

Prognostic Significance of Myocardial Fibrosis in Hypertrophic Cardiomyopathy

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Objectives	We investigated the significance of fibrosis detected by late gadolinium enhancement cardiovascular magnetic resonance for the prediction of major clinical events in hypertrophic cardiomyopathy (HCM).
Background	The role of myocardial fibrosis in the prediction of sudden death and heart failure in HCM is unclear with a lack of prospective data.
Methods	We assessed the presence and amount of myocardial fibrosis in HCM patients and prospectively followed them for the development of morbidity and mortality in patients over 3.1 ± 1.7 years.
Results	Of 217 consecutive HCM patients, 136 (63%) showed fibrosis. Thirty-four of the 136 patients (25%) in the fibrosis group but only 6 of 81 (7.4%) patients without fibrosis reached the combined primary end point of cardiovascular death, unplanned cardiovascular admission, sustained ventricular tachycardia or ventricular fibrillation, or appropriate implantable cardioverter-defibrillator discharge (hazard ratio [HR]: 3.4, $p = 0.006$). In the fibrosis group, overall risk increased with the extent of fibrosis (HR: 1.18/5% increase, $p = 0.008$). The risk of unplanned heart failure admissions, deterioration to New York Heart Association functional class III or IV, or heart failure-related death was greater in the fibrosis group (HR: 2.5, $p = 0.021$), and this risk increased as the extent of fibrosis increased (HR: 1.16/5% increase, $p = 0.017$). All relationships remained significant after multivariate analysis. The extent of fibrosis and nonsustained ventricular tachycardia were univariate predictors for arrhythmic end points (sustained ventricular tachycardia or ventricular fibrillation, appropriate implantable cardioverter-defibrillator discharge, sudden cardiac death) (HR: 1.30, $p = 0.014$). Nonsustained ventricular tachycardia remained an independent predictor of arrhythmic end points after multivariate analysis, but the extent of fibrosis did not.
Conclusions	In patients with HCM, myocardial fibrosis as measured by late gadolinium enhancement cardiovascular magnetic resonance is an independent predictor of adverse outcome. (The Prognostic Significance of Fibrosis Detection in Cardiomyopathy; NCT00930735) (J Am Coll Cardiol 2010;56:867–74) © 2010 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a relatively common inherited cardiac disorder with a population prevalence of 1 in 500. It is a cause of sudden cardiac death (SCD) and an important cause of heart failure (HF) (1–5). A key mechanism for adverse outcomes is believed to be myocardial fibrosis—a pathological hallmark of the condition (6). Although myocardial

fibrosis was previously only identifiable by biopsy, advances in cardiovascular magnetic resonance (CMR) have enabled its noninvasive detection and quantification in vivo with

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**Abbreviations
and Acronyms****BSA** = body surface area**CI** = confidence interval**CMR** = cardiovascular
magnetic resonance**FWHM** = full width half
maximum**HCM** = hypertrophic
cardiomyopathy**HF** = heart failure**HR** = hazard ratio**ICD** = implantable
cardioverter-defibrillator**LAVI** = left atrial volume
index**LGE** = late gadolinium
enhancement**LVOTO** = left ventricular
outflow tract obstruction**NSVT** = nonsustained
ventricular tachycardia**NYHA** = New York Heart
Association**SCD** = sudden cardiac
death

the late gadolinium enhancement (LGE) technique (7–10). The presence of fibrosis on CMR is known to be associated with the presence of risk factors for SCD, HF symptoms, and the occurrence of nonsustained ventricular tachycardia (NSVT) (11–16). It remains unclear, however, whether fibrosis is an independent predictor of major adverse events and survival.

Methods

From January 2000 to December 2006, consecutive patients with HCM referred for CMR at the Royal Brompton Hospital were recruited. Reasons for referral included diagnostic evaluation, confirmation of diagnosis, family screening and assessment of severity. The diagnosis of HCM was made on the basis of typical clinical, echocardiographic, and hemodynamic features, according to established criteria (5). We excluded patients with con-

founding comorbidities, such as significant coronary artery disease (>50% stenosis) (n = 6), previous myocardial infarction (n = 17), or prior gradient reduction therapy (n = 21). All patients >40 years of age had coronary artery disease excluded angiographically; in those under 40 years of age, angiography was performed according to clinical symptoms. The study was approved by the Institutional Ethics Committee.

