03	0.002	1.56	1.19–2.06	0.002	1.61	1.22–2.11	0.001
Hyperlipidemia	1.03	0.76–1.39	0.864									
Previous heart failure	1.42	1.03–1.94	0.030	1.35	0.98–1.88	0.070	1.37	0.99–1.90	0.061	1.37	0.98–1.90	0.062
Previous MI	1.84	1.09–3.10	0.023									
History of PCI	1.25	0.94–1.66	0.119									
Peripheral artery disease	1.50	0.74–3.04	0.263									
History of stroke	1.77	1.22–2.55	0.002	1.79	1.23–2.61	0.002	1.77	1.22–2.58	0.003	1.73	1.19–2.52	0.004
ESRD on dialysis	1.74	0.92–3.29	0.087									
Chronic lung disease	1.77	1.27–2.46	0.001	1.73	1.23–2.42	0.002	1.73	1.23–2.43	0.002	1.70	1.21–2.39	0.002
Pacemaker implanted	0.91	0.23–3.67	0.893									
Baseline creatinine level	1.07	0.98–1.18	0.122									
Baseline AV V_{max}	0.80	0.67–0.95	0.009	0.83	0.70–0.99	0.044	0.82	0.69–0.97	0.025	0.86	0.72–1.03	0.109
Baseline ejection fraction	1.00	0.99–1.01	0.804									
Baseline significant AR†	1.10	0.80–1.52	0.564									
Baseline significant MR†	1.02	0.70–1.50	0.908									
Conscious anesthesia	0.91	0.69–1.21	0.533									
Route												
Transfemoral	1.00											
Transapical	1.28	0.63–2.60	0.488									
Transaortic	2.03	0.65–6.35	0.224									
Baseline LVEDD	0.99	0.97–1.01	0.329									
Baseline LV mass	1.00	1.00–1.00	0.386									
Baseline LV mass index	1.00	0.99–1.00	0.215									

Multivariable model 1 included ECG left ventricular (LV) hypertrophy (LVH) by Sokolow-Lyon criteria; multivariable model 2 included ECG LVH by Romhilt-Estes score; multivariable model 3 included ECG LVH by Cornell criteria. AR indicates aortic regurgitation; AV, aortic valve; ESRD, end-stage renal disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEDD, left ventricular end-diastolic dimension; MACCE, major adverse cardiac or cerebrovascular event; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and STS, Society of Thoracic Surgery.

*Hazard ratios (HRs) were adjusted for age (continuous), sex (male or female), and statistically significant variables with *P* values <0.20 in univariate analysis.

†Significant refers to grade 3 (moderate) or grade 4 (severe) regurgitation.

measurements are the most simplistic and easily used diagnostic approach for characterizing LVH and also provide another electrical abnormality. Fourth, we did not directly assess cardiac amyloidosis or the extent of myocardial fibrosis, which are some of the main pathologic findings in patients with AS without ECG LVH.

Further studies investigating the association between ECG LVH and pathologic findings in patients with AS are needed. Fifth, considering the relatively small sample size of patients and clinical events, our study might have been underpowered to detect hard clinical end points according to different ECG LVH criteria. Sixth, we used linear cube formula for calculating LV mass index. Although the linear method is widely used, this method may not reflect well with actual LV mass in severe AS owing to a change of LV geometry. Last, the direct applicability of our study findings to other populations of different racial or ethnic groups might be questionable.

CONCLUSIONS

Among patients with severe AS undergoing TAVR, we found that the prevalence of baseline ECG LVH and their prognostic impact varied greatly according to the different ECG criteria used. While the presence of ECG LVH by the Cornell voltage criteria was significantly associated with lower risks of MACCE and mortality, such an association was absent with the Sokolow-Lyon criteria and Romhilt-Estes score. Further investigations are warranted to understand the underlying mechanisms and define optimal risk stratification in patients with discrepancies between electrical LVH on the 12-lead ECG and anatomic LVH on the echocardiogram.

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Disclosures

None.

Supplemental Material

Tables S1–S6

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Supplemental Material

Table S1. Univariate and Multivariate Analyses for the Predictors for the Presence of Electrocardiographic Left Ventricular Hypertrophy by the Sokolow-Lyon criteria.

