Predictors of Long-Term Outcomes in Hypertrophic Cardiomyopathy (HCM): The NHLBI HCM Registry

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KEY POINTS:

Question: What are the important historical, imaging, genetic, and blood biomarker predictor of risks in hypertrophic cardiomyopathy?

Findings: Primary composite outcomes in HCM were predicted by cardiac magnetic resonance (CMR) imaging measures of left ventricular (LV) structure including mass and replacement fibrosis/scar extent, LV function, heart failure history, and N-terminal pro B-type natriuretic peptide (NTproBNP). Sudden cardiac death outcomes, including appropriately treated ventricular arrhythmias, were predicted by LV structure and function and NTproBNP.

Meaning: These results provide strong prospective evidence for incorporating CMR and NTproBNP in the evaluation of HCM patients.

ABSTRACT

Importance. Current risk prediction guidelines for hypertrophic cardiomyopathy (HCM) predict only sudden cardiac death (SCD) and are imperfect, leading to avoidable deaths and unnecessary implantable cardioverter-defibrillator implantations.

Objective. We hypothesized that combining prospectively collected clinical history, imaging, genetic, and biomarker data could improve risk prediction of adverse events in HCM.

Design. 2750 HCM patients underwent a health history questionnaire, blood sampling for biomarkers and genotyping, and contrast-enhanced cardiac magnetic resonance imaging (CMR). The predefined composite adjudicated primary endpoint was time to first event for: 1) HCM-related deaths; 2) Nonfatal sustained ventricular arrhythmias (VA) requiring cardioversion or defibrillation; 3) Left ventricular (LV)

assist device implantation/heart transplantation. A secondary endpoint was a composite of SCD and nonfatal VA events. Elastic-net methodology identified the most important predictors. Cox proportional hazards regression assessed associations with time to first endpoint. The 2750 patients were prospectively enrolled from 44 sites in North America and Europe with expertise in HCM and CMR. 2,698 (98%) had analysable data, as 9 were HCM phenocopies and 43 withdrew.

Exposure: Mean follow-up was 6.9±2.1 years. Patients were followed yearly by telephone and records review regarding event documentation.

Main Outcomes. Of the 2698 patients, 71% were male, mean age was 50±11 years, and 16% were from underrepresented groups. The primary event model (in 104 patients) included LV scar as % of LV mass by late gadolinium enhancement (LGE) (hazard ratio (HR) 1.86, $p<0.001$, Confidence interval (C.I.) (1.58 – 2.20)), LV mass index (LVMI) (HR 1.09, $p=0.030$, C.I. (1.01 – 1.17)), LV end-systolic volume index (HR 1.28, $p<0.001$, C.I. 1.12 – 1.46)), all per 10-unit increase, history of heart failure (HF) at study entry (HR 2.89, $p<0.001$, C.I. (1.75 – 4.77)), and log N-terminal pro B-type natriuretic peptide (NTproBNP) (HR 1.41, $p<0.001$, C.I. (1.17 – 1.70)) per log unit, (C-index for all 0.77). LGE% ≥9% substantially increased the primary composite event rate ($p = 0.001$). The secondary SCD/VA risk factor model (in 69 patients) included LGE %, LVMI, LV ejection fraction, and log(NTproBNP), (C-index 0.76).

Conclusions. These results provide strong prospective evidence for incorporating CMR and NTproBNP in the evaluation of HCM patients.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM), with a prevalence of 1 in 500, is the most frequent cause of sudden cardiac death (SCD) in young individuals[1-3] and is characterized by primary left ventricular hypertrophy, replacement and interstitial fibrosis, and myofibrillar disarray.[4] While some patients remain asymptomatic, others develop effort intolerance, exertional angina, progressive HF, atrial and ventricular arrhythmias and SCD. Current approaches to risk stratification are imperfect; the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines[1] have higher sensitivity[5] whereas the European Society of Cardiology (ESC) model for SCD prediction has higher specificity.[6] These approaches have relied on retrospective analyses focusing exclusively on risk of SCD, despite heart failure being a major disease burden in progressive HCM. Prospective studies with systematic data collection and follow-up to predict the risk of adverse events, including heart failure, in HCM have been lacking.