Events data. Patient events were recorded by communication with patients, their cardiologists, and family physicians. Medical records were reviewed after attendance at outpatient clinics or hospital stay. All patients were directly contacted at 3- to 6-month intervals during follow-up. Only new events from the time of recruitment were considered in the primary or secondary outcomes. The time of death was identified from the U.K. National Strategic Tracing Service database, and cause of death was confirmed through review of hospital records, general practitioner records, and the Office of National Statistics. No patient was lost to follow-up.

CMR acquisition. A standard volumes and LGE-CMR was performed on a dedicated scanner (Siemens Sonata/Avanto 1.5-T, Erlangen, Germany), with full myocardial coverage (17). The LGE images were acquired after intravenous gadolinium-diethylenetriamine penta-acetic acid (Bayer-Schering, Berlin, Germany; 0.1 mmol/kg) in identical short-axis planes to cine images with a breath-hold inversion-recovery gradient echo sequence (18). Inversion

times were optimized to null normal myocardium with images repeated in 2 separate phase-encoding directions to exclude artifact.

Image analysis. Ventricular function was analyzed with dedicated software (CMRtools, Cardiovascular Imaging Solutions, London) (19,20). All volumes and mass measurements were indexed to body surface area (21). The entire short-axis LGE stack of images were analyzed quantitatively for LGE extent by 2 independent readers with customized software (MRI-MASS, Medis, Leiden, the Netherlands). The endocardial and epicardial borders were traced for each short-axis slice. A region of interest (ROI) averaging 50 mm² was defined within the normal remote myocardium in an area with uniform myocardial suppression free of artifacts. A multipass region-growing algorithm was used to identify the fibrotic boundaries based on the “full width half maximum” (FWHM) technique, and fibrosis was expressed as present or absent, and its extent was quantified as a percentage of total left ventricular mass (22–24).

Statistical analysis. Results are summarized as mean (SD) or n (%) for continuous and categorical variables, respectively. Comparisons of demographic and clinical characteristics between fibrosis and no fibrosis groups were made with unpaired *t* tests or chi-square tests for continuous and categorical data.

The pre-specified primary end point was the composite of cardiovascular death, unplanned cardiovascular hospital stay, sustained ventricular tachycardia or ventricular fibrillation, or appropriate implantable cardioverter-defibrillator (ICD) discharge. Two separate secondary end points were predefined. A composite HF end point included unplanned HF hospital stay, progression to New York Heart Association (NYHA) functional class III or IV status, or HF-related death. A composite arrhythmic end point included sustained ventricular tachycardia or ventricular fibrillation, appropriate ICD discharge, or SCD. Start of follow-up was defined as the date of the initial CMR. Patients were censored at the time of their first event or the time of their last clinical follow-up.

Kaplan-Meier curves were used to estimate the survival distributions of the end points and to show the difference in survival between those with and without fibrosis. Demographic, clinical, and scan characteristics were all first tested with univariate analysis, and all variables with a *p* value <0.05 were then taken forward to be considered for inclusion in the multivariate model. The model was constructed with a forward selection procedure, with any variable that improved the likelihood ratio test statistic by an amount equivalent to *p* < 0.05 included. A Cox proportional hazards model was used to estimate the hazard ratio (HR) for the presence or absence of fibrosis and to estimate the effect on the outcomes of increased amounts of fibrosis. For each patient the predicted probability of having an event at 1, 2, and 3 years was calculated. This was done by obtaining the baseline

survival from the Cox model for the cohort at each time point and calculating the increased risk associated with increased levels of fibrosis. To test whether fibrosis was an independent predictor of risk, a multivariate analysis was performed (25). All analyses were performed with Stata version 10.1 (StataCorp, College Station, Texas).

Results

Baseline characteristics. A total of 217 patients were followed prospectively for 3.1 ± 1.7 years, representing 671 patient years of follow-up. The baseline population characteristics are summarized in Tables 1 and 2. Fibrosis was present in 63% of the total cohort. Within the fibrosis group, the mean percentage of fibrosis was 15.5% (range 1.4% to 54.9%). Groups with and without fibrosis had similar mean ages and baseline risk factors but different NYHA status, left ventricular mass index, left atrial volume index (LAVi), and maximum wall thickness.

Autopsy data. One patient with HCM who died underwent autopsy. Assessment of the macroscopic appearance of the cut surface of the heart showed focal fibrosis, which was confirmed histologically with Picrosirius Red staining. There was excellent agreement between the postmortem location and quantity of fibrosis and LGE on antemortem CMR. We quantified the amount of fibrosis with the FWHM technique in vivo and compared this with the amount of replacement fibrosis quantified histologically at postmortem, with an excellent agreement in the overall percentage of fibrosis quantified by the CMR technique versus histology. In this heart, LGE was specific for fibrosis rather than disarray (present in the septum) (Fig. 1). Representative patterns of fibrosis as imaged with LGE are shown in Figure 2.

