Myocardial Scar Visualized by Cardiovascular Magnetic Resonance Imaging Predicts Major Adverse Events in Patients With Hypertrophic Cardiomyopathy

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Objectives   We sought to establish the prognostic value of a comprehensive cardiovascular magnetic resonance (CMR) examination in risk stratification of hypertrophic cardiomyopathy (HCM) patients.

Background   With annual mortality rates ranging between 1% and 5%, depending on patient selection, a small but significant number of HCM patients are at risk for an adverse event. Therefore, the identification of and prophylactic therapy (i.e., defibrillator placement) in patients with HCM who are at risk of dying are imperative.

Methods   Two-hundred forty-three consecutive patients with HCM were prospectively enrolled. All patients underwent initial CMR, and 220 were available for clinical follow-up. The mean follow-up time was 1,090 days after CMR. End points were all-cause and cardiac mortality.

Results   During follow-up 20 of the 220 patients died, and 2 patients survived sudden cardiac death due to adequate implantable cardioverter-defibrillator discharge. Most events (n = 16) occurred for cardiac reasons; the remaining 6 events were related to cancer and accidents. Our data indicate that the presence of scar visualized by CMR yields an odds ratio of 5.47 for all-cause mortality and of 8.01 for cardiac mortality. This might be superior to classic clinical risk factors, because in our dataset the presence of 2 risk factors yields an odds ratio of 3.86 for all-cause and of 2.20 for cardiac mortality, respectively. Multivariable analysis also revealed the presence of late gadolinium enhancement as a good independent predictor of death in HCM patients.

Conclusions   Among our population of largely low or asymptomatic HCM patients, the presence of scar indicated by CMR is a good independent predictor of all-cause and cardiac mortality.   (J Am Coll Cardiol 2010;56:875–87) © 2010 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder (1). With annual mortality rates ranging between 1% and 5% depending on patient selection, a small but significant number of patients are at risk for an adverse event (2). Therefore, the identification and prophylactic therapy (i.e., defibrillator placement) in patients with HCM who are at risk of dying are imperative. This is underscored by the fact that HCM has a high

socioeconomic impact, because it is the most common cause for sudden cardiac death (SCD) in young people (3).

Currently, several clinical markers are accepted for risk stratification in patients with HCM, including an adverse family history, prior cardiac arrest, spontaneous ventricular tachycardias or syncope, left ventricular (LV) wall thickness, and ventricular outflow tract obstruction. However, risk stratification in HCM is still limited by low positive predictive values of the clinical markers described in the preceding text (4,5).

Recently, it has been described that myocardial scarring detected by late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) is related to long-term clinical outcome and thus might be a much better predictor of lethal adverse events (Fig. 1) than established clinical

markers (6). Consequently, the primary objective of this study was to establish the prognostic value of a comprehensive CMR examination in risk stratification of patients with hypertrophic cardiomyopathy. Specifically, we sought to demonstrate that the presence of scar visualized by CMR predicts future cardiac death. In addition, we aimed to compare the incremental value of different CMR parameters in predicting adverse events with that of the established clinical markers.

Methods

Patient population. Two-hundred forty-three consecutive patients presenting at our institutions in Essen and Stuttgart for work-up of known or suspected HCM were prospectively enrolled between January 2003 and April 2008. All patients gave informed consent to the protocol, which was approved by

the local institutional review boards, and underwent CMR as well as centralized clinical follow-up. The HCM was diagnosed (or confirmed) by the presence of a nondilated and hypertrophied LV on 2-dimensional echocardiography or CMR (maximal wall thickness ≥15 mm in adult index patients or ≥13 mm in adult relatives of HCM patients) in the absence of another disease that could account for the hypertrophy (7). Patients who were known to have coronary artery disease, aortic stenosis, amyloidosis, systemic hypertension, or contraindications to CMR imaging were not included. We also did not include patients with previous septal ablation or myectomy.

CMR protocol. All images were acquired on a 1.5-T scanner (Siemens Sonata or Siemens Avanto, Siemens Healthcare, Erlangen, Germany) with a phased array receiver coil during breath-holds (approximately 8 s) gated to the electrocardiogram. Cine images were acquired in multiple short-axis and 2 to 3 long-axis views with a steady state free precession technique (8). Short-axis views were prescribed every 10 mm (slice thickness 6 mm) from base to apex (6 to 8 cine slices/heart) (9). A gadolinium-based contrast agent (gadolinium diethylenetriamine penta-acetic acid or gadoteridol, 0.15 mmol/kg) was then administered intravenously, and contrast-enhanced images were acquired in the same views used for cine imaging on average 10 min
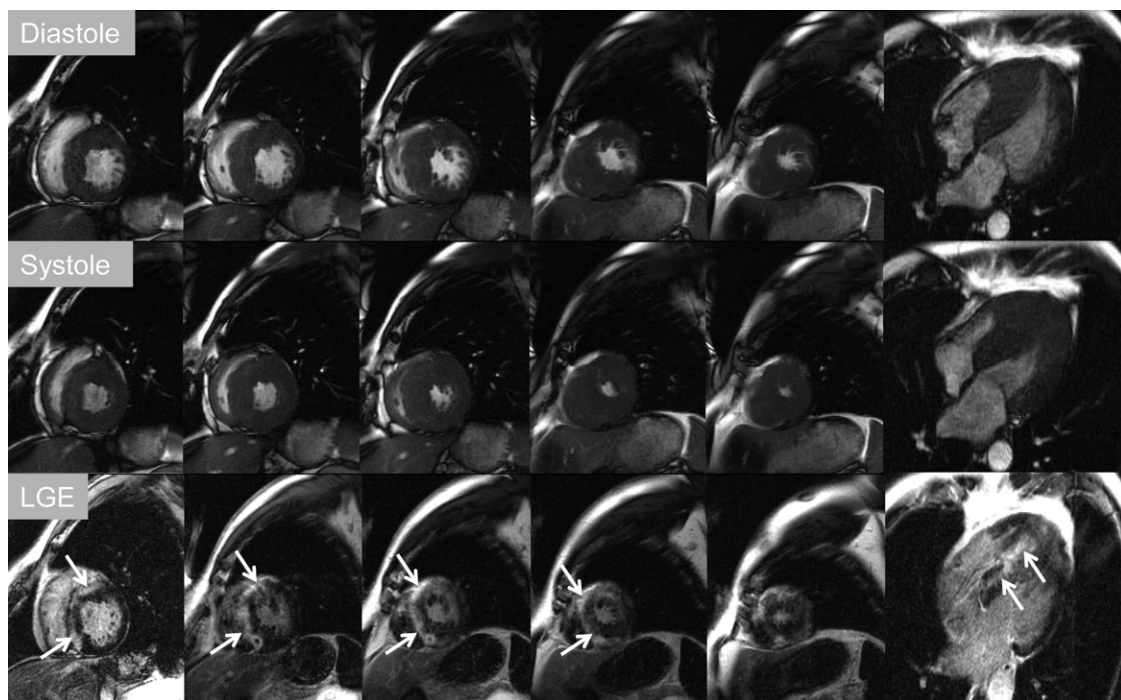
Figure 1   CMR Images of a 48-Year-Old White Man With 3 Recognized Clinical Risk Factors for SCD