Based on prior observational data suggesting incremental prognostic value,[7,8] extensive late gadolinium enhancement (LGE) observed on contrast-enhanced cardiac magnetic resonance (CMR), a non-invasive marker of myocardial fibrosis/scar, is now incorporated into recent guidelines as an adjunctive factor to enhance risk stratification for SCD and inform decision making for placement of primary prevention implantable cardioverter defibrillators (ICD).[1,2] Most prior studies evaluating the role of LGE in HCM have been based on retrospective data from specialized tertiary referral centers including higher risk patients, with uncertain generalizability.[7-9] Although the presence of pathogenic sarcomere variants[10] and blood biomarkers[11] are associated with SCD in HCM, neither have been included in algorithms to predict risk of adverse outcomes.

The Hypertrophic Cardiomyopathy Registry (HCMR) was established as a National Heart Lung and Blood Institute (NHLBI)-funded prospective registry including 44 sites in North America and Europe, with a standardized CMR protocol with core laboratory quantitation, as well as genetic and

blood biomarker analysis, aimed to improve risk stratification.[12,13] The HCMR investigators hypothesized that combining prospectively collected clinical history, imaging, genetic, and blood biomarker data, when examined together, could provide high prognostic value to predict risk for adverse events in HCM, including sudden cardiac death and heart failure.

METHODS

Inclusion and exclusion criteria for entry into HCMR (NCT 01915615), as well as details of the CMR protocol and analysis, genotyping, biomarker analysis and statistical methods, have been published previously.[12,13] Of note, patients with preceding ICD placement were excluded, resulting in a low-to-intermediate risk cohort. Briefly, between April 2014 and April 2017, patients were enrolled at 44 sites in the U.S. (18), Canada (4), United Kingdom (13), Italy (4), Germany (3), and the Netherlands (2). The research protocol was approved by institutional review boards or ethics committees at each site and all participants gave written informed consent.

Patients responded to a questionnaire and clinical data were collected including clinical echocardiographic reports. Patients underwent a blood draw for biomarkers and genotyping and underwent a comprehensive, standardized CMR examination. The CMR protocol included scout imaging, T1 mapping before and after gadolinium contrast, short and long axis cine imaging, and LGE imaging. CMR image analysis was performed in the Brigham and Women's Hospital and Beth Israel Deaconess Hospital (Boston, MA) core labs. Quantification of LGE was performed according to Society for Cardiovascular Magnetic Resonance standards[14] visually and quantitatively using 6 standard deviations in the signal intensity threshold above noise in non-enhanced segments.[15] Sequencing of 36 cardiomyopathy genes was performed at the Oxford Regional Genetics Laboratory (Oxford, UK).[13]

Serum biomarker analysis was performed at the Biomarker Research and Clinical Trials Laboratory at the Brigham and Women's Hospital core laboratory (Boston, MA).[13]

The primary endpoint was a composite of: 1) HCM-related cardiovascular deaths including sudden arrhythmic, stroke, HF, and peri-procedural (septal reduction therapy); 2) non-fatal sustained VA (≥200 bpm) that required intervention (either appropriate ICD therapy with defibrillation or anti-tachycardia pacing, or external cardioversion/defibrillation) for termination; and 3) left ventricular assist device (LVAD) insertion or heart transplantation. The primary analysis was performed for time to first event. Secondary analyses were 1) multiple event analysis and 2) sudden cardiac death outcomes including non-fatal VA as defined above.[16] Both primary and secondary events were prespecified. Event adjudication was performed by a Clinical Event Committee of four highly experienced cardiologists with electrophysiology or heart failure expertise (JPD, BG, MSL, GSF).

Data were collected at sites and entered into a centralized database. Follow-up data were collected by telephone call or office visit. All data collected from core laboratories and clinical sites formed the study database, which was kept at the data coordinating center at MedStar Health Research Institute/Georgetown University (Washington, DC).

Statistical Analysis

Multiple imputation was used to generate 20 complete data sets for the primary analyses. The number of missing values necessitated a large number of imputed data sets.[17] A 2-stage analytic strategy was used, with elastic-net regression[18] for candidate screening followed by Cox proportional hazards regression for final model estimation.[19,20] This 2-stage approach was used to retain clinically interpretable final models while evaluating whether parsimonious models preserved discrimination and calibration. The proportional hazards assumption was checked by scaled Shoenfeld residuals.[20] "Full models" were defined by elastic-net selected variables that appeared in 2 or more of the 20 imputed data

sets. Reduced models were assessed by the log-likelihood ratio test and comparing the c-indices of the "full" and "reduced" models. A non-significant ($p > 0.05$) likelihood ratio test and a c-index difference of 5% or less was considered to indicate that the more parsimonious model was appropriate.

