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Prognostic Role of Late Gadolinium Enhancement in patients with Hypertrophic Cardiomyopathy and low to intermediate Sudden Cardiac Death Risk Score.

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Running title: LGE in HC with low/intermediate risk

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ABSTRACT

Sudden cardiac death (SCD) is the most life-threating complication of hypertrophic cardiomyopathy (HC). ESC Guidelines suggest the implantation of a ICD in primary prevention according to a 5-year Risk SCD score ≥ 6%. The aim of the study is to evaluate the prognostic role of late gadolinium enhancement (LGE) in patients with a 5-year Risk SCD score <6%. In this multicenter study, we performed CMR in 354 consecutive HC patients (257 males, range of age 54±17) with a risk SCD score <6% (302 with <4% and 52 with ≥4 and <6% risk). Hard cardiac events, including SCD, resuscitated cardiac arrest, appropriate ICD interventions, sustained ventricular tachycardia, occurred in 22 patients. LGE was detected in a high proportion (92%) of patients with hard cardiac events (p =0.002). At ROC curve analysis, LGE extent ≥10% was the best threshold to predict major arrhythmic events (AUC 0.74). Kaplan-Meier curves showed that patients with LGE≥10% had a worse prognosis than those with lower extent (p< 0.0001). LGE extent was the best independent predictor of hard cardiac events (HR 1.05; 95% CI 1.03-107; p<0.0001). The estimates 5-year risk of hard cardiac event was 2.5% (95% CI 0.8-4.2) in patients with LGE extent <10% and 23.4% (95% CI 10.2-36.5) for those with LGE extent ≥10%. In conclusion, this study demonstrates as the extent of LGE≥10% is able to recognize additional patients at increased risk for malignant arrhythmic episodes in a population with low-intermediate ESC SCD risk score.

Keywords

Cardiac Magnetic Resonance; hypertrophic cardiomyopathy; sudden cardiac death; late gadolinium enhancement; HC SCD risk score.

INTRODUCTION

Sudden cardiac death (SCD) is the most dramatic complication of Hypertrophic cardiomyopathy (HC) (1-3). ESC Guidelines suggest the use of a clinical risk prediction model, the HC risk score, to estimate the 5-years risk of SCD, using clinical and echocardiographic parameters (4). These guidelines prescribed ICD implantation for an estimated risk of ≥6%. When the 5-years risk SCD score is intermediate (≥4- <6%) there is not a clear recommendation for defibrillator implantation, and many sudden cardiac deaths occurs also in patients with lower risk (<4%)(5). Cardiac magnetic resonance (CMR) has an important role for the diagnosis of HC (6, 7) and for not invasive detection and quantification of myocardial fibrosis by the late gadolinium enhancement (LGE) (8-10). The prognostic role of extensive and diffuse LGE was demonstrated in patients with HC in a multicenter study (11). However, the extent of LGE was not included in the 5-year risk SCD score. In this study we aimed to evaluate the prognostic role of the extent of LGE in a population of patients with a low-intermediate risk score (<6%).

METHODS

This study was a multicenter investigation, including data from 5 hospitals. CMR was performed from January 2006 to January 2014 in a cohort of consecutive patients with a previous diagnosis of HC using the following inclusion criterion presence of a wall thickness ≥15 mm in one or more LV myocardial segments in absence of secondary causes of LV hypertrophy, with the exception of those with systemic hypertension under effective drug therapy with family history of HC or with consistent genotype (3). We excluded patients with contraindications for CMR and

those with contraindications for gadolinium-based contrast agent. Accordingly to current ESC guidelines, the risk of sudden death of these patients was reclassified using the HC risk score and a population of 360 patients with an intermediate (5-year risk from 4 to <6%) or low (5-year risk <4%) score was included in the current study (3). Finally six patients were excluded because of sub-optimal CMR images quality.