Case #107. Cine images in the **top and middle rows** reveal normal left ventricular function but massive septal hypertrophy. Contrast images **(bottom row)** visualize extensive scarring as indicated by late gadolinium enhancement (LGE) **(white arrows)**. With regard to 3 clinical risk factors (Table 3), this patient underwent implantable cardioverter-defibrillator (ICD) placement shortly after cardiovascular magnetic resonance (CMR). During follow-up this individual survived sudden cardiac death (SCD), due to 2 adequate ICD discharges in the setting of ventricular fibrillation.

after contrast administration with a segmented inversion-recovery sequence constantly adjusting the inversion time as described previously (10). In-plane image resolution for cine and contrast was typically 1.2 × 1.6 mm.

CMR analysis. For all patients, the CMR scans were placed in random order after the identity markers were removed. Two blinded observers evaluated the cine and contrast-enhanced images separately.

The endocardial and epicardial borders of the myocardium were planimetered on the short-axis cine images (11). Maximum wall thickness was evaluated with all short-axis cine images covering the entire ventricle. Volumes were derived by summation of discs, and the ejection fraction was calculated accordingly. The LV mass was calculated by subtracting endocardial from epicardial volume at end-diastole and multiplying by 1.05 g/cm^3 (11). The extent of scarred myocardium was determined automatically by computer counting of all hyperenhanced pixels in the myocardium on each of the short-axis images. Hyperenhanced pixels resembling LGE were defined as those with image intensities of 2 SDs above the mean of image intensities in a remote myocardial region in the same image, which has been shown to represent myocardial fibrosis/scarring in HCM by necropsy comparison (12). The scar volume was then calculated as a percentage of LV mass (%LV), as the sum of hyperenhanced pixels from each of the short-axis images divided by the total number of pixels within the LV myocardium multiplied by 100%. Also, the surface area was measured for every patient (Fig. 2).

All CMR analysis was performed with Siemens Argus Software (Siemens Healthcare) as well as the National Institutes of Health Image Analysis Software Package (National Institutes of Health, Bethesda, Maryland).

Clinical follow-up. Clinical follow-up was performed by the Institut für Herzinfarktforschung, Ludwigshafen, Germany, with a standardized telephone questionnaire. In case of a suspected event, all necessary medical records were obtained and reviewed by the authors acting as an end point committee.

Variables, end points, and definitions. All variables assessed were pre-defined and collected directly from patients and/or from medical records with a standard questionnaire and check list, except CMR parameters, which were evaluated as described in the preceding text. Variables include general characteristics, clinical risk factors for SCD, and follow-up results. Most variables are self-explanatory; all other variables are defined in the following paragraphs.

Clinical risk factors for SCD: 1) history of cardiac arrest; 2) history of spontaneous ventricular tachycardia; 3) extreme hypertrophy (maximum wall thickness ≥30 mm); 4) family history of SCD (≥1 first-degree relative, <50 years of age); 5) unexplained syncope; and 6) LV outflow tract gradient >30 mm Hg measured by continuous-wave Doppler. The LV outflow tract gradient as described in the preceding text was chosen as a surrogate parameter for obstruction (7), because exercise blood pressure response was not available in many patients.

There were 2 primary end points: 1) all-cause death; and 2) cardiac death. The explicit meaning of these is described as follows:

All-cause mortality: death from any cause, including aborted SCD.

Cardiac death: death from all cardiac causes, including SCD, heart failure, and aborted SCD.

SCD: unexpected arrest of presumed cardiac origin within 1 h after onset of any symptoms that could be interpreted as being cardiac in origin (e.g., death after 30 min of angina). If an arrest occurred between 1 and 24 h after onset of symptoms it was classified as "suspected" sudden death.

Death from congestive heart failure: documented by the presence of signs of either right ventricular or LV failure or both on physical exam or radiographic exam.

| Volume: | 31ml | 25.7ml | 20.4ml | Σ 132ml |
| Scar Surface Area: | 892 mm² | 944mm² | 661mm² | Σ 3422.7mm² |
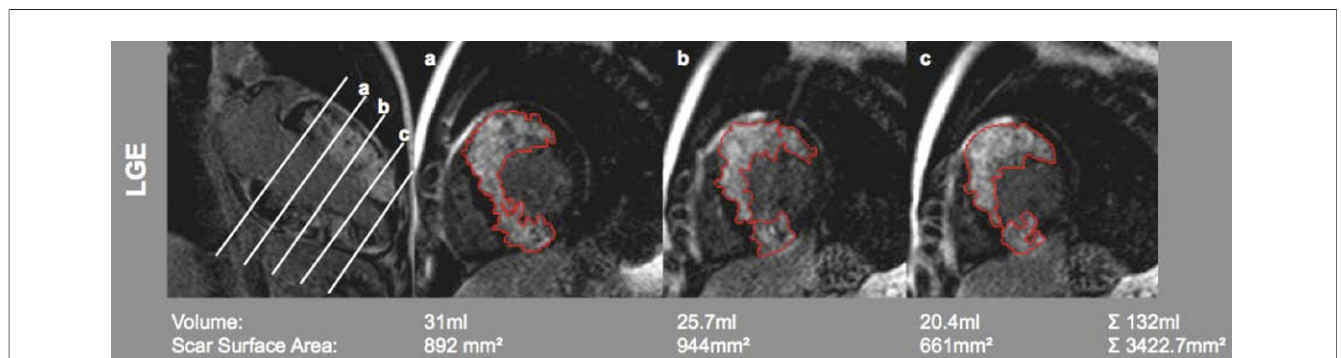
Figure 2   Contrast CMR Analysis

Areas of late gadolinium enhancement (LGE), as defined in the Methods section, were outlined by computer (**red area**) in every slice and multiplied with the inter-slice gap (10 mm). Scar volume was calculated by summation of discs. The scar surface area of each slice was calculated by multiplying the length of the **red outline** with the interslice gap (10 mm). The surface area of the entire scar was then also obtained by summation of discs.