Primary outcome. During follow-up, there were 9 cardiovascular deaths, 8 of which (89%) occurred in the fibrosis group. Overall, 40 of 217 (18.4%) patients reached the primary end point: 34 of 136 (25%) in the fibrosis group, and 6 of 81

Table 1 Baseline Characteristics of 217 Patients With HCM

	No Fibrosis (n = 81)	Fibrosis (n = 136)	Total (n = 217)	p Value
Age at diagnosis, yrs	52.2 (14.8)	50.4 (15.4)	51.1 (15.2)	0.40
Age at baseline CMR, yrs	52.8 (14.6)	53.2 (15.1)	53.2 (15.1)	0.84
Male (%)	59 (72.8)	94 (69.1)	153 (70.5)	0.56
BSA (m ²)	1.93 (0.23)	1.92 (0.18)	1.92 (0.18)	0.74
Ethnicity (%)				
White	69 (85.2)	123 (90.4)	192 (88.5)	0.002
Black	7 (8.6)	0 (0)	7 (3.2)	
Asian	3 (3.7)	12 (8.8)	15 (6.9)	
Other/unknown	2 (2.5)	1 (0.7)	3 (1.4)	
AF (%)	2 (2.5)	9 (6.6)	11 (5.1)	0.18
NYHA functional class (%)				
I	47 (58.0)	52 (38.8)	99 (46.1)	0.01
II	28 (34.6)	58 (43.3)	86 (40.0)	
III/IV	6 (7.4)	24 (17.9)	30 (13.9)	
Mean NYHA functional class	1.52 (0.71)	1.80 (0.74)	1.69 (0.74)	0.01
Risk factors for SCD				
Peak wall thickness, mm	17.5 (3.0)	23.3 (5.0)	21.1 (5.2)	<0.001
Wall thickness >30 mm	0 (0)	12 (8.8)	12 (5.5)	0.006
Rest LVOTO >30 mm Hg	18 (22.2)	39 (28.7)	57 (26.3)	0.30
Family history of SCD	6 (7.4)	19 (14.0)	25 (11.5)	0.14
Syncope	12 (14.8)	23 (16.9)	35 (16.1)	0.695
Sustained VT/VF	1 (1.1)	5 (3.7)	6 (2.8)	0.29
Nonsustained VT (total)	3 (3.7)	16 (11.8)	19 (8.8)	0.04
Nonsustained VT (age <45 yrs)	2	4	6	NS
Number of risk factors for SCD (%)				
0	50 (61.7)	65 (47.8)	115 (53.0)	0.06
1	24 (29.6)	45 (33.1)	69 (31.8)	
2+	7 (8.6)	26 (19.1)	33 (15.2)	
Beta-blockers (%)	23 (28.4)	60 (44.1)	83 (38.3)	0.02
Calcium antagonist (%)	7 (8.6)	24 (17.7)	31 (14.3)	0.07
Other antiarrhythmics (%)	6 (7.4)	23 (16.9)	29 (13.4)	0.05

According to presence or absence of fibrosis as detected by late gadolinium enhancement cardiovascular magnetic resonance (CMR). The p value represents the t test comparison between fibrosis and no-fibrosis groups. Values are mean \pm SD unless otherwise stated.

AF = atrial fibrillation; BSA = body surface area; HCM = hypertrophic cardiomyopathy; LAV = left atrial volume; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVOTO = left ventricular outflow tract obstruction; NYHA = New York Heart Association functional class; SCD = sudden cardiac death; VT/VF = ventricular tachycardia/ventricular fibrillation.

