






Original research

Prognosis of patients with hypertrophic cardiomyopathy and low-normal left ventricular ejection fraction

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ABSTRACT

Objective To investigate whether low-normal left ventricular ejection fraction (LVEF) is associated with adverse outcomes in hypertrophic cardiomyopathy (HCM) and evaluate the incremental value of predictive power of LVEF in the conventional HCM sudden cardiac death (SCD)-risk model.

Methods This retrospective study included 1858 patients with HCM from two tertiary hospitals between 2008 and 2019. We classified LVEF into three categories: preserved ($\geq 60\%$), low normal ($50\%–60\%$) and reduced ($<50\%$); there were 1399, 415, and 44 patients with preserved, low-normal, and reduced LVEF, respectively. The primary outcome was a composite of SCD, ventricular tachycardia/fibrillation and appropriate implantable cardioverter-defibrillator shocks. Secondary outcomes were hospitalisation for heart failure (HHF), cardiovascular death and all-cause death.

Results During the median follow-up of 4.09 years, the primary outcomes occurred in 1.9%, HHF, cardiovascular death, and all-cause death occurred in 3.3%, 1.9%, and 5.3%, respectively. Reduced LVEF was an independent predictor of SCD/equivalent events (adjusted HR (aHR) 5.214, 95% CI 1.574 to 17.274, $p=0.007$), adding predictive value to the HCM risk-SCD model (net reclassification improvement 0.625). Compared with patients with HCM with preserved LVEF, those with low-normal and reduced LVEF had a higher risk of HHF (LVEF $50\%–60\%$, aHR 2.457, 95% CI 1.423 to 4.241, $p=0.001$; LVEF $<50\%$, aHR 7.937, 95% CI 3.315 to 19.002, $p<0.001$) and cardiovascular death (LVEF $50\%–60\%$, aHR 2.641, 95% CI 1.314 to 5.309, $p=0.006$; LVEF $<50\%$, aHR 5.405, 95% CI 1.530 to 19.092, $p=0.009$), whereas there was no significant association with all-cause death.

Conclusions Low-normal LVEF was an independent predictor of HHF and cardiovascular death in patients with HCM.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy characterised by left ventricular (LV) hypertrophy in the absence of explainable abnormal loading conditions.¹ Although major advances in treating disease-related complications have made HCM a controllable disease with extended longevity,^{2,3} approximately 2%–5% of patients experience disease progression to end-stage HCM, defined as an LV ejection

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The 2020 American Heart Association/American College of Cardiology guideline for hypertrophic cardiomyopathy (HCM) recommends a left ventricular ejection fraction (LVEF) $<50\%$ as a predictor of sudden cardiac death (SCD) and an indication for an implantable cardioverter-defibrillator (class of recommendation IIa).

WHAT THIS STUDY ADDS

⇒ Low-normal left ventricular systolic function, in which LVEF is higher than 50% but not in the normal range (ie, LVEF of $50\%–60\%$), was a hazardous condition representing a higher risk of hospitalisation for heart failure and cardiovascular death in patients with HCM. Additionally, LVEF is an independent factor with incremental value for predicting SCD when added to the conventional HCM risk-SCD model.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides supportive evidence for the need for more aggressive management and surveillance of patients with HCM with low-normal left ventricular systolic function, who were previously overlooked. Also, our findings support that LVEF should be considered in the HCM risk-SCD model.

fraction (LVEF) $<50\%$.⁴ Although rare, the development of LV systolic dysfunction is considered an unfavourable HCM clinical course with a substantial risk of morbidity and mortality.^{5–7}

The 2020 American Heart Association/American College of Cardiology (AHA/ACC) guideline for HCM recommends an LVEF $<50\%$ as a predictor of sudden cardiac death (SCD).⁸ However, little is known about the clinical implication of low-normal LVEF $50\%–60\%$ in HCM.⁹ Moreover, an LVEF $<50\%$ is only a class IIa recommendation for an implantable cardioverter-defibrillator (ICD) indication,^{4,8} and the additional predictive value of an LVEF $<50\%$ to the 5-year risk-SCD score endorsed by the 2014 European Society of Cardiology (ESC) guidelines has not yet been determined.^{8,10} Therefore, we

Table 1 Baseline characteristics of patients stratified based on left ventricular (LV) ejection fraction (LVEF)

Variable	Total N=1858	LV systolic function			P value
		LVEF ≥60% N=1399	LVEF 50%–60% N=415	LVEF <50% N=44	
Demographic data					
Age, years	60.0 (52.0–71.0)	63.0 (53.0–71.0)*	61.0 (51.0–72.0)	57.0 (45.5–66.0)†	0.010
Male, n (%)	1263 (68.0)	924 (66.0)‡	311 (74.9)†	28 (63.6)	0.002
Systolic blood pressure, mm Hg	129.0 (118.0–140.0)	129.0 (119.0–140.0)	128.0 (117.0–140.0)	122.0 (110.0–141.5)	0.223
Diastolic blood pressure, mm Hg	75.0 (69.0–82.0)	75.0 (69.0–81.0)‡	77.0 (70.0–84.0)†*	75.0 (65.0–80.75)‡	0.022
Body mass index, kg/m ²	24.8 (22.9–26.8)	24.8 (23.0–26.8)	24.8 (22.8–27.0)	23.6 (20.9–26.4)	0.196
Comorbidities, n (%)					
Hypertension	1031 (55.5)	778 (55.6)	235 (56.6)	18 (40.9)	0.135
Diabetes mellitus	387 (20.8)	289 (20.7)	90 (21.7)	8 (18.2)	0.820
Dyslipidaemia	670 (36.1)	516 (36.9)	137 (33.0)	17 (38.6)	0.329
End-stage renal disease	17 (1.0)	15 (1.1)	1 (0.2)	1 (2.3)	0.173
Atrial fibrillation	267 (14.4)	175 (12.5)†*	80 (19.3)†	12 (27.3)†	<0.001
Ischaemic stroke	212 (11.4)	167 (12.0)	38 (9.2)	7 (15.9)	0.182
Mitral regurgitation	40 (2.2)	30 (2.1)	9 (2.2)	1 (2.3)	0.998
Percutaneous coronary intervention	86 (4.6)	63 (4.5)	18 (4.3)	5 (11.4)	0.097
Beta-blocker	865 (46.6)	643 (46.0)	196 (47.2)	26 (59.1)	0.217
ICD implantation	54 (2.9)	38 (2.7)*	11 (2.7)*	5 (11.4)††	<0.001
Risk factors for SCD, n (%)					
Family history of SCD	133 (7.2)	95 (6.8)*	30 (7.2)*	8 (18.2)††	0.016
Unexplained syncope	188 (10.1)	141 (10.1)	46 (11.1)	1 (2.3)	0.181
Non-sustained VT (N=960)§	238 (24.8)	167 (23.1)	64 (30.3)	7 (29.2)	0.085
Echocardiographic data					
LV end-diastolic volume, mL	64.6 (52.7–80.0)	64.0 (52.4–78.9)†*	65.0 (52.0–82.4)†*	98.6 (79.5–115.0)††	<0.001
LV end-systolic volume, mL	23.0 (18.1–51.0)	21.6 (17.1–27.0)†*	28.0 (22.0–35.3)†*	53.8 (44.3–66.2)††	<0.001
LVEF, %	63.9 (60.0–67.4)	65.5 (63.0–68.6)†*	57.4 (55.7–58.7)†*	43.9 (40.8–47.4)††	<0.001
e' velocity, m/s	4.9 (4.0–6.0)	4.9 (4.0–6.0)*	4.9 (4.0–6.0)*	4.0 (3.1–4.5)††	<0.001
E/e' ratio	12.5 (9.8–16.2)	12.3 (9.6–16.1)*	12.1 (10.0–15.7)*	16.7 (14.1–19.5)††	<0.001
LA dimension, mm	43.3 (39.0–49.0)	43.0 (39.0–48.0)†*	44.5 (40.0–50.2)†*	51.5 (42.0–57.5)††	<0.001
LA volume index, mL/m ²	43.8 (34.5–56.5)	42.9 (34.0–55.4)†*	44.7 (36.2–59.1)†*	62.4 (39.4–79.9)††	<0.001
PASP, mm Hg	31.0 (26.2–36.6)	31.0 (26.2–36.0)	30.0 (25.8–35.0)	33.0 (28.8–39.4)	0.159
LV-MWT, mm	18.0 (16.0–20.0)	17.8 (16.0–20.0)	18.0 (16.0–20.0)	17.0 [15.0–19.7]	0.098
LV-MWT ≥30 mm	16 (0.9)	10 (0.7)	6 (1.4)	0 (0.0)	0.302
LVOTmaxPG, mm Hg	6.5 (4.0–14.6)	6.7 (4.3–18.3)*†	5.6 (3.6–10.2)†	4.0 (2.6–8.6)†	<0.001