Parameter		ECG LVH by Sokolow-Lyon					
		Univariate			Multivariable		
		OR	95% CI	p Value	OR	95% CI	p Value
Age		0.985	0.96–1.02	0.323	0.982	0.95–1.02	0.303
Male sex		1.150	0.83–1.59	0.399	1.313	0.91–1.90	0.147
Body mass index (kg/m^2)		0.948	0.90–1.00	0.031	0.946	0.90–1.00	0.051
Logistic EuroSCORE		0.992	0.98–1.01	0.322			
STS score		1.030	0.97–1.09	0.317			
NYHA class	1	1		0.927			
	2	1.112	0.66–1.87	0.690			
	3	1.188	0.68–2.08	0.546			
	4	0.998	0.41–2.41	0.996			
Atrial fibrillation/flutter		0.425	0.25–0.71	0.001	0.471	0.27–0.83	0.009
Hypertension		1.301	0.81–2.09	0.276			
Diabetes		0.662	0.48–0.92	0.013			
Hyperlipidemia		1.328	0.91–1.93	0.137	1.604	1.05–2.44	0.027
Previous heart failure		0.833	0.54–1.28	0.407			
Previous MI		1.135	0.52–2.49	0.751			
History of PCI		1.064	0.74–1.53	0.735			
Peripheral artery disease		2.584	0.83–8.02	0.100			
History of stroke		1.069	0.65–1.77	0.794			
ESRD on dialysis		1.170	0.47–2.91	0.735			
Chronic lung disease		0.966	0.60–1.55	0.884			
Baseline creatinine level		1.013	0.88–1.16	0.856			

Baseline AV V_{max}	2.140	1.70–2.7	0.000	1.820	1.42–2.34	0.000
Baseline ejection fraction	0.984	0.97–1.00	0.053			
Baseline significant AR	1.307	0.87–1.96	0.197			
Baseline significant MR	1.266	0.78–2.05	0.338			
LV-end diastolic dimension	1.049	1.02–1.08	0.000			
LV mass	1.013	1.01–1.02	0.000			
LV mass index	1.024	1.02–1.03	0.000	1.020	1.01–1.03	0.000

ECG LVH; electrocardiographic left ventricular hypertrophy, OR; odds ratio, CI; confidence interval, STS: Society of Thoracic Surgery, NYHA; New York Heart Association, MI; myocardial infarction, PCI; percutaneous coronary intervention, ESRD; end-stage renal disease, AV; aortic valve, AR; aortic regurgitation, MR: mitral regurgitation, LV; left ventricle.

†Independent predictors of ECG LVH were determined using a stepwise multivariate logistic regression model including age, sex, and clinical, anatomic, and hemodynamic variables with p-values <0.20 in univariate analysis.

Table S2. Univariate and Multivariate Analyses for the Predictors for the Presence of Electrocardiographic Left Ventricular Hypertrophy by the Romhilt-Estes score criteria.

Parameter		ECG LVH by Romhilt-Estes score					
		Univariate			Multivariable		
		OR	95% CI	p Value	OR	95% CI	p Value
Age		0.981	0.95–1.01	0.232	0.977	0.94–1.01	0.221
Male sex		1.641	1.16–2.33	0.006	1.757	1.16–2.66	0.008
Body mass index (kg/m^2)		0.899	0.85–0.95	0.000	0.920	0.86–0.98	0.015
Logistic EuroSCORE		1.005	0.99–1.02	0.564			
STS score		0.955	0.89–1.02	0.171			
NYHA class	1	1		0.529			
	2	0.807	0.46–1.41	0.450			
	3	1.069	0.59–1.92	0.824			
	4	0.800	0.31–2.09	0.649			
Atrial fibrillation/flutter		0.384	0.20–0.75	0.005	0.289	0.13–0.63	0.002
Hypertension		0.971	0.58–1.62	0.909			
Diabetes		1.067	0.75–1.51	0.713			
Hyperlipidemia		1.030	0.69–1.54	0.885			
Previous heart failure		1.558	1.00–2.44	0.052			
Previous MI		1.114	0.49–2.53	0.797			
History of PCI		0.804	0.54–1.19	0.276			
Peripheral artery disease		2.570	0.98–6.77	0.056	2.610	0.85–8.05	0.095
History of stroke		0.853	0.49–1.48	0.571			
ESRD on dialysis		1.499	0.60–3.73	0.384			
Chronic lung disease		1.739	1.08–2.81	0.024			
Baseline creatinine level		1.026	0.89–1.18	0.727			

Baseline AV V_{max}	1.805	1.44–2.26	0.000	1.794	1.37–2.35	0.000
Baseline ejection fraction	0.949	0.93–0.97	0.000	0.955	0.94–0.98	0.000
Baseline significant AR	1.052	0.69–1.61	0.815			
Baseline significant MR	1.394	0.85–2.28	0.185			
LV-end diastolic dimension	1.085	1.05–1.12	0.000			
LV mass	1.016	1.01–1.02	0.000			
LV mass index	1.028	1.02–1.03	0.000	1.021	1.01–1.03	0.000

The abbreviations are as outlined in table S1.