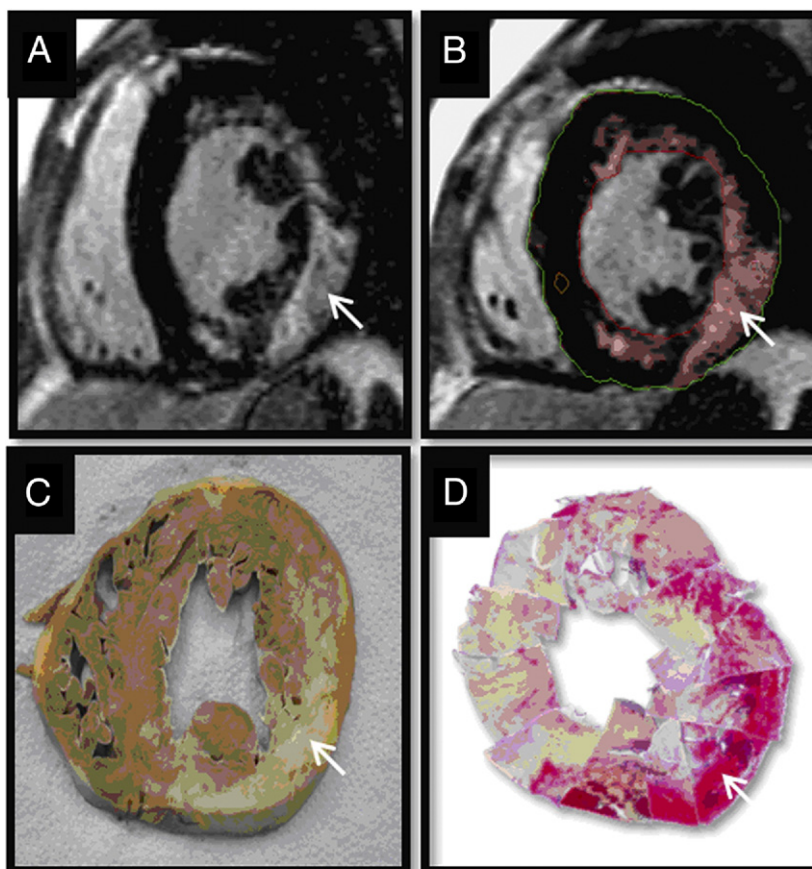


Figure 1 Autopsy Correlation of Fibrosis With In Vivo LGE-CMR

Comparison of in vivo late gadolinium enhancement (LGE) images (**A, B**, white arrows) matching macroscopic assessment from autopsy (**C**), and confirmed fibrosis on histology sections stained with Picrosirius red (**D**). CMR = cardiovascular magnetic resonance.

(7.4%) in the no-fibrosis group (HR: 3.4, 95% confidence interval [CI]: 1.4 to 8.1, $p = 0.006$) (Fig. 3A). The breakdown of events for the primary end point is shown in Table 3. In the fibrosis group, the overall risk of the primary end point increased with the percentage of fibrosis present (HR: 1.18/5% fibrosis increase, 95% CI: 1.05 to 1.33, $p = 0.008$) (Fig. 3B). The presence and amount of fibrosis remained independent predictors of the primary outcome after multivariable analysis (fibrosis \pm HR: 2.7, 95% CI: 1.01 to 7.1, $p = 0.046$; fibrosis % HR: 1.15, 95% CI: 1.01 to 1.30, $p = 0.03$). Hence, for every 5% increase in fibrosis the risk of reaching the primary end point increases by 15%. Other variables that were found to be independently associated with the primary outcome in the multivariate model were LAVi (HR: 1.016, 95% CI: 1.008 to 1.024, $p < 0.001$) and NYHA functional class (HR: 1.6, 95% CI: 1.07 to 2.31, $p = 0.021$).

Secondary outcomes. HF. Overall, 41 of 217 (19%) of the cohort reached the secondary HF end point: 33 of 136 (24.5%) in the fibrosis group, and 8 of 81 (9.9%) in the no fibrosis group (HR: 2.51, 95% CI: 1.1 to 5.5, $p = 0.021$) (Fig. 4A). In the fibrosis group, the overall risk increased

with the percentage of fibrosis present (HR: 1.16, 95% CI: 1.03 to 1.31, $p = 0.017$ /5% fibrosis increase) (Fig. 4B). Both the presence and amount of fibrosis remained significant predictors of HF outcome after multivariate analysis (fibrosis \pm HR: 2.6, 95% CI: 1.08 to 6.5, $p = 0.033$; fibrosis % HR: 1.21 95% CI: 1.06 to 1.37) $p = 0.004$). Other variables that were found to be independently associated with HF outcomes included LAVi (HR: 1.021, 95% CI: 1.01 to 1.03, $p < 0.001$) and the presence of a left ventricular outflow gradient of >30 mm Hg (HR: 2.45, 95% CI: 1.2 to 4.9, $p = 0.013$). In multivariate analysis, after adjustment for baseline differences in NYHA status, the amount of fibrosis remained a significant predictor of HF outcomes (HR: 1.27, 95% CI: 1.02 to 1.6, $p = 0.035$). In addition, in subset analysis for patients in NYHA functional classes I and II with no previous HF hospital stay, the presence and amount of fibrosis remained predictive of the secondary HF end points (fibrosis \pm HR: 2.73, 95% CI: 1.2 to 6.3, $p = 0.019$; fibrosis % HR: 1.16, 95% CI: 1.01 to 1.34, per 5% increase, $p = 0.035$). Furthermore, the overall percentage of fibrosis was a stronger predictor in this

