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Background—We conducted a prospective longitudinal study to investigate the yet unknown clinical significance of myocardial fibrosis in patients with non–ischemic cardiomyopathy without history of congestive heart failure (CHF).

Methods and Results—At 3 tertiary referral centers, 228 patients with non–ischemic cardiomyopathy without history of CHF were studied with cardiovascular magnetic resonance for late gadolinium enhancement (LGE) detection and quantification and prospectively followed up for a median of 23 months. The end point was a composite of cardiac death, onset of CHF, and aborted sudden cardiac death. LGE was detected in 61 (27%) patients. Thirty-one of 61 (51%) patients with LGE reached combined end point when compared with 18 of 167 (11%) patients without LGE (hazard ratio, 5.10 [2.78–9.36]; $P<0.001$). Patients with LGE had greater risk of developing CHF than patients without LGE (hazard ratio, 5.23 [2.61–10.50]; $P<0.001$) and higher rate of aborted sudden cardiac death (hazard ratio, 8.31 [1.66–41.55]; $P=0.010$). Multivariate analysis showed that LGE was associated with high likelihood of composite end point independent of other prognostic determinants, including age; duration of cardiomyopathy; and left ventricular volumes, mass, and ejection fraction (hazard ratio, 4.02 [2.08–7.76]; $P<0.001$). Improvement χ^2 analysis disclosed that LGE addition to models, including clinical data alone or in combination with parameters of left ventricular remodeling and function, yielded an improvement in outcome prediction ($P<0.001$). Addition of LGE to age and left ventricular ejection fraction improved risk stratification for composite end point (net reclassification improvement, 29.6%) and onset of CHF (net reclassification improvement, 25.4%; both $P<0.001$).

Conclusions—In patients with non–ischemic cardiomyopathy without history of CHF, myocardial fibrosis is a strong and independent predictor of outcome, providing incremental prognostic information and improvement in risk stratification beyond clinical data and degree of left ventricular dysfunction. **(*Circ Heart Fail*. 2014;7:448-456.)**

Key Words: cardiomyopathies ■ fibrosis ■ magnetic resonance imaging

Non–ischemic cardiomyopathy (NICM) is a common cause of congestive heart failure (CHF) with a prevalence of ≥1 in 2500 adults[1] and a 5-year mortality as high as 20%.[2] A preclinical phase may precede the development of CHF in patients with NICM.[3–5] However, information on the clinical course of this condition is scarce, given that most of the data are focused on preclinical left ventricular (LV) systolic dysfunction (SD) because of ischemic heart disease.[6–9] Population-based, cross-sectional cohort studies have shown that preclinical LVSD is as prevalent as CHF in the general population[6–9] and is associated with an increased risk of CHF and mortality irrespective of the pathogenesis causing ventricular dysfunction.[6,7] The identification of prognostic predictors in patients with preclinical LVSD is crucial for an effective risk stratification and surveillance of patients. In fact, optimization of medical therapy at this early stage may delay or may prevent progression to CHF,[10] lessening the social and economic burden imposed by this condition.

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Clinical Perspective on p 456

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In patients with NICM and history of CHF replacement myocardial fibrosis detected by late gadolinium enhancement (LGE) technique using cardiovascular magnetic resonance (CMR) has been shown to be a strong and an independent predictor of outcome.[3,11–14] To date, there are no data on the clinical value of fibrosis in patients with NICM without history of CHF. On the basis of these premises, we performed a multicenter longitudinal prospective study in a cohort of patients with NICM without history of CHF to investigate the prognostic significance of myocardial fibrosis detected by LGE technique using contrast-enhanced CMR.

Methods

Study Design and Subjects

This is a prespecified multicenter longitudinal prospective study conducted in a cohort of patients with NICM without history of CHF as part of a larger prospective registry of consecutive patients with NICM referred for CMR. Between July 2004 and December 2012, 765 consecutive patients with NICM were evaluated at 3 referral centers (585 at Fondazione CNR-Regione Toscana 'G.Monasterio', Pisa, Italy [center A]; 105 at Gasthuisberg University Hospital, Leuven, Belgium [center B], and 75 at Centro Cardiologico Monzino, Milano, Italy [center C]) for study enrollment. The inclusion criteria were (1) reduced LV ejection fraction at transthoracic echocardiography based on published reference ranges,[15] (2) absent significant coronary artery stenosis at invasive coronary angiography or cardiac computed tomography,[16] (3) absent history of CHF based on Framingham Criteria.[6] Before inclusion, the diagnosis of LVSD was confirmed by CMR on the basis of reduced LV ejection fraction when compared with published reference ranges normalized for age and sex.[17] Exclusion criteria included age <18 years old, recent myocarditis, peripartum cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy, severe primary valvular disease, untreated hypertension, end-stage hypertrophic cardiomyopathy, cardiac amyloidosis, estimated glomerular filtration rate <30 mL/min, and contraindications to CMR. Each subject underwent complete clinical history, physical examination, ECG, and CMR. Clinical and CMR data were collected at each center by 2 experienced physicians in charge of the study. All data were then anonymized and transferred to center A for analysis. The protocol was approved by each Institution Ethical Committee, and all patients gave written informed consent.