Model performance was evaluated by discrimination and calibration measures.[19] Internal validation was assessed by bootstrapping,[20] , with the model-building procedure repeated within bootstrap samples to estimate optimism in parameter estimates and model performance. Validation was also assessed by generating a separate set of imputed data sets and applying the model developed from the original imputed data sets. For each model, a complete case (CC) analysis was performed to compare hazard ratios and 95% confidence intervals with imputed results. Stata v.19 (Stata Corp. College Station, TX) was used for all analyses. Further details are given in eAppendix A.

RESULTS

Patient and event characteristics

A total of 2,698 HCM patients (98% of the 2750 enrolled) were available for analysis **(Figure 1)**, as 9 were phenocopies of HCM determined by genetic or other analysis and 43 withdrew or had no follow-up data. Mean follow-up was 6.9±2.1 years. At baseline, the ESC risk score of the population was 2.4, C.I. (2.1-2.8). Sixty seven % of the patients had 0 ACC/AHA risk markers for SCD,[1] 27.7% had 1 risk factor, and 5.3% had 2 or more risk factors.

There were 117 primary composite events among 104 (3.9%) patients. **Figure 2** presents a breakdown of the 117 primary event types. The 63 deaths included 34 SCD, 11 HF deaths, 6 fatal strokes, and 12 other HCM-related deaths. The 43 nonfatal VA events included 18 resuscitated cardiac

arrests, 5 sustained ventricular tachycardia episodes, and 20 ventricular tachycardia or fibrillation events terminated by ICD shocks or anti-tachycardia pacing. There were 10 heart transplantations and 1 LVAD implantation. **Table 1** presents summary descriptive statistics for 50 demographic, clinical, echocardiographic, CMR, genetic and biomarker variables for those subjects with and without primary outcome events. A total of 77 sudden cardiac deaths or ventricular arrhythmia events occurred in 69 patients (2.6%).

Variable selection

The variables in **Table 1** were first evaluated in the elastic net analysis to determine the most appropriate variables for further analysis. LGE and LGE% were colinear (r = 0.94) (see eAppendix B, Table B1). Given that LGE% is the measure most commonly used clinically, further analyses included only LGE%. LGE%, LV mass index (LVMI), and LV end systolic volume index (LVESVI) were the first three variables selected in all 20 data sets for both the primary outcome and the multiple event analysis. Variables selected in all 20 data sets for the SCD event analysis included LGE%, LVMI, LVEF and log(NTProBNP).

Predictive models

The models for each analysis are presented in **Table 2**. The proportional hazards assumption in the multiple event analysis was not met for log(NTProBNP). Thus, log(NTProBNP) was stratified for the analysis: 1st tertile (< 5), 2nd tertile (5 – 6) and 3rd tertile (> 6). For the primary composite event analysis, LGE%, LVMI and LVESVI increased the hazard by 86%, 9% and 28% respectively for every 10-unit increase. History of HF at study entry, defined as HF hospitalization or intensified diuretic therapy for HF, increased the hazard by 189% and log(NTProBNP) increased the hazard by 41% for every 1 unit increase. **Figure 3** includes plots of the Cox regression curves to 9 years for several values of each of the predictive variables in the model. The event-free probability curve for LGE% ≥ 9% (95th

percentile of the LGE% distribution) indicated significantly lower probabilities than LGE% values < 9% (p = 0.001, **Figure 3**, **A**). First and multiple event results were similar for all predictors, except log(NTProBNP) which was stratified by tertiles. For multiple events, the hazard was increased by 110% for every increase in tertile. For SCD events, results were similar to the composite event for LGE%, LVMI and log(NTProBNP) **(Figure 4)**. LVEF decreased the hazard by 32% for every 10-unit increase.