The diagnosis should be confirmed by noninvasive or hemodynamic measurements.

Aborted SCD: resuscitation after cardiac arrest defined as performance of the physical act of cardioversion, appropriate implantable cardioverter-defibrillator (ICD) shocks, or cardiopulmonary resuscitation in a patient who remains alive 28 days later.

Appropriate ICD shocks: defibrillator discharges were considered appropriate, including automatic defibrillation shocks triggered by ventricular tachycardia or fibrillation and documented by stored intracardiac electrocardiographic or cycle-length data.

Statistical analysis. Absolute numbers and percentages were computed to describe the patient population. Medians (with quartiles) or means (with SD) were computed as appropriate. Categorical values were compared by chi-square test or Fisher exact test as appropriate. Kaplan Meier curves were calculated for visualizing the cumulative survival of patients with and without scar indicated by LGE. A log-rank test was performed to compare both survival curves. A multivariable Cox proportional hazard model was used for analyzing independent associations with all-cause and cardiac mortality. The covariates included in the regression model as potential confounders were selected with the present data and are limited in number due to the number of observed events. Therefore, the predictive value of LGE might be slightly lower than the current estimates from the multivariable analysis, due to over-fitting when applying the method to future cases. Values of $p < 0.05$ were considered significant. All p values are results of 2-tailed tests. All statistical analyses were performed with the SAS statistical package, version 9.1 (SAS Institute, Cary, North Carolina).

Results

Patient characteristics. Two-hundred twenty of all 243 patients were available for clinical follow-up as described in the preceding text, yielding a follow-up rate of 90.5%. The remaining 23 patients were lost due to no contact. The following paragraphs describe the characteristics of the 220 patients who underwent clinical follow-up.

At the time of the CMR study, patients were 58 years of age (interquartile range 47 to 68 years). Despite significant myocardial hypertrophy, most patients were asymptomatic (n = 132) or only mildly symptomatic (New York Heart Association functional class I and II, n = 46), respectively (Table 1). The remaining baseline characteristics can be viewed in Table 1.

More than 75% of all patients did not have any recognized clinical risk factors for SCD (n = 167). One clinical risk factor was present in 43 patients (19.5%), and 10 patients had 2 (n = 7) or 3 (n = 3) clinical risk factors for SCD. Twelve patients were offered prophylactic ICD insertion shortly after the CMR scan, in line with the current European guidelines (7). However, 4 patients initially re-

Table 1	Baseline Patient Characteristics	
		n or IQR
All patients with follow-up (%)	100	220
Time to follow-up (days, median)	1,090	466–1,869
Height (cm)	174	168–182
Weight (kg)	80	70–91
Female (%)	38.6	85/220
Symptoms (%)		
Chest pain	11.3	25/220
NYHA functional class I	1.4	3/220
NYHA functional class II	19.5	43/220
NYHA functional class III	7.72	17/220
Pattern (%)		
Septal	84.1	185/220
Apical	8.2	18/220
Concentric	7.7	17/220
CMR parameters		
LVEF (%)	71	65–77
Maximal wall thickness (mm)	19	16–23
LV mass (g)	156	127–196
LV mass index (g/m^2)	84	68–97
LVOT obstruction (%)	31.4	69/220
LGE mass (g)	2.2	0.0–8.5
LGE (% of LVM)	1.3	0.0–5.5
Surface area/LV mass (mm^2/g)	0.6	0.0–1.9
Surface area LGE (mm^2)	100.0	0.0–333.4
SCD risk factors (%)		
Maximal wall thickness >30 mm	3.6	8/220
History of sustained VT	5.5	12/220
Family history of SCD	4.5	10/220
Unexplained syncope	5.5	12/220
LVOT obstruction >30 mm Hg	10.9	24/220
Events (%)		
All-cause mortality	10.0	22/220
Cardiac mortality	7.2	16/220

All patients with follow-up.

CMR = cardiovascular magnetic resonance; EF = ejection fraction; IQR = interquartile range; LGE = late gadolinium enhancement; LV = left ventricle; LVOT = left ventricular outflow tract; NYHA = New York Heart Association functional class; SCD = sudden cardiac death; VT = ventricular tachycardia.

fused ICD placement, mostly due to the lack of clinical symptoms.

CMR findings. The mean LV ejection fraction was 71%, ranging from 22% to 89%. Most patients had septal hypertrophy, followed by apical and concentric patterns defined according to Klues et al. (13) (Table 1). The average maximum LV wall thickness was 19 mm, and the average LV mass was 156 g (Table 1).

Wall motion abnormalities were present in 17 of our 220 patients. In all 17 patients the wall motion abnormality was within the area of hypertrophy and scarring except in 3 patients, in whom the wall motion abnormality was confined to the thinned apical segments in the setting of massive mid-ventricular septal hypertrophy.

LGE was present in 148 (67.2%) of our 220 mostly mildly or asymptomatic patients. In those patients scar burden ranged from 0.9% to 39.9% of LV mass. The distribution of scar burden throughout the patient cohort
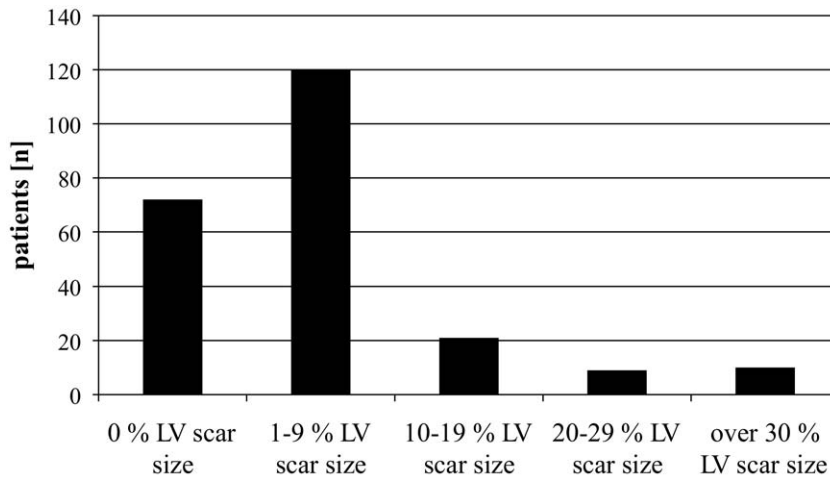
Figure 3   **Bar Graph Visualizing the Distribution of Scar Burden in Our Patient Cohort**

Median scar percentage of left ventricular mass (%LV). It is important to note that, among most individuals in our largely low or asymptomatic hypertrophic cardiomyopathy population, scarring was present as indicated by late gadolinium enhancement.

as a percentage of the LV mass can be viewed in Figure 3. Table 2 compares the characteristics of patients with LGE (n = 148) with those without LGE (n = 72). In general there were no differences between groups, except that patients with scar had a higher burden of hypertrophy as well as a history of arrhythmias more frequently.