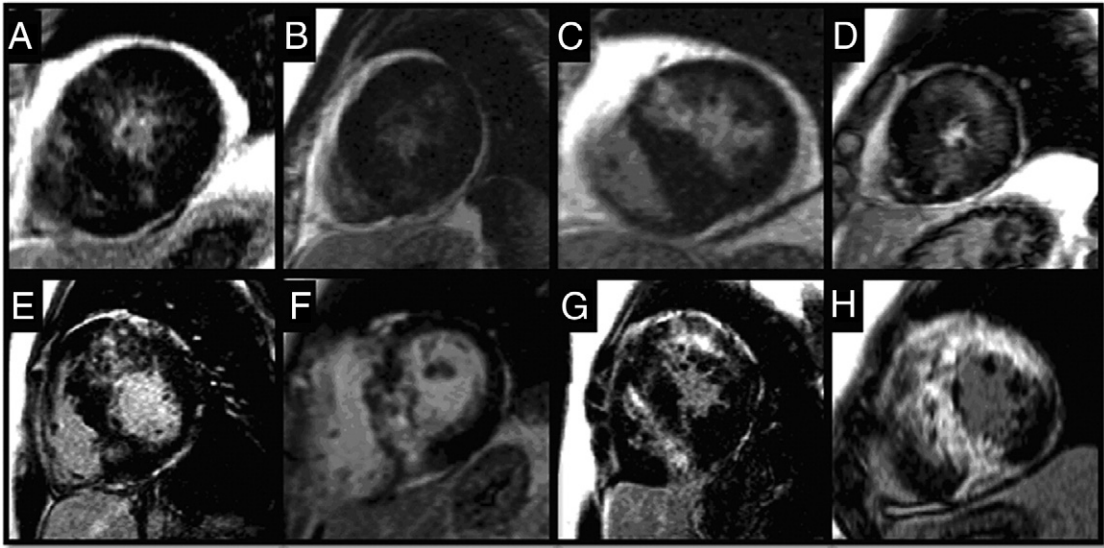


Figure 2 Representative Patterns and Severities of Fibrosis in HCM as Detected With LGE-CMR

Patchy and focal insertion point fibrosis (**A to C**), with other focal areas of patchy mid-wall fibrosis in the basal anteroapical wall (**A**) and anterolateral wall (**B**). A more circumferential diffuse mid-wall fibrosis (**D**), primarily at the apex. (**E to H**) Increasing severities of myocardial fibrosis with more diffuse insertion point fibrosis in **E**; extensive inferoseptal fibrosis in **F**; extensive anterior and anteroseptal fibrosis in **G**; and widespread anterolateral, septal, and inferoseptal fibrosis in **H**. HCM = hypertrophic cardiomyopathy; other abbreviations as in [Figure 1](#).

cohort of HF outcomes than the presence of left ventricular outflow tract obstruction (LVOTO) >30 mm Hg.

Arrhythmic outcome. Of the entire cohort, 12 of 217 reached the secondary arrhythmic end point: 10 of 136 (7.3%) in the fibrosis group, and 2 of 81 (2.5%) in the no-fibrosis group (HR: 3.15, 95% CI: 0.69 to 14.4, $p = 0.138$). Univariate predictors of this end point were the presence of NSVT and the overall percentage of fibrosis. None of the other standard clinical risk factors were predictive in this cohort. The amount of fibrosis was significantly associated with the outcome in univariate analysis (HR: 1.30, 95% CI: 1.05 to 1.61, $p = 0.014$), but in the multivariable analysis NSVT was the strongest

predictor, and after this no other variables were added to the model owing to the low event numbers.

Discussion

There are limited data on the prognostic significance of fibrosis in patients with HCM. The main findings are that the presence and severity of fibrosis are associated with a greater risk of major adverse events.

Hypertrophic cardiomyopathy is an important cause of SCD throughout life and progressive HF and stroke in older patients. Established risk markers mainly focus on identifying those at risk of SCD (approximately 0.5%/year).