*P<0.05 compared with the group with reduced LVEF.

†P<0.05 compared with the group with preserved LVEF.

‡P<0.05 compared with the group with low-normal LVEF.

§Among 1858 patients, 960 patients underwent 24-hour Holter monitoring.

E/e', ratio of peak early diastolic transmitral inflow velocity to e' velocity; e' velocity, early diastolic mitral annular velocity; ICD, implantable cardioverter-defibrillator; LA, left atrium; LV-MWT, maximal LV wall thickness; LVOTmaxPG, maximal LV outflow tract pressure gradient; PASP, pulmonary arterial systolic pressure; SCD, sudden cardiac death; VT, ventricular tachycardia.

aimed to investigate the prognostic value of LVEF 50%–60% in a large cohort of patients with HCM. Also, we attempted to confirm the prognostic value of LVEF <50% as an imaging biomarker of SCD/equivalent events to support the 2020 AHA/ACC guideline for HCM.⁸

METHODS

Study design and study population

This cohort study recruited 1936 consecutive patients diagnosed with HCM between 2008 and 2019 from two tertiary university hospitals. An end-diastolic maximal LV wall thickness (LV-MWT) ≥15 mm on echocardiography without abnormal loading conditions that sufficiently explain LV hypertrophy is generally considered diagnostic for HCM.^{8–10} Furthermore, LV-MWT ≥13 mm can be considered diagnostic in family members of patients with HCM⁸ and patients with an LVEF <50% were included regardless of their LV-MWT if they had prior objective evidence of HCM on echocardiography and/or cardiac MRI.¹¹ In this study, all recruited patients

met this diagnostic criterion after reviewing the electronic medical records. Based on exclusion criteria (online supplemental methods), a total of 1858 patients (median age, 60.0 years (52.0–71.0 years); 1263 men (68.0%)) were included in the final analysis (online supplemental figure 1).

Echocardiography and measurement of LVEF

Comprehensive transthoracic echocardiography was performed in a standard fashion using commercially available ultrasound machines (Vivid 7, GE Healthcare, Chicago, Illinois, USA; i33, Philips, Amsterdam, The Netherlands; Sequoia, Siemens Medical Solutions, Malvern, Pennsylvania, USA) according to current guidelines by expert sonographers and reviewed by an echocardiographer.^{12–13} LVEF was calculated using the biplane method of discs as recommended by the current guideline.¹⁴ LVEF measurement reproducibility was calculated in 20 randomly selected patients by demonstrating the intraclass correlation coefficient (ICC).

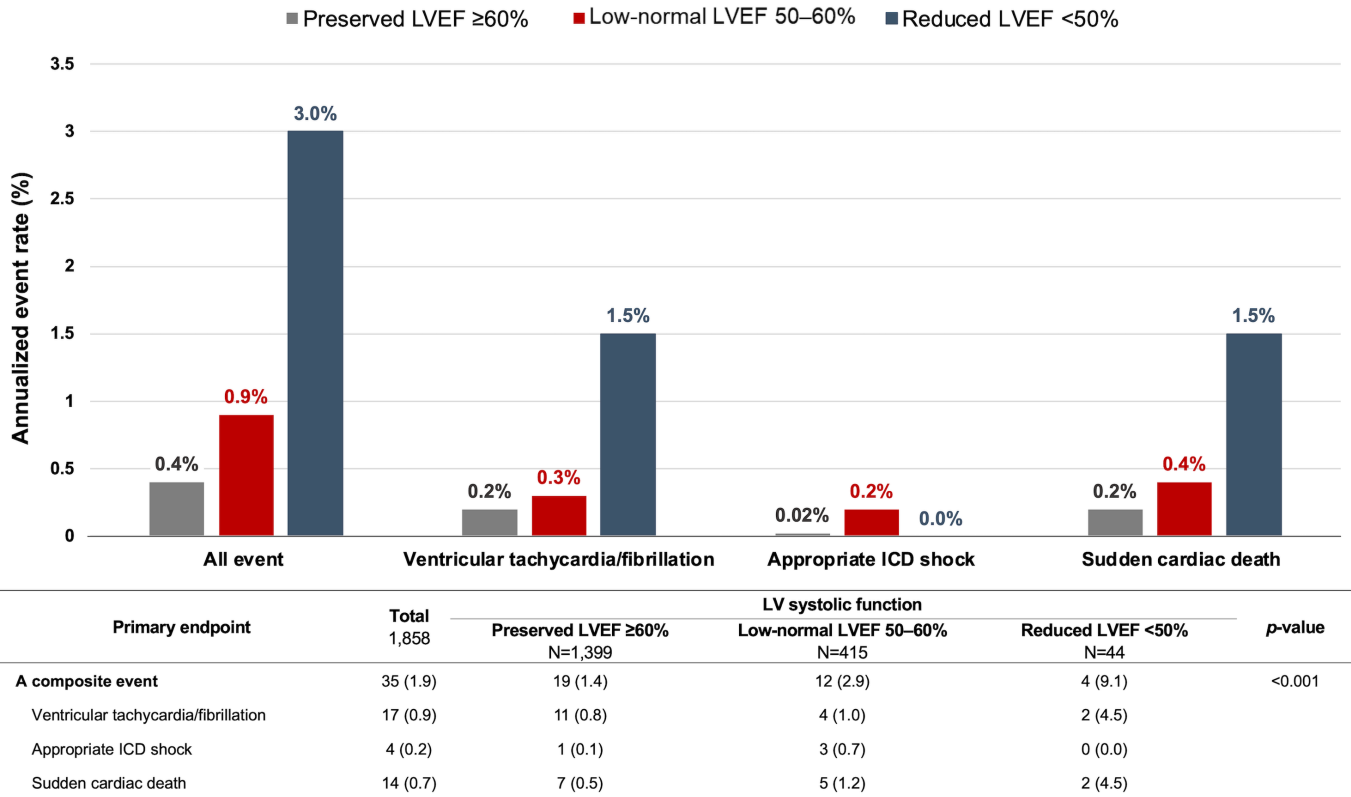


Figure 1 Annualised event rates of the primary outcomes. Annualised event rates of primary outcome including ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator (ICD) shock and sudden cardiac death, in patients with hypertrophic cardiomyopathy are classified based on left ventricular ejection fraction (LVEF).