Table 2   **Patients Without LGE Compared With Patients With LGE**

	No LGE	LGE	p Value	OR (95% CI)
LGE (n)	72	148	—	—
Age (yrs)	55.0	59.5	0.50	1.01 (0.99–1.03)
Pattern				
Septal	88.9 (64/72)	81.8 (121/148)	0.17	0.56 (0.24–1.30)
Apical	5.6 (4/72)	8.8 (13/148)	0.40	1.64 (0.51–5.21)
Concentric	5.6 (4/72)	9.5 (14/148)	0.32	1.78 (0.56–5.60)
CMR				
LVEF (%)	70.5	71.0	0.95	0.99 (0.97–1.02)
Maximal wall thickness (mm)	18.0	20.0	<0.01	1.13 (1.05–1.21)
LV mass (g)	147.0	162.0	0.05	1.01 (1.00–1.01)
LV mass index (g/m^2)	76.0	85.0	0.001	1.01 (1.00–1.02)
LVOT obstruction (%)	34.7	29.7	0.45	0.80 (0.44–1.45)
LGE (g)	0	5.7	—	—
LGE (% of LVM) (%)	0	3.2	—	—
Surface area LGE (mm^2)	0	211.6	—	—
Surface area/LV mass (mm^2/g)	0	1.4	—	—
SCD risk factors				
Maximal wall thickness >30 mm	0 (0/72)	5.4 (8/148)	<0.05	N/A
History of spontaneous VT	0 (0/72)	8.1 (12/148)	<0.05	N/A
Family history of SCD	2.8 (2/72)	5.4 (8/148)	0.38	2.00 (0.41–9.67)
Unexplained syncope	4.2 (3/72)	6.1 (9/148)	0.56	1.49 (0.39–5.68)
LVOT obstruction >30 mm Hg	14.3 (9/63)	11.4 (15/132)	0.56	0.77 (0.32–1.87)
Number of SCD risk factors				
0	83.3 (60/72)	73.8 (107/148)	0.07	0.52 (0.25–1.07)
1	13.9 (10/72)	21.3 (33/148)	0.14	1.78 (0.82–3.85)
2	2.8 (2/72)	9.1 (5/148)	0.81	1.22 (0.23–6.47)
3	0.0 (0/72)	2.0 (3/148)	0.22	N/A

Values are % (n/N) unless otherwise indicated.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

Table 3	Characteristics of All Patients With Events

Case #	Event Type	Age, yrs	NYHA	CCS	MWT >30 mm	Spontaneous VT	History of SCD	Unexplained Syncope	LVOT >30	LVEF	MWT	LV Mass	LGE	LGE (g)	LGE (% LV)	Surface Area	Surface Area/ LV Mass
3	Cancer	71	—	—	—	—	—	—	—	80	15	82	X	0.9	1.2	51.4	0.6
5	SCD	60	—	—	—	—	—	—	—	72	18	132	X	19.5	14.8	374.2	2.8
7	Suspected SCD	60	—	—	—	—	—	—	X	85	23	214	X	14.1	6.6	483.2	2.3
11	Heart failure	83	—	—	—	—	—	—	—	65	15	123	X	8.1	6.6	190.6	1.6
28	Cancer	78	2	—	—	—	—	—	—	59	15	162	X	1.5	0.9	112.6	0.7
42	Cancer	74	—	—	—	—	—	—	—	78	23	264	X	44.0	16.6	878.9	3.3
70	SCD	62	—	—	—	—	—	—	—	30	21	210	X	83.6	39.9	2,347.7	11.2
74	Suspected SCD	64	—	—	—	—	—	—	—	53	18	117	X	27.0	23.1	1,034.8	8.9
80	Heart failure	79	—	—	—	—	—	—	X	89	26	177	X	8.0	4.5	284.9	1.6
107	Aborted SCD	48	—	—	X	X	—	X	—	67	32	265	X	92.9	35.1	1,924.5	7.3
112	Suspected SCD	51	—	—	—	—	—	—	—	22	13	454	X	3.9	0.9	172.7	0.4
113	Cancer	66	—	—	—	—	—	—	X	58	25	282	X	2.9	1.0	174.9	10.6
119	Heart failure	76	—	—	—	—	—	—	—	68	20	158	X	3.6	2.3	169.3	11.1
124	SCD	61	—	—	—	—	—	—	—	58	18	216	X	18.9	8.7	664.9	3.1
136	SCD	53	—	—	—	—	—	—	—	79	26	196	—	0.0	0.0	0.0	0.0
139	Suspected SCD	61	—	—	—	—	—	—	—	78	20	173	X	9.7	5.6	249.2	1.4
154	Accident	60	—	—	—	—	—	—	—	72	18	190	X	14.5	7.6	681.3	3.6
161	Suspected SCD	67	—	—	—	—	—	—	—	68	23	154	X	17.2	11.2	508.4	3.3
163	Aborted SCD	54	—	—	—	X	—	—	—	69	29	259	X	51.3	19.8	1,655.0	18.0
169	Heart failure	76	3	1	—	—	X	X	—	49	17	243	X	19.8	8.2	412.0	1.7
201	Heart failure	70	—	—	—	—	—	—	—	46	16	147	X	2.4	1.6	180.7	1.2
236	Cancer	86	—	—	—	—	—	X	X	70	18	168	—	0.0	0.0	0.0	0.0

CCS = Canadian Cardiovascular Society Angina Score; MWT = maximum wall thickness; NYHA = New York Heart Association functional class; SCD = sudden cardiac death; other abbreviations as in Table 1.