Definition of CHF

The diagnosis of CHF was based on Framingham Criteria, consisting in the presence of 2 major or 1 major and 2 minor clinical criteria, which could not be attributed to another diagnosis.[6] Major criteria were paroxysmal nocturnal dyspnea or orthopnea, pulmonary edema, increased central venous pressure (distended neck veins and hepatojugular reflux), rales at pulmonary auscultation, third heart sound, and weight loss on diuretic therapy. Minor criteria were bilateral ankle edema, night cough, dyspnea on exertion, pleural effusion and pulmonary vascular redistribution, tachycardia, and hepatomegaly and decreased in vital capacity.

CMR Protocol

CMR studies were performed at center A with 1.5-T unit (CVi; GE-Healthcare, Milwaukee, WI), at center B with 1.5-T unit (Intera-CV; Philips, Best, The Netherlands), and at center C with 1.5-T unit (Discovery MR450; GE-Healthcare). All studies were performed using dedicated cardiac software, phased-array surface receiver coil, and ECG triggering. A similar CMR study protocol was followed in all centers (see Data Supplement). In brief, cine images in horizontal, vertical, and short-axis views were acquired using breath-hold cine steady-state free-precession sequence. For the quantification of LV volumes, stroke volume, ejection fraction, and mass, cine images were acquired in a stack of contiguous short-axis slices from base to apex. Postcontrast breath-hold T1-weighted 2-dimensional (2D; CVi; GE Healthcare/Discovery MR450; GE-Healthcare) or 3D (Intera-CV; Philips) inversion-recovery segmented gradient-echo sequence was used for detection and quantification of LGE. Ten to 20 minutes after intravenous bolus of 0.1 mmol/kg of gadolinium-gadobenate dimeglumine (Multihance; Bracco, Milan, Italy; center C) or 0.2 mmol/kg gadolinium-tetraazacyclododecane-tetraacetic acid (Dotarem, Guerbet, France; centers A and B), LGE images were acquired using the same views used for cine images. The inversion time was individually adapted to suppress the signal of normal myocardium (220–350 ms).

Image Analysis

All CMR studies were centrally analyzed in center A using a workstation (Advantage; GE-Healthcare) with a dedicated software (MASS 6.1; Medis, Leiden, Netherlands). The analysis started with postcontrast images. The presence of LGE was assigned by the consensus of 2 experienced operators (A.D.T. and A.B.) blinded to clinical data. Myocardial LGE was considered present if the hyperenhanced myocardium was confined to midwall or subepicardial layers detectable in 2 perpendicular views.[13] A third operator (P.G.M.) blinded to clinical data adjudicated the presence or absence of LGE in case of disagreement (n=3). When present, LGE was semiquantitatively graded by an operator (A.B.). LV was segmented based on 17-segment model according to American Heart Association recommendation,[18] segment 17 was excluded from further analysis. Using short-axis stack of LGE images, a segment was considered involved when the hyperintense myocardium occupied >50% of its circumferential extent. Sum of segments showing LGE was used as a semiquantitative score of LGE extent. LV volumes, stroke volume, mass, and ejection fraction were quantified using the stack of cine short-axis images. LV volumes, stroke volume, and mass were normalized to body surface area.

Clinical Follow-Up and End Points

Follow-up was performed till July 2013. All events were centrally adjudicated at center A by the consensus of 2 experienced cardiologists blinded to CMR results (M.E. and M.L.). At 6- to 12-month intervals, all patients were followed up for nonfatal event by telephone interview, review of outpatient clinics or hospitalization records, and contact with primary care physician or cardiologists of patients. After hospitalization, medical records were reviewed to define the cause of admission. The cause of death was defined from a combination of death certification, postmortem data (when available), medical records, and communication with primary care physician or cardiologist of patients. Type of death was classified according to a modified Hinkle–Thaler system.[19] Patients who died of noncardiac causes were considered censored at the time of the event. Sudden cardiac death (SCD) was defined as unexpected death either within 1 hour of cardiac symptoms in the absence of progressive deterioration and during sleep or within 24 hours of last being seen alive. Aborted SCD was diagnosed in patients who received an appropriate implantable cardioverter-defibrillator (ICD) intervention for ventricular arrhythmia or had a nonfatal episode of ventricular fibrillation or spontaneous sustained ventricular tachycardia (>30 s in duration), causing hemodynamic compromise and requiring cardioversion. CHF death was defined as death associated with unstable, progressive deterioration of pump function, despite active therapy. Onset of CHF was defined according to Framingham Criteria as indicated above. The predefined end point was a composite of cardiac death, onset of CHF, and aborted SCD.