We classified patients into three groups based on their LVEF: preserved LVEF ≥60%, low-normal LVEF 50%–60% and reduced LVEF <50%.

Risk factors for SCD and the 5-year HCM risk-SCD score

Patients had undergone a comprehensive personal and family history and physical examination as part of the routine clinical care, two-dimensional transthoracic echocardiography and 24-hour Holter monitoring at baseline. The 5-year risk-SCD scores were calculated for each patient using the 5-year HCM risk-SCD model endorsed by the 2014 ESC guidelines (online supplemental methods).¹⁰ We classified patients into three categories: low risk (<4%), intermediate risk (4%–6%) and high risk (≥6%) of SCD.¹⁰

Definition of clinical outcomes

The primary outcome was a composite of SCD and equivalent events, including documented ventricular tachycardia/fibrillation, appropriate ICD shocks and aborted SCD. Only sustained pulseless or unstable ventricular tachycardia or ventricular fibrillation was considered SCD equivalent events. The secondary outcomes were hospitalisation for heart failure (HHF), cardiovascular death and all-cause death. Detailed definitions of each outcome are described in online supplemental methods.¹⁵

Patients were censored when they underwent heart transplantation due to end-stage HCM. Each patient was followed from the date of the initial echocardiography until either the occurrence of any of the clinical outcomes, death from any cause, the end of the study follow-up (31 December 2020) or completion of 5 years of follow-up, whichever came first.

Potential incremental predictive value

We calculated the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) by comparing the

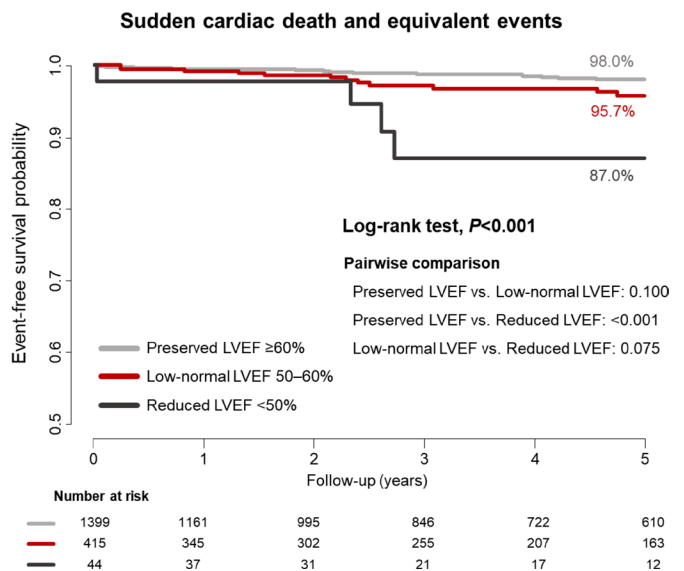


Figure 2 Kaplan-Meier curves for the primary outcomes in patients with hypertrophic cardiomyopathy classified based on their left ventricular ejection fraction (LVEF). The Kaplan-Meier event-free survival curves for primary outcome, a composite of ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator shocks and aborted sudden cardiac death.

Table 2 Multivariate Cox proportional regression analysis for the primary and secondary outcomes

Variable	Multivariate analysis*			Multivariable analysis†		
	HR	95% CI	P value	HR	95% CI	P value
Primary outcomes (SCD/equivalent events)						
LVEF, % (as a continuous variable)	0.954	0.917 to 0.993	0.020	–	–	–
Preserved LVEF ≥60%	–	–	–	1.000	Reference	–
Low-normal LVEF 50%–60%	–	–	–	1.838	0.886 to 3.812	0.102
Reduced LVEF <50%	–	–	–	5.214	1.574 to 17.274	0.007
Secondary outcomes						
Hospitalisation for HF						
LVEF, % (as a continuous variable)	0.940	0.912 to 0.970	<0.001	–	–	–
Preserved LVEF ≥60%	–	–	–	1.000	Reference	–
Low-normal LVEF 50%–60%	–	–	–	2.457	1.423 to 4.241	0.001
Reduced LVEF <50%	–	–	–	7.937	3.315 to 19.002	<0.001
Cardiovascular death						
LVEF, % (as a continuous variable)	0.936	0.901 to 0.973	<0.001	–	–	–
Preserved LVEF ≥60%	–	–	–	1.000	Reference	–
Low-normal LVEF 50%–60%	–	–	–	2.641	1.314 to 5.309	0.006
Reduced LVEF <50%	–	–	–	5.405	1.530 to 19.092	0.009
All-cause death						
LVEF, % (as a continuous variable)	0.967	0.937 to 0.999	0.044	–	–	–
Preserved LVEF ≥60%	–	–	–	1.000	Reference	–
Low-normal LVEF 50%–60%	–	–	–	1.524	0.942 to 2.466	0.086
Reduced LVEF <50%	–	–	–	2.349	0.834 to 6.613	0.106

The primary outcome was a composite of SCD and equivalent events, including documented ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator shocks and aborted SCD.

*Adjusted for baseline variables with a p<0.1 in the univariate analysis with LVEF as a continuous variable (%) (refer to online supplemental table 2).

†Adjusted for baseline variables with a p<0.1 in the univariate analysis with LVEF as a categorical variable (LVEF ≥60%, LVEF 50%–60% and LVEF <50%) (refer to online supplemental table 2).

HF, heart failure; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

predictive probabilities of the HCM risk-SCD risk category alone with the predictive probabilities of the HCM risk-SCD risk category endorsed by the 2014 ESC guidelines¹⁰ in combination with LVEF as a continuous or categorical variable, respectively. The conventional HCM risk-SCD model uses seven risk factors to calculate the risk-SCD score (online supplemental methods). Therefore, NRI and IDI were calculated only in patients with all seven risk factors (N=897).

Statistical analysis

Continuous variables were expressed as means±SD or medians (IQR), and categorical variables were expressed as frequencies (percentages). We compared the three LVEF groups using either the one-way analysis of variance or Kruskal-Wallis test for continuous variables and the X² test or Fisher's exact test for categorical variables. In the post hoc analysis, we used the Tukey honest significant difference test for pairwise comparisons.

Cumulative event-free survival was estimated using the Kaplan-Meier method and compared with the log-rank test. We performed pairwise post hoc analysis for a log-rank test using a Bonferroni adjustment for multiple comparisons. The proportional hazards assumption was checked using a statistical test based on Schoenfeld residuals and their plots. Time zero was defined as the date of the initial echocardiography. HR was calculated in the Cox proportional hazards model and presented as the 95% CI and p value. Variables that first achieved a p<0.1 in the univariate Cox regression were assessed in a multivariable model. Two different multivariable Cox proportional hazards models were created, where LV systolic function was entered as

either a continuous (LVEF in %) or categorical variable (LVEF ≥60%, LVEF 50%–60% and LVEF <50%).

NRI and IDI were computed using the package 'Hmisc' in R programming based on the methods described by Pencina *et al.*¹⁶ Moreover, a competing risk analysis of HHF was performed with mortality as a competing risk.