Table 2 Baseline CMR Characteristics of 217 Patients With HCM				
CMR Parameters	No Fibrosis (n = 81)	Fibrosis (n = 136)	Total (n = 217)	p Value
LVEF, %	75.9 (8.4)	72.7 (11.6)	73.9 (10.6)	0.03
LVEDV, ml	130.6 (38.9)	129.5 (35.9)	129.9 (37.0)	0.82
LVESV, ml	33.8 (22.6)	37.3 (21.4)	36.0 (21.9)	0.25
LVEDV indexed, ml/BSA	67.5 (16.4)	67.5 (16.7)	67.5 (16.5)	0.99
LVESV indexed, ml/BSA	17.2 (10.5)	19.5 (11.2)	18.6 (11.0)	0.14
LV mass, g	179.8 (49.7)	227.5 (85.6)	209.8 (77.7)	<0.001
LV mass indexed, g/BSA	93.2 (22.3)	118.2 (41.3)	108.9 (37.4)	<0.001
LAV, ml	89.7 (33.1)	112.1 (57.5)	103.9 (51.0)	0.002
LAV indexed, ml/BSA	46.8 (16.6)	58.3 (28.5)	54.1 (25.4)	0.002
Fibrosis, mean % (range)	0	15.5 (1.4–54.9)	9.7 (0–54.9)	NA

Values are mean ± SD unless otherwise stated. According to presence or absence of fibrosis as detected by LGE-CMR. The p value represents the t test comparison between fibrosis and no fibrosis groups.
Abbreviations as in [Table 1](#).

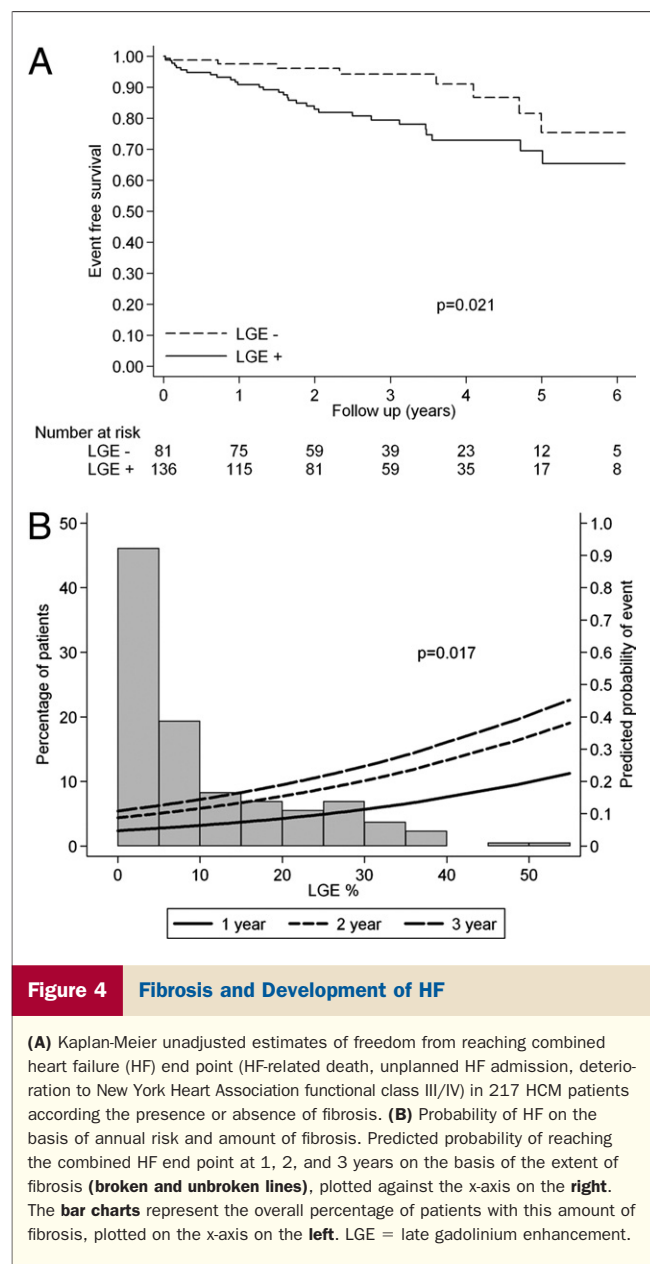
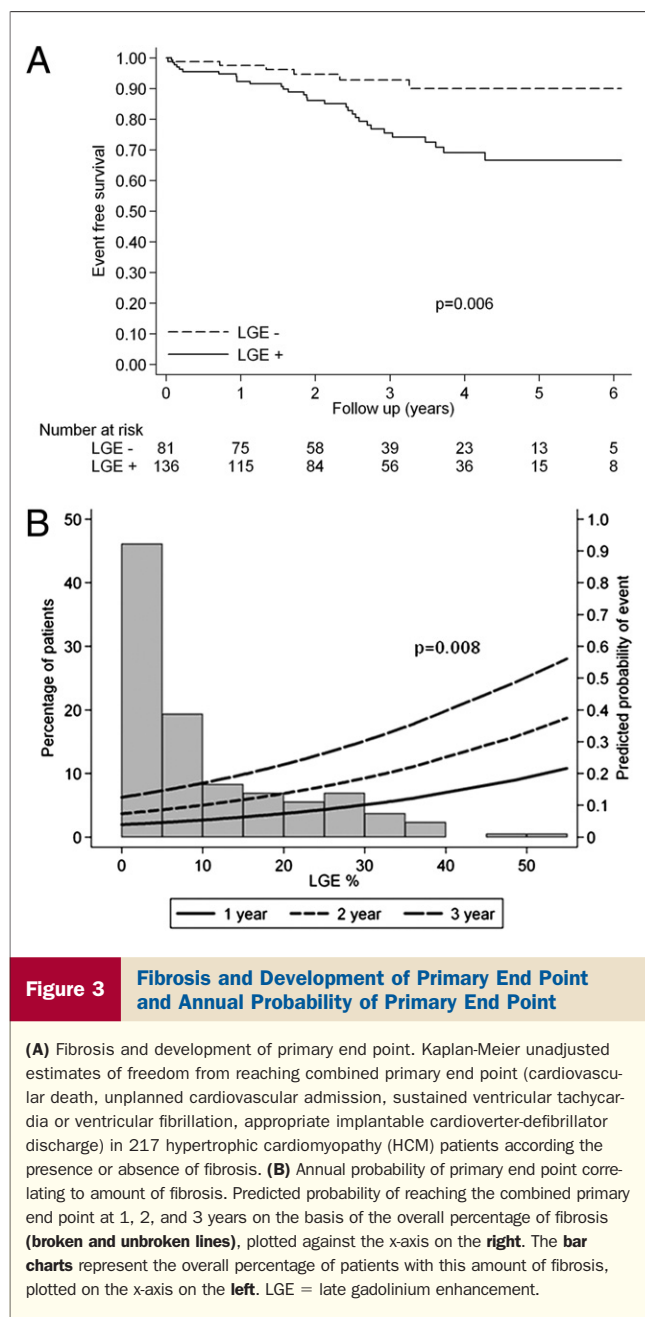