†Independent predictors of ECG LVH were determined using a stepwise multivariate logistic regression model including age, sex, and clinical, anatomic, and hemodynamic variables with p-values <0.20 in univariate analysis

Table S3. Univariate and Multivariate Analyses for the Predictors for the Presence of Electrocardiographic Left Ventricular Hypertrophy by the Cornell criteria.

Parameter		ECG LVH by Cornell					
		Univariate			Multivariable		
		OR	95% CI	p Value	OR	95% CI	p Value
Age		0.997	0.97–1.03	0.849	0.994	0.96–1.03	0.721
Male sex		0.410	0.29–0.57	0.000	0.307	0.21–0.45	0.000
Body mass index (kg/m^2)		0.987	0.941.04	0.585			
Logistic EuroSCORE		1.026	1.01–1.04	0.003			
STS score		0.990	0.94–1.05	0.708			
NYHA class	1	1		0.042			
	2	1.514	0.88–2.59	0.130			
	3	2.108	1.19–3.74	0.011			
	4	2.347	0.96–5.74	0.062			
Atrial fibrillation/flutter		0.709	0.43–1.18	0.187			
Hypertension		1.059	0.66–1.70	0.814			
Diabetes		0.961	0.70–1.33	0.809			
Hyperlipidemia		1.062	0.73–1.54	0.752			
Previous heart failure		1.239	0.80–1.91	0.331			
Previous MI		0.525	0.23–1.19	0.122	0.377	0.14–1.00	0.049
History of PCI		0.813	0.57–1.16	0.257			
Peripheral artery disease		1.222	0.47–3.21	0.684			
Hhistory of stroke		0.818	0.50–1.35	0.429			
ESRD on dialysis		Infinity		1.000			
Chronic lung disease		0.797	0.50–1.28	0.347			
Baseline creatinine level		1.388	1.13–1.71	0.002	1.655	1.22–2.24	0.001

Baseline AV V_{max}	2.024	1.62–2.53	0.000	1.864	1.43–2.42	0.000
Baseline ejection fraction	0.972	0.96–0.99	0.000	0.970	0.95–0.99	0.003
Baseline significant AR	1.149	0.77–1.71	0.495			
Baseline significant MR	1.159	0.72–1.86	0.540			
LV-end diastolic dimension	1.040	1.01–1.07	0.002			
LV mass	1.011	1.01–1.01	0.000			
LV mass index	1.023	1.02–1.03	0.000	1.017	1.01–1.02	0.000

The abbreviations are as outlined in table S1.

†Independent predictors of ECG LVH were determined using a stepwise multivariate logistic regression model including age, sex, and clinical, anatomic, and hemodynamic variables with p-values <0.20 in univariate analysis

Table S4. Independent Predictors for the Presence of Electrographic Left Ventricular Hypertrophy According to 3 Different Criteria*

	ECG-LVH by Sokolow-Lyon			ECG-LVH by Romhilt-Estes score			ECG-LVH by Cornell		
Parameter	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Age	0.98	0.95–1.02	0.303	0.98	0.94–1.01	0.221	0.99	0.96–1.03	0.721
Male sex	1.31	0.91–1.90	0.147	1.76	1.16–2.66	0.008	0.31	0.21–0.45	<0.001
Body mass index (kg/m^2)	0.95	0.90–1.00	0.051	0.92	0.86–0.98	0.015			
Atrial fibrillation/flutter	0.47	0.27–0.83	0.009	0.29	0.13–0.63	0.002			
Hyperlipidemia	1.60	1.05–2.44	0.027						
Previous MI							0.38	0.14–1.00	0.049
Peripheral artery disease				2.61	0.85–8.05	0.095			
History of stroke									
Baseline creatinine level							1.65	1.22–2.24	0.001

Baseline AV V_{max}	1.82	1.42–2.34	<0.001	1.79	1.37–2.35	<0.001	1.86	1.43–2.42	<0.001
Baseline ejection fraction				0.96	0.94–0.98	<0.001	0.97	0.95–0.99	0.003
LV mass index	1.02	1.01–1.03	<0.001	1.02	1.01–1.03	<0.001	1.02	1.01–1.02	<0.001

*Independent predictors of ECG-LVH by 3 criteria were determined using a stepwise multivariate logistic regression model including age, sex, and variables selected by backward elimination. OR; odds ratio and other abbreviations as Tables S1 and S2.