Statistical Analysis

Continuous variables were expressed as mean±SD or median and 25th to 75th percentiles and categorical variables as frequency with percentage. Student independent *t* or Mann–Whitney tests were used as appropriate to compare continuous variables between patients with and without LGE. Comparisons between groups on categorical variables were performed by χ^2 or by Fisher exact test if the expected cell count was <5. Survival curves were obtained by Kaplan–Meier analysis and compared by log-rank test. The time to events was calculated from the CMR date. Univariate Cox proportional hazard models were used to

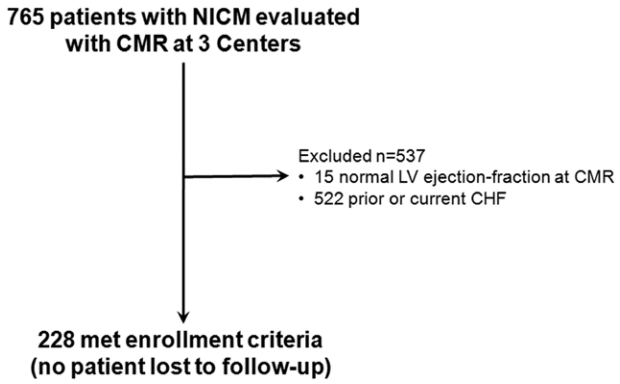

Figure 1. Study protocol. CHF indicates congestive heart failure; CMR, cardiovascular magnetic resonance; LV, left ventricular; and NICM, non–ischemic cardiomyopathy.

assess the association between baseline covariates and composite end point (results presented as hazard ratio and 95% confidence interval). Variables with $P<0.10$ at univariate analysis were then included as covariates in multivariate Cox proportional hazard models to test which variables were independently associated with the composite end point.

Considering the strong correlation between LV ejection fraction and LV end-systolic volume index (Pearson correlation coefficient, $r=-0.811$; $P<0.001$), LV ejection fraction (model 1) and LV end-systolic volume index (model 2) were introduced separately in the multivariate analysis. The presence and extent of LGE were introduced separately in both model 1 (LGE presence in model 1a and LGE extent in model 1b) and model 2 (LGE presence in model 2a and LGE extent model 2b). For each model, the incremental value in predicting composite end point by stepwise inclusion of CMR parameters of LV remodeling and function (LV volumes, mass, and ejection fraction) and fibrosis (presence or extent of LGE) in addition to clinical data (age and duration of cardiomyopathy) was assessed by the χ^2 using Omnibus test of model coefficients. For each model, goodness-of-fit statistics were obtained by means of log likelihood and Akaike Information Criterion, as well as Bayesian Information Criterion. Reclassification of patients was determined using net reclassification improvement analysis for combined end point and onset of CHF. For each end point, the net reclassification improvement and risk reclassification tables were used to determine reclassification of patients obtained by adding LGE status to the model based on age and LV ejection fraction.[20] Because no conventional cutoff values exist for composite end point and onset of CHF in such population, risk categories were determined on the basis of mean event rate at 2 years of follow-up. For composite end point, a threshold of 15% was used to stratify patients in low-risk (<15%) and high-risk (≥15%) categories. For onset of CHF, a threshold of 10%

Table 1. Baseline Characteristics in Whole Study Population and in Patients With and Without LGE

Variables	All (n=228)	Patients With LGE (n=61)	Patients Without LGE (n=167)	*P* Value
Age, y	50±15	50±15	50±15	0.868
Women, n (%)	47 (21)	10 (16)	37 (22)	0.341
BMI, kg/m^2	26±4	26±3	25±4	0.599
Duration of CM, mo	7 (1–48)	9 (2–73)	6 (1–43)	0.178
Family history of CM	51 (22)	15 (25)	36 (22)	0.627
Hypertension, n (%)	67 (29)	15 (25)	52 (31)	0.324
Diabetes mellitus, n (%)	20 (9)	7 (11)	13 (8)	0.383
Smoking, n (%)	88 (39)	22 (36)	66 (39)	0.635
Dyslipidemia, n (%)	58 (25)	18 (30)	40 (24)	0.394
Alcohol abuse	15 (7)	4 (7)	11 (7)	0.991
Hemoglobin, g/dL	13±1	13±1	13±2	0.876
Creatinine, mg/dL	0.90±0.20	0.95±0.20	0.92±0.21	0.439
Atrial fibrillation, n (%)	16 (7)	5 (8)	11 (7)	0.674
LBBB, n (%)	56 (25)	13 (21)	43 (26)	0.491
QRS duration, ms	120±27	122±26	120±27	0.750
CMR data				
LGE, n (%)	61 (27)	…	…	…
LGE no. of segments	0 (0–1)	3 (2–6)	…	…
LVEDVi, mL/m^2	115±31	117±28	115±32	0.674
LVESVi, mL/m^2	68±30	68±26	68±31	0.905
LVMi, g/m^2	83±23	88±26	82±22	0.061
LVSVi, mL/m^2	48±10	49±11	47±9	0.360
LVEF, %	43±10	43±10	43±10	0.925
LVEF<35%, n (%)	52 (23)	14 (23)	38 (23)	0.975
Medications				
ACEi/ARBs, n (%)	201 (88)	51 (84)	150 (89)	0.456
β-Blockers, n (%)	187 (82)	50 (82)	145 (87)	0.495
Spironolactone, n (%)	56 (25)	15 (24)	41 (25)	0.911

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II inhibitor; BMI, body mass index; CM, cardiomyopathy; CMR, cardiovascular magnetic resonance; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass index; and SVi, stroke volume index.

was used to stratify patients in low-risk (<10%) and high-risk (≥10%) categories. All tests were 2-tailed, and $P<0.05$ was considered statistically significant. Analyses were performed using SSPS version 15 (SPSS, Chicago, IL) and R-statistic 2.15.