Table 3 Breakdown of Events Contributing to Overall MACE Rate in 217 HCM Patients With and Without Fibrosis						
Outcome	No Fibrosis (n = 81)	Fibrosis (n = 136)	Total (n = 217)	HR	95% CI	p Value
Primary outcome	6 (7.4)	34 (25.0)	40 (18.4)	3.367	1.406–8.063	0.006
CV mortality	1 (1.2)	8 (5.9)	9 (4.2)	4.452	0.548–36.204	0.163
Unplanned CV hospital stay	5 (6.2)	24 (17.7)	29 (13.4)	2.825	1.072–7.448	0.036
VT/VF	1 (1.2)	8 (5.9)	9 (4.2)	4.973	0.622–39.762	0.131
ICD discharge	0 (0)	2 (1.5)	2 (0.9)	NA	—	—
Sudden death	1 (1.2)	1 (0.7)	2 (0.9)	0.648	0.041–10.360	0.759
HF death	0 (0)	6 (4.4)	6 (2.8)	—	—	—
CVA death	0 (0)	1 (0.7)	1 (0.4)	NA	—	—

CI = confidence interval; CV = cardiovascular; CVA = cardiovascular accident; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; VT/VF = ventricular tachycardia/ventricular fibrillation.

However, there remain many patients where additional risk stratification would be beneficial, particularly those with a single risk factor. In addition, there is limited guidance to identify those at risk of progressive HF, which affects up to 10% of patients (14). Understanding processes occurring at the myocardial tissue level—in particular, fibrosis—might provide a novel marker to predict both arrhythmic and HF outcomes. Fibrous tissue promotes re-entrant ventricular arrhythmias and contributes to increased ventricular stiffness (26–29). In histopathological studies, there is an 8-fold increase in the amount of matrix collagen in adults and children who die suddenly from HCM compared with normal control subjects (8). This is also reflected in greater levels of serum markers of collagen turnover (30). Microscopic fibrosis is greater in hearts of patients with the dilated phase of HCM than in nondilated hearts (26).