Table S4. Univariate and Multivariate Predictors for All-Cause Mortality*

Parameter		Univariate			Multivariable-1			Multivariable-2			Multivariable-3		
		HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
ECG LVH by Sokolow-Lyon		0.67	0.43–1.05	0.080	0.77	0.49–1.22	0.268						
ECG LVH by Romhilt-Estes score		1.37	0.87–2.17	0.177				1.26	0.78–2.04	0.348			
ECG LVH by Cornell		0.54	0.34–0.86	0.010							0.55	0.34–0.90	0.017
Age		1.03	0.99–1.08	0.119	1.03	0.98–1.07	0.253	1.03	0.99–1.08	0.160	1.02	0.98–1.06	0.401
Male sex		1.30	0.83–2.04	0.247	1.47	0.92–2.33	0.106	1.38	0.87–2.20	0.175	1.29	0.81–2.06	0.285
Body mass index (kg/m^2)		0.93	0.86–0.99	0.027									
Smoking		0.79	0.34-1.83	0.580									
Logistic EuroSCORE		1.03	1.01–1.04	0.007	1.02	1.00–1.04	0.015	1.02	1.00–1.04	0.013	1.03	1.01–1.04	0.009
STS score		0.99	0.91–1.06	0.706									
NYHA class	1	1.00			1.00			1.00			1.00		
	2	0.47	0.25–0.90	0.024	0.41	0.21–0.78	0.007	0.42	0.22–0.82	0.011	0.38	0.20–0.74	0.004
	3	0.80	0.42–1.53	0.501	0.68	0.35–1.34	0.266	0.71	0.36–1.39	0.314	0.68	0.35–1.33	0.258
	4	1.32	0.50–3.47	0.574	0.75	0.27–2.04	0.567	0.81	0.29–2.22	0.679	0.80	0.29–2.20	0.662
Atrial fibrillation/flutter		0.73	0.34–1.60	0.435									

Hypertension	1.32	0.65–2.66	0.441									
Diabetes	1.97	1.25–3.09	0.003	2.08	1.31–3.31	0.002	2.11	1.33–3.34	0.001	2.22	1.40–3.52	0.001
Hyperlipidemia	0.85	0.51–1.42	0.529									
Previous heart failure	1.59	0.97–2.59	0.064									
Previous MI	4.64	2.37–9.11	<0.001	4.59	2.28–9.25	0.000	4.65	2.30–9.37	<0.001	4.18	2.08–8.41	<0.001
Previous history of PCI	1.24	0.77–2.00	0.373									
Peripheral artery disease	1.56	0.49–4.97	0.449									
History of stroke	1.54	0.82–2.89	0.175									
ESRD on dialysis	2.90	1.26–6.70	0.013									
Chronic lung disease	1.99	1.20–3.33	0.008	1.80	1.07–3.05	0.028	1.84	1.09–3.11	0.023	1.75	1.04–2.96	0.036
Pacemaker implanted	1.55	0.22–11.19	0.663									
Baseline creatinine level	1.18	1.05–1.33	0.006									
Baseline AV V_{max}	0.75	0.56–1.00	0.050									
Baseline ejection fraction	0.98	0.96–1.00	0.034									
Baseline significant AR†	1.48	0.89–2.46	0.135									
Baseline significant MR†	1.71	0.98–2.98	0.057									
Conscious anesthesia	0.98	0.60–1.59	0.928									

Route	Transfemoral	1.00		
	Transapical	2.09	0.76–5.73	0.152
	Transaortic	1.77	0.25–12.79	0.569
LV-end diastolic dimension		1.00	0.97–1.04	0.990
LV mass		1.00	1.00–1.00	0.743
LV mass index		1.00	0.99–1.01	0.964

*Hazard ratios were adjusted for age (continuous), sex (male or female), and variables selected by backward elimination. Multivariable 1 included ECG LVH by Sokolow-Lyon criteria; Multivariable 2 included ECG LVH by Romhilt-Estes score; Multivariable 3 included ECG LVH by Cornell criteria. HR; hazard ratio, CI: confidence interval and other abbreviations as outlined in Tables 1 and 2.

