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ORIGINAL RESEARCH

# Performance of 2020 AHA/ACC HCM Guidelines and Incremental Value of Myocardial Strain for Predicting SCD

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## ABSTRACT

**BACKGROUND** The 2020 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for sudden cardiac death (SCD) risk stratification in hypertrophic cardiomyopathy (HCM) need further international validation.

**OBJECTIVES** Performance of the guidelines and the incremental value of myocardial strain for predicting SCD in HCM were investigated.

**METHODS** In 1,416 HCM patients, SCD risk was stratified according to the 2020 AHA/ACC and 2014 European Society of Cardiology (ESC) guidelines. Left ventricular (LV) global longitudinal strain (GLS) and left atrial reservoir strain (LARS) were measured. The main outcome consisted of SCD events.

**RESULTS** Overall, 29.1% had major risk factors (RFs), and 14.7% had nonmajor RFs in the absence of major RFs; estimated 5-year SCD event rates were 6.8% and 2.3%, respectively. SCD risk was significantly increased in the former group but not in the latter. When stratified by the number of RFs, 5-year SCD event rates were 1.9%, 3.0%, 4.9%, and 18.4% for patients with 0, 1, 2, and 3 or more RFs, respectively. SCD risk was elevated in patients with multiple RFs but not in those with a single RF. Performance of the AHA/ACC and ESC guidelines did not differ significantly over 10 years (5-year time-dependent area under the curve: 0.677 vs 0.724; $P = 0.235$). Decreased LV GLS and LARS were independently associated with SCD events with optimal cutoffs of LV GLS <13% and LARS <21%. Adding LV GLS and LARS to the guidelines had incremental predictive value.

**CONCLUSIONS** The 2020 AHA/ACC guidelines were predictive of SCD events with modest power in a large Asian HCM cohort. Implantable cardioverter-defibrillators are reasonable in patients with multiple RFs, and consideration of myocardial strain can improve SCD prediction. (JACC: Asia 2024;4:10–22) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Sudden cardiac death (SCD) is the most devastating complication of hypertrophic cardiomyopathy (HCM), but implantable cardioverter-defibrillators (ICDs) have provided an effective lifesaving therapy in high-risk patients with HCM since 2000.[1] Although there is no disagreement that ICDs should be implanted for secondary SCD prevention, risk stratification strategies for the

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primary prevention of SCD differ between the American and European guidelines.[2-4] The 2014 European Society of Cardiology (ESC) guidelines recommended calculation of the 5-year SCD risk score and defined patients with a 5-year SCD risk ≥6% to be at high risk.[2] The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines use a risk factor-based strategy to identify HCM patients at high risk of SCD. These guidelines were updated in 2020 to include new risk factors such as left ventricular (LV) apical aneurysm, reduced LV ejection fraction (LVEF), and extensive late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging,[3] thus adding up to a total of 7 risk factors, 5 major and 2 nonmajor. Limited data are available, however, on the validation of the 2020 AHA/ACC risk factor strategy for SCD prediction, especially considering the type of risk factor.[5-7]

Myocardial disarray, hypertrophy, and fibrosis are the histopathologic hallmarks of HCM and likely comprise the substrate for the development of fatal arrhythmias. CMR can image myocardial fibrosis and disarray,[8,9] and LGE, which is a measure of myocardial scar, was included as a risk factor in the latest American guidelines. Myocardial strain measured with speckle tracking echocardiography is a sensitive marker of myocardial dysfunction, and it can be measured from routine echocardiography examinations without additional CMR imaging. LV global longitudinal strain (GLS) was associated with the histologic features of HCM,[10] and it was also predictive of SCD events.[11] Additionally, left atrial reservoir strain (LARS) is a marker of atrial function and also reflects increased LV filling pressure[12]; LARS was associated with greater LV hypertrophy and fibrosis in HCM.[13] These parameters may provide additional value for the prediction of SCD in HCM.

Thus, this study aimed to assess the performance of the 2020 AHA/ACC risk factor strategy and the additive value of myocardial strain for the prediction of SCD in a large cohort of Asian patients with HCM.

## METHODS

**ETHICS STATEMENTS.** This study conforms to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (Seoul, Korea; H-2206-169-1336).

**STUDY GROUP.** The study is based on the prospective registries of 2 tertiary hospitals in Korea. Consecutive patients with HCM (aged ≥16 years) who underwent evaluation at Seoul National University Hospital (n = 971) and Samsung Medical Center (n = 445) between January 2007 and July 2020 were included (Supplemental Figure 1). HCM was diagnosed on the basis of LV hypertrophy ≥15 mm (or ≥13 mm in patients with a family history of HCM) in the absence of other conditions that could account for the observed degree of hypertrophy.[2,3] Patients with indications for ICD implantation for secondary prevention before the initial evaluation and patients with infiltrative cardiomyopathies, metabolic diseases, or congenital heart disease causing LV hypertrophy were excluded.

**SCD RISK ASSESSMENT.** Clinical examination, including history taking and echocardiography, was performed in all patients. Holter monitoring was performed in 1,011 patients (71.4%), and CMR with LGE imaging was performed in 939 patients (66.3%) at the discretion of the attending physician. The presence of SCD risk factors according to the 2020 AHA/ACC guidelines[3] was assessed as follows: 5 major risk factors (with Class 2a recommendation for ICD implantation), including: 1) a family history of SCD;2) massive LV hypertrophy (≥30 mm); 3) unexplained syncope;4) LV apical aneurysm detected on echocardiography or CMR; and 5) LV ejection fraction <50%; and 2 nonmajor risk factors (with Class 2b recommendation for ICD implantation), including: 1) extensive LGE; and 2) nonsustained ventricular tachycardia documented by Holter monitoring. The 5-year SCD risk score was calculated according to the 2014 ESC guidelines.[2]

Transthoracic echocardiography and CMR were performed as reported previously,[11,13] and details are provided in the Supplemental Methods. LGE was quantified using a threshold-based algorithm defining positive LGE as a pixel of the myocardium with a signal intensity >6 SD of the normal remote myocardium, and extensive LGE was defined as LGE ≥15%.[3,14] Missing data on nonsustained ventricular tachycardia (NSVT) and LGE risk factors were coded as absent.

**MYOCARDIAL STRAIN MEASUREMENT.** Measurements of myocardial strain were performed according to the guidelines,[15,16] as detailed in the Supplemental Methods and in previous publications.[11,13] Briefly, LV GLS and LARS were measured offline at a core laboratory blinded to clinical information and using vendor-independent postprocessing software (Imaging Arena 4.6, TomTec Imaging Systems). Absolute values for LV GLS were used here.