All analyses used a two-sided p value, and a p<0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, V.25.0 (IBM Corp) and R software, V.4.2.2 (<http://www.R-project.org>); The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

The median LVEF in the entire cohort of 1858 patients with HCM was 63.9% (60.0%–67.4%), among which 1399 (75.3%), 415 (22.3%), and 44 (2.4%) patients had a preserved LVEF of ≥60%, low-normal LVEF of 50%–60%, and reduced LVEF of <50%, respectively. The intraobserver and interobserver variability for LVEF measurement were good, with ICCs of 0.860 (95% CI 0.664 to 0.945) and 0.879 (95% CI 0.715 to 0.952), respectively.

The baseline demographic and clinical characteristics of the study population in the three LVEF groups are outlined in [table 1](#). The median age of the study population was 60.0 years (52.0–71.0 years), and the prevalence of hypertension was 55.5%. Patients with reduced LVEF were significantly younger than those with preserved LVEF (63.0 years (53.0–71.0 years) vs 57.0 years (45.5–66.0 years); p<0.001). Atrial fibrillation

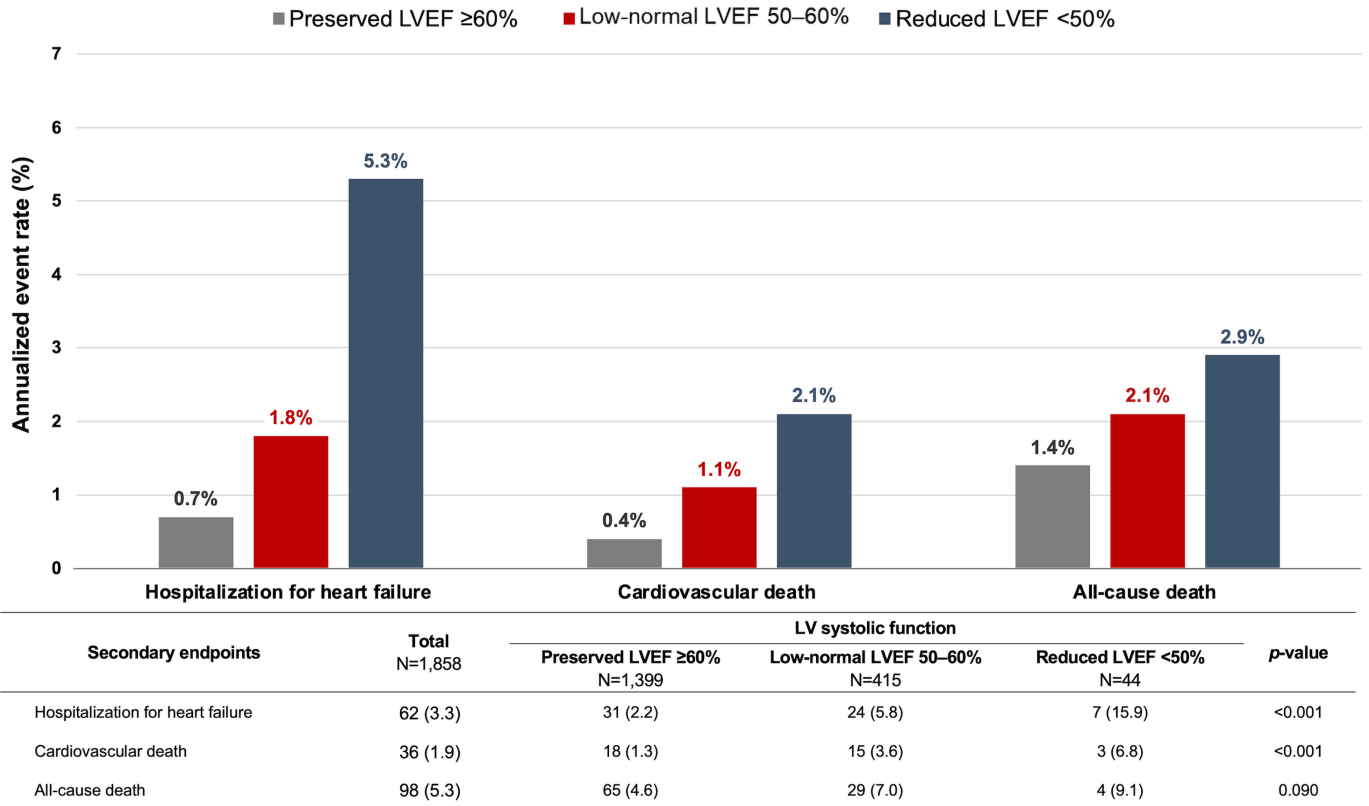


Figure 3 Annualised event rates of the secondary outcomes. Annualised event rates of secondary outcomes, such as hospitalisation for heart failure, cardiovascular death and all-cause death in patients with hypertrophic cardiomyopathy, are classified based on left ventricular ejection fraction (LVEF).

was more frequent in patients with low-normal and reduced LVEF than in those with preserved LVEF (19.3% and 27.3% vs 12.5%, $p < 0.001$). Compared with patients with preserved and low-normal LVEF, those with reduced LVEF had the highest prevalence of a family history of SCD (6.8% and 7.2% vs 18.2%, $p = 0.016$). Regarding echocardiographic parameters, patients with reduced LVEF had the largest LV volumes and largest left

atrial (LA) sizes, the lowest e' velocities and the highest E/e' ratios (all $p < 0.001$). The maximal LV outflow tract pressure gradient was smaller in patients with low-normal and reduced LVEF than in those with preserved LVEF ($p < 0.001$). During follow-up, there were two patients who underwent heart transplantation; one patient each in LVEF <50% and LVEF 50%–60% groups after HHF.

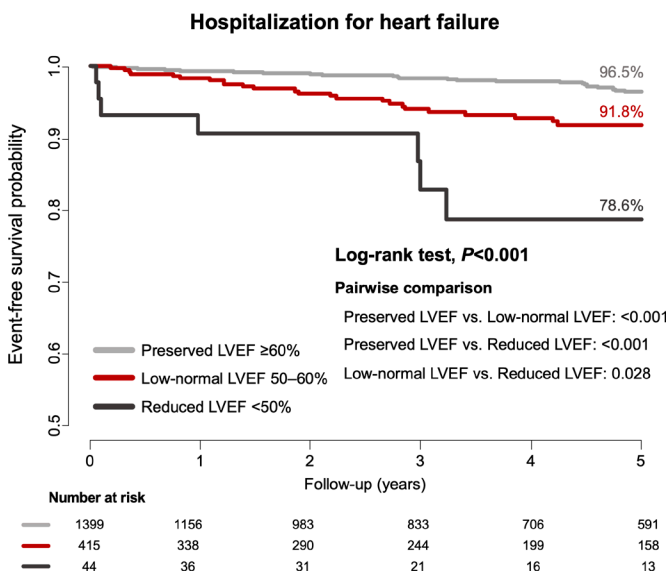


Figure 4 Kaplan-Meier curves for hospitalisation for heart failure in patients with hypertrophic cardiomyopathy classified based on their left ventricular ejection fraction (LVEF).

