Association of Fibrosis With Mortality and Sudden Cardiac Death in Patients With Nonischemic Dilated Cardiomyopathy

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Importance Risk stratification of patients with nonischemic dilated cardiomyopathy is primarily based on left ventricular ejection fraction (LVEF). Superior prognostic factors may improve patient selection for implantable cardioverter-defibrillators (ICDs) and other management decisions.

Objective To determine whether myocardial fibrosis (detected by late gadolinium enhancement cardiovascular magnetic resonance [LGE-CMR] imaging) is an independent and incremental predictor of mortality and sudden cardiac death (SCD) in dilated cardiomyopathy.

Design, Setting, and Patients Prospective, longitudinal study of 472 patients with dilated cardiomyopathy referred to a UK center for CMR imaging between November 2000 and December 2008 after presence and extent of midwall replacement fibrosis were determined. Patients were followed up through December 2011.

Main Outcome Measures Primary end point was all-cause mortality. Secondary end points included cardiovascular mortality or cardiac transplantation; an arrhythmic composite of SCD or aborted SCD (appropriate ICD shock, nonfatal ventricular fibrillation, or sustained ventricular tachycardia); and a composite of HF death, HF hospitalization, or cardiac transplantation.

Results Among the 142 patients with midwall fibrosis, there were 38 deaths (26.8%) vs 35 deaths (10.6%) among the 330 patients without fibrosis (hazard ratio [HR], 2.96 [95% CI, 1.87-4.69]; absolute risk difference, 16.2% [95% CI, 8.2%-24.2%]; $P<.001$) during a median follow-up of 5.3 years (2557 patient-years of follow-up). The arrhythmic composite was reached by 42 patients with fibrosis (29.6%) and 23 patients without fibrosis (7.0%) (HR, 5.24 [95% CI, 3.15-8.72]; absolute risk difference, 22.6% [95% CI, 14.6%-30.6%]; $P<.001$). After adjustment for LVEF and other conventional prognostic factors, both the presence of fibrosis (HR, 2.43 [95% CI, 1.50-3.92]; $P<.001$) and the extent (HR, 1.11 [95% CI, 1.06-1.16]; $P<.001$) were independently and incrementally associated with all-cause mortality. Fibrosis was also independently associated with cardiovascular mortality or cardiac transplantation (by fibrosis presence: HR, 3.22 [95% CI, 1.95-5.31], $P<.001$; and by fibrosis extent: HR, 1.15 [95% CI, 1.10-1.20], $P<.001$), SCD or aborted SCD (by fibrosis presence: HR, 4.61 [95% CI, 2.75-7.74], $P<.001$; and by fibrosis extent: HR, 1.10 [95% CI, 1.05-1.16], $P<.001$), and the HF composite (by fibrosis presence: HR, 1.62 [95% CI, 1.00-2.61], $P=.049$; and by fibrosis extent: HR, 1.08 [95% CI, 1.04-1.13], $P<.001$). Addition of fibrosis to LVEF significantly improved risk reclassification for all-cause mortality and the SCD composite (net reclassification improvement: 0.26 [95% CI, 0.11-0.41]; $P=.001$ and 0.29 [95% CI, 0.11-0.48]; $P=.002$, respectively).

Conclusions and Relevance Assessment of midwall fibrosis with LGE-CMR imaging provided independent prognostic information beyond LVEF in patients with nonischemic dilated cardiomyopathy. The role of LGE-CMR in the risk stratification of dilated cardiomyopathy requires further investigation.

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NONISCHEMIC DILATED CARDIOmyopathy is a common heart muscle disease with a prevalence of at least 1 in 2500 adults.[1] It is characterized by left ventricular cavity enlargement and impaired contractility in the absence of significant coronary artery disease.[1] The condition is associated with significant morbidity and mortality due to progressive heart failure (HF) and sudden cardiac death (SCD).[2] Despite

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therapeutic advances, 5-year mortality remains as high as 20%.[2] Risk stratification in dilated cardiomyopathy therefore constitutes a crucial part of patient management with implications for surveillance, treatment, and outcome. Currently, risk stratification is heavily dependent on the assessment of left ventricular ejection fraction (LVEF), as exemplified by its use as the key determinant of device implantation.[3] Although LVEF is an important prognostic factor in dilated cardiomyopathy,[4,5] effective risk stratification remains challenging, particularly with respect to SCD.[6,7] Most patients who experience SCD do not have severely reduced LVEF, and many patients with significant impairment of LVEF may still be at low risk for SCD.[7,8] Identification of better independent prognostic factors is necessary to enable clinicians to more accurately stratify risk in patients with dilated cardiomyopathy and tailor management accordingly.

Attention has recently focused on whether detection of myocardial replacement fibrosis may assist with risk stratification in dilated cardiomyopathy. Fibrosis is associated with contractile impairment,[9,10] and provides a substrate for ventricular reentrant arrhythmia.[11,12] Late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) imaging enables identification and quantification of myocardial replacement fibrosis in vivo.[13,14] Approximately 30% of patients with dilated cardiomyopathy have a characteristic midwall pattern of replacement fibrosis on LGE-CMR.[13,15] Although several studies have suggested that midwall fibrosis may predict adverse outcomes in patients with dilated cardiomyopathy,[16-19] the true prognostic value of midwall fibrosis with respect to mortality and SCD is unknown. Therefore, we prospectively evaluated whether midwall fibrosis predicts mortality, independently of LVEF and other established prognostic factors, in a large cohort of consecutive patients with dilated cardiomyopathy during a long follow-up period. Second, we assessed if midwall fibrosis was an independent predictor of SCD risk and major HF events.

METHODS

Patients

We performed a prospective, longitudinal study of the prognostic value of midwall fibrosis in a cohort of consecutive patients with dilated cardiomyopathy who were referred to the Royal Brompton Hospital in London, England, for CMR between November 2000 and December 2008. Eligible patients had a diagnosis of dilated cardiomyopathy, in accordance with the criteria of the World Health Organization/International Society and Federation of Cardiology,[20] of at least 6 months' duration. Prior to inclusion, the diagnosis of dilated cardiomyopathy was confirmed by CMR on the basis of (1) increased left ventricular end-diastolic volume indexed to body surface area and reduced LVEF compared with published reference ranges normalized for age and sex[21]; and (2) absence of subendocardial LGE indicative of previous myocardial infarction.[13] All patients provided written informed consent. The study was approved by the Royal Brompton Hospital ethics committee.