**ABBREVIATIONS AND ACRONYMS**

**ACC** = American College of Cardiology

**AHA** = American Heart Association

**AUC** = area under the curve

**CMR** = cardiac magnetic resonance

**ESC** = European Society of Cardiology

**HCM** = hypertrophic cardiomyopathy

**ICD** = implantable cardioverter-defibrillator

**LA** = left atrial

**LARS** = left atrial reservoir strain

**LGE** = late gadolinium enhancement

**LGS** = global longitudinal strain

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**NSVT** = nonsustained ventricular tachycardia

**ROC** = receiver-operating characteristic

**SCD** = sudden cardiac death

**CLINICAL OUTCOMES.** The primary endpoint consisted of SCD events, defined as a composite of SCD, aborted SCD, or appropriate ICD shock. SCD was defined as witnessed sudden death with or without documented ventricular fibrillation or sudden death presumed to be of cardiac cause within 1 day of new symptoms or unexplained sudden death without an antecedent history of worsening symptoms.[17] Patients with ICDs underwent annual interrogation by the attending electrophysiologists. The index date was that of the initial echocardiography, and follow-up was until occurrence of the endpoint or censoring as a result of death, loss of follow-up, or end of the study period (January 2021 for Seoul National University Hospital and August 2019 for Samsung Medical Center). Outcome events were assessed from review of medical records and telephone calls to the family members. Data on mortality and the causes of death for the study cohort were obtained from the National Death Registration Records of Korea.

**STATISTICAL ANALYSIS.** Details are provided in the Supplemental Methods. Kaplan-Meier survival curves with log-rank tests were used to estimate event rates and compare event-free survival according to stratification by type and number of SCD risk factors, and multiple pairwise comparisons were corrected by the Benjamini-Hochberg method. Cox proportional hazards regression analyses were performed to assess the association between variables and the risk of SCD events, and effect sizes were expressed as HRs with 95% CIs. The discriminating performance of the risk stratification models using parameters at the index evaluation at fixed time points was assessed with time-dependent receiver-operating characteristic (ROC[t]) curves constructed using the inverse probability of censoring weighting method and that across the full-time range with Harrell's C-index. The 2020 AHA/ACC risk factor strategy was coded as a continuous variable (number of risk factors, including both major and minor) for this analysis. The time-dependent area under the curve (AUC) for the ROC(t) curves was estimated and compared at each time point over 10 years. The sensitivity, specificity, positive predictive value, and negative predictive value of the guidelines for 5-year SCD events using thresholds corresponding to the classes of recommendation for ICD implantation were calculated. The relationship between myocardial strain parameters and SCD events was plotted using restricted cubic splines in the Cox regression setting. The optimal thresholds of LV GLS and LARS for predicting SCD events were determined using receiver-operating characteristic (ROC) curves on the basis of the Youden index. The potential incremental value of adding myocardial strain to the guidelines for SCD risk stratification models was assessed using the global chi-square score with the likelihood ratio test and Harrell's C-indices in nested Cox regression models. Two-sided $P$ values $<0.05$ were considered statistically significant. Analyses were conducted using R software version 4.1 (R Foundation).

## RESULTS

**BASELINE CHARACTERISTICS OF THE STUDY GROUP WITH AND WITHOUT SCD EVENTS.** The baseline characteristics of the 1,416 patients with HCM included in the study are summarized in Table 1. Their mean age was 59.3 ± 13.2 years, and 71.8% were men. ICDs were implanted in 41 patients (2.9%) during the study. During a median 5.5 years (Q1-Q3: 2.4-8.9 years) of follow-up, 43 (3.0%) SCD events occurred (35 SCD events during 5 years), including 32 SCDs, 1 aborted SCD, and 10 appropriate ICD shocks. Compared with the Western HCM cohorts, our study cohort patients were several years older, had a greater proportion of men, and had similar SCD event rates.[5,17]

Patients with SCD events included more women and had worse symptoms of dyspnea, more atrial fibrillation, slightly lower LVEF, greater left atrial (LA) size, higher E/e′ ratio (ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity), higher pulmonary artery systolic pressure, and a higher maximum LV outflow tract gradient than patients free from SCD events (Table 1). The prevalence of AHA/ACC risk factors (69.8% vs 43.0%; $P = 0.001$) and the ESC risk scores (4.4 ± 4.6 vs 2.4 ± 2.0; $P = 0.008$) were higher in patients with SCD events than in those without SCD events. All AHA/ACC risk factors were more prevalent in patients with SCD events, except for the criterion of maximum LV wall thickness ≥30 mm. Among the 43 patients with SCD events, 13 (30.2%) did not have any AHA/ACC risk factor, and 28 (65.1%) were categorized as having a low SCD risk by the ESC risk score.

When categorized by the number of AHA/ACC risk factors, patients with more risk factors were younger and had greater symptoms of dyspnea, less hypertension, slightly lower LVEF, greater LA size, greater maximum LV wall thickness, and lower LV GLS and LARS than patients with fewer risk factors (Supplemental Table 1). There were minimal differences in the baseline characteristics of patients

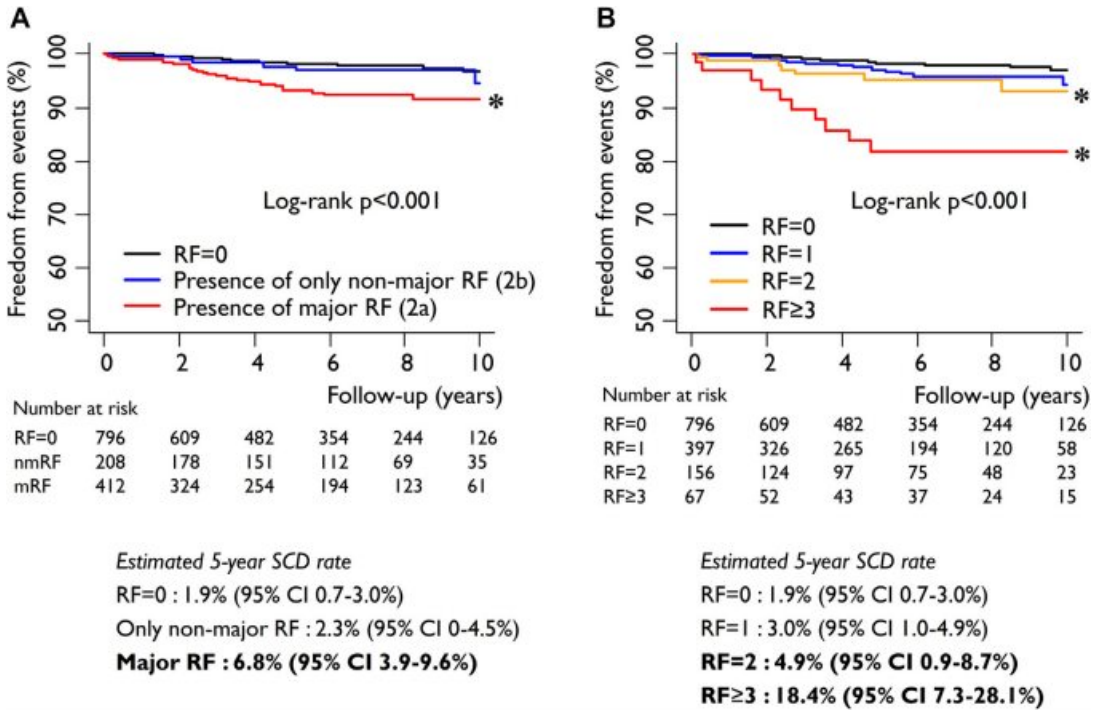
**TABLE 1 Baseline Characteristics of the Study Group With and Without Incident SCD Events**