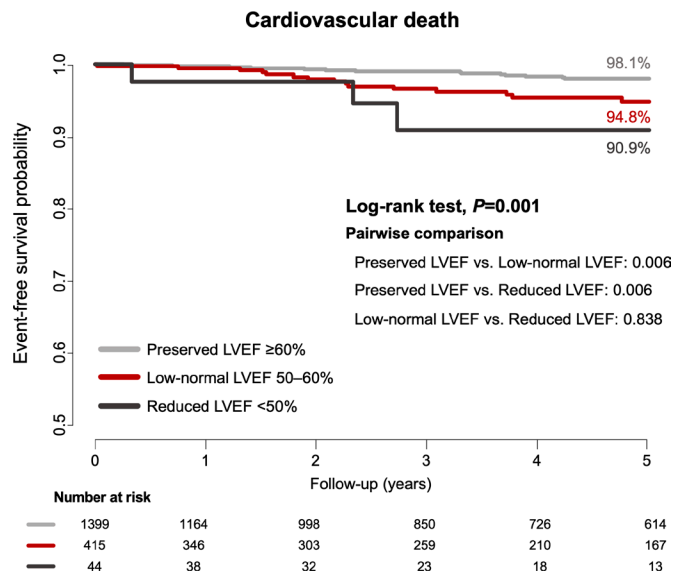


Figure 5 Kaplan-Meier curves for cardiovascular death in patients with hypertrophic cardiomyopathy classified based on their left ventricular ejection fraction (LVEF).

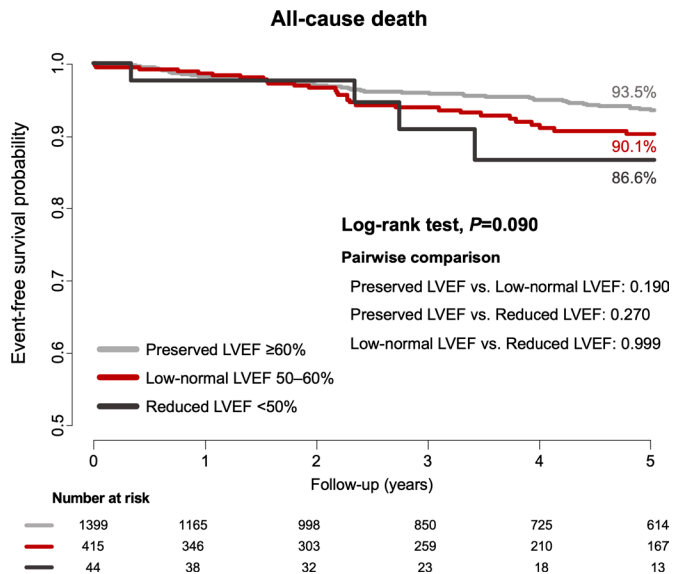


Figure 6 Kaplan-Meier curves for all-cause death in patients with hypertrophic cardiomyopathy classified based on their left ventricular ejection fraction (LVEF).

Primary outcome

During the median follow-up duration of 4.09 years (1.66–5.00 years), the primary outcome was attained in 35 (1.9%). Ventricular tachycardia/fibrillation occurred in 17 (0.9%), appropriate ICD shocks in 4 (0.2%) and SCD in 14 (0.7%). The annualised event rate of the primary outcome according to LVEF categories is shown in [figure 1](#) and online supplemental table 1.

Kaplan-Meier curves showed that the event-free survival probability for the primary outcome was significantly different among the three groups being 98.0%, 95.7%, and 87.0% in patients with preserved, low-normal, and reduced LVEF, respectively (log-rank test, $p < 0.001$, [figure 2](#)). In the univariate Cox analysis, SCD/equivalent events were associated with LVEF (%) and the LVEF categories, as were age, a family history of SCD, unexplained syncope and LA dimension (online supplemental table 2). The multivariable Cox analysis indicated that a higher LVEF (%) was associated with a significantly lower risk of SCD/equivalent events (adjusted HR 0.954, 95% CI 0.917 to 0.993, $p = 0.020$). In addition, a reduced LVEF was an independent predictor of SCD/equivalent events compared with preserved LVEF (adjusted HR 5.214, 95% CI 1.574 to 17.274, $p = 0.007$), whereas low-normal LVEF did not increase the risk of SCD/equivalent events compared with preserved LVEF ([table 2](#)). There was no effect modification by age on the association between LVEF and primary outcomes (online supplemental table 3).

Secondary outcomes

Overall, HHF occurred in 62 (3.3%), cardiovascular death in 36 (1.9%) and all-cause death in 98 (5.3%). The annualised event rates of each secondary outcome according to LVEF categories are shown in [figure 3](#) and online supplemental table 1. The reasons for cardiovascular death included SCD (N=14)/ventricular fibrillation (N=1), heart failure-related death (N=11) and ischaemic stroke-related death (n=6). Other causes include acute myocardial infarction and cardiovascular operation-related or procedure-related complications.

Kaplan-Meier curves showed a significant difference in the event-free survival probability between the three groups in terms of HHF (log-rank test, $p < 0.001$, [figure 4](#)) and cardiovascular

death (log-rank test, $p = 0.001$, [figure 5](#)), but not all-cause death (log-rank test, $p = 0.090$, [figure 6](#)). In the multivariable Cox analysis, both LVEF (%) and the LVEF categories were significantly associated with risks of HHF and cardiovascular death ([table 2](#)). There was no effect modification by age on the association between LVEF and secondary outcomes (online supplemental table 3). When mortality was considered a competing risk, LVEF was again significantly associated with the risk of HHF (online supplemental table 4).

Incremental value of LVEF in predicting SCD

The incremental predictive value of LVEF was assessed in the 897 patients for whom all seven risk factors can be identified. Among them, 681 (75.9%), 194 (21.6%), and 22 (2.5%) patients had preserved, low-normal, and reduced LVEF, respectively. The median 5-year HCM risk-SCD score was highest in patients with reduced LVEF (median score, 2.05% (1.40%–3.35%), 2.37% (1.52%–3.73%) and 2.55% (1.82%–3.52%) in patients with preserved, low-normal and reduced LVEF, respectively; $p = 0.019$), whereas the proportion of the three risk-SCD risk categories did not differ statistically between the three groups ($p = 0.109$) (online supplemental table 5). When added to the 5-year HCM risk-SCD category, LVEF as a continuous and categorical variable significantly improved the risk classification for SCD/equivalent events (LVEF (%): NRI 0.576 and IDI 0.041; the LVEF categories: NRI 0.625 and IDI 0.042) (online supplemental table 6).

DISCUSSION

This large cohort study of patients with HCM evaluated the clinical implications of low-normal LVEF in predicting adverse long-term clinical outcomes including SCD/equivalent events, HHF, cardiovascular death and all-cause death. The main findings are twofold: in patients with HCM, (1) low-normal LV systolic function, defined as an LVEF 50%–60%, was strongly associated with the risk of HHF and cardiovascular death, but not SCD/equivalent events; and (2) reduced LV systolic function, defined as an LVEF $< 50\%$, was an independent predictor for SCD/equivalent events, HHF and cardiovascular death, and provided an added predictive value for SCD/equivalent events to the 5-year HCM risk-SCD model.

Low-normal LV systolic function in HCM

HCM research on the prediction and prevention of SCD to date has focused on end-stage HCM with an LVEF $< 50\%$.^{6,7} Contrastingly, only limited attention has been paid to HCM with LVEF ranges from 50% to 60%. Olivotto *et al* proposed four clinical stages of HCM: non-hypertrophic HCM, classic HCM phenotype, adverse remodelling and overt dysfunction.¹⁷ Among these, the *adverse remodelling stage* represents worsening LV systolic function with relatively preserved clinical and haemodynamic balance. During this stage, several structural and functional features, including an LVEF in the low-normal range may coexist.^{10,18} However, all of these phenomena are not expected to be present in a single patient simultaneously, given that HCM is a heterogeneous disease, and all clinical and pathological manifestations are not always found concomitantly.¹⁷ Nevertheless, there has been no compelling evidence for the clinical and prognostic implications of low-normal LVEF in HCM.¹⁰ In this context, the novel findings of our study illustrate that the risks of HHF and cardiovascular death progressively increased from preserved, low-normal LVEF to end-stage HCM. This suggests that low-normal LVEF is not simply the preceding or transition

phase of end-stage HCM but needs to be considered an independent high-risk population requiring close clinical attention and monitoring.