The examination was performed using 1.5 Tesla systems (Signa Hdx, General Electric Healthcare, Milwaukee, Wisconsin; Magnetom Avanto Siemens Medical System, Erlangen, Germany; Gyroscan NT, Philips Healthcare, Amsterdam, the Netherlands) with dedicated cardiac coil. Study protocol included functional evaluation with short axis cine images, acquired from the mitral plane valve to the left ventricular (LV) apex, and these images were acquired using a steady-state free precession pulse sequence with the following parameters: 30 phases, slice thickness 8 mm, no gap, views per segment 8, FOV 35-40 cm, phase FOV 1, matrix 224×224, reconstruction matrix 256×256, 45° flip angle, and a TR/TE near to 2. Cine images with the same parameters were acquired also in 2-,3- and 4 chamber views. LGE images were acquired 10 minutes after the administration of Gd-DTPA with a dosage of 0.2 mmol/kg in short-axis views. An inversion recovery T1-weighted gradient- echo (GRE) sequence was used with the following parameters: field of view 35-40 mm, slice thickness 8 mm, no gap between each slice, repetition time 3-5 msec, echo time 1-3, a flip angle of 25°, matrix 224×224, reconstruction matrix 256×256. The appropriate inversion time was set to null for normal myocardium using a TI-scout.

All CMR studies were analyzed offline in the core laboratory of Pisa by three experienced observers with III level EACVI accreditation for CMR investigators who were blinded to the

clinical data. A commercially available research software package (Mass Analysis, Leyden, The Netherlands) was used to quantify the functional parameters using conventional method. Left ventricular mass was measured by the analysis of the cine short-axis images. The endocardial and epicardial contours of LV myocardium were manually traced in the end-diastolic and the end-systolic phases. End-diastolic volume index, end-systolic volume index, mass, and mass index were measured as previously described (12, 13). Maximal LV end diastolic wall thickness was measured as previously described (7). The extent of LGE was measured using a previously validated method (10,14). Briefly, the endocardial and epicardial contours in each image were manually traced to identify the LV myocardium in each image. To obtain the standard deviations (SD) of the signal noise of the images, a region of interest was placed in a region of myocardium without LGE. The mean signal intensity and SD were measured in this region of interest. Myocardial voxels with a signal intensity higher than the average signal intensity of the region of interest ≥6 SD were considered enhanced. The percentage of enhanced voxels in the entire LV myocardium was measured. The extent of LGE was expressed in grams and the percentage of the LV mass.

After the CMR examination, a follow-up was performed for all patients. A clinical questionnaire was compiled by a clinical physician during periodic ambulatory visitations in each hospital, by contacting their relatives by telephone, or by a general practitioner. The clinical questionnaire included the definition of the following hard cardiac events: cardiac death, resuscitated cardiac arrest and appropriate implantable cardioverter defibrillator (ICD) shock, anti-tachycardia pacing, sustained ventricular tachycardia on Holter electrocardiogram monitoring, as well as secondary endpoints (heart failure hospitalization, Stroke, atrial fibrillation and acute

coronary syndrome). A complete analysis of the ICD was performed by the referring cardiologist in order to confirm the appropriateness of the shock. A panel of expert investigators adjudicated the occurrence of hard cardiac events.

Values are presented as the mean +- standard deviations (SD) or as the median (interquartile range IQR) for variables with normal and non-normal distributions, respectively. Values with non-normal distribution according to Kolmogorov-Smirnov test were logarithmically transformed for parametric analysis. Qualitative data are expressed as percentages. Categorical variables were compared by the chi-square test or the Fisher exact test when appropriate. Continuous variables were compared by the ANOVA t test and analysis of variance or by the Wilcoxon nonparametric test when appropriate. Bonferroni correction was used when needed. the Receiver Operating Characteristic (ROC) curve was used to determine the best threshold of LGE for predicting cardiac events. The Kaplan-Meier time-to-event method was used to calculate and compare longitudinal curves among groups. Logistic regression analysis was used to explore the impact of each significant variable in univariate analysis to predict the occurrence of hard cardiac endpoint. A p value lower than 0.05 was considered statistically significant.