Scarring was always located in the area of hypertrophy, either patchy with multiple foci (62.8%) or in a more diffuse distribution (37.2%). In contrast to subendocardial scarring in ischemic or subepicardial scarring in inflammatory heart disease, scars were predominantly located within the mid-myocardium in the HCM patient group.

Follow-up results. During the follow-up time (mean 1,090 days) (Table 1) 20 (9%) of the 220 patients died, and 2 patients survived SCD due to adequate ICD discharge. Those 2 patients were also counted as events as described in the Methods section. Most events (n = 16) occurred for cardiac reasons, the remaining 6 events were related to cancer and accidents. The clinical and imaging characteristics of all patients with events are displayed in Table 3. Note that 20 of the 22 (91%) patients who died during follow-up had no previous clinical symptoms. In addition, 8 of the 11 patients (73%) suffering from SCD during follow-up had no recognized clinical risk factors for SCD.

Predictors of events. For evaluation of predictors for events we looked at: 1) all patients who suffered any type of death during follow-up (all-cause mortality); 2) the subgroup of patients who suffered cardiac death (cardiac mortality); and 3) the subgroup of patients suffering SCD. The univariate analysis comparing different general, clinical, and imaging characteristics between groups with and without an

event during follow-up is displayed in Table 4 (all-cause mortality), Table 5 (cardiac mortality), and Table 6 (SCD only). There was no significant correlation among the hypertrophy pattern (septal, apical, or concentric), LV function, and the presence of wall motion abnormalities. In fact, none of the 17 patients with wall motion abnormalities suffered an event. Furthermore, we found no significant correlation between the occurrence of an adverse event and the presence of any single clinical risk factor. Also the presence of any 2 (n = 6) clinical risk factors was not significant for prediction of events (Tables 4, 5, and 6). However, besides the LV mass and patient age, only the presence of LGE as well as all LGE-related parameters reached statistical significance. In fact, the presence of any LGE yielded an odds ratio for death of 5.47 in the all-cause mortality and 8.01 in the cardiac mortality group. When focusing on the subgroup of patients suffering SCD only, the presence of LGE almost reached statistical significance, yielding an odds ratio for SCD of 5.14 (Table 6).

Figure 4 displays the relationship of scar burden assessed as %LV and the number of clinical risk factors as well as adverse events (right 2 columns). In general, patients with clinical risk factors for SCD had a larger amount of scar by CMR than patients without risk factors. However, even patients with 2 clinical risk factors had significantly less scarring than patients

Table 4	Univariate Analysis: All-Cause Mortality			
	No Event (n = 198)	**All-Cause Mortality (n = 22)**	**p Value**	**OR (95% CI)**
Age, yrs	56.5 (46.0–68.0)	65.0 (60.0–76.0)	<0.01	1.06 (1.02–1.02)
Pattern				
Septal	84.3 (167)	81.8 (18)	0.76	0.84 (0.26–2.64)
Apical	7.1 (14)	13.6 (3)	0.39	2.08 (0.55–7.87)
Concentric	8.6 (17)	4.5 (1)	1.00	0.51 (0.06–4.01)
CMR parameter				
LVEF, %	71.0 (64.9–76.7)	68.0 (58.0–78.0)	0.17	0.96 (0.93–1.00)
Maximal wall thickness, mm	19.0 (16.0–22.0)	19.0 (17.0–23.0)	0.57	1.03 (0.94–1.13)
LV mass, g	154.0 (126.8–190.3)	183.0 (153.5–243.2)	<0.05	1.01 (1.00–1.01)
LV mass index, g/m^2				
LVOT obstruction, %	36.4 (61)	30.8 (8)	0.59	1.28 (0.51–3.22)
LGE	64.6 (128)	90.1 (20)	0.01	5.47 (1.24–24.08)
LGE, g	1.8 (0.0–7.4)	11.9 (2.9–19.8)	<0.001	1.02 (1.00–1.03)
LGE, % LV	1.2 (0.0–4.6)	6.6 (1.2–14.8)	<0.01	1.04 (1.00–1.07)
Surface area LGE, mm^2	74.1 (0.0–263.6)	329.6 (172.7–681.3)	<0.001	1.00 (1.00–1.00)
Surface area/LV mass, mm^2/g	0.5 (0.0–1.7)	1.7 (0.7–3.3)	<0.001	1.16 (1.02–1.32)
SCD risk factors				
Maximal wall thickness >30 mm	3.5 (7)	4.5 (1)	0.58	1.30 (0.15–11.08)
History of spontaneous VT	5.0 (10)	9.1 (2)	0.34	1.88 (0.38–9.19)
Family history of SCD	2.0 (9)	4.5 (1)	1.00	1.00 (0.12–8.29)
Unexplained syncope	2.0 (9)	13.6 (3)	0.11	3.32 (0.83–13.30)
LVOT obstruction >30 mm Hg	10.0 (20)	19.0 (4)	0.30	1.81 (0.55–5.92)
Number of SCD risk factors				
0	76.7 (152)	68.2 (15)	0.37	0.65 (0.25–1.69)
1	19.6 (39)	18.2 (4)	1.00	0.91 (0.29–2.83)
2	2.5 (5)	9.1 (2)	0.15	3.86 (0.7–21.2)

Values are median (interquartile range) or % (n).
Abbreviations as in Tables 1 and 2.