†significant refers to grade 3 (moderate) or grade 4 (severe) regurgitation.

Table S6. Univariate and Multivariate Predictors for Cardiovascular Death*

Parameter	Univariate			Multivariable-1			Multivariable-2			Multivariable-3		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
ECG LVH by Sokolow-Lyon	0.65	0.36-1.16	0.141	0.59	0.32-1.08	0.088						
ECG LVH by Romhilt-Estes score	1.56	0.87-2.81	0.137				1.20	0.63-2.28	0.573			
ECG LVH by Cornell	0.57	0.31-1.04	0.065							0.40	0.20-0.79	0.008
Age	1.01	0.96-1.07	0.660	1.01	0.96-1.07	0.730	1.02	0.97-1.08	0.405	1.02	0.96-1.07	0.580
Male sex	1.09	0.61-1.95	0.773	0.90	0.49-1.65	0.741	0.92	0.50-1.69	0.800	0.73	0.39-1.37	0.324
Body mass index (kg/m^2)	0.94	0.86-1.03	0.181	0.94	0.86-1.03	0.170						
Smoking	1.20	0.47-3.10	0.705									
Logistic EuroSCORE	1.03	1.01-1.06	0.005									
STS score	0.98	0.89-1.08	0.696									
NYHA class 1	1.00											
2	0.51	0.22-1.17	0.111									
3	0.75	0.32-1.77	0.517									
4	1.49	0.44-4.99	0.519									
Atrial fibrillation/flutter	1.08	0.45-2.56	0.863									

Hypertension	1.42	0.56-3.62	0.462									
Diabetes	2.52	1.39-4.55	0.002	2.75	1.49-5.06	0.001	2.68	1.47-4.90	0.001	2.48	1.33-4.62	0.004
Hyperlipidemia	0.83	0.43-1.62	0.589									
Previous heart failure	2.00	1.08-3.71	0.027							1.58	0.83-3.01	0.162
Previous MI	2.18	0.67-7.08	0.196									
Previous history of PCI	1.44	0.79-2.64	0.239									
Peripheral artery disease	1.76	0.43-7.29	0.435									
History of stroke	1.05	0.41-2.67	0.925									
ESRD on dialysis	2.57	0.79-8.29	0.116									
Chronic lung disease	2.15	1.13-4.10	0.020	2.16	1.13-4.15	0.021	2.11	1.09-4.07	0.025	1.96	1.02-3.77	0.042
Pacemaker implanted	2.51	0.34-18.3	0.363									
Baseline creatinine level	1.20	1.04-1.39	0.011							1.18	1.00-1.40	0.053
Baseline AV V_{max}	0.73	0.50-1.07	0.109									
Baseline ejection fraction	0.96	0.94-0.98	<0.001	0.97	0.95-0.99	0.015	0.97	0.95-1.00	0.021	0.97	0.94-0.99	<0.001
Baseline significant AR†	1.76	0.93-3.35	0.085									
Baseline significant MR†	2.13	1.08-4.21	0.030	1.72	0.84-3.54	0.140	1.74	0.85-3.56	0.129			
Conscious anesthesia	0.57	0.30-1.11	0.100	0.50	0.25-1.00	0.05	0.53	0.27-1.04	0.06	0.56	0.28-1.12	0.10

Route	Transfemoral	1.00		
	Transapical	1.71	0.41-7.08	0.458
	Transaortic	inf		
LV-end diastolic dimension		1.02	0.97-1.06	0.489
LV mass		1.00	1.00-1.01	0.604
LV mass index		1.00	0.99-1.01	0.775

*Hazard ratios were adjusted for age (continuous), sex (male or female), and variables selected by backward elimination. Multivariable 1 included ECG LVH by Sokolow-Lyon criteria; Multivariable 2 included ECG LVH by Romhilt-Estes score; Multivariable 3 included ECG LVH by Cornell criteria. HR; hazard ratio, CI: confidence interval and other abbreviations as outlined in Tables 1 and 2.

†significant refers to grade 3 (moderate) or grade 4 (severe) regurgitation.