RESULTS

The study comprised of 354 patients with 5-years risk SCD score <6% (257 males, range of age 54+-17). Three hundred two patients had a low risk of SCD (risk score <4%) and 52 an intermediate risk (risk score ≥4 and <6%). Basal clinical characteristics of population, included

drug therapy, risk factors for obtaining risk SCD model and CMR results, are summarized on table 1.

Two hundred and thirty (65%) patients were positive for LGE at visual assessment (example in figure 1).

During the median follow-up of 1219 (572-2020) days, 27 (8%) patients underwent to ICD implantation based on clinical decision. Episodes of hard cardiac events occurred in 22 patients (6 episodes of cardiac sudden death; 8 resuscitated cardiac arrests; 1 episode of sustained ventricular tachycardia; and 7 appropriate interventions of ICD). As evident in table 2, patients with hard cardiac events had higher maximal end-diastolic wall thickness, greater indexed LV mass and higher extent of LGE than those with no events. Based on the analysis of the Receiver Operating Characteristic (ROC) curve, ≥10% of LGE extent was chosen as the best threshold to predict the occurrence of hard cardiac events in this population (AUC of 0.74, specificity 82%, sensitivity 73%). LGE extent ≥10% was found in 73 patients who showed a greater incidence of hard cardiac events (n=14, 18.7%) than those with lower LGE extent (n=8, 3% p<0.0001).

The analysis of Kaplan-Meier survival curves, showed that patients with LGE extent ≥10% had worse prognosis than those with lower extent (p<0.0001) (figure 2). The estimates 5-year risk of hard cardiac event was 2.5% (95% CI 0.8-4.2) in patients with LGE extent <10% and 23.4% (95% CI 10.2-36.5) for those with LGE extent ≥10%. As evident in table 3, the estimates 5-year risk of hard events was higher when LGE extent was ≥10% either in patients with low or in those with intermediate risk SCD score.

At univariate analysis subjects with higher LV end-diastolic volume, LGE extent ≥10%, dimensions of left atrium and extreme LV hypertrophy, are significantly related to frequent incidence of sudden cardiac death.

Based on the logistic regression analysis, LGE extent ≥10% was the only independent predictor of malignant arrhythmic events and mortality (HR 8.8; 95% CI 2.03-37.8; p<0.0001) (table 4).

DISCUSSION

In this multicenter study, we evaluated the prognostic role of LGE in patients with a low-intermediate 5-years HC risk SCD score. The main result was that the presence of LGE extent ≥10% was associated with worse prognosis in both patients with low-intermediate risk. LGE was the best independent predictor of hard cardiac events in these patients.

As recommended by current ESC guidelines for HC, ICD is indicated for patients with 5-year risk ≥6%, excluded for a risk <4, and it may be considered for risk ≥4 and <6%. However, despite the lower 5-year risk, most of SCD/aborted cardiac arrest occurs in patients with low-intermediate risk, because they constituted the majority of HC population. In the study by Maron et al (5) cardiac events occurred in 12% of patients with high risk, 8% in those with intermediate risk and in 3.7% in subjects with low risk.

The HC SCD risk score doesn't include LGE assessment which is a marker of myocardial fibrosis and is generally considered a potential substrate for malignant ventricular arrhythmias. The association of the presence of LGE with sudden death/aborted sudden death was demonstrated in two recent meta-analysis (15,16). However, at the first diagnosis, the majority (ranging from 50