| | Total Group (N = 1,416) | No SCD Events (n = 1,373) | SCD Events (n = 43) | *P* Value |
|---|---|---|---|---|
| Age, y | 59.3 ± 13.2 | 59.2 ± 13.1 | 63.1 ± 14.0 | 0.058 |
| Male | 1,017 (71.8) | 994 (72.4) | 23 (53.5) | 0.011 |
| NYHA functional class | | | | 0.009 |
| I | 962 (67.9) | 942 (68.6) | 20 (46.5) | |
| II | 385 (27.2) | 365 (26.6) | 20 (46.5) | |
| III-IV | 69 (4.9) | 66 (4.8) | 3 (7.0) | |
| SCD risk stratification | | | | |
| Family history of SCD | 134 (9.5) | 122 (8.9) | 12 (27.9) | <0.001 |
| Max LVWT ≥30 mm | 28 (2.0) | 27 (2.0) | 1 (2.3) | >0.999 |
| Unexplained syncope | 166 (11.7) | 157 (11.4) | 9 (20.9) | 0.096 |
| LV apical aneurysm | 117 (8.3) | 109 (7.9) | 8 (18.6) | 0.026 |
| LVEF <50% | 41 (2.9) | 36 (2.6) | 5 (11.6) | 0.003 |
| NSVT | 224/1,011 (22.2) | 211/984 (21.4) | 13/27 (48.1) | 0.002 |
| LGE ≥15% | 216/939 (23.0) | 204/915 (22.3) | 12/24 (50.0) | 0.003 |
| 2020 AHA/ACC guidelines | | | | |
| Presence of major RF | 412 (29.1) | 388 (28.3) | 24 (55.8) | <0.001 |
| Presence of major or minor RF | 620 (43.8) | 590 (43.0) | 30 (69.8) | 0.001 |
| No. of RF | 0.7 ± 0.9 | 0.6 ± 0.9 | 1.4 ± 1.3 | 0.001 |
| 0 | 796 (56.2) | 783 (57.0) | 13 (30.2) | <0.001 |
| 1 | 397 (28.0) | 384 (28.0) | 13 (30.2) | |
| 2 | 156 (11.0) | 149 (10.9) | 7 (16.3) | |
| ≥3 | 67 (4.7) | 57 (4.2) | 10 (23.3) | |
| 2014 ESC guidelines | | | | |
| 5-y SCD risk score | 2.5 ± 2.2 | 2.4 ± 2.0 | 4.4 ± 4.6 | 0.008 |
| Risk group according to 5-y SCD risk score | | | | |
| Low risk (<4%) | 1,232 (87.0) | 1,204 (87.7) | 28 (65.1) | <0.001 |
| Intermediate risk (4% to <6%) | 105 (7.4) | 99 (7.2) | 6 (14.0) | |
| High risk (≥6%) | 79 (5.6) | 70 (5.1) | 9 (20.9) | |
| Comorbidities | | | | |
| Atrial fibrillation | 263 (18.6) | 244 (17.8) | 19 (44.2) | <0.001 |
| Coronary artery disease | 43 (3.0) | 42 (3.1) | 1 (2.3) | >0.999 |
| Hypertension | 618 (43.6) | 600 (43.7) | 18 (41.9) | 0.934 |
| Diabetes | 239 (16.9) | 232 (16.9) | 7 (16.3) | >0.999 |
| End-stage renal disease | 13 (0.9) | 12 (0.9) | 1 (2.3) | 0.864 |
| Echocardiography parameters | | | | |
| LVEDD, mm | 48.0 (44.0-51.0) | 48.0 (44.0-51.0) | 47.0 (44.0-50.5) | 0.900 |
| LVESD, mm | 28.0 (25.0-31.0) | 28.0 (25.0-31.0) | 30.0 (25.5-32.0) | 0.215 |
| LVEF, % | 65.0 (60.0-69.0) | 65.0 (60.0-69.0) | 61.0 (56.0-67.5) | 0.005 |
| LA diameter, mm | 44.0 (40.0-50.0) | 44.0 (40.0-49.0) | 52.0 (46.0-56.7) | <0.001 |
| LAVI, mL/m$^2$ | 42.3 (33.1-55.2) | 42.0 (32.9-54.4) | 60.0 (46.5-87.1) | <0.001 |
| E/septal e′ | 12.3 (9.7-16.3) | 12.2 (9.6-16.1) | 15.2 (11.0-21.1) | 0.002 |
| PASP, mm Hg | 32.0 (29.0-37.0) | 32.0 (29.0-36.0) | 36.5 (31.1-41.2) | 0.005 |
| Max LVWT, mm | 17.1 (16.0-20.0) | 17.0 (15.8-20.0) | 18.9 (17.0-20.0) | 0.169 |
| Max LVOT gradient, mm Hg | 5.0 (3.6-8.8) | 5.0 (3.6- 8.5) | 6.9 (3.9-25.4) | 0.044 |
| Obstructive (≥30 mm Hg) | 201 (14.2) | 193 (14.1) | 8 (18.6) | 0.537 |
| LV GLS, % (absolute) | 14.1 (11.6-17.4) | 14.2 (11.6-17.4) | 11.9 (9.4-14.0) | <0.001 |
| LARS, % | 24.2 (17.7-31.0) | 24.4 (17.9-31.2) | 18.2 (10.6-21.7) | <0.001 |

Values are mean ± SD, n (%), or median (Q1-Q3).

ACC = American College of Cardiology; AHA = American Heart Association; E/septal e′ = ratio of early diastolic septal mitral inflow velocity to early diastolic mitral annulus velocity; ESC = European Society of Cardiology; GLS = global longitudinal strain; LARS = left atrial reservoir strain; LAVI = left atrial volume index; LGE = late gadolinium enhancement; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; Max = maximum; NSVT = nonsustained ventricular tachycardia; RF = risk factor; PASP = pulmonary artery systolic pressure; SCD = sudden cardiac risk.