It is only recently that fibrosis in HCM could be detected noninvasively *in vivo* with the CMR LGE technique, where gadolinium-contrast agents accumulate in areas of interstitial expansion due to fibrosis, which can then be imaged (7). Fibrosis detection by the LGE technique has prognostic significance in ischemic heart disease and dilated cardiomyopathy (31,32). The importance in HCM is unclear, although we and others have shown an association with markers for SCD (12,33). It also seems to correlate with systolic dysfunction and the development of NSVT (10,14). Several methods have been described to quantify the amount of myocardial fibrosis. In this study we used an established and validated method of quantification based on the FWHM technique. Several groups have recently shown that this technique correlates accurately with *ex vivo* quantification of fibrosis and has the best reproducibility (22–24). Some groups have used an alternative method based on thresholding with the use of silicon cutoff values of between 2 and 6 SDs above the remote noninjured myocardium and in particular 6 SDs. Work by Spiewak *et al.* (24) has demonstrated no significant difference between techniques for quantifying fibrosis in HCM on the basis of 6 SDs and FWHM thresholding methods compared with visual analysis, with the best intraobserver agreement noted for the FWHM method. The findings of this study suggest that either method of quantification is likely to be valid. Further work is ongoing to assess whether one method is more accurate, compared with histological validation in HCM.

The findings in this study indicate that CMR fibrosis identifies patients at increased risk of disease progression. Both the presence and the amount of fibrosis are of independent prognostic significance. The presence of fibrosis is associated with a 3.4-fold greater risk of major adverse events, and the risk is proportional with increased amounts of LGE-detected fibrosis. These results are predominantly driven by the development of HF (2.5-fold increase in risk). This risk is independent of baseline NYHA status. In this study, the prevalence of LVOTO was similar in both groups, and although it was shown to be an independent predictor of the HF outcomes, it was a weaker predictor than the amount of LGE and a similar

strength predictor for the presence or absence of LGE. Regarding the potential that LVOTO might promote the development of LGE, this has not as yet been demonstrated in published reports and would be the basis for further important work. It is likely that several factors contribute to the development of fibrosis in HCM, a fact supported by the finding of LGE in patients without LVOTO and in apical HCM phenotypes. Although it is thought-provoking to highlight that 83% (10 of 12) of major arrhythmic events occurred in the group with fibrosis, this study was underpowered to show this to be statistically significant. Both the overall percentage of fibrosis and NSVT were important independent predictors of major arrhythmic end points, but owing to the small numbers of these events over the time course of this study, fibrosis percentage did not reach statistical significance after multivariable analysis. This relationship to arrhythmic end points might prove to be more relevant over a longer-term follow-up. At present, the data suggest the need for closer monitoring of patients with HCM and fibrosis for the development of HF. That even small amounts of replacement fibrosis are associated with increased risk of development of HF might be a marker of more significant underlying interstitial fibrosis. Further work will be required to identify whether early therapy with an antifibrotic agent has an impact. The findings do not, at present, support the routine deployment of an ICD on the basis of the presence or amount of fibrosis *per se*. This is consistent with other recent work (34).

Study limitations. Although this was a single-center study in a tertiary hospital, this allowed for a consistent scanning protocol and close follow-up of all patients. To ensure a representative cohort, consecutive HCM referrals from a large network of referring hospitals were recruited. Further work is required to identify whether these findings are applicable to a community-based population. The accrued 671 patient-years of follow-up was underpowered to assess fibrosis incrementally to other risk factors for SCD, and ongoing prospective follow-up in a larger cohort will be required. The LGE technique detects only focal fibrosis and not microscopic diffuse fibrosis. Patients with an ICD at baseline were excluded from enrollment, owing to the contraindication for CMR. It is unclear how their inclusion would influence the present results, although other groups have previously shown that the incidence of fibrosis in this high-risk cohort to be higher than lower-risk populations. Further work is required to determine whether specific patterns and locations of fibrosis correlate with differing outcomes.

Conclusions

In vivo fibrosis detection by CMR is an independent predictor of adverse outcome in HCM. As a novel marker it seems to detect those at risk of progressive disease and might guide specific therapies for HF prevention and treatment. As a risk factor for SCD, it is likely that longer follow-up in a larger cohort will clarify the role of fibrosis detection.

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Key Words: cardiovascular magnetic resonance ■ hypertrophic cardiomyopathy ■ late gadolinium enhancement ■ myocardial fibrosis.