Model performance and validation

Discrimination was excellent and consistent across the three analyses. The c-indices were 0.77 (0.76 to 0.78) for the time to first event, 0.78 (0.77 to 0.79) for multiple events and 0.76 (0.75 to 0.79) for the SCD event analysis (**Table 2**). Calibration was also excellent and consistent across the three analyses. Calibration slopes were 0.88 (0.86 to 0.89), 0.85 (0.82 to 0.86) and 0.89 (0.87 to 0.91) for first event, multiple events and SCD events respectively. Calibration curves for each analysis are presented in eAppendix C. They show close agreement between observed and predicted event-free curves for all three outcomes. Model validation results are presented in eTable B2. Bootstrap results indicated very small differences (bias) between observed and bootstrapped hazard ratios and 95% confidence intervals for all three outcomes. Similarly, validation by generating additional imputed data sets also indicated little difference in model parameters for all three analyses.

Complete Case analyses

Complete case results are presented in eAppendix D and these are consistent with the imputed results presented above.

DISCUSSION

The HCMR investigators comprehensively measured historical, genetic, blood biomarker, and imaging data from 2698 low-to-intermediate risk HCM subjects and followed them prospectively for a mean of nearly 7 years for cardiovascular outcome events. Associations with primary composite outcome events (including HCM-related deaths, nonfatal VA events, and transplantation/LVAD implantation) included several CMR markers, history of heart failure, and a blood biomarker, log(NTproBNP). CMR markers included the extent of myocardial fibrosis/scar (based on LGE), LVMI, and LVESVI. LV scar extent, LVMI, LV systolic function, and log(NTproBNP). These were associated with both the primary composite and SCD endpoints, whereas history of HF was linked only to the primary composite endpoint, likely because the latter included HF endpoints. LGE comprising ≥ 9% of LV mass was associated with a significant increase in the primary composite event rate. The excellent C-indices achieved by our models ranged from 0.76 to 0.78, providing clinically important added precision to event prediction for both SCD and HF events.

The European Society of Cardiology (ESC) HCM Risk-SCD score was validated in a cohort of 3703 patients with a c-index of 0.70.[21] When the ESC risk score was included in the present analysis, it was not identified as an independent risk marker of SCD. This risk calculator includes measurement of age, maximal wall thickness, left atrial size and LV outflow tract gradient (LVOT). None of these variables were identified in HCMR as predictors of either the primary or SCD endpoint, although LVMI is more representative than maximal wall thickness because it takes the entire LV into consideration. Specific risk markers for SCD named in the 2024 AHA/ACC guidelines[1] such as family history of SCD, syncope, and apical aneurysm were not identified in the HCMR risk model for the SCD endpoint. One of the strengths of the risk markers identified in HCMR, including LGE %, LVMI, and LVESVI or EF, is that they are continuous variables rather than dichotomous thresholds.

LGE provides a substrate for re-entrant ventricular arrhythmias in HCM,[22] particularly at the interface between scar and adjacent non-scarred myocardium. LGE% ≥ 9% significantly increased the likelihood both the primary composite and the SCD endpoint in HCMR. In the 2024 ACC/AHA guidelines, extensive LGE as a risk marker for SCD was suggested to be more than 15%; however, a significant number of SCD events occur in HCM subjects with 5-15% LGE.[9] A recent meta-analysis of 11 studies with 5500 patients and over 5 years of follow-up identified the optimal LGE cutoff for sensitivity and specificity for SCD as 10%[23], in line with our finding of 9% as a strong discriminator. Interstitial fibrosis, as estimated by extracellular volume (ECV) measured by CMR, was not a predictor in any of the models in HCMR, suggesting that dense scar is a more important marker of risk in HCM.

In most prior retrospective studies, individual risk markers have been identified as important. Biomarkers including high-sensitivity troponin T and NTproBNP have shown independent association with outcomes; for troponin in two modest-sized studies[24,25] and for NTproBNP in several studies[11,26,27] and a network meta-analysis.[28] The latter study included 112 studies with 58,732 patients and the composite endpoint was similar to HCMR, although it also included all-cause deaths.

In the present study, additional structural CMR findings played an important role in risk prediction. In particular, LVMI predicted both primary and sudden cardiac death endpoints, whereas maximal LV wall thickness did not. Higher LVMI was previously identified as a marker of HCM-related death in a study of 264 patients and was more sensitive than LV maximal wall thickness of 30 mm.[29] This underscores the importance of 3-dimensional measures of LV hypertrophy over unidimensional measures such as wall thickness In addition, LV mass accounts for chamber size. LVESVI takes into account overall cardiac size and was identified as a risk marker for the composite primary outcome in HCMR, as it has been for HF events in a prior study of 543 patients in which it was an independent predictor along with LGE and mitral regurgitation.[30] Some patients in HCMR demonstrated borderline low EF's when measured by CMR at baseline.[13] LVEF was a marker of the