**FIGURE 1 Incidence of SCD Events by RF Type and Number**




Patients were stratified by the type and number of 2020 American Heart Association/American College of Cardiology risk factors (RF). (A) The incidence of sudden cardiac death (SCD) events is significantly increased in patients with major risk factors (mRF) (Class 2a recommendation for implantable cardioverter-defibrillator) but not in patients with only nonmajor risk factors (nmRF) (Class 2b recommendation for implantable cardioverter-defibrillator). (B) The incidence of sudden cardiac death events is significantly increased in patients with multiple (≥2) risk factors but not in patients with a single risk factor. Asterisks denote a significant difference in event-free survival from the reference group (no risk factor) in adjusted pairwise comparisons.

according to loss of follow-up (Supplemental Table 2), thereby supporting no bias related to informative censoring.

**INCIDENCE OF SCD EVENTS ACCORDING TO THE 2020 AHA/ACC RISK FACTOR PROFILE.** Overall, among the 1,416 patients in the study, major risk factors were present in 412 (29.1%) and nonmajor risk factors in the absence of major risk factors were present in 208 (14.7%). Meanwhile, 79 (5.6%) and 105 (7.4%) patients had ESC risk scores ≥6% and ≥4% to <6%, respectively, corresponding to Class 2a and Class 2b recommendation for ICD implantation in the 2014 ESC guidelines. The number of SCD events stratified by the type and number of AHA/ACC risk factors and ESC risk categories are shown in Supplemental Figures 2A to 2C.

The estimated 5-year SCD event rates were 6.8% (95% CI: 3.9%-9.6%) in patients with major risk factors, 2.3% (95% CI: 0%-4.5%) in patients with only nonmajor risk factors, and 1.9% (95% CI: 0.7%-3.0%) in patients with no risk factors (**Figure 1A**). Of note, the risk of SCD events was significantly higher in patients with ≥1 major risk factor (HR: 3.49; 95% CI: 1.78-6.86) but not in patients with only nonmajor risk factors ($P = 0.383$) (**Figure 1A**, Supplemental Table 3).

When stratified by the number of risk factors (counting all major and nonmajor risk factors), the estimated 5-year SCD event rates were 1.9% (95% CI: 0.7%-3.0%), 3.0% (95% CI: 1.0%-4.9%), 4.9% (95% CI: 0.9%-8.7%), and 18.4% (95% CI: 7.3%-28.1%) for patients with 0, 1, 2, and ≥3 risk factors, respectively (**Figure 1B**). The risk of SCD events tended to increase progressively in proportion to the number of risk factors (HR: 1.83 per 1 increase in number of risk factors; 95% CI: 1.45-2.32; $P < 0.001$). The risk of SCD events was significantly increased in patients with

**TABLE 2 Risk of SCD Events Associated With Individual 2020 AHA/ACC Risk Factors**

| | N | Events (IR[a]) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| No risk factors | 796 | 13 (1.9) | 1.00 (reference) | |
| SCD risk associated with each AHA/ACC risk factor[b] | | | | |
| Major risk factors (Class 2a recommendation for ICD) | | | | |
| Family history of SCD | 134 | 12 (10.3) | 5.16 (2.36-11.3) | <0.001 |
| Max LVWT ≥30 mm | 28 | 1 (3.7) | 1.84 (0.24-14.1) | 0.557 |
| Unexplained syncope | 166 | 9 (7.9) | 3.47 (1.48-8.13) | 0.004 |
| LV apical aneurysm | 117 | 8 (6.0) | 3.71 (1.54-8.96) | 0.004 |
| LVEF <50% | 41 | 5 (14.3) | 10.1 (3.57-28.5) | <0.001 |
| Nonmajor risk factors (Class 2b recommendation for ICD) | | | | |
| NSVT | 224 | 13 (6.7) | 3.31 (1.53-7.14) | 0.002 |
| LGE ≥15% | 216 | 12 (6.1) | 3.11 (1.42-6.81) | 0.002 |
| SCD risk associated with each AHA/ACC risk factor,[b] stratified by the presence or absence of other risk factors | | | | |
| Major risk factors (Class 2a recommendation for ICD) | | | | |
| Family history of SCD | | | | |
| Lone risk factor | 56 | 3 (4.6) | 2.97 (0.85-10.04) | 0.089 |
| Coexistence of other risk factors | 78 | 9 (14.6) | 6.84 (2.92-16.0) | <0.001 |
| Max LVWT ≥30 mm | | | | |
| Lone risk factor | 7 | 0 (0) | – | – |
| Coexistence of other risk factors | 21 | 1 (5.0) | – | – |
| Unexplained syncope | | | | |
| Lone risk factor | 85 | 1 (2.7) | 0.85 (0.11-6.52) | 0.878 |
| Coexistence of other risk factors | 81 | 8 (12.2) | 5.64 (2.34-13.6) | <0.001 |
| LV apical aneurysm | | | | |
| Lone risk factor | 60 | 3 (3.7) | 2.59 (0.74-9.11) | 0.137 |
| Coexistence of other risk factors | 57 | 5 (8.6) | 5.00 (1.78-14.0) | 0.002 |
| LVEF <50% | | | | |
| Lone risk factor | 11 | 1 (14.3) | 9.13 (1.18-70.9) | 0.034 |
| Coexistence of other risk factors | 30 | 4 (14.4) | 10.4 (3.4-31.9) | <0.001 |
| Nonmajor risk factors (Class 2b recommendation for ICD) | | | | |
| NSVT | | | | |
| Lone risk factor | 89 | 4 (4.0) | 2.41 (0.79-7.39) | 0.124 |
| Coexistence of other risk factors | 135 | 9 (8.6) | 3.97 (1.70-9.28) | 0.001 |
| LGE ≥15% | | | | |
| Lone risk factor | 89 | 1 (0) | 0.59 (0.08-4.48) | 0.607 |
| Coexistence of other risk factors | 127 | 11 (11.6) | 5.10 (2.28-11.39) | <0.001 |

Values are n (IR: %/5 years) unless otherwise indicated. [a]5-year incidence rate of SCD, estimated by the Kaplan-Meier method. [b]Cox regression analysis with patients with no risk factors (n = 796) as reference.

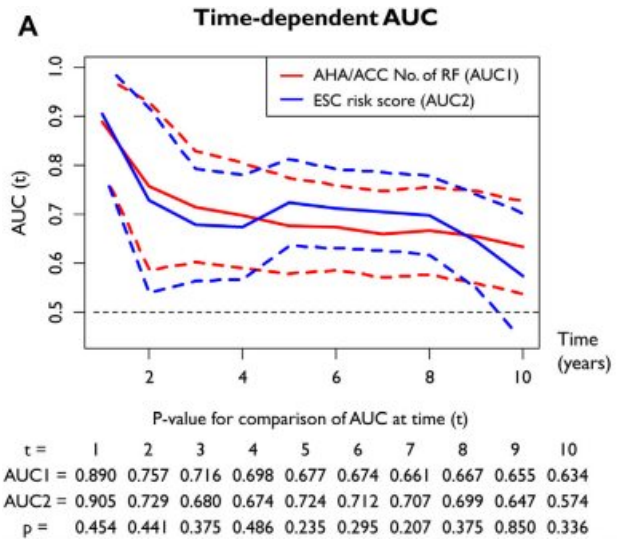
ICD = implantable cardioverter-defibrillator; IR = incidence rate; other abbreviations as in Table 1.

multiple (≥2) risk factors but not in those with a single risk factor (*P* = 0.113) (Figure 1B, Supplemental Table 3).