CMR Image Acquisition

Cardiovascular magnetic resonance imaging was performed using a 1.5-T scanner (Siemens Sonata/Avanto) and a standardized protocol. Cine images were acquired with a steady-state, free-precession sequence in long-axis planes and contiguous short-axis slices from the atrioventricular ring to the apex as previously described.[21] Ten minutes after intravenous injection of 0.1 mmol/kg of gadolinium - contrast agent (gadopentetate dimeglumine or gadobutrol, Schering), LGE images were obtained using an inversion-recovery gradient echo sequence in identical long-axis and short-axis planes. Inversion times were optimized to null normal myocardium, and images were repeated in 2 separate phase-encoding directions to exclude artifacts.[16]

Image Analysis

Left ventricular volumes, ejection fraction, and mass were measured using dedicated software (CMRtools, Cardiovascular Imaging Solutions).[21] Left ventricular volumes and mass were indexed to body surface area. The presence and location of midwall fibrosis were assessed by 2 independent expert readers (E.D.P. and M.R.D.) who were blinded to all clinical data. Midwall fibrosis was only considered present if the area of enhancement was confined to intramural and/or subepicardial layers,[22] visible in both phase-encoding directions and in 2 orthogonal views. A third blinded reader (F.A.) adjudicated in cases in which there was disagreement (n=10). The extent of midwall fibrosis was quantified by a single experienced operator as a percentage of left ventricular mass using the full-width half-maximum technique and semiautomated software (CMR42, Circle Cardiovascular Imaging Inc).[23]

Follow-up and End Points

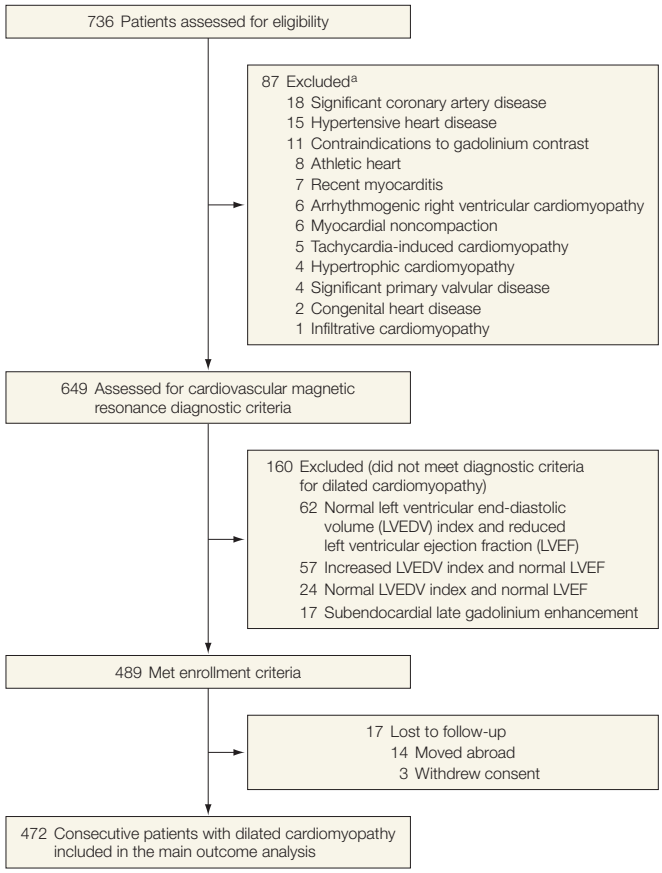
Follow-up was performed until December 2011. All events were adjudicated by the consensus of an independent committee blinded to the CMR results. Mortality status was verified from the UK National Strategic Tracing Service at 6 monthly intervals. Cause of death was established from a combination of death certification, postmortem data when available, communication with the patients' primary care physicians and cardiologists, and review of medical records for patients who died while hospitalized.

All patients were followed up for nonfatal events by telephone, postal questionnaire, or both at 6-month intervals. The patients' primary care physician and cardiologist were contacted every 6 months to facilitate review of all correspondence documenting outpatient clinic attendance or hospitalization during the follow-up period. After hospitalization, the medical records were examined to document the reason for admission and inpatient course. There were 17 patients lost to

follow-up and therefore not included in the analyses.

The predefined primary end point was all-cause mortality. The principal secondary end point was a composite of cardiovascular mortality (SCD, HF, stroke, or thromboembolic event) or cardiac transplantation. Two additional secondary end points were prespecified: an arrhythmic composite end point of SCD or aborted SCD and a HF composite end point of HF death, unplanned HF hospitalization, or cardiac transplantation. Mode of death was classified according to a modified Hinkle-Thaler system.[24] Sudden cardiac death was defined as unexpected death either within 1 hour of cardiac symptoms in the absence of progressive cardiac deterioration, during sleep, or within 24 hours of last being seen alive. Heart failure death was defined as death associated with unstable, progressive deterioration of pump function despite active therapy. Aborted SCD was diagnosed in patients who received an appropriate implantable cardioverter-defibrillator (ICD) shock for ventricular arrhythmia, or had a nonfatal episode of ventricular fibrillation or spontaneous sustained ventricular tachycardia (>30 seconds in duration) causing hemodynamic compromise and requiring cardioversion. Heart failure hospitalization was categorized in patients admitted to the hospital with signs and symptoms of decompensated HF requiring treatment with an intravenous HF medication (diuretics, vasodilators, or inotropic agents). Patient data were censored at the time of any cardiac transplantation. For composite end points, only the first event for each patient was included in the analysis.

Figure 1. Derivation of the Study Cohort



[a]Significant coronary artery disease was defined as >50% luminal stenosis in any epicardial coronary artery on angiography. Athletic heart was defined as left ventricular dilatation with preserved/mildly reduced ejection fraction and high stroke volume, on a background of regular organized endurance training, with raised maximal oxygen uptake on cardiopulmonary exercise testing. Significant primary valvular disease was defined as moderate or higher valvular stenosis/regurgitation, with the exception of functional mitral regurgitation. Functional mitral regurgitation was defined as mitral regurgitation secondary to left ventricular remodeling resulting in failure of leaflet coadaptation, in the setting of normal mitral valve anatomy, on echocardiography and cardiovascular magnetic resonance imaging.

Statistical Analysis

Baseline characteristics, available for all participants, grouped by the dichotomous presence or absence of midwall fibrosis, are presented as frequency (percentage) for categorical data and mean (standard deviation) for continuous data unless otherwise stated. Comparison between groups was made using the χ^2 or Fisher exact tests for categorical variables and unpaired *t* tests for continuous variables. Survival curves were generated by the Kaplan-Meier method and compared by the log-rank test. Event times were measured from the date of CMR study. A univariate Cox proportional hazards model was used to test the association between the end points and baseline covariates, with results presented as hazard ratios (HRs) with 95% confidence intervals. To determine whether midwall fibrosis was independently associated with outcome, multivariable analysis was performed with a forward-selection modeling process.

For each end point, 2 multivariate models were constructed based on inclusion of midwall fibrosis as a categorical (presence or absence) or continuous (percentage extent) variable. The proportional hazards assumption was tested and verified for each covariate. The predicted risk of each end point at 5 years was estimated from a Cox proportional hazards model that contained LVEF alone or LVEF combined with the presence or absence of midwall fibrosis. This was derived by first running a Cox model to obtain the baseline survival function at 5 years expressed as S0(5). A risk score

for each value of LVEF, with or without midwall fibrosis, was calculated by multiplying the observed value for the model parameter by its corresponding coefficient from the Cox model. The estimated probability of observing an event at 5 years was then calculated using the formula: $P(5) = 1 - S0(5) \times \exp(\text{risk score})$.

Reclassification of patient risk was determined using net reclassification improvement for all-cause mortality and the arrhythmic composite end point.[25] For each patient, the predicted overall risk of an adverse event was determined on the basis of a model using LVEF alone, and the relative improvement in patient reclassification associated with midwall fibrosis status (presence or absence) was then assessed. For all-cause mortality, reclassification was examined using the thresholds of 0%-5%, 5%-10%, 10%-20% and 20% or greater to stratify level of risk. For the arrhythmic composite end point, a risk threshold of 15% was used to stratify patients into high- and low-risk categories.

All statistical analyses were conducted using Stata version 12 (StataCorp). A 2-tailed *P* value of less than .05 was considered significant. For the comparison of those with vs those without midwall fibrosis, there was 90% power to detect a significant difference in mortality.