Results

Study Population

Overall 228 patients met the enrollment criteria, and no patients were lost to follow-up (Figure 1). Of the whole population, 151 patients complained with a specific symptoms not fulfilling the diagnosis of CHF,[6] namely palpitations (n=80; 35%), atypical chest pain (n=55; 24%), and presyncope/syncope (n=16; 7%). Importantly, none was symptomatic for undue dyspnea or asthenia on ordinary physical activity or was receiving loop diuretic at study entry. The remaining 77 patients were completely asymptomatic and underwent clinical investigation because of family history of NICM (n=39; 17%), history of hypertension-associated left bundle branch block (n=31; 14%), and anthracycline exposure (n=7; 3%). Significant coronary artery disease was excluded by means of invasive coronary angiography in 203 patients and of cardiac computed tomography in the remaining 25 patients. Sixty-one (27%) patients showed LGE, and the median extent of LGE was 3 segments (range, 1–10). Baseline characteristics in the overall study population and in patients with and without LGE are reported in Table 1. Baseline characteristics were well balanced in the 2 groups, with the exception of LV mass index that tended to be higher in patients with LGE (P=0.061).

Clinical Follow-Up

The median follow-up duration was 23 months (13–37 months). During follow-up, we identified 49 events. Thirty-one of 61 patients with LGE reached the combined end point when compared with 18 of 167 (11%) patients without LGE (hazard ratio, 5.10 [2.78–9.36]; P<0.001; Figure 2; Table 2). All cardiac deaths were because of CHF and occurred at a similar rate in patients with and without LGE. However, patients with LGE had a greater risk of developing CHF when compared with patients without LGE (hazard ratio, 5.23 [2.61–10.50]; P<0.001; Figure 3; Table 2). During follow-up, 16 patients (7%) underwent device implantation, of which 11 received an ICD combined with cardiac resynchronization therapy and 5 received an ICD alone. Six patients implanted the device after the onset of CHF. Among the remaining 10 patients, 9 had severe LVSD (ejection fraction, <35%), despite treatment with optimal medical therapy for ≥12 months and arrhythmic burden documented at 24-hour Holter monitoring or ECG monitoring (8 patients had >1 episode of nonsustained ventricular tachycardia and 1 patient had an episode of sustained ventricular tachycardia), and 1 patient had moderate LVSD (ejection fraction, 43%) and an episode of sustained ventricular tachycardia documented at 24-hour Holter monitoring. During follow-up, patients with LGE had higher rate of aborted SCD when compared with patients without LGE (hazard ratio, 8.31 [1.66–41.55]; P=0.010; Table 2). All cases of aborted SCD (n=8) were because of appropriate ICD intervention.

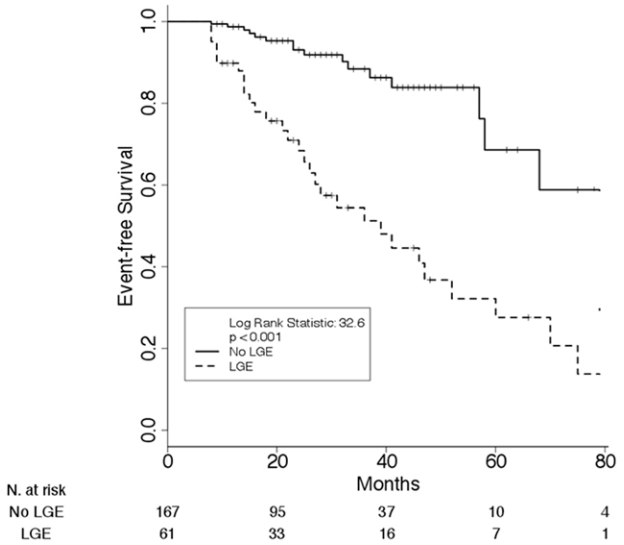

Figure 2. Kaplan–Meier curves for composite end point. LGE indicates late gadolinium enhancement.

Predictors of Clinical Outcomes at Univariate and Multivariate Analyses

At univariate analysis, the presence and extent of LGE predicted the combined primary end point. Advanced age, longer history of cardiomyopathy, higher LV volumes and mass, and lower LV ejection fraction were the other covariates associated with the occurrence of combined end point during follow-up (Table 3). However, at multivariate analysis, only the presence and extent of LGE and age remained independent predictors of the combined end point (model 1a and 1b; Table 4). These results were confirmed when LV end-systolic volume index replaced LV ejection fraction in the multivariate models (model 2a and 2b; Table 4).

Incremental Value of LGE for Prediction Clinical Outcomes

Information on the presence and extent of LGE made a sizeable difference in the prediction of combined end point. In particular, the addition of parameters of LV remodeling and function (ie, LV volumes, mass, and ejection fraction) to the model, including only clinical data (age and duration of cardiomyopathy), did not yield any improvement in the prediction of outcome. However, the addition of information on the presence or extent of LGE to the multivariate models yielded a significant improvement in outcome prediction (Figure 4).