In addition, despite no statistical significance in the multivariate analysis, SCD/ventricular fibrillation (15 of 36) accounted for a non-negligible fraction of cardiovascular deaths in the low-normal LVEF group. Therefore, large-scale longitudinal independent studies are necessary to establish knowledge of this unnoticed but unique population.

LV systolic dysfunction in HCM

LV systolic dysfunction in HCM is associated with substantial myocardial fibrosis and haemodynamic decompensation, potentially causing the fatal arrhythmia.^{19,20} Notably, end-stage HCM has a few clinical and histopathological characteristics, including HCM occurrence at a young age, heterogeneous patterns of LV remodelling and extensive myocardial fibrosis,^{4,21} all of which are associated with ventricular tachyarrhythmias.^{22,23} We also observed similar findings in the current study; that is, patients with HCM with LVEF <50% were the youngest and had the highest cases in family history of SCD.

Recently, Rowin *et al* demonstrated that end-stage HCM with an LVEF <50% is a significant risk for SCD, with no difference in the frequency of these events in patients with an LVEF <35%, and suggested an LVEF <50% as the threshold for recommending an ICD for primary prevention of SCD in HCM.⁶ In this regard, our study demonstrated that patients with HCM with an LVEF <50% had a fivefold higher risk of SCD/equivalent events than those with preserved LVEF. On the other hand, patients with low-normal LVEF were not at higher risk of SCD/equivalent events than those with preserved LVEF, supporting an LVEF <50% as an appropriate threshold for primary prevention ICDs. Moreover, we showed that a reduced LVEF can predict SCD/equivalent events and has incremental predictive value when added to the 5-year HCM risk-SCD prediction model. This is of value in that the 5-year HCM risk-SCD model does not consider LV systolic dysfunction.⁸ Hence, our findings do support the adoption of an LVEF <50% as a new indication for the primary prevention of SCD in the 2020 AHA/ACC guideline.⁸ Furthermore, the present study provides supportive evidence that LVEF is an additional risk factor that needs to be considered in the 5-year HCM-SCD risk score, especially for low and intermediate-risk patients.^{10,24}

LVEF as an easy-to-use and clinically useful prognostic factor in HCM

HCM is a highly heterogeneous disease with variable timings of disease onset and progression, phenotypes and clinical courses, such as normal longevity, progression to end-stage heart failure or SCD.^{25,26} Therefore, disease progression requiring medical management cannot be effectively predicted, necessitating an individualised approach and periodical follow-up. Although a few imaging markers were suggested as potential prognostic factors in patients with HCM,^{10,15} LVEF remains the most validated and commonly used indicator of LV systolic function because of its high reproducibility and ease of use.²⁷ We found that LVEF not only predicts SCD/equivalent events but also long-term clinical outcomes, such as HHF and cardiovascular death in HCM. Consequently, this easy-to-measure and well-validated imaging marker is an important tool for the clinical monitoring of patients with HCM.

Meanwhile, we did not observe an association between reduced LVEF and all-cause mortality in this study. We cannot

explain this comprehensively but assume that with the substantial improvement in HCM management, a 5-year follow-up might be too short to elucidate the impact of LV systolic dysfunction on all-cause mortality. Of note, a recently reported study demonstrated the supplemental role of LV global longitudinal strain for predicting SCD in HCM.²⁸ Therefore, further studies regarding the clinical implications of the LV global longitudinal strain are warranted to aid risk stratification in patients with HCM and low-normal LVEF.

Study limitations

First, this study was retrospectively analysed on pre-existing data of the prospective HCM registry. Accordingly, there could be missing values of variables to be used in the HCM-SCD risk model, leading to the possibility of selection bias. Second, our study cohort mainly consisted of Asian patients. Thus, the results of our study may not be generalisable given the potential racial and genetic differences among populations with HCM.^{29,30} Moreover, we did not provide genetic information for this population with HCM because only 198 patients underwent genetic testing. Fourth, despite our large HCM cohort, including almost 2000 patients, the number of patients with an LVEF <50% was relatively small, but statistical significance could be confirmed even with a wide CI. This might be partly explained by the fact that we excluded patients who required secondary prevention, who might be already in the burnout stage of HCM. Finally, we did not demonstrate serial changes in LVEF. We believe that this issue is of clinical interest and requires further studies.

CONCLUSIONS

In this large HCM cohort, we observed that patients with low-normal LVEF were at an increased risk of HHF and cardiovascular death compared with patients with preserved LVEF. In addition, LV systolic dysfunction, defined as an LVEF <50%, provided additional prognostic information above and beyond the 5-year HCM risk-SCD score.

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Contributors YJ Choi and HK Kim designed the study. HK Kim developed the theory and performed the computations. HKK, ICH, JBP, YEY, SPL, GYC, and YJK acquired data (patient recruitment). HK Kim, IC Hwang, and YJ Choi verified the analytical methods. HK Kim and IC Hwang encouraged YJ Choi to investigate and supervised the findings of this work. CS Park, TM Rhee, HJ Lee, JB Park, YE Yoon, SP Lee, GY Cho, and YJ Kim contributed to the interpretation of the results. YJ Choi, IC Hwang, and HK Kim wrote the manuscript. All authors approved the final version and are accountable for the integrity of the work. HKK and ICH accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Supplemental Material

Title: Prognosis of patients with hypertrophic cardiomyopathy and low-normal left ventricular ejection fraction

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Detailed Methods

Study population

This cohort study recruited 1936 consecutive patients diagnosed with hypertrophic cardiomyopathy (HCM) between 2008 and 2019 from two tertiary university hospitals. HCM was diagnosed by only experienced cardiologists who have more than 10 years of clinical and echocardiographic experience, based on the guidelines (1). All echocardiographic images were thoroughly reviewed and double-checked. In cases where HCM diagnosis was ambiguous, cardiac magnetic resonance imaging was performed in cooperation with cardiovascular radiologists. Additionally, in order to verify HCM diagnosis, we re-confirmed the diagnosis of HCM based on the morphology of left ventricular (LV) hypertrophy pattern (apical, asymmetrical septal hypertrophy, etc.), as well as the extent of blood pressure control.

We applied the following exclusion criteria: competitive sports and other causes of LV hypertrophy, such as Noonan syndrome, Fabry disease, glycogen storage disease, cardiac amyloidosis, and mitochondrial disease; and eligibility for secondary prevention of sudden cardiac death (SCD) (i.e., history of spontaneous ventricular tachycardia, ventricular fibrillation, or cardiac arrest) or ischemic cardiomyopathy (i.e., LV ejection fraction [LVEF] \leq 40% with a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery). Based on these criteria, 22 patients were excluded because they were candidates for secondary prevention and four because they had combined ischemic cardiomyopathy. Additionally, 49 patients were excluded due to inadequate echocardiographic data and five due to lack of data for follow-up.