RESULTS

Study Population

A total of 489 patients met the enrolment criteria (FIGURE 1). Seventeen patients (3.5%) were lost to follow-up, resulting in a final cohort of 472 patients. Of these 472 patients, 101 patients were included in an earlier investigation,[16] and are reported herein with extended follow-up. The mean (SD) LVEF was 37% (13%) (range: 10%-59%). Significant coronary artery disease was excluded by angiography in 348 patients (74%) and stress imaging studies in 52 patients (11%). The remaining 72 patients (15%) were aged 40 years or younger, had no history of angina, and 1 or 0 risk factors for coronary artery disease. Patients were prospectively followed up for a median duration of 5.3 years (range, 31 days to 11.0 years), representing 2557 patient-years of follow-up. Midwall fibrosis was present in 142 patients (30%). The median extent of midwall fibrosis was 2.5% (interquartile range, 1.2%-4.8%; range, 0.4%-24.4%). Patients with midwall fibrosis were more likely to be male, have a history of malignant ventricular arrhythmia, have lower systolic and diastolic blood pressure levels, and have more symptomatic HF coupled with higher loop diuretic and aldosterone antagonist treatment rates compared with patients without midwall fibrosis (TABLE 1). The CMR measurements re-

Table 1. Baseline Characteristics

	All Patients (N = 472)	Presence of Midwall Fibrosis		*P* Value[a]
		No (n = 330)	Yes (n = 142)	
Age, mean (SD), y	51.1 (14.7)	51.2 (15.0)	50.9 (14.1)	.84
Male sex, No. (%)	324 (68.6)	214 (64.9)	110 (77.5)	.007
Diabetes, No. (%)	35 (7.4)	27 (8.2)	8 (5.6)	.33
Smoker, No. (%)	94 (19.9)	65 (19.7)	29 (20.4)	.86
Medical history, No. (%)				
VF or sustained VT	25 (5.3)	11 (3.3)	14 (9.9)	.004
Atrial fibrillation	82 (17.4)	59 (17.9)	23 (16.2)	.66
Alcohol excess[b]	59 (12.5)	41 (12.4)	18 (12.7)	.94
Family history of DCM, No. (%)	36 (7.6)	21 (6.4)	15 (10.6)	.12
Heart rate, mean (SD), beats/min	74.4 (14.7)	74.0 (14.2)	75.3 (15.7)	.35
Blood pressure, mean (SD), mm Hg				
Systolic	120.1 (18.7)	122.2 (18.9)	115.1 (17.8)	<.001
Diastolic	72.8 (11.2)	73.7 (11.2)	70.8 (10.8)	.009
Left bundle-branch block, No. (%)	129 (27.3)	86 (26.1)	43 (30.3)	.35
NYHA functional class, No. (%)				
I	194 (41.1)	148 (44.9)	46 (32.4)	.03
II	174 (36.9)	120 (36.4)	54 (38.0)	
III	95 (20.1)	57 (17.3)	38 (26.8)	
IV	9 (1.9)	5 (1.5)	4 (2.8)	
Medications at baseline, No. (%)				
ACE inhibitor or ARB	427 (90.5)	293 (88.8)	134 (94.4)	.06
β-Blocker	322 (68.2)	223 (67.6)	99 (69.7)	.65
Loop diuretic	243 (51.5)	145 (43.9)	98 (69.0)	<.001
Aldosterone antagonist	150 (31.8)	93 (28.2)	57 (40.1)	.01
Aspirin	148 (31.4)	103 (31.2)	45 (31.7)	.92
Warfarin	130 (27.5)	90 (27.3)	40 (28.2)	.84
Statin	128 (27.1)	95 (28.8)	33 (23.2)	.21
Digoxin	77 (16.3)	48 (14.6)	29 (20.4)	.11
Amiodarone	36 (7.6)	21 (6.4)	15 (10.6)	.12
Cardiovascular magnetic resonance measurements, mean (SD)				
LV end-diastolic volume index, mL/m^2	135.1 (44.3)	128.9 (39.1)	149.7 (51.7)	<.001
LV end-systolic volume index, mL/m^2	88.6 (45.6)	81.7 (40.6)	104.7 (52.3)	<.001
LV stroke volume, mL	92.1 (28.4)	93.3 (27.5)	89.3 (30.3)	.16
LV ejection fraction, %	37.2 (13.1)	39.1 (12.5)	32.8 (13.4)	<.001
LV mass index, g/m^2	101.3 (29.8)	99.3 (30.0)	106.1 (28.8)	.02
Extent of late gadolinium enhancement, median (IQR), %			2.5 (1.2-4.8)	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; DCM, dilated cardiomyopathy; LV, left ventricular; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a] Calculated using either the *t* test for continuous variables or χ^2 test for categorical data.
[b] Defined as consistent intake of 4 or more units/d for men and 3 or more units/d for women.[26]

vealed more severe left ventricular adverse remodeling in the group with midwall fibrosis, as evidenced by higher left ventricular end-diastolic and end-systolic volumes indexed and lower ejection fraction.