SCD endpoint in HCMR and is known to be associated with adverse outcomes in HCM,[31] including HF and death, even in the setting of low-normal EF.[32,33]

Some previously identified markers of risk in HCM such as pathogenic sarcomere variants and apical aneurysms were not independent risk factors in HCMR. The presence of a pathogenic sarcomere variant has been previously recognized as a lifetime marker of adverse risk in HCM.[10] Those with pathogenic sarcomere variants generally have higher LV mass due to the more frequent presence of reverse septal curvature morphology and they have more extensive LGE.[13] Thus, genetic factors, at least in part, may drive the presence of increased LVMI and LGE. Apical aneurysm morphology was not an independent predictor in HCMR, likely due to being underpowered given its low prevalence (3%) in the cohort. In a dedicated cohort of HCM patients with apical aneurysms, the size of the aneurysm was strongly associated with VA risk,[34] and the most recent guidelines include apical aneurysm as a class 2A indication for an ICD.[1]

Limitations

The patient population was predominantly male and only 16% were from underrepresented groups despite the consortium's best efforts. Due to exclusion of patients with ICDs at study entry because of CMR considerations, the patient population was relatively lower risk at baseline, although this makes the findings generalizable to similar populations. Forty percent of patients were missing values for history of non-sustained ventricular tachycardia (NSVT) as measured on electrocardiographic monitoring, as the latter data were captured if available, but were not required for study entry. This also led to missing data for calculation of the ESC risk score. However, the complete case analysis suggested no change in the identified risk markers in all endpoint analyses. Data from clinically performed echocardiograms was captured at entry into the study and research echocardiograms were not specifically performed. Thus, provocative maneuvers to demonstrate LV outflow tract gradients may not

have been complete in some instances, and thus the number of patients with significant LVOT obstruction may have been underestimated. Only 76% of the patients had T1 mapping available due to software limitations at some sites.[13]

Twenty percent of the population underwent disease modifying interventions during the follow-up period (451 myectomy and 112 alcohol septal ablations) that may have altered the course of disease. Septal myectomy has not been studied in a randomized fashion but in an observational study was shown to reduce the risk of heart failure and stroke,[35] and overall post-operative mortality is similar to an age- and gender-matched U.S. population.[36] A definitive effect of myectomy on SCD is less clear.[37] In addition, predictor selection involved an elastic-net screening step prior to fitting the final Cox models; therefore, confidence intervals and p-values should be interpreted cautiously as post-selection inferential quantities. For this reason, we emphasize discrimination, calibration, and internal validation as the primary measures of model performance. Alternative approaches, including grouped or stacked penalized methods applied across multiply imputed data sets, are also reasonable and may be attractive when the primary goal is predictive optimization. Our modeling strategy reflects a tradeoff between prediction-focused penalized modeling and clinical interpretability of the final reported model, for which hazard ratios and confidence intervals from conventional Cox regression are better understood in clinical settings. Lastly, external validation is currently not possible, as there are no other available databases with similar comprehensive data including CMR, genotyping, and biomarkers.

Conclusions and Future Directions

The multicenter international HCMR registry is the largest study to date of HCM patients with strictly standardized state-of-the-art CMR imaging, genotyping, blood biomarkers and prospective long-term follow-up. HCMR provides strong prospective evidence for incorporating CMR and NTproBNP in the evaluation and risk assessment of HCM patients. Future work will include development of a risk

score from HCMR as well as external validation from future databases with similar comprehensive measures.

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Table 1. Patients with primary composite events, those without an event, and all patients.