Table 5	Univariate Analysis: Cardiac Mortality			
	No Cardiac Mortality (n = 204)	Cardiac Mortality (n = 16)	p Value	OR (95% CI)
Age, yrs	57.0 (46.0–68.0)	61.5 (57.0–73.0)	<0.05	1.04 (1.00–1.08)
Pattern				
Septal	84.3 (172)	81.2 (13)	0.72	0.81 (0.22–2.99)
Apical	7.4 (15)	12.5 (2)	0.36	1.80 (0.37–8.67)
Concentric	8.3 (17)	6.2 (1)	1.00	0.73 (0.09–5.90)
CMR parameter				
LVEF, %	71.0 (64.8–76.9)	68.0 (51.2–75.2)	<0.05	0.95 (0.92–0.99)
Maximal wall thickness, mm	19.0 (16.0–22.5)	20.0 (17.5–24.5)	0.35	1.05 (0.95–1.16)
LV mass, g	154.8 (126.8–190.9)	186.0 (150.3–229.7)	0.05	1.01 (1.00–1.01)
LV mass index, g/m^2	81.4 (66.2–95.3)	97.1 (82.0–126.0)	<0.01	1.02 (1.00–1.03)
LVOT obstruction, %	30.9 (63.0)	37.5 (6.0)	0.58	1.34 (0.47–3.86)
LGE	65.2 (133.0)	93.8 (15.0)	<0.05	8.01 (1.04–61.9)
LGE, g	1.8 (0.0–7.4)	15.6 (5.9–23.4)	<0.001	1.02 (1.00–1.04)
LGE, % LV	1.1 (0.0–4.6)	7.4 (3.4–17.3)	<0.001	1.05 (1.01–1.09)
Surface area LGE, mm^2	75.6 (0.0–272.3)	393.1 (185.7–849.9)	<0.001	1.00 (1.00–1.00)
Surface area/LV mass, mm^2/g	0.5 (0.0–1.7)	2.0 (1.3–4.8)	<0.001	1.20 (1.05–1.38)
SCD risk factors				
Maximal wall thickness >30 mm	3.4 (7.0)	6.3 (1.0)	0.46	1.88 (0.22–16.27)
History of spontaneous VT	4.9 (10.0)	12.5 (2.0)	0.21	2.77 (0.55–13.90)
Family history of SCD	4.4 (9.0)	6.3 (1.0)	0.54	1.44 (0.17–12.18)
Unexplained syncope	4.9 (10.0)	12.5 (2.0)	0.21	2.77 (0.55–13.90)
LVOT obstruction >30 mm Hg	12.2 (22.0)	13.3 (2.0)	1.00	1.10 (0.23–5.23)
Number of SCD risk factors				
0	76.5 (156.0)	68.8 (11.0)	0.54	0.68 (0.22–2.04)
1	19.6 (40.0)	18.8 (3.0)	1.00	0.95 (0.26–3.48)
2	2.9 (6.0)	6.3 (1.0)	0.38	2.20 (0.25–19.48)

Values are median (interquartile range) or % (n).
  Abbreviations as in Tables 1 and 2.

with an event. So the mean scar burden of patients with 2 risk factors was 3.8%, whereas the mean scar burden was 11.8% in the group of individuals who suffered from cardiac death and 9.8% when all-cause mortality was considered.

Kaplan-Meier survival curves—for all-cause mortality, cardiac mortality, and SCD comparing patients with scar with patients without scar—can be viewed in Figures 5A to 5C. Note that during the first 1,825 days of follow-up not a single patient without scar suffered from any cardiac death, including SCD (Figs. 5B and 5C).

Multivariable Cox regression analysis, including the presence of LGE, LV ejection fraction, and LV myocardial mass, also revealed LGE as a good independent predictor of cardiac death (p = 0.035; hazard ratio [HR]: 4.81). In this model ejection fraction (p = 0.067; HR: 0.96), and LV mass (p = 0.40; HR: 1.00) did not reach statistical significance. When the presence of 1 and 2 clinical risk factors for SCD as well as the presence of LGE was included in the multivariable regression analysis, the presence of LGE was a good independent predictor of cardiac death (p = 0.038, HR: 8.6), whereas the presence of 1 (p = 0.63, HR: 0.73) or 2 clinical risk factors (p = 0.68, HR: 1.37) did not reach statistical significance in our cohort. We did not perform multivariable analysis in the subgroup of patients suffering SCD (n = 11), due to the limited number of events.

Discussion

This study was unique in that we could demonstrate that the presence of scar visualized by LGE CMR is a predictor for death in HCM patients. In comparison with those of previous studies, our primary end points were not arrhythmias (6,14) or ventricular remodeling (15) but all-cause and cardiac mortality only. Our data indicate that the presence of LGE might be useful for noninvasive risk stratification in asymptomatic and mildly symptomatic HCM patients, yielding an odds ratio of 5.47 for all-cause and 8.01 for cardiac mortality. This might be superior to classic clinical risk factors, because in our dataset the presence of 2 risk factors yields an odds ratio of 3.86 for all-cause and 2.20 for cardiac mortality, respectively (Tables 4 and 5). Furthermore, multivariable analysis revealed the presence of LGE as a good independent predictor of death in HCM patients. **Patient characteristics.** Most patients were only mildly or completely asymptomatic (81%), which is similar to our previous results (95%) (11) as well as to patient cohorts of Moon et al. (15) (97%) and Adabag et al. (6) (95%). The finding that most HCM patients are low or asymptomatic underscores the importance of new risk stratification strategies, because SCD might be the first clinical symptom, occurring without any warning years after the initial diagnosis of HCM has been made (2,3).

Table 6	Univariate Analysis: SCD			
	No SCD (n = 209)	SCD (n = 11)	p Value	OR (95% CI)
Age, yrs (IQR)	57.0 (46.0–68.0)	60.0 (53.0–62.0)	0.77	1.07 (0.97–1.05)
Pattern				
Septal	84.2 (176.0)	81.8 (9.0)	0.69	0.84 (0.17–4.08)
Apical	7.7 (16.0)	9.1 (1.0)	0.60	1.21 (0.15–10.03)
Concentric	8.1 (17.0)	9.1 (1.0)	1.00	1.13 (0.14–9.36)
CMR parameter				
LVEF, % (IQR)	71.0 (64.7–76.7)	68.2 (53.2–78.0)	<0.05	0.95 (0.92–0.99)
Maximal wall thickness, mm (IQR)	19.0 (16.0–22.0)	21.0 (18.0–26.0)	0.13	1.09 (0.98–1.21)
LV mass, g (IQR)	155.2 (126.8–190.3)	210.0 (153.5–259.2)	<0.05	1.01 (1.00–1.02)
LV mass index, g/m^2	81.5 (66.9–95.5)	97.0 (83.9–135.8)	<0.05	1.02 (1.01–1.04)
LVOT obstruction, % (IQR)	30.6 (64.0)	45.5 (5.0)	0.33	1.89 (0.55–6.41)
LGE	66.0 (138.0)	90.9 (10.0)	0.10	5.14 (0.65–41.0)
LGE, g (IQR)	1.9 (0.0–7.6)	18.9 (9.7–51.3)	<0.001	1.02 (1.01–1.04)
LGE, % LV (IQR)	1.3 (0.0–4.7)	11.2 (5.6–23.1)	<0.01	1.06 (1.02–1.11)
Surface area LGE, mm^2 (IQR)	79.9 (0.0–280.9)	508.4 (249.2–1,655.0)	<0.001	1.00 (1.00–1.00)
Surface area/LV mass, mm^2/g (IQR)	0.6 (0.0–1.7)	3.1 (1.4–7.3)	<0.01	1.26 (1.08–1.47)
SCD risk factors				
Maximal wall thickness >30 mm	3.3 (7.0)	9.1 (1.0)	0.34	2.89 (0.32–25.77)
History of spontaneous VT	4.8 (10.0)	18.2 (2.0)	0.11	4.42 (0.84–23.23)
Family history of SCD	2.0 (9.0)	0 (0.0)	1.00	N/A
Unexplained syncope	2.0 (9.0)	9.1 (1.0)	0.47	1.80 (0.21–15.35)
LVOT obstruction >30 mm Hg	12.4 (23.0)	10.0 (1.0)	1.00	0.78 (0.09–6.47)
Number of SCD risk factors				
0	76.1 (159.0)	72.7 (8.0)	0.73	0.84 (0.21–3.28)
1	19.6 (39.0)	18.2 (2.0)	1.00	0.91 (0.19–4.38)
2	3.3 (7.0)	0.0 (0)	1.00	N/A