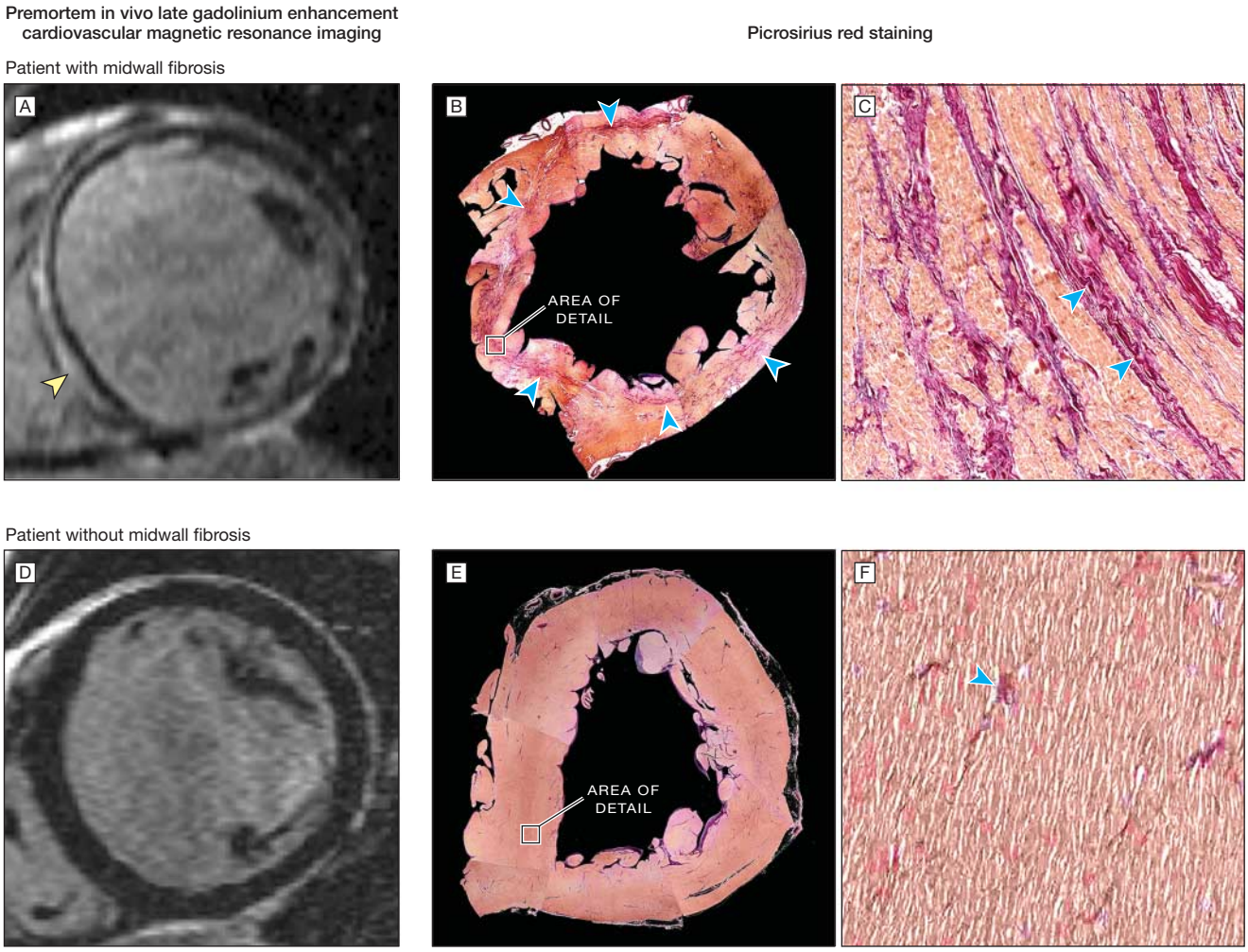
Histological Correlation

In 7 patients with midwall fibrosis, the hearts were explanted following death (n=3) or cardiac transplantation (n=4) and underwent detailed histopathological examination (eMethods at http://www.jama.com). In all cases, there was excellent agreement between the location and pattern of midwall fibrosis from the in vivo CMR scan and regions of replacement fibrosis seen in the explanted hearts (FIGURE 2). The hearts of 9 patients with no midwall fibrosis on CMR, who either died (n=7) or underwent transplantation (n=2), were also reviewed. Histopathological assessment of these specimens revealed no areas of replacement fibrosis (Figure 2).

Primary End Point: All-Cause Mortality

During the follow-up period, 73 deaths were recorded. Overall, 38 of 142 patients with midwall fibrosis (26.8%) reached the primary end point compared with 35 of 330 patients without

Figure 2. A Patient With Midwall Fibrosis Who Experienced Sudden Cardiac Death and a Patient Without Midwall Fibrosis Who Underwent Cardiac Transplantation



A, Premortem late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) demonstrated a near-circumferential pattern of midwall LGE (yellow arrow) in the anterior, septal, inferior, and inferolateral segments at midventricular level. B, Picrosirius red staining in the corresponding postmortem macroscopic short-axis section revealed a prominent linear band of collagen (blue arrows), which mirrored the distribution of LGE on CMR. C, Microscopic examination confirmed the presence of extensive replacement fibrosis (blue arrows) in an area of staining seen on the macroscopic section (area of detail in part B); magnification ×300. D, On LGE-CMR performed prior to cardiac transplantation, there were no areas of LGE. E, Following explantation, macroscopic assessment revealed no detectable regions of collagen with Picrosirius red stain. F, Microscopic section from the septal midwall (area of detail in part E) showed small amounts of perivascular fibrosis (blue arrow) but no replacement fibrosis; magnification ×300. The macroscopic images (B and E) were recomposited from 156 overlapping digital images taken at ×100 magnification with an Olympus digital microscope camera. The image was composited using Microsoft Image Composite Editor (version 1.4.4.0) and Microsoft Office Publisher 2007.

midwall fibrosis (10.6%) (HR, 2.96 [95% CI, 1.87-4.69]; absolute risk difference, 16.2% [95% CI, 8.2%-24.2%]; $P<.001$, FIGURE 3A and TABLE 2). After multivariable Cox regression analysis, both the presence (HR, 2.43 [95% CI, 1.50-3.92]; $P<.001$) and percentage extent (HR, 1.11 [95% CI, 1.06-1.16]; $P<.001$) of midwall fibrosis were significant independent predictors of all-cause mortality (TABLE 3). Other covariates that were found to be independently associated with all-cause mortality in the multivariable models were LVEF, age, heart rate, New York Heart Association functional class, and systolic blood pressure.

Cardiovascular Mortality or Cardiac Transplantation

Of the 73 deaths, the principal cause was cardiovascular in 58 patients (79%). These deaths included 26 SCDs, 30 HF deaths, and 2 deaths due to stroke and pulmonary embolism (other cardiovascular death). Orthotopic cardiac transplantation was performed in 9 patients (1.9%) for end-stage HF. The presence of midwall fibrosis was associated with a markedly higher risk of the secondary composite of cardiovascular mortality or cardiac transplantation (28.9% vs 7.9%; HR, 4.11 [95% CI, 2.51-6.72]; absolute risk difference, 21.0% [95% CI, 13.0%-29.0%]; $P<.001$, Figure 3B). This association was unchanged following adjustment for other significant prognostic variables (by fibrosis presence: HR, 3.22 [95% CI, 1.95-5.31]; $P<.001$; TABLE 4). Similarly, midwall fibrosis remained significantly associated with the principal secondary outcome when fibrosis extent was substituted for fibrosis presence in the multivariable model (HR, 1.15 [95% CI, 1.10-1.20], $P<.001$; Table 4).

Arrhythmic and HF Secondary End Points

A total of 144 patients (30%) were treated with device implantation during the follow-up period, of which 51 (35%) received an ICD, 34 (24%) received cardiac resynchronization therapy (CRT) alone, and 59 (41%) received CRT combined with a defibrillator (Table 2). Patients with midwall fibrosis had higher implantation rates of ICD (HR, 3.80 [95% CI, 2.17-6.64]; $P<.001$) and CRT combined with a defibrillator (HR, 2.40 [95% CI, 1.44-4.01]; $P=.001$). There was no significant difference in CRT alone implantation rates between the 2 midwall fibrosis groups (HR, 1.03 [95% CI, 0.49-2.16]; $P=.93$).

The arrhythmic composite end point occurred in 65 patients (14%). Univariate analysis revealed that patients with midwall fibrosis were more than

Figure 3. Kaplan-Meier Estimates of the Time to Events by Midwall Fibrosis Status