Variable	Primary composite event n = 104	No primary event n = 2594	All patients n = 2698
Demographic/Clinical			
Age (years)	51.4 (45-60)	50.0 (43–59)	50.0 (43-59)
Male	77 (74.0)	1842 (71.0)	1919 (71.3)
Minority	18 (17.3)	405 (15.6)	423 (15.7)
BMI (kg/m^2)	30.2 (25.1-33.6)	29.3 (25.3-32.3)	29.3 (25.3-32.4)
Hx hypertension	35 (34.0)	943 (36.5)	978 (36.4)
Hx heart failure	17 (16.5)	122 (4.7)	139 (5.2)
Hx hospitalization for HF	10 (9.7)	43 (1.7)	53 (2.0)
Hx stroke	6 (5.8)	70 (2.7)	76 (2.8)
Family Hx HCM	34 (33.0)	871 (33.7)	905 (33.7)
Family Hx of SCD	11 (10.7)	317 (12.3)	328 (12.2)
Type II diabetes	11 (10.7)	200 (7.7)	211 (7.8)
Hx syncope	10 (9.7)	349 (13.5)	359 (13.3)
Hx dyspnea	55 (53.4)	1108 (42.8)	1163 (43.3)
NYHA Class III/IV	12 (11.6)	181 (7.1)	193 (7.3)
Current smoker	15 (14.6)	364 (14.1)	378 (14.1)
LVOT gradient > 30mmHg	25 (24.0)	470 (18.1)	495 (18.3)
Hx atrial fibrillation	15 (14.4)	226 (8.7)	241 (8.9)
Mitral regurgitation II/III	1 (1.0)	67(2.6)	68 (2.5)
NSVT	18 (25.4)	177 (11.5)	195 (12.1)
ESC risk score	2.6 (2.2-2.9)	2.4 (2.0-2.8)	2.4 (2.1-2.8)
Morphology			
Isolated basal septal	31 (31.3)	1157 (46.1)	1188 (45.5)
Reverse curvature	54 (54.6)	998 (39.7)	1052 (40.3)
Apical	5 (5.1)	219 (8.7)	224 (8.6)
Concentric	4 (4.0)	32 (1.3)	36 (1.4)
Apical aneurysm	4 (4.0)	73 (2.9)	77 (3.0)
Other morphology	1 (1.0)	32 (1.3)	33 (1.3)
Sarcomere mutation +	38 (36.9)	893 (35.9)	931 (36.0)
CMR			
LVMI (g/m^2)	103.8 (77.6-123.6)	84.7 (66.0-97.5)	85.4 (66.4-98.6)
LGE (g)	10.4 (0.0-12.2)	2.9 (0.0-3.0)	3.2 (0.0-3.3)
LGE / LVM (%)	5.8 (0.0-7.2)	1.7 (0.0-1.8)	1.8 (0.0-2.0)
ECV (%)	0.34 (0.28-0.39)	0.30 (0.26-0.33)	0.30 (0.26-0.33)
LVEDVI (ml/m^2)	94.5 (81.6-101.5)	84.5 (73.4-93.9)	84.9 (73.7-94.2)
LVESVI (ml/m^2)	40.5 (28.5-45.7)	30.8 (23.0-36.7)	31.1 (23.2-37.0)
LVEF (%)	58.1 (51.5-67.5)	64.2 (59.1-70.1)	64.0 (58.8-70.0)
LVSVI (ml/m^2)	54.0 (46.4-62.0)	53.7 (47.2-59.8)	53.8 (47.1-60.0)
LVM/Volume	1.1 (0.9-1.3)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
RVEDVI (ml/m^2)	76.5 (63.3-86.7)	75.3 (63.9-85.1)	75.3 (63.9-85.1)
RVESVI (ml/m^2)	26.4 (18.0-32.3)	24.4 (16.3-30.9)	24.4 (16.4-30.9)
RVEF (%)	65.9 (57.5-74.5)	68.4 (61.0-76.1)	68.3 (61.0-76.0)

Max wall thickness (mm)	22.3 (18.9-25.2)	20.6 (17.1-23.2)	20.7 (17.2-23.3)
LAVI (ml/m^2)	68.3 (52.5-76.0)	58.4 (44.2-69.5)	58.7 (44.3-69.9)
LA Reservoir (%)	29.9 (23.5-36.7)	35.2 (29.8-41.9)	35.0 (29.6-41.8)
LA Contractile (%)	38.1 (29.5-50.1)	46.9 (39.9-56.1)	46.6 (38.5-56.0)
Biomarkers			
NTProBNP (pg/ml)	1087.9 (280.6-1416.0	525.1 (104.9-601.4)	547.0 (107.0-639.1)
cTnT (ng/ml)	24.5 (11.1-27.8)	15.5 (7.4-15.4)	15.9 (7.5-15.9)
GAL3 (pg/ml)	6762.5 (5388.0-7334.0)	6966.9 (5099.0-7554.0)	6959.1 (5105.0-7538.0)
ST2 (pg/ml)	21,470.4 (12,517.0-26,288.0)	19,195.5 (13,101.0-22,838.0)	19,281.8 (13,084.0-22,939.0)
MMP1 (pg/ml)	432.6 (175.0-587.0)	468.6 (194.0-570.0)	467.2 (194.0 - 571.0)
TIMP1 (pg/ml)	125,640.9 (97,094.0-139,398.0)	120,754.9 (99,512.0-135,695.5)	120,938,4 (99,255-136,031)
CICP (ng/ml)	11.7 (8.1-14.0)	10.3 (7.2-12.1)	10.3 (7.3-12.2)
BAP (U/ml)	19.8 (14.8-23.9)	18.5 (14.6-21.4)	18.6 (14.6-21.5)