Risk factors for SCD and 5-year HCM Risk-SCD score

All patients had undergone a comprehensive personal and family history and physical examination at baseline. The following factors were systematically assessed to determine the 5-year Risk-SCD scores (1); (i) age at initial evaluation, (ii) family history of SCD, defined as SCD in one or more first-degree relatives under 40 years of age or in a first-degree relative with confirmed HCM at any age, (iii) the history of unexplained syncope, (iv) non-sustained ventricular tachycardia, documented by 24-hour Holter monitoring or pacemaker/ICD recording, which was defined as ≥ 3 beats at a rate of ≥ 120 beats per minute, and lasting < 30 seconds; and (v) echocardiographic parameters including maximal LV outflow tract pressure gradient (mmHg), maximal LV wall thickness (mm), and left atrial dimension (mm).

LV wall thickness was assessed at end-diastole using two-dimensional echocardiography, and maximal LV wall thickness was measured as the thickest segment of the LV wall (2). The left atrial anteroposterior dimension was measured at end-systole from the parasternal view. The maximal LV outflow tract pressure gradient was recorded as the largest value using continuous-wave Doppler at rest and/or during the Valsalva manoeuvre.

Definition of primary and secondary outcomes

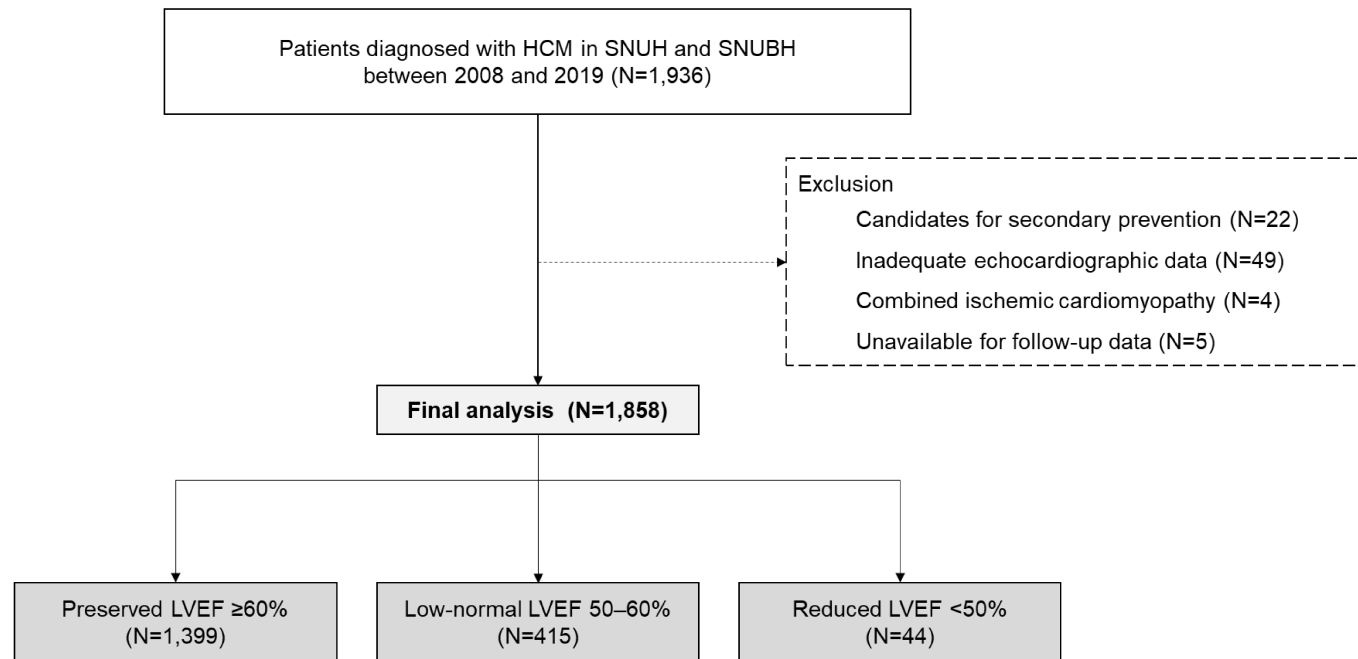
The primary endpoint was a composite of SCD and equivalent events, including documented ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator (ICD) shocks, and aborted SCD. SCD was defined as an unexpected, witnessed arrest within hours of the patient being in a previously stable clinical condition or within 1 hour of a new onset of any symptom that could be interpreted as originating in the heart. Death occurring in bed overnight with no antecedent history of worsening symptoms was also considered SCD and aborted SCD was considered a successful resuscitation after cardiac arrest (3). An ICD shock was considered appropriate if the tachyarrhythmia had originated from the ventricle,

documented by stored electrocardiographic data. Patients with an ICD were evaluated regularly by an experienced electrophysiologist (4). The secondary endpoints were hospitalization for heart failure (HHF), cardiovascular death, and all-cause death. HHF was defined as hospitalizing a patient with new or worsening symptoms and/or signs of heart failure requiring new heart failure medication or the addition of intravenous medications for improvement (5).

Deaths and their causes were ascertained using the National Death Registration Records of Korea and/or witness interviews in the case of death outside of the hospital and using hospital electrical medical records in the case of death in the hospital. Patients were censored when they underwent heart transplantation due to end-stage HCM.

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Supplemental Figures**Supplemental Figure 1.** Flow chart of the study population

HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; SNUH, Seoul National University Hospital; SNUBH, Seoul National University Boondang Hospital.

Supplemental Tables

Supplemental Table 1. Annualized event rate according to LVEF category

Outcomes	Annualized event rate (95% confidence interval)		
	Preserved LVEF $\geq 60\%$ N=1,399	Low-normal LVEF 50–60% N=415	Reduced LVEF $< 50\%$ N=44
Primary outcomes			
Ventricular tachycardia/fibrillation	0.41 (0.244–0.633)	0.87 (0.449–1.518)	0.56 (0.809–7.606)
Appropriate ICD shock	0.23 (0.117–0.420)	0.29 (0.079–0.742)	1.49 (0.180–5.365)
Sudden cardiac death	0.02 (0.001–0.119)	0.22 (0.045–0.635)	0.00 (0.000–0.000)
	0.15 (0.060–0.308)	0.36 (0.118–0.845)	1.49 (0.180–5.365)
Secondary outcomes			
Hospitalization for heart failure	0.67 (0.455–0.951)	1.79 (1.150–2.670)	5.31 (2.135–10.941)
Cardiovascular death	0.38 (0.227–0.604)	1.08 (0.603–1.776)	2.14 (0.442–6.258)
All-cause death	1.38 (1.066–1.760)	2.08 (1.394–2.990)	2.86 (0.778–7.310)

Abbreviations: LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.