Values are median (interquartile range) or % (n).
 Abbreviations as in Tables 1 and 2.

Only 12 of our 220 patients were eligible for prophylactic ICD insertion according to the current European guidelines (7). However, 4 patients initially refused ICD placement due to the lack of clinical symptoms, reflecting the current difficulties in real-world clinical HCM patient management.

CMR findings. As expected, septal hypertrophy was detected most frequently, whereas apical and concentric patterns were present in approximately 8% of patients each. The average maximum wall thickness of 19 mm nicely demonstrates that significant hypertrophy can be present in
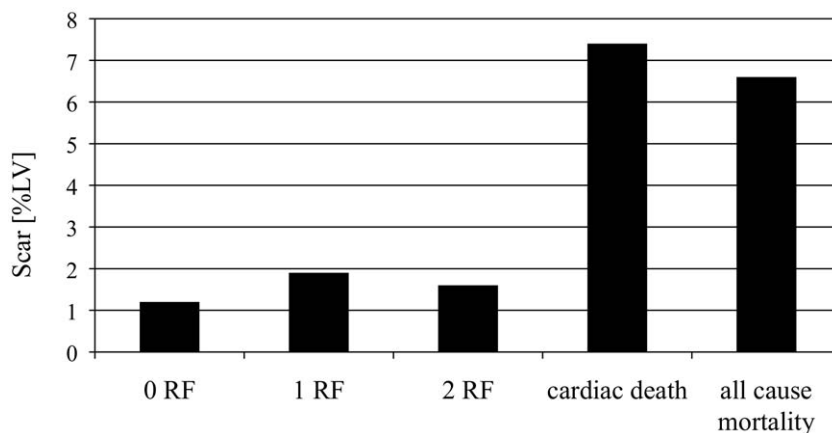
| Figure 4 | Bar Graph Plotting the Number of Sudden Cardiac Death Risk Factors and All-Cause and Cardiac Mortality Versus the Amount of Scarring |

Percentage of left ventricular mass (%LV). Note that patients who suffered an event during follow-up had the highest scar burden. Interestingly, patients without clinical risk factors (RF) also had scars.
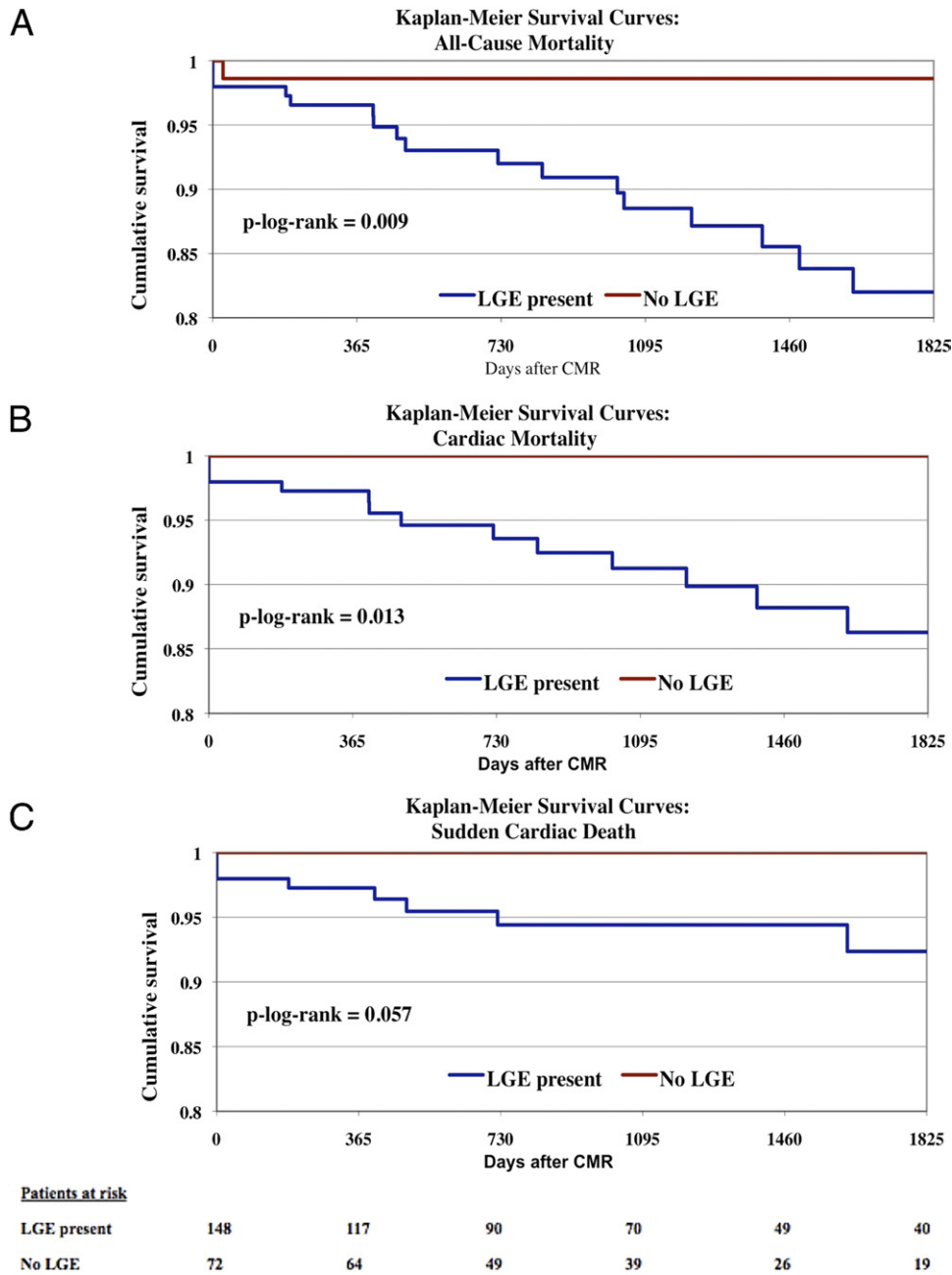
Figure 5   Kaplan-Meier Survival Curves With Regard to All-Cause Mortality, Cardiac Mortality, and SCD