Risk Reclassification

For the composite end point, the addition of LGE status to the model based on age and LV ejection fraction resulted in an overall correct reclassification of 29.6% (95 confidence interval, 17.4%–41.7%; P<0.001). Among 179 patients who did not experience the composite end point, 37 patients were correctly reclassified in the low-risk group, whereas 6 patients were incorrectly upgraded in the high-risk group (Table 5). Among the 49 patients who had the composite end point during follow-up, 6 patients were correctly reclassified in the high-risk category. For the onset of CHF, the addition of LGE status to the model based on age and LV ejection fraction yielded an overall correct reclassification of 25.4% (95% confidence

Table 2. Outcome Data

Outcome	Overall (n=228)	Patients With LGE (n=61)	Patients Without LGE (n=167)	Hazard Ratio (95% CI)	*P* Value
Combined end point, n (%)	49 (21)	31 (51)	18 (11)	5.104 (2.783–9.361)	<0.001
Cardiovascular deaths	4 (2)	1 (2)	3 (2)	1.241 (0.110–13.941)	0.861
CHF	37 (16)	24 (39)	13 (8)	5.234 (2.609–10.500)	<0.001
Aborted SCD	8 (4)	6 (10)	2 (1)	8.314 (1.664–41.548)	0.010

Hazard ratio is calculated for patients with LGE vs those without LGE. *P* values are obtained from univariate Cox proportional hazard models. CHF indicates congestive heart failure; CI, confidence interval; LGE, late gadolinium enhancement; and SCD, sudden cardiac death.

interval, 11.5%–39.2%; *P*<0.001). Among 191 patients who did not develop CHF during follow-up, 41 patients were correctly reclassified in the low-risk group, whereas 8 patients were incorrectly reclassified in the high-risk category. Among the 37 patients who experienced CHF, 4 patients were correctly reclassified in the high-risk category and 1 patient was incorrectly downgraded in the low-risk group (Table 6).

Discussion

We found that in patients with NICM without history of CHF, the presence and extent of LGE were associated with an increased likelihood of the composite end point, including cardiac death, development of CHF, and aborted SCD. These associations were independent of other important prognostic determinants, including age, duration of cardiomyopathy, and the degree of LV remodeling and dysfunction. Moreover, the addition of the presence or extent of LGE to models, including clinical data alone or in combination with parameters of LV remodeling and function, yielded a significant improvement in outcome prediction. Net reclassification improvement analyses disclosed that the addition of LGE status to models based on age and LV ejection fraction resulted in a correct reclassification of nearly one third of patients for the composite end point and the development of CHF.

Reactive (interstitial and perivascular) and replacement myocardial fibrosis are hallmarks of NICM.[21,22] Contrast-enhanced CMR with LGE technique is accurate for an in vivo detection and quantification of replacement fibrosis, a scarring process that occurs in response to myocytes necrosis.[11,14] Studies by several groups underscored that LGE is an independent predictor of outcome in patients with NICM and history of CHF based on a composite of cardiovascular death, CHF hospitalization, or appropriate ICD interventions.[3,11–14] Recently, in a cohort of 472 consecutive patients with NICM, Gulati et al[14] demonstrated that the presence and extent of LGE provided an independent prognostic information for all cause of mortality and SCD. However, more than half of patients complained with symptoms of CHF at study entry, and the proportion of asymptomatic patients at enrollment but with antecedent episodes of CHF was not specified. The present study expands

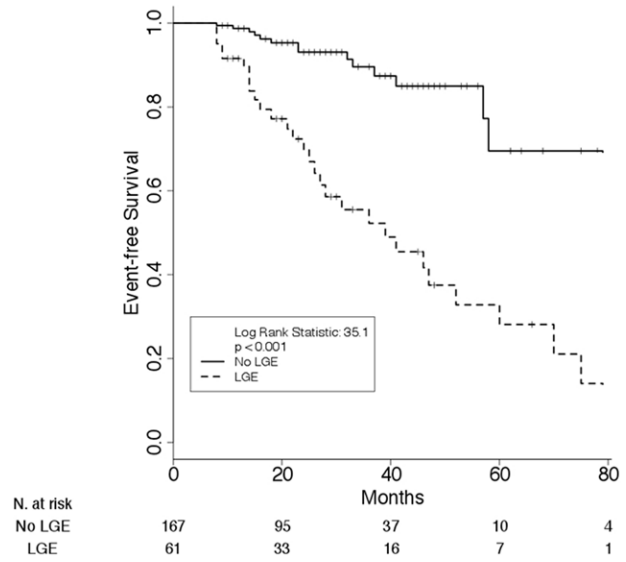

Figure 3. Kaplan–Meier curves for the development of congestive heart failure. LGE indicates late gadolinium enhancement.

Table 3. Univariate Cox Proportional Hazards Analysis for Composite End Point

Variables at Baseline	HR (95% CI)	*P* Value
Age, y	1.040 (1.018–1.062)	<0.001
Sex (women)	0.669 (0.321–1.396)	0.284
BMI, kg/m^2	1.051 (0.997–1.131)	0.184
Family history of CM	0.935 (0.505–1.876)	0.935
Diabetes mellitus	1.031 (0.367–2.896)	0.953
Hypertension	0.893 (0.464–1.719)	0.735
Dyslipidemia	0.966 (0.522–1.788)	0.913
Smoking	1.392 (0.785–2.467)	0.258
Alcohol abuse	0.907 (0.219–3.764)	0.893
Duration of CM, mo	1.007 (1.003–1.012)	0.002
Hemoglobin, g/dL	1.046 (0.798–1.371)	0.744
Creatinine, mg/dL	1.251 (0.262–5.969)	0.779
Atrial fibrillation	1.391 (0.492–3.932)	0.533
Presence of LBBB	1.243 (0.672-2.2.300)	0.489
QRS duration, ms	1.007 (0.993–1.021)	0.322
Presence of LGE	5.104 (2.783–9.361)	<0.001
LGE extent (no. of segment)	1.168 (1.069–1.277)	0.001
LVEDVi, mL/m^2	1.008 (1.000–1.016)	0.044
LVESVi, mL/m^2	1.009 (1.002–1.017)	0.013
LVSVi, mL/m^2	0.987 (0.959–1.015)	0.369
LVMi, g/m^2	1.018 (1.006–1.030)	0.004
LVEF, %	0.962 (0.934–0.990)	0.009