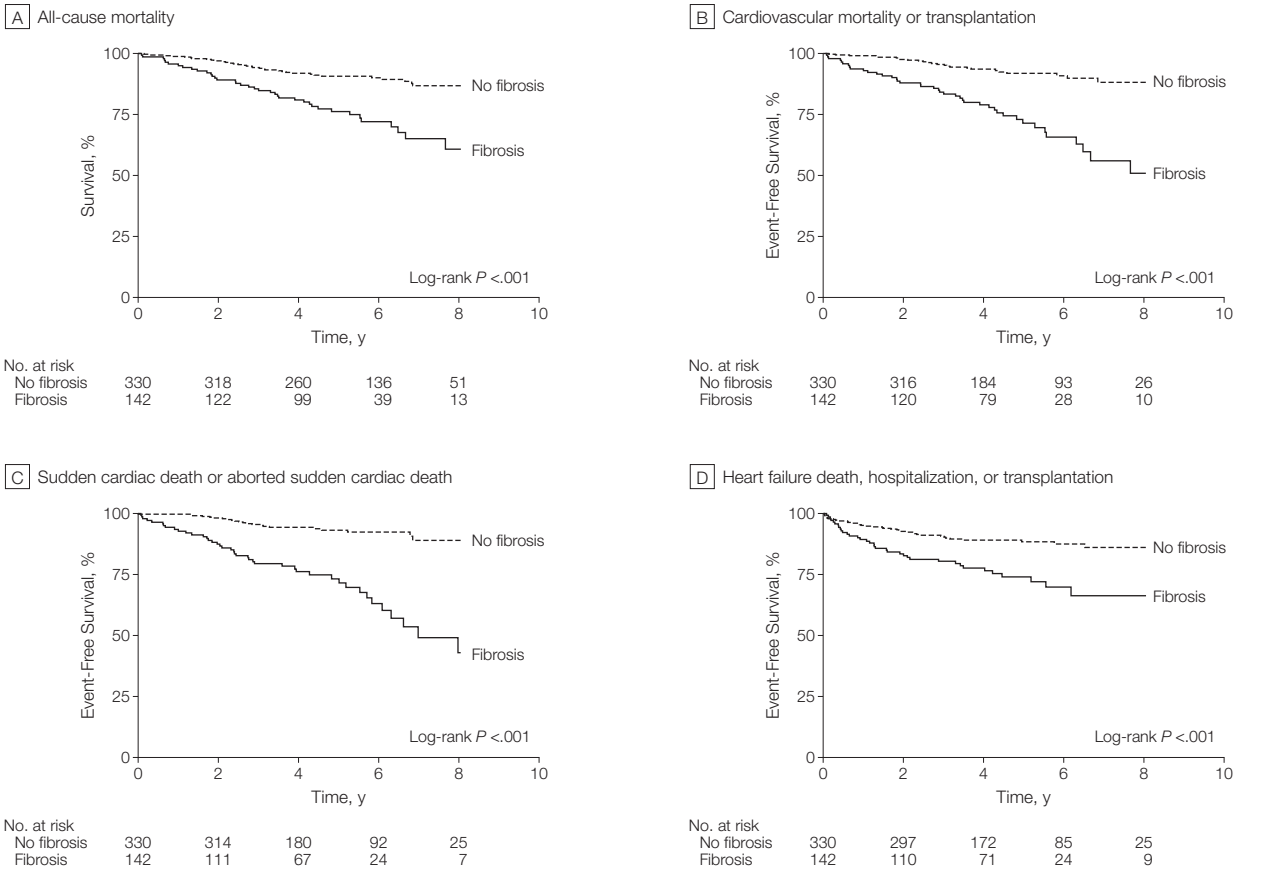


Table 2. Study Outcome Data

Outcome	No. (%) of Patients by Presence of Midwall Fibrosis: No (n = 330)	Yes (n = 142)	Hazard Ratio (95% CI)	*P* Value[a]
Primary end point (all-cause mortality)	35 (10.6)	38 (26.8)	2.96 (1.87-4.69)	<.001
Principal secondary outcomes				
Cardiovascular mortality or cardiac transplantation	26 (7.9)	41 (28.9)	4.11 (2.51-6.72)	<.001
Cardiovascular death	24 (7.3)	34 (23.9)	3.88 (2.30-6.55)	<.001
Cardiac transplantation	2 (0.6)	7 (4.9)	8.63 (1.79-41.58)	.007
Arrhythmic secondary composite end point				
Sudden cardiac death or aborted sudden cardiac death[b]	23 (7.0)	42 (29.6)	5.24 (3.15-8.72)	<.001
Sudden cardiac death	11 (3.3)	15 (10.6)	3.81 (1.75-8.33)	.001
Aborted sudden cardiac death	12 (3.6)	29 (20.4)	6.93 (3.53-13.61)	<.001
Heart failure secondary composite end point				
Heart failure death, heart failure hospitalization, or cardiac transplantation[b]	37 (11.2)	36 (25.4)	2.49 (1.57-3.95)	<.001
Heart failure death	12 (3.6)	18 (12.7)	4.05 (1.95-8.41)	<.001
Heart failure hospitalization	35 (10.6)	30 (21.1)	2.21 (1.36-3.60)	.001
Device implantation				
Implantable cardioverter-defibrillator	21 (6.4)	30 (21.1)	3.80 (2.17-6.64)	<.001
Cardiac resynchronization therapy without defibrillator	24 (7.3)	10 (7.0)	1.03 (0.49-2.16)	.93
Cardiac resynchronization therapy with defibrillator	31 (9.4)	28 (19.7)	2.40 (1.44-4.01)	.001

[a] *P* values are derived from a Cox proportional hazards model.
[b] The number of patients who experienced an index composite outcome.

5 times more likely to experience SCD or aborted SCD compared with patients without midwall fibrosis (29.6% vs 7.0%, respectively; HR, 5.24 [95% CI, 3.15-8.72]; absolute risk difference, 22.6% [95% CI, 14.6%-30.6%], $P<.001$; Figure 3C and Table 2). In the multivariable models that incorporated history of malignant ventricular arrhythmia, systolic blood pressure, and LVEF, presence of midwall fibrosis (HR, 4.61 [95% CI, 2.75-7.74]; $P<.001$) and extent (HR, 1.10 [95% CI, 1.05-1.16]; $P<.001$) were significant independent predictors of the arrhythmic outcome (Table 4). Midwall fibrosis remained a significant independent predictor of the arrhythmic composite end point if appropriate ICD discharge was removed from the analysis (by fibrosis presence: HR, 4.15 [95% CI, 2.36-7.31], $P<.001$; by fibrosis extent: HR 1.13 [95% CI, 1.07-1.19], $P<.001$).

The HF composite end point was reached by 36 patients with midwall fibrosis (25.4%) and 37 patients without

Table 3. All-Cause Mortality in Univariable and Multivariable Analyses[a]

	No. (%)		Univariable Analysis		Multivariable Analysis: Model 1[b]		Multivariable Analysis: Model 2[c]	
	Alive	Dead	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age, per year			1.02 (1.01-1.04)	.005	1.03 (1.01-1.05)	.001	1.02 (1.00-1.04)	.01
Sex								
Female	131 (88.5)	17 (11.5)	1 [Reference]					
Male	268 (82.7)	56 (17.3)	1.53 (0.89-2.63)	.13				
History of VF or sustained VT								
No	377 (84.3)	70 (15.7)	1 [Reference]					
Yes	22 (88.0)	3 (12.0)	0.76 (0.24-2.42)	.64				
History of atrial fibrillation								
No	327 (83.9)	63 (16.2)	1 [Reference]					
Yes	72 (87.8)	10 (12.2)	0.75 (0.38-1.46)	.40				
Diabetes								
No	373 (85.4)	64 (14.7)	1 [Reference]					
Yes	26 (74.3)	9 (25.7)	1.58 (0.78-3.19)	.20				
Smoker								
No	319 (84.4)	59 (15.6)	1 [Reference]					
Yes	80 (85.1)	14 (14.9)	0.96 (0.54-1.72)	.89				
History of alcohol excess								
No	355 (86.0)	58 (14.0)	1 [Reference]					
Yes	44 (74.6)	15 (25.4)	1.81 (1.02-3.20)	.04				
Family history of DCM								
No	369 (86.4)	67 (15.4)	1 [Reference]					
Yes	30 (83.3)	6 (16.7)	1.08 (0.47-2.50)	.85				

(continued)

Table 3. All-Cause Mortality in Univariable and Multivariable Analyses[a] (continued)