The presence of each AHA/ACC risk factor was associated with a higher risk of SCD events compared with patients without risk factors, with the exception of maximum LV wall thickness ≥30 mm, which did not confer an increased risk of SCD in this HCM cohort (Table 2). LVEF <50% was associated with the greatest increase in SCD risk. However, much of the association between risk factors and SCD events could be attributed to the presence of multiple risk factors. The estimated 5-year SCD event rate in the presence of a lone risk factor, either major or minor, was <6% for all risk factors except for LVEF <50% (Table 2). In particular, the lone presence of unexplained syncope or maximum LV wall thickness ≥30 mm was not associated with SCD events (Table 2, Supplemental Figure 3).

**PERFORMANCE OF THE 2020 AHA/ACC GUIDELINES COMPARED WITH THE 2014 ESC GUIDELINES.** The performance of the AHA/ACC risk factor strategy and the ESC risk score did not differ significantly up to 10 years (Figure 2A). Time-dependent AUCs were 0.890 (95% CI: 0.794-0.985) and 0.905 (95% CI: 0.797-0.999) at 1 year (*P* for comparison = 0.454), and they were 0.677 (95% CI: 0.580-0.774) and 0.724 (95% CI: 0.607-0.841) at 5 years (*P* for comparison = 0.235), respectively (Figure 2B). Both models showed best

**FIGURE 2 Comparison of the Performance of the AHA/ACC and ESC Guidelines**




Performance of the 2020 American Heart Association (AHA)/American College of Cardiology (ACC) and 2014 European Society of Cardiology (ESC) guidelines were compared using time-dependent receiver-operating characteristic (ROC) analyses. (A) Comparison of the area under the curve (AUC) up to 10 years shows no significant difference. The performances of both models are best within 2 years and then show deterioration. The dotted lines indicate 95% CI bands for each pointwise estimate of the area under the curve at time (t). (B) Time-dependent (t) receiver-operating characteristic curves and the area under the curve at 5 years are shown. RF = risk factor.

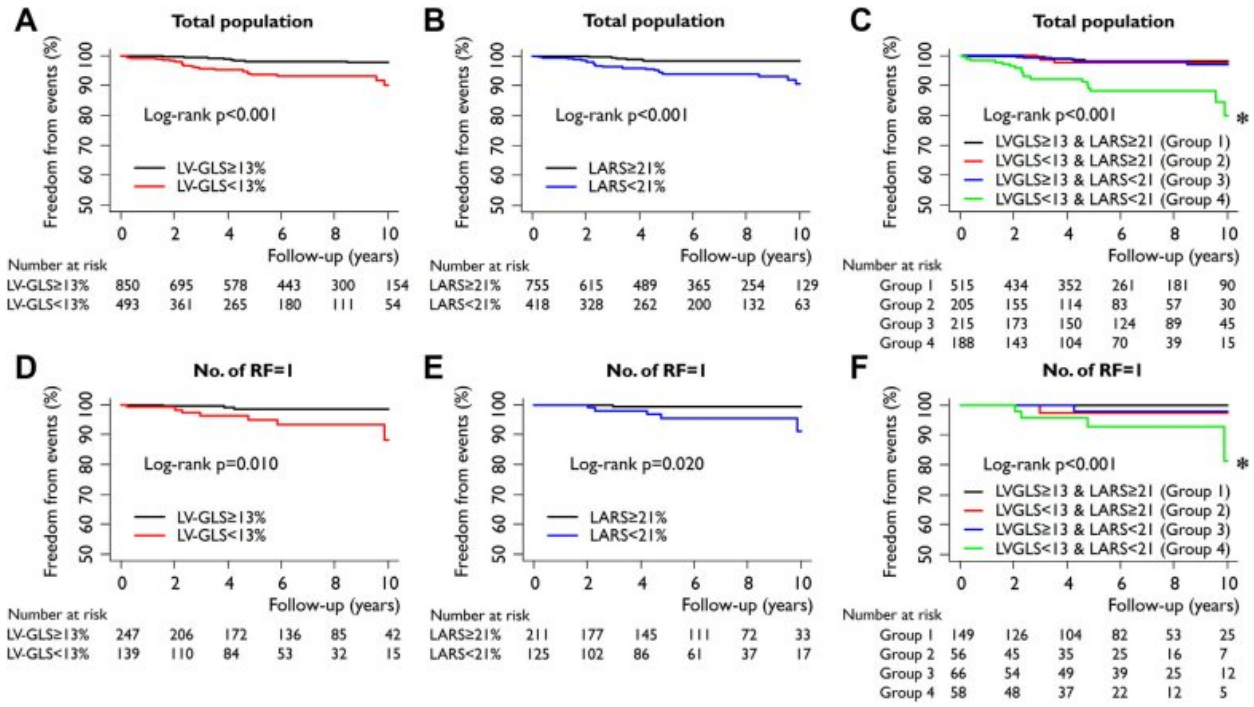
performance within 2 years after the index evaluation, and performance slowly deteriorated on nearing 10 years. Harrell's C-index was 0.686 (95% CI: 0.600-0.772) and 0.701 (95% CI: 0.619-0.783) for the AHA/ACC risk factor strategy and the ESC risk score, respectively ($P$ for comparison = 0.640).

The sensitivity and specificity for predicting 5-year SCD events by using recommendations from the guidelines are shown in Supplemental Table 4. For both Class 2a and Class 2b recommendations, the 2020 AHA/ACC guidelines had higher sensitivity but lower specificity compared with the 2014 ESC guidelines, and the positive predictive value for a Class 2a recommendation was only 6.7%. Using the threshold of multiple (≥2 or ≥3) risk factors improved the specificity of the 2020 AHA/ACC model, although sensitivity was decreased, becoming similar to the 2014 ESC model.

**MYOCARDIAL STRAIN AS A PREDICTOR OF SCD EVENTS.** LV GLS was measured in 1,343 patients (94.8%), and LARS was measured in 1,173 (82.8%). Patients with SCD events had lower LV GLS (11.9% vs 14.2%; $P < 0.001$) and LARS (18.2% vs 24.4%; $P < 0.001$) than patients without SCD events (**Table 1**). The associations among LV GLS, LARS, and established SCD risk factors are shown in Supplemental Tables 5 and 6.