BMI indicates body mass index; CI, confidence interval; CM, cardiomyopathy; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; HR, hazard ratio; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass index; and SVi, stroke volume index.

Table 4. Multivariate Cox Proportional Hazards Analysis for Composite End Point

Variables at Baseline	Model 1				Model 2			
	Model 1a		Model 1b		Model 2a		Model 2b	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y	1.038 (1.013–1.063)	0.003	1.049 (1.021–1.078)	0.001	1.036 (1.011–1.062)	0.004	1.049 (1.020–1.078)	0.001
Duration of CM, mo	1.004 (0.998–1.009)	0.175	1.003 (0.998–1.009)	0.282	1.004 (0.998–1.009)	0.162	1.003 (0.998–1.009)	0.278
Presence of LGE	4.020 (2.082–7.762)	<0.001	N/A	N/A	4.152 (2.142–8.048)	<0.001	N/A	N/A
LGE extent (no. of segment)	N/A	N/A	1.239 (1.111–1.382)	<0.001	N/A	N/A	1.241 (1.114–1.383)	<0.001
LVEDVi, mL/m^2	1.006 (0.993–1.019)	0.378	1.007 (0.994–1.020)	0.318	0.991 (0.959–1.025)	0.603	0.999 (0.966–1.034)	0.974
LVESVi, mL/m^2	N/A	N/A	N/A	N/A	1.020 (0.986–1.056)	0.250	1.010 (0.975–1.046)	0.578
LVMi, g/m^2	0.998 (0.982–1.013)	0.770	0.999 (0.983–1.015)	0.884	0.998 (0.983–1.014)	0.828	0.999 (0.983–1.015)	0.912
LVEF, %	0.997 (0.934–1.021)	0.305	0.989 (0.944–1.035)	0.625	N/A	N/A	N/A	N/A

CI indicates confidence interval; CM, cardiomyopathy; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass index; and N/A, not applicable.

the current knowledge about the clinical significance of fibrosis in the risk stratification of patients with NICM by reporting the strong and independent prognostic value of LGE in NICM subjects without history of CHF.

Most of the information on preclinical LVSD derives from large epidemiological cohort studies, showing that this condition is as common as CHF in the general population and is predominantly associated with ischemic heart disease.[6,8,9] In a community-based cross-sectional cohort study, Wang et al[6] reported that subjects with preclinical LVSD had increased risk of developing CHF and death when compared with those with normal LV systolic function irrespective of baseline cardiovascular risk factors and the cause of ventricular dysfunction. To the best of our knowledge, our study is the first to show that in patients with NICM without history of CHF, the presence of LGE at baseline CMR conferred a 5-fold increased risk of experiencing the composite end point, and the strong prognostic predictive value of LGE was independent of other important prognostic determinants, including age, duration of cardiomyopathy, LV volumes, mass, and ejection fraction. Myocardial LGE was also an independent prognostic predictor when semiquantitatively graded as number of LV segments with LGE, indicating that not only the presence but also the burden of fibrosis is an important determinant of outcome. Of note, most of the events were related to the development of CHF during follow-up, suggesting that baseline LGE detection is capable to predict the transition from preclinical to symptomatic stage. Fibrosis has been regarded as a marker of disease severity, reflecting the burden of initial myocardial damage and subsequent injury because of adverse LV remodeling.[23] However, there are cumulating evidences supporting the knowledge that fibrosis is not a fixed marker of disease severity[24] but rather a dynamic process that may play a causative role in the progression of LVSD and ensuing onset of CHF.[25]

Currently, risk stratification in patients with preclinical LVSD is primarily based on the degree of LVSD in the view of the fact that the likelihood of CHF and death augments with increasing the degrees of LVSD.[6] In patients with NICM and CHF, LV ejection fraction is a validated independent prognostic predictor[26,27] even though the relationship between LV systolic function and outcome is not linear and becomes weaker in patients with severe LVSD.[1,28] Risk stratification based on LV ejection fraction is also limited by the fact that more than one third of patients with NICM experiences a consistent and sustained improvement of LV ejection fraction after optimization of medical therapy irrespective of the severity of initial LV dilatation and dysfunction.[24,29] Thus, effective risk stratification remains challenging in NICM particularly in subjects without history of CHF also because of the paucity of the data in this specific subgroup of patients. A remarkable finding of our study is that the addition of presence or extent of LGE to clinical data alone or in combination with parameters of LV remodeling and function significantly improved the outcome prediction. Furthermore, net reclassification improvement analyses showed that the addition of LGE status to models based on age and LV ejection fraction yielded an improvement of risk stratification for both composite end point and onset of CHF. For example, in patients who did not experience the composite end point, the use of LGE status correctly reclassified in low-risk group as many as 56% of patients incorrectly allocated to high-risk category by the model based on age and LV ejection fraction. Similarly, in patients who had the composite end point during follow-up, the addition of LGE status to the model, including age and LV ejection fraction, correctly reclassified 24% in the high-risk group. Overall, these findings suggest that LGE improves the prediction of outcome and risk stratification in patients with NICM without history of CHF.