to 85%) of patients with HC had LGE (17-21) and a fast progression of its extent and of its prevalence was demonstrated by serial CMR exams (22, 23). In the multicenter trial by Chan and colleagues (7), the prognostic role of quantitative LGE was evaluated, and a LGE extent >15% of LV mass was associated to hard cardiac events with a significant addictive value over conventional arrhythmic risk factors. In our study, we assessed the prognostic role of LGE extent in patients with intermediate or low HC risk score and a cut-off ≥10% of myocardial fibrosis was identified as a predictor of hard cardiac events. In the manuscript by Chan, 39% of patients were at high risk, defined as > 2 conventional arrhythmic risk factors for SCD, and the average extent of LGE was higher than in our study, probably because of more advanced stage of the disease. Despite this, Chan used a visual technique where the grayscale threshold was manually chosen case by case and reported a prevalence of positive LGE in 42% of HC patients. On contrast we used a conventional ≥ 6SD greyscale threshold and found a positive LGE in 65% in our study. Indeed, the current study was the first study evaluating the prognostic role of LGE extent using the widely accepted ≥6SD method of quantification. The reproducibility of a semi automatic method of quantification as ≥6SD is surely greater than those of the visual greyscale threshold that requires great expertise in CMR.

In a recent single-center study, Mentias and coworkers demonstrated the prognostic role of LGE extent ≥15% in patients with HC and low-intermediate 5-years risk score (24). In our multicenter study we prospectively enrolled consecutive patients with HC, while in the retrospective study by Mentias and coworkers patients with LV dysfunction were excluded and the majority of patients were obstructive (68%), and 48% of the patients of the entire population underwent to myectomy during follow-up. Our population of unselected patients is more similar to

real life as regards the prevalence of obstructive HC (only in a minority of the population), LV dysfunction and for the average age.

On the clinical point of view, recent evidences (5,25) demonstrated that the current ESC HC risk SCD model potentially leaves more subjects unprotected from sudden cardiac death. On the other hand, defibrillator treatment may be associated with adverse sequelae, as inappropriate discharge or infective complications and this underlines the importance of the appropriate selection of the patient for ICD implantation. We found that in presence of LGE extent ≥10%, the 5-year risk of hard cardiac events passed from 3% to 14% in patients with intermediate HC risk SCD score and from 2 to 26% in those with low risk score. LGE ≥10% permits to reclassify patients from a low-intermediate risk to a high risk category for SCD. In the opposite way, patients with intermediate SCD risk score and LGE<10% may be relocated to a low risk group. According to our results, LGE should be used to stratify HC patients with low-intermediate risk score for SCD as proposed in our modified diagnostic algorithm for risk stratification of SCD (figure 3).

Some study limitations should be mentioned. First, as for the design of the study, we decided not to include patients with SCD risk score ≥6% and data about the potential addictive prognostic role of LGE extent in such patients are not available. However, in high risk patients the indication of ICD implantation is already recommended.

Second, T1 mapping and Extracellular Volume measurement are novel promising CMR techniques permitting to assess fibrosis and potentially able to detect microscopic fibrosis. However, a previous study demonstrated that extracellular volume was not significantly different in myocardium with no

LGE of HC patients than in myocardium of Healthy controls (26). The prognostic role of native T1 mapping in HC should be investigated in future studies.

In conclusion, these suggest that quantitative LGE should be considered in the decision making for ICD implantation, because a LGE extent ≥10% of LV mass allows reclassification of 5-year risk of SCD from low/intermediate to high risk. Therefore, the current HC SCD risk score should be integrated with LGE extent quantification to obtain a more complete and accurate risk assessment of HC patients as we proposed in diagnostic algorithm reported in the figure 3.

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Figure legends:

Figure 1: Examples of two patients with hypertrophic cardiomyopathy with LGE extent ≥10% and <10% (respectively in upper and lower panels). Patient of upper panels had a HC-risk score of 2.7% but presented an episode of sustained ventricular tachycardia. Patient of lower panel had a risk score of 4.8% but without cardiac events during the follow-up.

Figure 2: Kaplan Meier survival curve demonstrated that patients with LGE extent≥10% had worse prognosis than others.

Figure 3: Modified algorithm for selection of patients for ICD implantation based on current ESC guidelines combined with the results of the current study.