The respective 1% decreases in LV GLS and LARS were associated with approximately 15% and 10% increases in the risk for SCD events, independent of age, sex, and the number of AHA/ACC risk factors or the ESC risk score (**Table 3**). These associations between myocardial strain and SCD events were also independent of decreased LVEF (<50%), extensive LV fibrosis (LGE ≥15%), and LV wall thickness (Supplemental Table 7). Restricted cubic spline plots of HRs demonstrated a consistently increased risk of SCD events with lower LV GLS and LARS (Supplemental Figure 4A). The optimal thresholds for discriminating an increased SCD risk determined by ROC analysis were approximately <13% for LV GLS and <21% for LARS (Supplemental Figure 4B). Event-free survival rates were significantly worse in patients with LV GLS <13% and LARS <21% than in their counterparts (**Figures 3A to 3C**). The estimated 5-year SCD event rates were 6.4% (95% CI: 3.7%-9.1%) vs 1.9% (95% CI: 0.1%-3.0%) for patients with LV GLS <13% vs ≥13% ($P < 0.001$) and 6.1% (95% CI: 4.7%-13.8%) vs 1.9% (95% CI: 0.1%-3.0%) for patients with LARS <21% vs. ≥21% ($P < 0.001$). Patients with both LV GLS <13%

**FIGURE 3** Incidence of Sudden Cardiac Death Events According to LV GLS and LARS Cutoffs




Patients were stratified by the suggested thresholds of left ventricular global longitudinal strain (LV GLS) and left atrial reservoir strain (LARS). In the (A to C) total study group and in (D to F) patients with a single risk factor (RF), decreased left ventricular global longitudinal strain (<13%) and left atrial reservoir strain (<21%) were associated with a significantly increased incidence of sudden cardiac death events. (C and F) Asterisks denote a significant difference in event-free survival from the reference group (group 1) in adjusted pairwise comparisons.

and LARS <21% had the highest risk for SCD events within with an estimated 5-year SCD event rate of 11.8% (95% CI: 6.0%-17%) (Figure 3C).

LV -GLS <13% and LARS <21% were independently associated with a 3- to 4-fold increase in the risk for SCD events, after adjustment for age, sex, and guideline-established SCD risk models (Table 3).

**INCREMENTAL PROGNOSTIC VALUE OF MYOCARDIAL STRAIN TO THE GUIDELINES.** In the 1,123 patients with both LV GLS and LARS measurements, there were 32 SCD events. In nested Cox regression models, the addition of LV GLS <13% or LARS <21% to the AHA/ACC risk factor strategy (Figure 4A) or the ESC risk score (Figure 4B) resulted in significant increases in the global chi-square and Harrell's C-indices of models, thus demonstrating the incremental prognostic value of LV GLS and LARS for predicting SCD events. The addition of LV GLS <13% and LARS <21% simultaneously further improved SCD prediction.

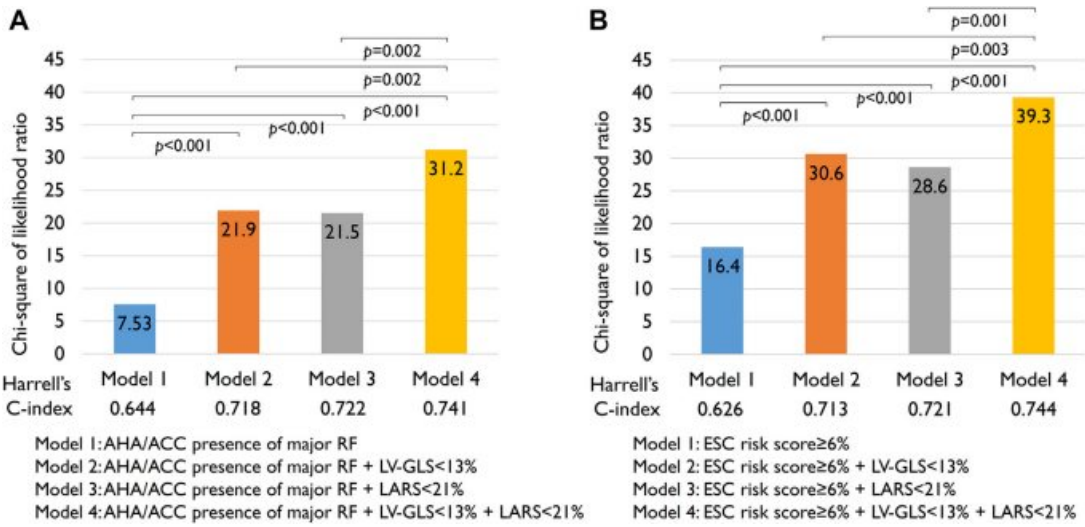
We performed exploratory analyses on various ways to integrate myocardial strain into the AHA/ACC SCD risk stratification strategy. Models adding either 1 or both of LV GLS <13% and LARS <21% as risk factors in addition to the 7 risk factors in the 2020 AHA/ACC guidelines, when the number of risk factors was coded as a continuous variable, had similar performance for prediction of SCD events over 10 years in ROC(t) analyses (Supplemental Figure 5A). These

**TABLE 3** Independent Association of LV GLS and LARS With SCD Events

| | HR (95% CI) | *P* Value |
|---|---|---|
| Adjusted for the 2020 AHA/ACC model (no. of risk factors), age, and sex | | |
| LV GLS (per 1% decrease) (absolute) | 1.14 (1.06-1.22) | <0.001 |
| LARS (per 1% decrease) | 1.10 (1.06-1.16) | <0.001 |
| LV GLS (absolute) <13% | 3.66 (1.86-7.20) | <0.001 |
| LARS <21% | 3.30 (1.54-7.08) | 0.002 |
| Adjusted for the 2014 ESC model (5-y SCD risk score), age, and sex | | |
| LV GLS (per 1% decrease) (absolute) | 1.17 (1.08-1.26) | <0.001 |
| LARS (per 1% decrease) | 1.09 (1.04-1.14) | <0.001 |
| LV GLS (absolute) <13% | 4.86 (2.41-9.83) | <0.001 |
| LARS <21% | 2.86 (1.30-6.26) | 0.009 |

Abbreviations as in Table 1.

**FIGURE 4 Incremental Value of LV GLS and LARS to the Guidelines**




The addition of left ventricular global longitudinal strain (LV GLS) <13% and left atrial reservoir strain (LARS) <21% to the (A) 2020 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines and (B) 2014 European Society of Cardiology (ESC) guidelines demonstrated incremental prognostic value for sudden cardiac death events in nested Cox regression models. RF = risk factor.

models also had a tendency for better performance compared with the original 2020 AHA/ACC and 2014 ESC guideline models (Supplemental Figure 5B), especially in the immediate period within 5 years of index evaluation. Adding LV GLS <13% and/or LARS <21% as additional 2020 AHA/ACC risk factors also resulted in significant improvement in Harrell's C-index, the category-free net reclassification index, and the integrated discrimination improvement index (Supplemental Table 8). Of note, if decreased myocardial strain is included as a risk factor, the threshold for ICD should be considered at a higher number of risk factors, for instance in patients with ≥3 or ≥2 risk factors (Supplemental Figures 6A and 6B).