All-cause mortality **(A)**, cardiac mortality **(B)**, and SCD **(C)**. The number of patients at risk is shown at the bottom of the figure. Note that in the group without any scar not a single patient suffered cardiac death **(B, C)** during the first 5 years of follow-up. Abbreviations as in Figure 1.

largely low or asymptomatic patients, confirming data from other groups (6,15).

LGE was present in almost 70% of patients, mostly confined to the area of hypertrophy, either in focal or diffuse patchy distribution, confirming previous findings (11). Figure 3 displays the distribution of scar burden throughout the patient cohort, demonstrating that most patients had a scar volume between 1% and 9% of

their LV mass. Only 36 patients had more than 10% of scar.

Follow-up results and predictors of events. In the group of 22 patients suffering death during follow-up, most individuals died from cardiac events (n = 16), emphasizing that cardiac events are the main cause of mortality among largely low or asymptomatic HCM patients. In this clinical scenario, however, risk stratification based on conventional

Figure 6   **CMR Images**

(A) CMR images of a 39-year-old white man without recognized risk factors for SCD. Cine images **(top and middle rows)** reveal normal left ventricular ejection fraction in the presence of severe septal hypertrophy. However, no scarring could be detected by contrast CMR **(bottom rows)**. As expected, this patient did not suffer any event during follow-up. **(B)** CMR images of a 64-year-old white man (case #74, Table 3), also without any recognized risk factors. However, despite similar morphology and left ventricular function compared with the patient in **A (upper 2 rows)**, LGE revealed significant myocardial scarring **(white arrows)**. This patient suffered SCD during follow-up in the absence of any recognized risk factor, underscoring that myocardial scarring might be a better predictor of major adverse cardiac events. Abbreviations as in Figure 1.

clinical risk factors (4,5) remains difficult, because 20 of the 22 patients (91%) who died during follow-up had no clinical symptoms, and only 3 of the 11 patients (27%) suffering SCD had any recognized risk factors for SCD (Table 3).

Thus, CMR might hold promise to improve clinical patient management and ultimately save lives. We found that the presence of scar as demonstrated by LGE is the strongest predictor for death in HCM patients with an odds

ratio of 5.47 for all-cause and 8.01 for cardiac mortality, respectively. Albeit limited by the relatively low number of cases and events, multivariable Cox regression analysis confirmed the presence of LGE as a good independent predictor of cardiac death when compared with LV function and LV mass (p = 0.035; HR: 4.81) as well as when compared with the presence of 1 or 2 clinical risk factors (p = 0.038, HR: 8.6), respectively.

This finding nicely fits with the fact that ventricular arrhythmias are the pathophysiological substrate of SCD in HCM patients (16) and that the presence of LGE was associated with a 7-fold increase in the risk of nonsustained ventricular tachycardia at follow-up in the cohort of Adabag et al. (6). In addition, as shown by Moon et al. (15), LGE is related not only to arrhythmias but also to ventricular remodeling and heart failure in HCM patients. All these previous results might explain why in the present study not a single patient without myocardial scarring suffered cardiac death (including SCD) during the first 1,825 days of follow-up (Figs. 5B and 5C).

This concept is also highlighted by Figure 6, displaying 2 typical examples of patients without any traditional risk factors but remarkable differences in scar size and outcome. Patient A with no presence of scar by LGE had no event during the follow-up period. However, Patient B, with a prominent scar, died from SCD. In fact, 8 of the 11 patients suffering from SCD during follow-up had no recognized clinical risk factors, but all had scars except 1. This patient, who suffered SCD without any recognized clinical risk factors and without any LGE (Table 3, Case #136), underscores that additional parameters such as genotype (17) or undetected coronary artery disease might also play a role in the clinical course of HCM.

Despite our encouraging data, however, it is important to keep in mind that there is not a 1:1 relationship between the presence of LGE and cardiac death. Thus, to further improve possible CMR risk stratification, we looked at the incremental value of several additional CMR-related parameters, such as the scar surface area (Fig. 2), which is thought to cause electrical instability (18). Interestingly, all these parameters reached statistical significance in the univariate analysis (Tables 4 to 6). However, we were not able to discriminate their individual predictive potential, due to the limited number of cases and events available in the present study. This topic as well as the question of whether the location of scarring within the ventricle might also help predict events (19) will be revisited as soon as the HCM data of the EuroCMR Registry (20,21) will be available.

Clinical implications. Although our data demonstrate an association between LGE and death in HCM patients, prospectively designed studies in large patient populations—such as the EuroCMR Registry (20,21)—are still required to definitively establish LGE as causally related to the death risk. However, with regard to our data and the results from other groups demonstrating that LGE is the substrate for ventricular arrhythmias in HCM (6,14) as well

as associated to ventricular remodeling and heart failure (15), it might be time to start regarding LGE as a primary risk factor for HCM patients.

Consequently, we believe that some weight can already be given to the presence of LGE as an arbitrator in reaching recommendations for prophylactic ICDs, when ambiguity remains concerning individual patient risk of cardiac death after assessing the conventional risk factors (22). Nevertheless, large longitudinal follow-up studies are needed to definitely establish LGE as an independent predictor of cardiac death in HCM.

Conclusions

Among our population of largely low or asymptomatic HCM patients, the presence of scar indicated by LGE is a good independent predictor of all-cause mortality as well as of cardiac mortality. These data support the necessity for future large longitudinal follow-up studies to definitely establish LGE as an independent predictor of cardiac death in HCM as well as to evaluate the incremental prognostic value of additional CMR parameters, such as scar surface area.

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