Table 1. Clinical characteristics of the population (n=354)

Variables:	**Value:**
Age (years)	54±17
Males	257 (72%)
Systemic Hypertension	165 (47%)
Hypercholesterolemia	92 (26%)
Diabetes Mellitus	30 (8%)
Smoker	37 (10%)
Dyspnea (NYHA class>I)	124 (35%)
5-years risk of sudden cardiac death <4%	302 (85%)
5-years risk of sudden cardiac death 4-6%	52 (15%)
CMR findings:	
Maximal wall thickness>=30 mm	14 (4%)
Family history of sudden cardiac death	66 (19%)
Syncope	32 (9%)
Non-sustained ventricular tachycardia	157 (44%)
Obstructive HC	79 (22%)
Left ventricular outflow gradient (mmHg)	59 ±30
Left ventricular atrium (mm)	38 (33-44)
Left ventricular end-diastolic volume index (ml/m2)	72 ± 19
Left ventricular end-systolic volume index (ml/m2)	23 ± 9
Left ventricular ejection fraction (%)	69 ± 11
Left ventricular mass index (gr/m2)	114 ±51
Right ventricular end-diastolic volume index (ml/m2)	62 ±17
Right ventricular end-systolic volume index (ml/m2)	19 ±8
Right ventricula ejection fraction (%)	68 ±9
Extent of Late Gadolinium Enhancement (% of LV mass)	2 (1-8)
Late Gadolinium enhancemt > 15% of LV mass	39 (11%)
Therapy:	
Beta Blockers	164 (46%)
Calcium antagonists	27 (8%)
Antiarrhythmics	12 (3%)
Diuretics	43 (12%)
ACE inhibitors	118 (33%)
Aldosterone blockers	12 (3%)

Table 2: Characteristics of the population with and without hard cardiac events.

Variables	"Hard" cardiac events		P value
	No (n=332)	Yes (n=22)	
n.	332	22	
Age	54±16	53±17	0.79
Men	253	12	0.81
Hypertension	162	3	0.014
Hypercholesterolemia	89	3	0.56
Diabetes Mellitus	30	0	0.22
Smoker	36	1	0.61
Beta-blockers	160	4	0.07
Calcium antagonists	26	1	0.85
Antiarrhythmics	12	0	0.38
Diuretics	42	1	0.11
ACE-inhibitors	115	3	0.22
Aldosterone blockers	12	0	0.38
Dyspnea (NYHA>1)	119	5	0.99
Family history of sudden death	63	3	0.94
Syncope	32	0	0.19
Non-sustained Ventricular Tachycardia	148	9	0.44
Obstructive HC	78	1	0.35
Old sudden cardiac death risk score >=2	54	3	0.78
risk of sudden cardiac death score	2.39±1.3	2.56±1.5	0.60
Left ventricular ejection fraction (%)	69±11	65±13	0.23
Left ventricular end-diastolic volume index(ml/m2)	72±19	76±25	0.47
Left ventricula Mass index (gr/m2)	113±50	140±67	0.034
Right ventricular ejection fraction (%)	68±10	69±7	0.97
Right ventricular end-diastolic volume index (ml/m2)	63±17	58±15	0.39
Maximal wall thickness (mm)	19±5	22±6	0.04
Late Gadolinium Enhancement (%)	2 (0-7)	10 (2-17)	0.002
Atrial dimensions	39±8	41±12	0.26
Wall motion score index	1.04±0.19	1.07±0.18	0.69

Table 3: incidence of cardiac events during the follow-up

	Sudden death risk			
Variables	**4 to <6%**	**4 to <6%**	**<4%**	**<4%**
	LGE<10%	**LGE≥10%**	**LGE<10%**	**LGE≥10%**
	(n=38)	**(n=15)**	**(n=243)**	**(n=58)**
Hard cardiac events	1(2.6%)	2(13.3%)	7(2.9%)[d]	12(20.6%)[c]
Sudden Cardiac Death	0	1(6.6%)	2(0.8%)[d]	3(5.2%)[c]
Appropriate Implanted cardioverter shock	1(2.6%)	0	3(1.2%)	3(5.2%)
Resuscitated Cardiac Arrest	0	1(6.6%)	2(0.8%)[d]	5(8.6%)[c]
Sustained ventricular tachycardia	0	0	0	1(1.7%)
5-year event probability (95% CI)	0.03(0.01-0.05)	0.14(0.09-0.21)	0.02(0.01-0.02)	0.26(0.11-0.43)

[d], significant vs <4% SCD risk with LGE≥10%; [c], significant vs <4% SCD risk with LGE<10%;

Table 4: Cox Logistic regression analysis for the risk of hard cardiac events.