Current guidelines recommend ICD implantation for primary prevention of SCD in patients with NICM, symptoms of CHF, and LV ejection fraction <35%, despite ≥3 months of treatment with optimal pharmacological therapy.[30] In the present study, 16 patients (7%) underwent ICD implantation alone or in combination with cardiac resynchronization therapy. Six patients with severe LVSD received device after the onset of CHF; whereas among the remaining 10 patients, 9 had severe LVSD not responding to optimized medical therapy and documented ventricular arrhythmic burden and 1 patient had moderate LVSD and an episode of sustained ventricular tachycardia. Patients with LGE had an 8-fold increased risk of appropriate ICD intervention when compared with those without LGE.

The validity of this result is limited by the few cases of aborted SCD. Nonetheless, this can be regarded as a

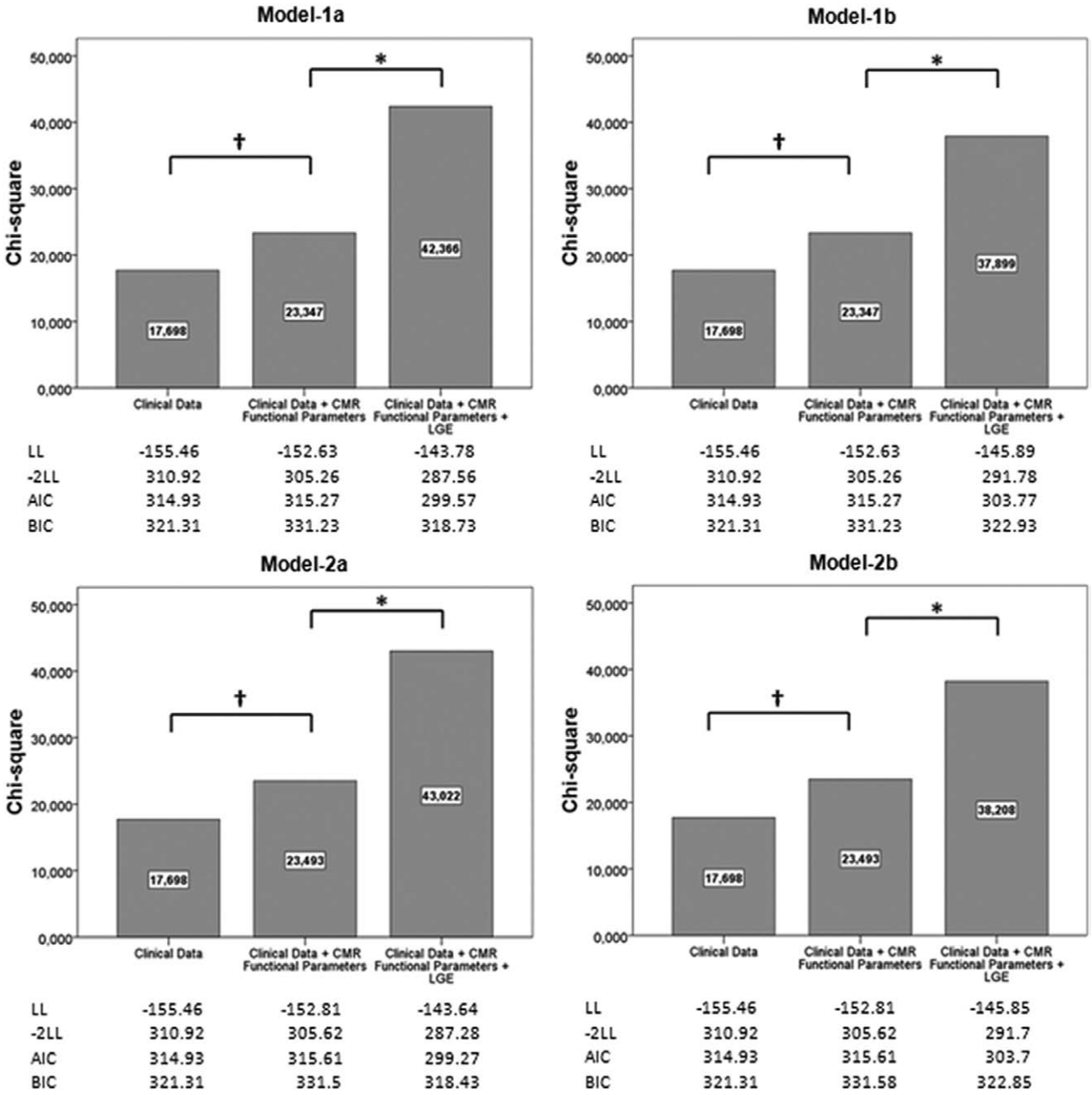

Figure 4. Multivariate analyses showing the incremental value of late gadolinium enhancement (LGE) in predicting outcome when compared with models, including clinical data alone (age and duration of cardiomyopathy) or in combination with cardiovascular magnetic resonance (CMR) parameters of left ventricular (LV) remodeling and function (LV volumes, mass, and ejection fraction). AIC indicates Akaike Information Criterion; BIC, Bayesian Information Criterion; and LL, log likelihood. **P*<0.001; †*P*>0.050.