	No. (%)		Univariable Analysis		Multivariable Analysis			
					Model 1[b]		Model 2[c]	
	Alive	Dead	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Heart rate, per 1 beat/min			1.03 (1.02-1.05)	<.001	1.02 (1.00-1.03)	.03	1.02 (1.00-1.04)	.01
Blood pressure, per 1 mm Hg								
Systolic			0.98 (0.96-0.99)	.001	0.98 (0.97-1.00)	.01		
Diastolic			0.97 (0.95-0.99)	.006				
Left bundle-branch block								
No	290 (84.6)	53 (15.5)	1 [Reference]					
Yes	109 (84.5)	20 (15.5)	0.99 (0.59-1.66)	.98				
NYHA functional class, per class			2.36 (1.79-3.11)	<.001			1.71 (1.23-2.37)	.001
LV end-diastolic volume index, per 10 mL/m^2			1.09 (1.05-1.13)	<.001				
LV end-systolic volume index, per 10 mL/m^2			1.10 (1.06-1.14)	<.001				
LV stroke volume, per 10 mL			0.89 (0.82-0.97)	.009				
LV ejection fraction, per 1%			0.95 (0.93-0.96)	<.001	0.97 (0.95-0.99)	.007	0.97 (0.95-1.00)	.02
LV mass index, per 10 g/m^2			1.12 (1.04-1.19)	.002				
Fibrosis								
No	295 (89.4)	35 (10.6)	1 [Reference]					
Yes	104 (73.2)	38 (26.8)	2.96 (1.87-4.69)	<.001	2.43 (1.50-3.92)	<.001		
Fibrosis extent, per 1% increment			1.11 (1.06-1.17)	<.001			1.11 (1.06-1.16)	<.001

Abbreviations: DCM, dilated cardiomyopathy; HR, hazard ratio; LV, left ventricular; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a] *P* values are derived from a Cox proportional hazards model.
[b] Midwall fibrosis was included as a categorical variable (presence or absence).
[c] Midwall fibrosis was included as a continuous variable (percentage extent).

Table 4. Secondary End Points in Multivariable Analysis[a]

	Multivariable Analysis[b]			
	Model 1[c]		Model 2[d]	
	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Cardiovascular mortality or cardiac transplantation				
Heart rate, per 1 beat/min			1.02 (1.00-1.04)	.02
Systolic blood pressure, per 1 mm Hg	0.98 (0.97-1.00)	.02		
LV end-diastolic volume index, per10 mL/m^2			1.05 (1.00-1.10)	.03
LV ejection fraction, per 1%	0.96 (0.94-0.98)	<.001	0.96 (0.94-0.99)	.002
Fibrosis presence	3.22 (1.95-5.31)	<.001		
Fibrosis extent, per 1% increment			1.15 (1.10-1.20)	<.001
Sudden cardiac death or aborted sudden cardiac death				
History of VF or sustained VT	3.24 (1.63-6.43)	.001	4.08 (2.06-8.10)	<.001
Systolic blood pressure, per 1 mm Hg	0.98 (0.97-1.00)	.01		
LV ejection fraction, per 1%			0.97 (0.95-0.99)	.005
Fibrosis presence	4.61 (2.75-7.74)	<.001		
Fibrosis extent, per 1% increment			1.10 (1.05-1.16)	<.001
Heart failure death, heart failure hospitalization, or cardiac transplantation				
Diastolic blood pressure, per 1 mm Hg	0.97 (0.94-0.99)	.002	0.97 (0.95-0.99)	.008
NYHA functional class, per class	1.85 (1.32-2.59)	<.001	1.77 (1.27-2.48)	.001
LV ejection fraction, per 1%	0.95 (0.93-0.97)	<.001	0.94 (0.92-0.97)	<.001
Fibrosis presence	1.62 (1.00-2.61)	.049		
Fibrosis extent, per 1% increment			1.08 (1.04-1.13)	<.001

Abbreviations: HR, hazard ratio; LV, left ventricular; NYHA, New York Heart Association, VF, ventricular fibrillation; VT, ventricular tachycardia.
[a] *P* values are derived from a Cox proportional hazards model.
[b] All baseline covariates with a *P* value of less than .05 on univariable analysis were entered into the multivariable model. Only those covariates that were selected as independent predictors of outcome on forward-stepwise multivariable analysis appear in the table. The unadjusted HRs for all baseline covariates appear in eTables 1-3 at http://www.jama.com.
[c] Midwall fibrosis was included as a categorical variable (presence or absence).
[d] Midwall fibrosis was included as a continuous variable (percentage extent).

midwall fibrosis (11.2%) (HR, 2.49 [95% CI, 1.57-3.95]; absolute risk difference, 14.1% [95% CI, 6.2%-22.1%], $P < .001$; Figure 3D and Table 2). Midwall fibrosis presence (HR, 1.62 [95% CI, 1.00-2.61]; $P = .049$) and extent (HR, 1.08 [95% CI, 1.04-1.13]; $P < .001$) were significant independent predictors of HF outcome in multivariable analysis (Table 4).

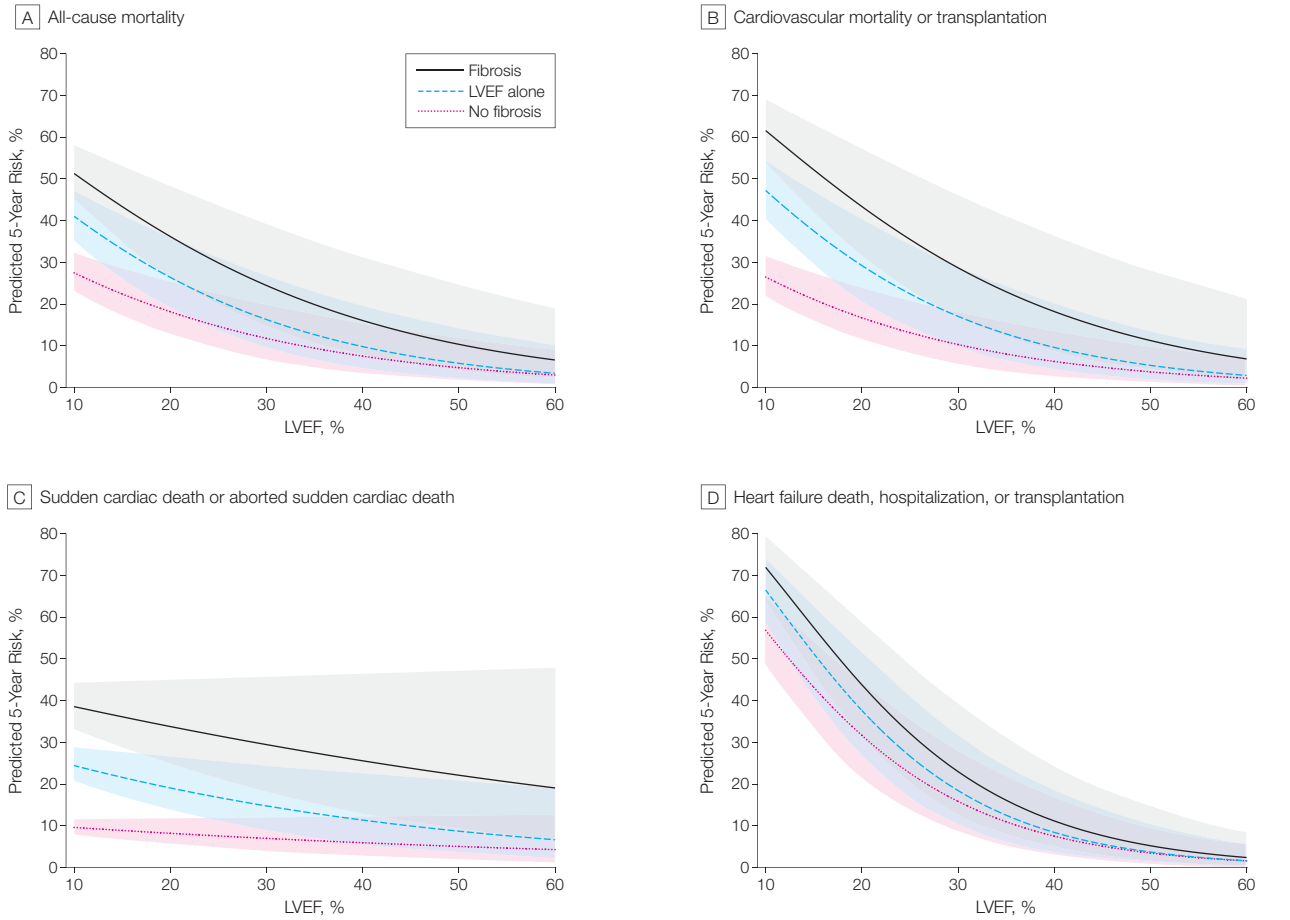
Incremental Prognostic Value of Midwall Fibrosis