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age	0.58	0.17-1.98	0.47			
Left ventricular ejection fraction	0.32	0.1-0.99	0.07			
Left ventricular end-diastolic volume index	5.1	0.48-52.8	0.007			
Left ventricular Mass index	1.01	1.0-1.01	0.001			
Maximal Wall thickness	1.8	0.7-48	0.25			
Wall thickness>=30 mm	6.3	1.4-28.4	0.017			
Late Gadolinium Enhancement (%)	1.06	1.04-1.08	<0.0001			
Late gadolinium enhancement extent ≥10%	8.6	3.06-20.9	<0.0001	8.8	2.03-37.8	<0.0001
Left atrial dimensions	4.2	1.1-16	0.002			
Familiar history of Sudden cardiac death	0.9	0.273-3.0	0.88			
Non-sustained ventricular tachycardia	1.2	0.48-3.06	0.68			
Obstructive HC	0.28	0.08-1.01	0.41			

Figure 1

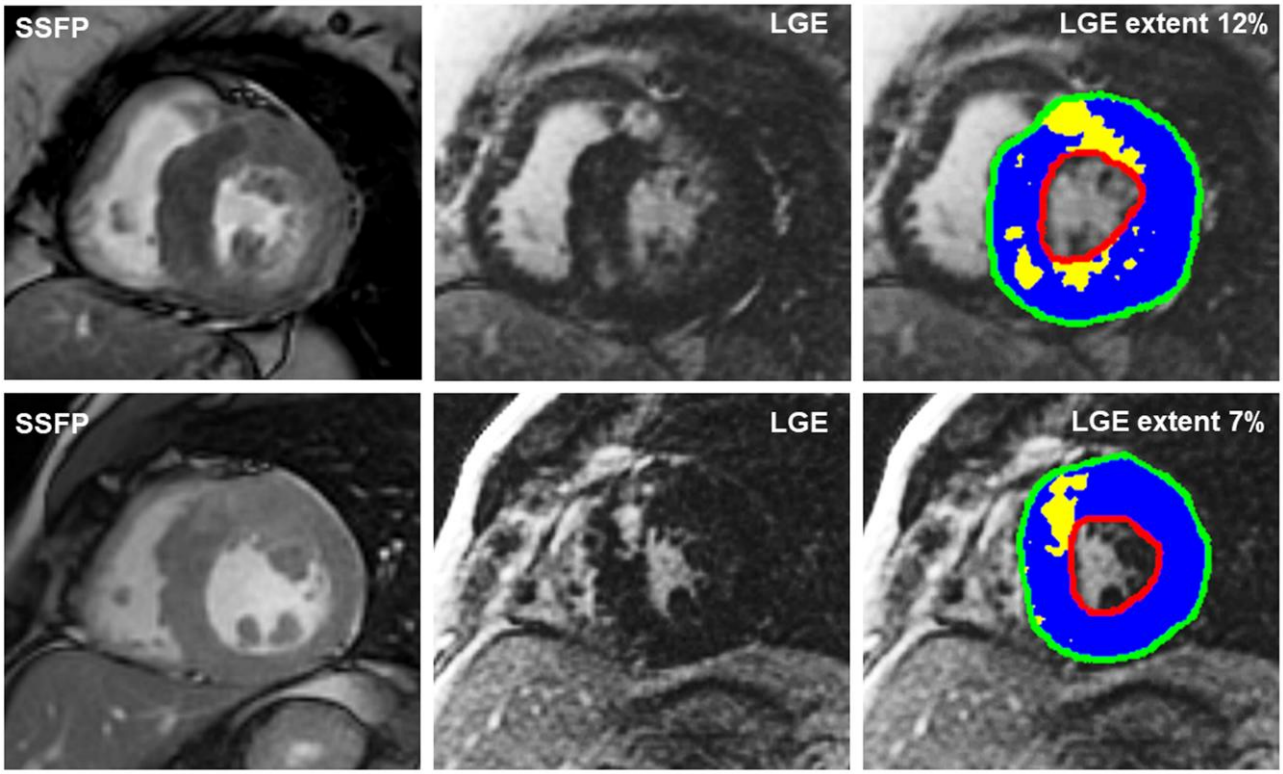
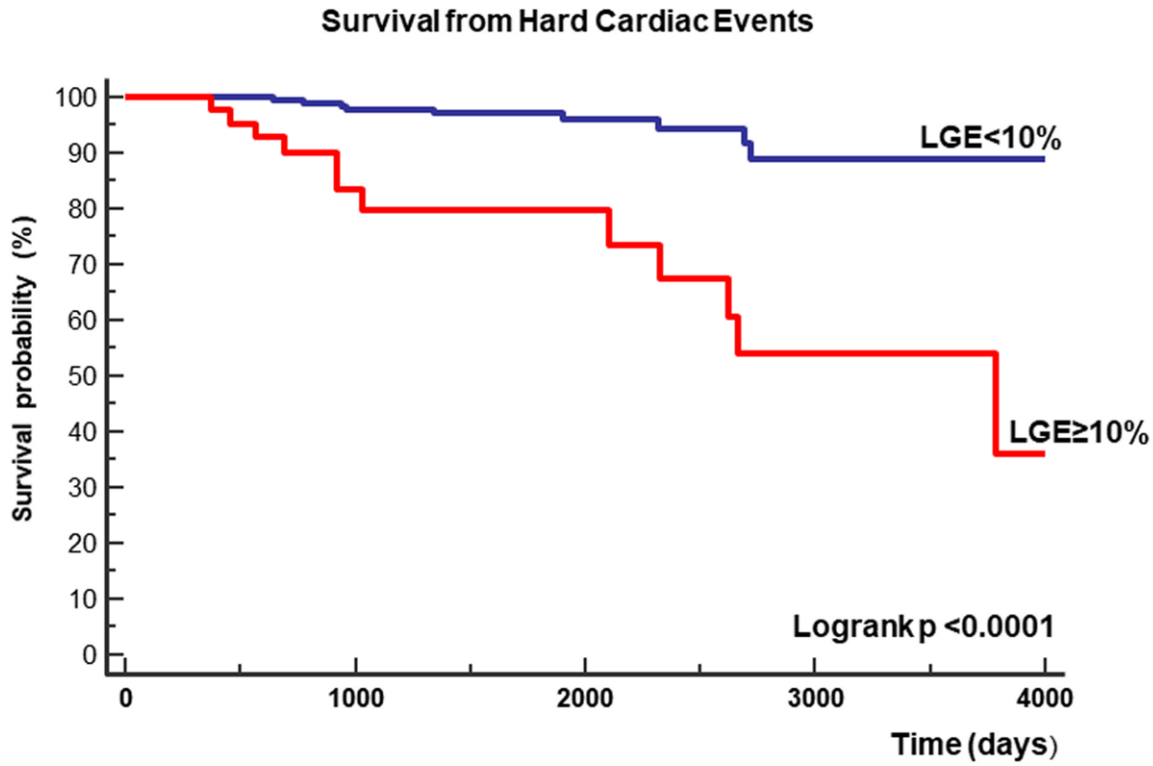


Figure 2



Number at risk

LGE<10%:	261	164	69	27	6
LGE≥10%:	70	22	14	3	2

Figure 3