In patients with only a single risk factor, additional stratification with myocardial strain could help identify patients at higher risk of SCD events. The estimated 5-year SCD event rates were 4.9% (95% CI: 0.5%-9.1%) vs 1.6% (95% CI: 0.0%-3.4%) for patients with LV GLS <13% vs ≥13% ($P = 0.010$) (**Figure 3D**). The same was true for LARS <21%; the estimated 5-year SCD event rates were 4.4% (95% CI: 0.1%-8.5%) vs 0.6% (95% CI: 0.0%-1.9%) for patients with LARS <21% vs ≥21% ($P = 0.020$) (**Figure 3E**). Combining LV GLS <13% and LARS <21% could discriminate patients at the highest risk for SCD events with an estimated 5-year SCD event rate of 7.2% (95% CI: 0%-15%) among those patients with a single risk factor (**Figure 3F**).

## DISCUSSION

The main findings of the current study can be summarized as follows:

1. In a large Asian HCM cohort, a high proportion of patients would be recommended to undergo ICD implantation when applying the 2020 AHA/ACC guidelines (29% had Class 2a and 15% had Class 2b recommendations); however, SCD events occurred in only 24 or 412 (5.8%) and 6 of 208 (2.9%) of patients with Class 2a and Class 2b recommendations, respectively.
2. SCD risk was significantly increased in patients with multiple risk factors but not in patients with a single risk factor in general. However, LVEF <50% as a lone risk factor was associated with an increased SCD risk.
3. Performances of the 2020 AHA/ACC risk factor strategy and 2014 ESC risk score did not differ significantly up to 10 years, and both models showed greatest performance within 2 years of the index evaluation. The AHA/ACC guidelines showed higher sensitivity but lower specificity compared with the ESC guidelines.

4. Decreased LV GLS and LARS were independently associated with a higher SCD risk.
5. The addition of LV GLS and LARS provided incremental prognostic value to the established SCD risk models.

This study is the first to provide an in-depth evaluation of the SCD risk factor profiles and their association with SCD events according to the 2020 AHA/ACC guidelines in a large cohort of Asian patients with HCM. We demonstrated that the 2020 AHA/ACC guidelines, compared with the 2014 ESC guidelines, showed higher sensitivity and low specificity despite similar performance for SCD risk discrimination. This finding is in line with results of previous studies that compared the AHA/ACC and ESC guidelines.[5,18] However, the higher sensitivity of the 2020 AHA/ACC guidelines reinforces the dilemma of deciding who should receive an ICD for the primary prevention of SCD. Additional risk factors were included in the guidelines, adding up to a total of 7, which resulted in >40% of the study cohort possessing at least 1 risk factor. This situation can inevitably lead to overestimation of the need for ICD implantation for primary prevention. The findings that 30% of the patients with SCD events did not have an AHA/ACC risk factor and 65% were categorized as low risk by the ESC risk score also bespeak the need for further refinement of the SCD risk stratification models.

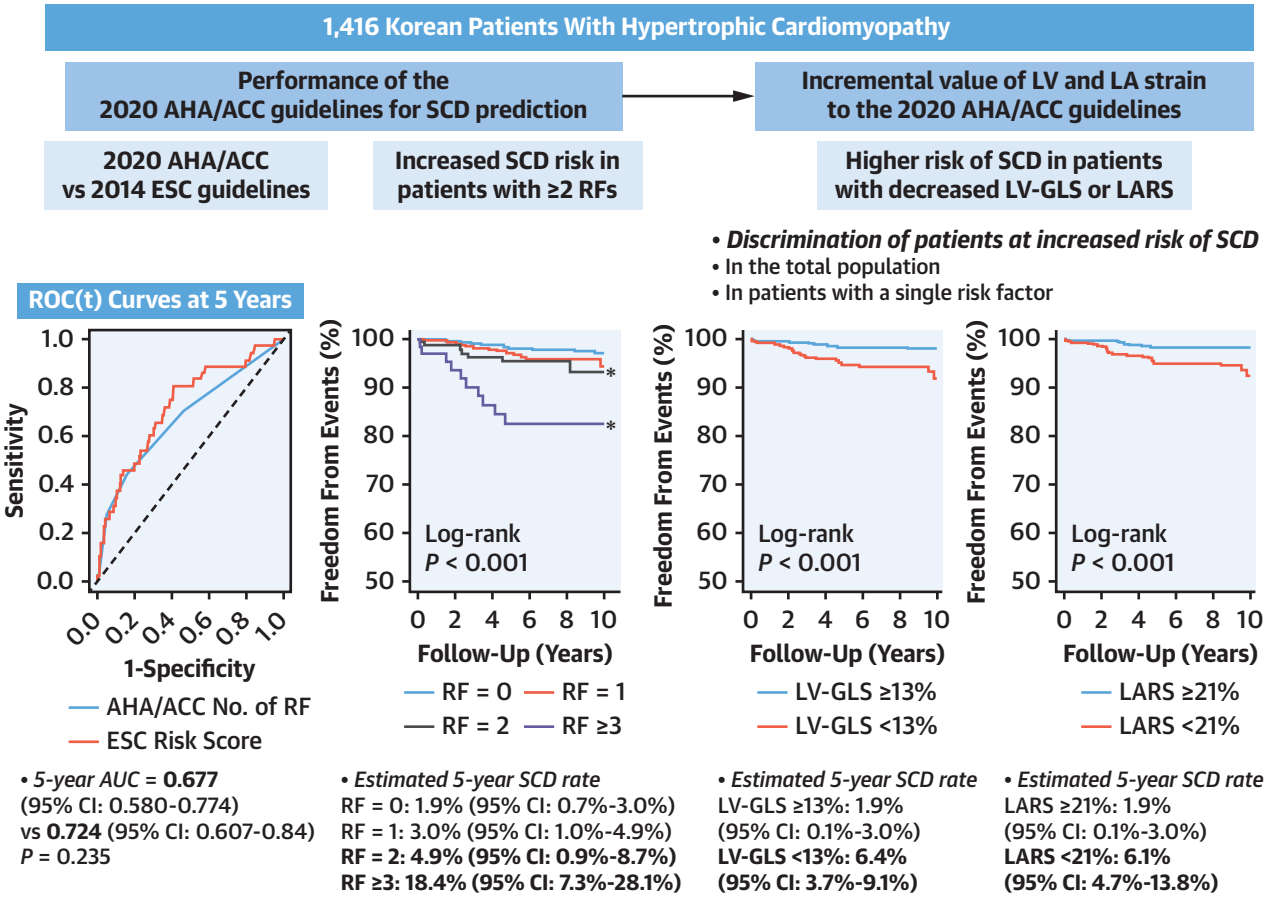
Previous cohort studies reported that risk stratification on the basis of the presence of the 2020 AHA/ACC risk factors had performance that was better than or comparable to the 2014 ESC risk score.[5-7] However, previous studies did not categorize the risk factors into major and nonmajor risk factors as recommended in the guidelines, nor did they provide the time-dependent performance comparison of the risk factor construct. The 2020 AHA/ACC guidelines state that ICD implantation is reasonable in patients with the 5 major risk factors (Class 2a recommendation) and may be considered in patients with only nonmajor risk factors, namely extensive LGE or NSVT (Class 2b recommendation).[3] Our study provides evidence for these recommendations in part, considering that the SCD risk was significantly increased in patients with ≥1 major risk factor, whereas the SCD risk associated with the presence of only nonmajor risk factors did not reach statistical significance. However, the current study also suggests that ICD recommendation on the basis of the presence of a single risk factor needs to be reconsidered or considered on a case-by-case basis, except in patients with "end-stage" HCM (ie, LVEF <50%). It seems that the number rather than the presence of risk factors more accurately reflects the risk of SCD events, and thus our study suggests that the strength of recommendations for ICD should be fine-tuned on the basis of the number of risk factors (**Central Illustration**).