Supplemental Table 2. Univariate Cox proportional hazard regression analysis for primary and secondary outcomes

Variable	Univariate analysis		
	HR	95% CI	P
Primary outcomes (SCD/equivalent events)			
LVEF, % (<i>as a continuous variable</i>)	0.938	0.905–0.972	<0.001
Preserved LVEF $\geq 60\%$	1.000	(reference)	-
Low-normal LVEF 50–60%	2.148	1.043–4.425	0.038
Reduced LVEF <50%	7.295	2.479–21.467	<0.001
Age, years	0.976	0.953–0.999	0.041
Male	0.960	0.511–2.128	0.910
Atrial fibrillation	1.022	0.397–2.634	0.964
Family history of SCD	3.056	1.335–6.997	0.008
Unexplained syncope	3.718	1.785–7.740	<0.001
LA dimension, mm	1.053	1.013–1.095	0.009
LV-MWT, mm	1.025	0.940–1.117	0.578
LVOTmaxPG, mmHg	1.005	0.996–1.014	0.281
Hospitalization for HF			
LVEF, %	0.937	0.913–0.962	<0.001
Preserved LVEF $\geq 60\%$	1.000	(reference)	-
Low-normal LVEF 50–60%	2.688	1.577–4.580	<0.001
Reduced LVEF <50%	7.977	3.510–18.130	<0.001
Age, years	1.049	1.026–1.073	<0.001
Male, n (%)	0.382	0.232–0.630	<0.001
Atrial fibrillation	2.627	1.518–4.548	<0.001
Family history of SCD	1.049	0.421–2.618	0.918
Unexplained syncope	1.530	0.755–3.101	0.238
LA dimension, mm	1.092	1.062–1.122	<0.001
LV-MWT, mm	1.065	1.004–0.130	0.037
LVOTmaxPG, mmHg	1.000	0.991–1.009	0.976
Cardiovascular death			
LVEF, %	0.936	0.905–0.969	<0.001
Preserved LVEF $\geq 60\%$	1.000	(reference)	-
Low-normal LVEF 50–60%	2.799	1.411–5.555	0.003
Reduced LVEF <50%	5.542	1.632–18.826	0.006
Age, years	1.074	1.040–1.109	<0.001
Male, n (%)	0.477	0.248–0.916	0.026

Atrial fibrillation	2.059	0.969–4.379	0.061
Family history of SCD	0.696	0.167–2.899	0.619
Unexplained syncope	0.532	0.128–2.216	0.386
LA dimension, mm	1.076	1.037–1.116	<0.001
LV-MWT, mm	1.033	0.950–1.123	0.451
LVOTmaxPG, mmHg	1.006	0.998–1.015	0.121
All-cause death			
LVEF, %	0.975	0.947–1.003	0.079
Preserved LVEF \geq 60%	1.000	(reference)	-
Low-normal LVEF 50–60%	1.510	0.975–2.339	0.065
Reduced LVEF <50%	2.040	0.743–5.600	0.167
Age, years	1.078	1.057–1.100	<0.001
Male, n (%)	0.635	0.426–0.947	0.026
Atrial fibrillation	2.004	1.265–3.176	0.003
Family history of SCD	0.374	0.118–1.179	0.093
Unexplained syncope	1.024	0.533–1.970	0.943
LA dimension, mm	1.056	1.031–1.080	<0.001
LV-MWT, mm	1.017	0.965–1.072	0.536
LVOTmaxPG, mmHg	1.005	0.995–1.010	0.073

The primary outcome was a composite of SCD and equivalent events, including documented ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator shocks, and aborted SCD. Abbreviations: CI, confidence interval; HR, hazard ratio; LA left atrium; LV, left ventricle; LVEF, LV ejection fraction; LVOTmaxPG, maximal LV outflow tract pressure gradient; LV-MWT, maximal LV wall thickness; SCD, sudden cardiac death.

Supplemental Table 3. Effect modification of age on primary and secondary outcomes

Variable	<i>P</i> for interaction
Primary outcomes (SCD/equivalent events)	
LVEF, %	0.586
Preserved LVEF $\geq 60\%$	-
Low-normal LVEF 50–60%	0.368
Reduced LVEF $< 50\%$	0.678
Hospitalization for HF	
LVEF, %	0.688
Preserved LVEF $\geq 60\%$	
Low-normal LVEF 50–60%	0.681
Reduced LVEF $< 50\%$	0.079
Cardiovascular death	
LVEF, %	0.718
Preserved LVEF $\geq 60\%$	
Low-normal LVEF 50–60%	0.878
Reduced LVEF $< 50\%$	0.178
All-cause death	
LVEF, %	0.233
Preserved LVEF $\geq 60\%$	
Low-normal LVEF 50–60%	0.341
Reduced LVEF $< 50\%$	0.662

Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

Supplemental Table 4. Cox proportional regression analysis for hospitalization for heart failure with mortality considered as a competing risk

Variable	Univariate analysis			Multivariate analysis ^a		
	HR	95% CI	P	HR	95% CI	P
Categorical variable						
LVEF category ^b	2.740	1.890–3.990	<0.001	2.538	1.639–3.930	0.001
Continuous variable						
LVEF, %	0.937	0.912–0.963	<0.001	0.941	0.910–0.972	0.001

^a Adjusted for age, gender, atrial fibrillation, left atrial size, and maximal wall thickness.

^b LVEF category was LVEF \geq 60%, LVEF 50–60%, and LVEF <50%

Abbreviations: CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

Supplemental Table 5. The 5-year HCM Risk-SCD score stratified based on LVEF in 897 HCM patients with a complete dataset of seven risk factors

Variable	LV systolic function			P
	Preserved LVEF $\geq 60\%$ N=681	Low-normal LVEF 50–60% N=194	Reduced LVEF $< 50\%$ N=22	
HCM Risk-SCD score, %^a	2.05 [1.40–3.35]	2.37 [1.52–3.73]	2.55 [1.82–3.52]	0.019
HCM Risk-SCD category				0.109
Low-risk ($< 4\%$)	557 (81.8)	147 (75.8)	18 (81.8)	
Intermediate-risk (4–6%)	80 (11.7)	25 (12.9)	1 (4.5)	
High-risk ($\geq 6\%$)	44 (6.5)	22 (2.5)	3 (13.6)	

Continuous variables were presented as median [interquartile range], and categorical variables were presented as frequencies (percentages).

Abbreviations: HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

^aRisk score was calculated by the 5-year HCM Risk-SCD model endorsed by the 2014 European Society of Cardiology guidelines on diagnosis and management of HCM.

Supplemental Table 6. Net reclassification index and integrated discrimination index for SCD/equivalent events ^a

Variable	Model 1			Model 2			Model 3		
	Value	95% CI	P	Value	95% CI	P	Value	95% CI	P
HCM Risk-SCD category^b plus LVEF (%)									
Net reclassification improvement	0.576	0.161–0.991	0.007	0.322	0.276–0.369	<0.001	0.249	0.201–0.297	<0.001
Integrated discrimination improvement	0.041	0.004–0.078	0.029	0.018	0.001–0.037	0.049	0.009	-0.005–0.019	0.064
HCM Risk-SCD category^b plus LVEF category^c									
Net reclassification improvement	0.625	0.205–1.045	0.004	0.531	0.489–0.573	<0.001	0.531	0.489–0.579	<0.001
Integrated discrimination improvement	0.042	0.003–0.081	0.035	0.021	0.001–0.042	0.040	0.013	0.007–0.025	0.038

Abbreviations: CI, confidence interval; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death.

Model 1 included 897 patients for whom all seven risk factors can be identified.

Model 2 included 1,614 patients without information on the presence or absence of NSVT. In this model, we put the missing value on NSVT as negative.

Model 3 included 1,614 patients without information on the presence or absence of NSVT. In this model, we put the missing value on NSVT as positive.

^a SCD-equivalent events included documented ventricular tachycardia/fibrillation, appropriate implantable cardioverter-defibrillator shocks, and aborted SCD.

^b HCM Risk-SCD category according to 2014 European Society of Cardiology guidelines; low risk (<4%), intermediate risk (4–6%), or high risk (≥6%).

^c LVEF was classified into three categories; preserved LVEF (≥60%), low-normal LVEF (50–60%), and reduced LVEF (<50%).