Values are mean (IQR) [interquartile range; 25th percentile to 75th percentile for continuous variables, n (%) for binary variables. Mean (IQR) and percentage calculations reflect number of patients with valid observations. Missing value information is presented in eAppendix B. I indicates “index”.

Atrial fibrillation includes paroxysmal or persistent.; BAP - bone alkaline phosphatase; BMI - body mass index; CICP - C-terminal propeptide of type 1 procollagen; CMR - cardiac magnetic resonance; cTnT - cardiac troponin T; ECG - electrocardiogram; ECV – extracellular volume; EDV - end diastolic volume; ESV - end systolic volume; GAL3 - galectin-3; HCM - hypertrophic cardiomyopathy; Hx – history; LA - left atrial; LAV - left atrial volume; LGE - late gadolinium enhancement; LV - left ventricular; LVEF - left ventricular ejection fraction; LVOT - left ventricular outflow tract; MMP1 – matrix metalloproteinase-1; MR - mitral regurgitation; NSVT - Non-sustained ventricular tachycardia; NTproBNP - N-terminal pro B-type natriuretic peptide; NYHA - New York Heart Association; PAF - paroxysmal atrial fibrillation; RV - right ventricular; RVEF – right ventricular ejection fraction; SCD –

sudden cardiac death; ST2 - suppression of tumorigenicity 2; SV - stroke volume; TIMP1 - tissue inhibitor metalloproteinase-1.

Table 2. Cox regression models for primary composite events, multiple events and sudden cardiac death events.

First primary event			Multiple events		SCD events		
Variables	**Hazard Ratio (95% CI)**	**p value**	**Hazard Ratio (95% CI)**	**p value**	**Variables**	**Hazard Ratio (95% CI)**	**p value**
LGE %	1.86 (1.58 – 2.20)	< 0.001	1.97 (1.69 – 2.29)	< 0.001	**LGE %**	1.92 (1.55 – 2.38)	< 0.001
LVMI	1.09 (1.01 – 1.17)	0.030	1.10 (1.02 – 1.20)	0.014	**LVMI**	1.12 (1.04 – 1.21)	0.004
LVESVI	1.28 (1.12 – 1.46)	< 0.001	1.26 (1.12 – 1.42)	< 0.001	**LVEF**	0.68 (0.52 – 0.89)	0.004
Hx heart failure	2.89 (1.75 – 4.77)	< 0.001	2.91 (1.76 – 4.83)	< 0.001	**Log (NTProBNP)**	1.39 (1.12 – 1.73)	0.003
Log (NTProBNP)	1.41 (1.17 – 1.70)	< 0.001	2.10 (1.36 – 3.00)	< 0.001			

Hazard ratios of LGE%, LVMI , LVESVI, and LVEF expressed in units of 10; NTProBNP 1 log unit.

log(NTProBNP) stratified by tertiles for multiple event analysis.

First event: c-index = 0.77 (0.76-0.78); calibration slope = 0.88 (0.86-0.89).

Multiple events: c-index = 0.78 (0.77-0.79); calibration slope = 0.85 (0.82-0.86).

Sudden cardiac death events: c-index = 0.76 (0.75-0.79); calibration slope = 0.89 (0.87-0.91).

Figure Legends

Figure 1. STROBE diagram of patient enrollment and study details.

Figure 2. Cox regression event-free curves for time to first event at various values of LGE% (A), history of heart failure (B), Log(NTProBNP) (C), LVESVI (D), and LVMI (E).

Figure 3. Cox regression event-free curves for time to SCD event at various values of LGE% (A), LVMI (B), LVEF (C) and Log (NTProBNP) (D).