Information regarding the presence or absence of midwall fibrosis made a sizeable difference to the risk profile of patients across the spectrum of LVEF for all end points (FIGURE 4). For example, a patient with an LVEF of 35% in our cohort had a risk of death by 5 years of 12.7% (95% CI, 6.8%-23.0%). When midwall fibrosis status was added to the risk model, the risk of death for a patient with an LVEF of 35% and no midwall fibrosis decreased to 9.4% (95% CI, 5.0%-17.5%), while those with midwall fibrosis now had a predicted risk of death of 19.9% (95% CI, 10.8%-35.0%).

Risk Reclassification

Reclassification of risk was assessed separately for all-cause mortality (TABLE 5) and the arrhythmic composite end point (TABLE 6) after addition of midwall fibrosis status to a risk model based on LVEF. For all-cause mortality, addition of midwall fibrosis status to LVEF resulted in 16 correct (up) reclassifications and 9 incorrect (down) reclassifications in the 73 patients who died. Additionally, 117 correct (down) reclassifications and 51 incorrect (up) reclassifications occurred in the 399 survivors. Overall, 26% of patients were correctly reclassified by the addition of midwall fibrosis status (net reclassification improvement, 0.26 [95% CI, 0.11-0.41]; $P = .001$). For the arrhythmic composite of SCD or aborted SCD, addition of midwall fibrosis status to LVEF yielded 23 correct (up) reclassifications and 11 incorrect (down) reclassifications in the 65 patients who experienced a major arrhythmic event. Additionally, 89 correct (down) reclassifications and 46 incorrect (up) reclassifications occurred in the 407 patients who did not have an arrhythmic event. Overall, 29% of patients were correctly reclassified after adding midwall fibrosis status to the risk model (net reclassification improvement, 0.29 [95% CI, 0.11-0.48]; $P = .002$).

Figure 4. Five-Year Risk Prediction Curves by Left Ventricular Ejection Fraction (LVEF) and Midwall Fibrosis Status



Shaded areas represent 95% CIs.

COMMENT

We found that both the presence and extent of midwall replacement fibrosis were associated with an increased likelihood of all-cause mortality in dilated cardiomyopathy. This association was independent of LVEF and other established prognostic factors in multivariable analysis. After controlling for LVEF and other significant covariates, the adjusted HRs for patients with midwall fibrosis were 2.43 ($P<.001$) for all-cause mortality and 3.22 ($P<.001$) for cardiovascular death or cardiac transplantation. The presence and extent of midwall fibrosis were also significant independent predictors of the secondary composite outcomes, SCD or aborted SCD, and HF death, HF hospitalization, or cardiac transplantation. Midwall fibrosis provided incremental prognostic value across the range of LVEF observed in our cohort. The addition of midwall fibrosis to LVEF resulted in significant improvements in risk reclassification for both all-cause mortality and the arrhythmic composite. Our findings suggest that detection and quantification of midwall fibrosis by LGE-CMR may represent useful markers for the risk stratification of death, ventricular arrhythmia, and HF for patients with dilated cardiomyopathy.

The histological basis for midwall LGE in dilated cardiomyopathy is focal replacement fibrosis, which is seen at autopsy in up to one-third of patients with dilated cardiomyopathy,[27] a prevalence which mirrors that of midwall fibrosis on LGE-CMR.[13] Replacement fibrosis refers to reparative microscopic scarring that follows myocyte death.[10,27] In keeping with previous reports,[16-18] patients with midwall fibrosis exhibited a greater degree of left ventricular dilatation and systolic impairment compared with patients without midwall fibrosis. Despite the close relationship between midwall fibrosis and ventricular remodeling, the presence of midwall fibrosis provided prognostic information that was independent of left ventricular parameters and incremental to LVEF. Midwall fibrosis retained its prognostic significance when assessed as a continuous variable, suggesting that not only the presence but also the burden of replacement fibrosis is an important determinant of outcome.

These findings support previous studies that have suggested that midwall fibrosis may be a helpful prognosticator in dilated cardiomyopathy. Early work from our group[16] showed that midwall fibrosis was the only independent predictor of a primary composite of death and cardiovascular hospitalization in 101 patients with dilated cardiomyopathy compared with standard left ventricular prognostic parameters. Two further studies have since demonstrated that midwall fibrosis appears to predict adverse outcome based on a composite of cardiovascular death, HF hospitalization, or appropriate ICD shock.[17,18] Although these studies have provided valuable insight into the potential prognostic implications of midwall fibrosis in patients with dilated cardiomyopathy, they were limited by small sample sizes of between 56 and 184 patients, short

Table 5. Risk Reclassification With the Addition of Midwall Fibrosis Status to a Risk Model Based on Left Ventricular Ejection Fraction (LVEF) for All-Cause Mortality[a]

Predicted Risk With LVEF Alone, %	Predicted Risk With LVEF and Midwall Fibrosis Status, % 0-5	5-10	10-20	≥20	Total
Deaths					
0-5	2	0	0	0	**2**
5-10	0	5	5	0	**10**
10-20	0	2	11	11	**24**
≥20	0	0	7	30	**37**
Total	**2**	**7**	**23**	**41**	**73**
Survivors					
0-5	22	4	0	0	**26**
5-10	46	76	26	0	**148**
10-20	0	39	66	21	**126**
≥20	0	0	32	67	**99**
Total	**68**	**119**	**124**	**88**	**399**

[a] Values represent the number of patients in each risk category (0%-5%, 5%-10%, 10%-20% and ≥20%) according to risk model based on LVEF alone and risk model based on LVEF and midwall fibrosis status (presence or absence) for patients who died or survived during follow-up. Correct reclassifications are shaded light gray and incorrect reclassifications are shaded dark gray.