In the current study, the lone presence of unexplained syncope or massive LV hypertrophy (≥30 mm) did not seem to confer an increased risk of SCD events. Although unexplained syncope that is unlikely to be neurally mediated is a traditional risk factor for SCD in HCM,[19,20] its definition and mechanisms are not clear, and there is no solid evidence on whether unexplained syncope itself in the absence of other risk factors increases the risk of SCD events. Moreover, data are conflicting on whether massive LV hypertrophy increases SCD risk and the optimal LV wall thickness threshold,[21-24] which may also differ according to imaging modality or ethnicity.[25,26] Data from large cohorts showed that an inverted U-shaped relationship seems to exist between maximum LV wall thickness and SCD risk.[23,24] This finding may account for the lack of association between massive LV hypertrophy and SCD observed in this study, especially considering that Asian patients with HCM have lower LV wall thickness than other ethnicities.[26]

Performances of the 2020 AHA/ACC and 2014 ESC guidelines for SCD prediction were good in the immediate period after the index evaluation (especially within 2 years), but they progressively deteriorated over time. Performances were modest at 5 years with AUCs of 0.677 and 0.724, respectively. This finding provides objective evidence for the guideline recommendation that SCD risk should be re-evaluated at 1- to 2-year intervals.[2,3]

We and others previously demonstrated that decreased LV GLS was independently associated with the SCD risk,[11,27] an association that was again confirmed here. We also found that decreased LARS was also independently associated with SCD events. This may be related to the fact that LARS reflects increased LV filling pressure and LV diastolic dysfunction,[12,13] driven by myocardial hypertrophy and fibrosis or scar change in HCM, which is also related to SCD risk. Atrial myopathy and arrhythmia may also contribute directly to an increased SCD risk.[28,29] The estimated 5-year SCD event rates in patients with decreased LV GLS (<13%) and LARS (<21%) were both >6%, which definitely signifies a high-risk group. Myocardial strain also showed prognostic value for SCD events in addition to the 2020 AHA/ACC risk factors or the 2014 ESC risk score. Of note, our study showed that SCD risk increased in

**CENTRAL ILLUSTRATION** **Performance of AHA/ACC Guidelines and Incremental Value of Myocardial Strain**




**Lee H-J, et al. JACC: Asia. 2024;4(1):10-22.**

The 2020 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines have similar performance to the 2014 European Society of Cardiology (ESC) guidelines, and the risk of sudden cardiac death (SCD) is proportional to the number of risk factors(RFs). Left ventricular global longitudinal strain (LV GLS) and left atrial reservoir strain (LARS) have incremental value to the guidelines for sudden cardiac death risk stratification. Asterisks denote a significant difference in event-free survival from the reference group (RF = 0) in adjusted pairwise comparisons. AUC = area under the curve; ROC(t) = time-dependent receiver-operating characteristic.

proportion to the number of 2020 AHA/ACC risk factors and that SCD risk was not significantly increased in most patients with only a single risk factor. Importantly, in patients with only a single risk factor, decreased LV GLS or LARS, alone or in combination, could discriminate between patients at low risk and at increased risk of SCD. Myocardial strain also has the merit of being easily extracted from routine echocardiography examinations without the expense or risk associated with additional imaging tests. Incorporation of myocardial strain into the current SCD risk assessment strategy should be considered to improve risk stratification in the decision to perform ICD implantation for primary prevention, especially in patients with only a single risk factor for SCD (Central Illustration).

**STUDY LIMITATIONS.** First, patients with missing Holter monitor or CMR results were considered as not having the risk factor of NSVT or LGE when assessing the presence of SCD risk factors. Although this approach may have undermined the performance of the SCD risk stratification models, it reflects the SCD risk assessment taking place in real-world clinical practice. Validation studies of the previous AHA/

ACC guidelines have used the same approach to missing data.[6,30] Second, the study group consisted of only Koreans, and there may be some ethnic differences in disease characteristics and clinical management affecting the study results. Third, although our study demonstrates that myocardial strain has incremental value to the AHA/ACC and ESC guidelines for SCD risk stratification, further studies are needed to confirm these results and decide the best method to integrate myocardial strain into SCD risk stratification models.

## CONCLUSIONS

In a large cohort of Asian patients with HCM, the 2020 AHA/ACC risk factor strategy was predictive of SCD events with modest predictive power. ICD implantation is reasonable in patients with multiple risk factors, but it needs to be reconsidered in those patients with only a single risk factor. Decreased LV GLS and LARS were independently associated with a risk of SCD events, and incorporation of myocardial strain into the current prediction models can improve SCD risk stratification.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** The 2020 AHA/ACC guidelines showed performance similar to that of the 2014 ESC guidelines for predicting SCD events. The number rather than the presence of risk factors may more accurately reflect SCD risk. Myocardial strain had additional prognostic value to both guidelines.

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** ICD placement is reasonable in patients with multiple risk factors according to the 2020 AHA/ACC guidelines, but it should be carefully considered in those with only a single risk factor. Decreased LV GLS and LARS can improve SCD risk stratification.

**TRANSLATIONAL OUTLOOK:** Further research should confirm the prognostic value of myocardial strain and the best method to integrate myocardial strain into SCD risk stratification models for patients with HCM.

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**KEY WORDS** echocardiography, hypertrophic cardiomyopathy, myocardial deformation, risk factors, sudden cardiac death

**APPENDIX** For an expanded Methods section and supplemental figures, tables, and references, please see the online version of this paper.