Table 6. Risk Reclassification With the Addition of Midwall Fibrosis Status to a Risk Model Based on Left Ventricular Ejection Fraction (LVEF) for the Secondary Arrhythmic Composite End Point[a]

Predicted Risk With LVEF Alone, %	Predicted Risk With LVEF Plus Midwall Fibrosis Status, % 0-15	>15	Total
Patients With Arrhythmic Event			
Predicted risk with LVEF alone			
0-15	12	23	**35**
>15	11	19	**30**
Total	**23**	**42**	**65**
Patients Without Arrhythmic Event			
Predicted risk with LVEF alone			
0-15	218	46	**264**
>15	89	54	**143**
Total	**307**	**100**	**407**

[a] Values represent the number of patients in each risk category (0%-15% and >15%) according to risk model based on LVEF alone and risk model based on LVEF and midwall fibrosis status (presence or absence) for patients who had an arrhythmic event or did not have an arrhythmic event. Correct reclassifications are shaded light gray and incorrect reclassifications are shaded dark gray.

follow-up periods (mean/median follow-up of 1.4-1.9 years), and reliance on broad composite primary end points. More recently, subgroup analysis of a mixed HF cohort preselected for CRT, has suggested that midwall fibrosis predicts cardiovascular death or transplantation among patients with dilated cardiomyopathy.[19] However, the low event rate (11 index events) in this study meant that there were insufficient data to accurately assess the prognostic significance of midwall fibrosis, controlling for all potentially confounding variables in multivariable analysis, in the dilated cardiomyopathy subgroup. As a result, the independent prognostic value of midwall fibrosis and its relationship to mortality and SCD have thus far remained open to question.

Current assessment of prognosis in patients with dilated cardiomyopathy is primarily based on LVEF, which has long been recognized as a strong predictor of mortality.[4,5] However, although mortality in patients with dilated cardiomyopathy increases with decreasing LVEF, this relationship is weaker in patients with severe systolic impairment.[28] A significant proportion of patients with severe systolic impairment at initial evaluation respond favorably to medical therapy with improvements in left ventricular functional indices.[29] Therefore, in patients with severely impaired left ventricular function, prediction of outcome purely on the basis of LVEF is difficult. Conversely, in patients with mild or moderate left ventricular systolic dysfunction, LVEF yields limited predictive value and yet such patients are still prone to substantial morbidity and mortality.[30] In the present study, detection of midwall fibrosis offered incremental prognostic information across the entire range of LVEF for all end points. The use of LGE-CMR may not only enable more reliable risk stratification of patients with dilated cardiomyopathy and severe left ventricular impairment, but also facilitate identification of high-risk patients with milder degrees of left ventricular dysfunction who are currently overlooked by assessment of global left ventricular function alone. Further study of patients stratified by LVEF is required to substantiate this.

In our study, patients with midwall fibrosis had worse prognosis despite higher implantation rates of ICD and CRT combined with a defibrillator, further emphasizing the negative prognostic implications of midwall fibrosis. Even though device implantation is known to improve outcome in dilated cardiomyopathy,[31-33] selection of patients for prophylactic defibrillator implantation is particularly problematic. Current guidelines for primary prevention of SCD in patients with dilated cardiomyopathy recommend defibrillator implantation in patients with New York Heart Association functional class II/III and a LVEF of less than 35%.[34,35] However, based on such guidelines, the annual rate of appropriate defibrillator discharge is only 5.1%; consequently, the majority of patients never receive an appropriate therapy.[32,36] Although SCD is less frequent in patients who do not meet LVEF criteria for defibrillator insertion, the proportion of SCD to all-cause mortality is higher in this group.[37] It is therefore increasingly recognized that LVEF lacks sensitivity and specificity for predicting SCD. Moreover, up to 1 in 5 patients with a prophylactic defibrillator will experience 1 or more inappropriate shocks within the first few years of implantation, with detrimental effects on mortality, HF progression, and psychological well-being.[38-40] Defibrillator implantation additionally carries a significant cost burden[39,41] and risk of procedural complications.[32,39] Improved risk stratification techniques for SCD in patients with dilated cardiomyopathy are therefore required to allow accurate identification of those patients who will maximally benefit from devices.

Although the mechanisms underlying SCD in patients with dilated cardiomyopathy are poorly characterized, there is emerging evidence to suggest that myocardial fibrosis forms the substrate for ventricular arrhythmias due to scar-related reentry.[11,12] This observation is supported by the findings of our study in which patients with midwall fibrosis had a 4-fold increase in the risk of the secondary composite of SCD or aborted SCD (HR, 4.61 [95% CI, 2.75-7.74]; $P < .001$). In the multivariable analysis, the presence and extent of midwall LGE were strongly associated with the arrhythmic composite end point, even allowing for conventional SCD risk factors such as previous malignant ventricular arrhythmia and LVEF. While there is contention regarding whether appropriate ICD discharge equates to aborted SCD,[39] midwall fibrosis still remained a significant independent predictor of arrhythmic outcome following exclusion of ICD therapy from the composite.

In the net reclassification improvement analysis, the addition of midwall fibrosis to LVEF was associated with improved risk stratification for SCD. There is no formal consensus regarding the level of SCD risk at which ICD implantation is justified in patients with dilated cardiomyopathy. In the present study, we selected a 15% SCD risk threshold to define high- and low-risk categories to direct ICD implantation, guided by the SCD event rates in the Marburg Cardiomyopathy Study.[42] Based on the incremental information provided by LGE-CMR in our cohort, of the 65 patients who reached the SCD composite, an additional 12 patients (18.5%) would now undergo ICD implantation. In addition, of the 407 patients who did not experience the SCD outcome, 43 patients would now avoid ICD implantation (10.6%). The use of LGE-CMR therefore improves detection of patients with dilated cardiomyopathy at high risk for SCD who are currently missed by stratification using LVEF. At the same time, LGE-CMR reduces the number of patients who would undergo ICD implantation without subsequently experiencing a SCD event. These data suggest that LGE-CMR may refine the SCD risk estimate in dilated cardiomyopathy, raising the possibility that this information could guide ICD implantation with po-

tential implications for public health and resource use.

Limitations

We have performed a single-center study that allowed for a standardized approach to both the CMR protocol and interpretation. Corroboration of our findings in a multicenter setting is required. Because our cohort consisted of patients with dilated cardiomyopathy clinically referred for CMR investigation, we accept that it may be subject to referral bias. However, our study population had similar demographic characteristics, medication usage, and disease severity profile compared with those reported in other large cohorts of patients with dilated cardiomyopathy such as the Trieste Cardiomyopathies Registry.[43] We therefore believe that our study cohort is representative of the wider dilated cardiomyopathy population at large. While each patient's LGE-CMR findings were available to their clinicians, current HF therapeutic guidelines do not recommend specific therapies based on midwall fibrosis assessment.[34] The midwall fibrosis status of patients in our cohort is therefore unlikely to have directly affected their treatment during the follow-up period. Furthermore, although patients with midwall fibrosis had higher defibrillator implantation rates, they still had worse outcomes. Coronary angiography was not performed in all patients. Those patients who did not undergo angiography were considered unlikely to have significant coronary artery disease in the absence of angina symptoms and previous myocardial infarction, coupled with normal stress imaging studies, low risk profile, or both. In line with current guidelines,[3] invasive angiographic investigation in such patients was not justified. Late gadolinium enhancement cardiovascular magnetic resonance detects focal areas of replacement fibrosis. Diffuse interstitial fibrosis is also present in patients with dilated cardiomyopathy.[27,44] Emerging T1-mapping CMR techniques offer promise for the evaluation of interstitial fibrosis but remain experimental and require optimization, standardization, and histological validation.[44,45]

CONCLUSIONS

Assessment of midwall fibrosis with LGE-CMR provided independent prognostic information in patients with nonischemic dilated cardiomyopathy. LGE-CMR imaging improved risk stratification beyond LVEF for all-cause mortality and SCD. The potential clinical utility of midwall fibrosis evaluated by LGE-CMR in the risk stratification of patients with dilated cardiomyopathy requires further investigation.

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