hypothesis-generating finding, warranting further investigations to assess the value of LGE in predicting SCD in patients with NICM without history of CHF. Of note, in patients with NICM and CHF, there are cumulating evidences, suggesting that fibrosis may be a useful marker for risk stratification of SCD.[12,14,31] Although the mechanisms of SCD in NICM are not yet completely understood, recent evidences suggest that fibrosis serves as anatomic substrate for reentry ventricular arrhythmias.[31,32]

Limitations

This is a multicenter study performed in 3 tertiary referral centers by adopting a prespecified standardized protocol for both clinical and CMR approaches and a centralized analysis of data. Referral bias might be a limitation of the study. The retrospective assignment of CHF could have led to misclassification. However, this potential limitation was minimized by the prospective and standardized collection of the data. The study comprised a limited number of subjects followed up for a median of 2 years who were mainly enrolled at center A. Larger studies with long-term follow-up are warranted to address the prognostic value of fibrosis fully in this subset of patients with NICM with particular respect to survival. With respect to CMR examination, the choice of contrast agent was left to each center's discretion. Although there are differences in contrast agent relaxivity, this aspect unlikely interfered with the visual discrimination and semiquantitative analysis

Table 5. Risk Reclassification Improvement With the Addition of LGE to Models, Including Age and LV Ejection Fraction, for the Composite End Point

Predicted Risk With Age and LV Ejection Fraction, %	Predicted Risk With Age, LV Ejection Fraction and LGE, %			
	<15	≥15	Total	Reclassified
Outcome absent				
<15	107	6*	113	5
≥15	37†	29	66	56
Outcome present				
<15	19	6†	25	24
≥15	0	24	24	0

Values indicate the number of subjects in each category of predicted risk for patients who did not experience composite end point (outcome absent) and for those who developed the composite end point (outcome present) during follow-up. LGE indicates late gadolinium enhancement; and LV, left ventricular.

*Incorrect classification.

†Correct reclassification.

of LGE. The latter was based on an easily obtainable semiquantitative grading based on several LV segments showing LGE. This approach was preferred to (semi)automatic quantification of LGE using signal intensity threshold because it reflects more closely what is routinely done in clinical practice. The definition of preclinical LVSD was based on reduced LV ejection fraction, detected at transthoracic echocardiography and confirmed by CMR, in the absence of history of CHF as defined by well-established diagnostic criteria.[6,33] However, the functional status was not evaluated by objective testing or a structured interview. Only 16 patients underwent ICD implantation and 8 of them received an appropriate ICD intervention during follow-up, a finding consistent with a particularly high risk of aborted SCD. Four of 8 patients with an appropriate ICD intervention had positive familial history for NICM, but we did not perform genetic counseling or testing. Thus, it cannot be excluded that some patients bore a sporadic or familiar mutation of genes associated with NICM phenotype and high risk of SCD.[34] Given the absence of established thresholds for defining the risk of composite end point and the development of CHF, in net reclassification improvement analyses, the choice of risk categories was based on the current study data. The adoption of different cutoff values might have yielded diverse results. Anyway, we performed multiple analyses (data not shown) using different categories of risk, and results remained consistent in all net reclassification improvement analyses. Furthermore, LGE technique allows the detection and quantification of replacement fibrosis. The quantification of interstitial fibrosis by T1 mapping may be of value in this setting.[35]

Table 6. Risk Reclassification Improvement With the Addition of LGE to Models, Including Age and LV Ejection Fraction, for Onset of CHF

Predicted Risk With Age and LV Ejection Fraction, %	Predicted Risk With Age and LV Ejection Fraction and LGE, %			
	<10	≥10	Total	Reclassified
CHF absent				
<10	98	8*	106	8
≥10	41†	44	85	48
CHF present				
<10	14	4†	18	22
≥10	1*	18	19	5

Values indicate the number of subjects in each category of predicted risk for patients who did not experience CHF (CHF absent) and for those who developed CHF (CHF present) during follow-up. CHF indicates congestive heart failure; LGE, late gadolinium enhancement; and LV, left ventricular.

*Incorrect classification.

†Correct reclassification.

Conclusions

Myocardial fibrosis is a strong and independent predictor of adverse outcome in patients with NICM without history of CHF, providing incremental prognostic information and significant improvement on risk stratification beyond clinical data and degree of LV dysfunction.

Disclosures

None.

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CLINICAL PERSPECTIVE

Non–ischemic cardiomyopathy (NICM) is a major cause of congestive heart failure (CHF) with 5-year mortality high as 20%. A preclinical phase may precede the development of CHF in patients with NICM. However, information on this condition is scarce, given that most of the data are focused on preclinical left ventricular dysfunction because of ischemic heart disease. In this multicenter longitudinal prospective study, we have investigated the prognostic significance of myocardial fibrosis detected by late gadolinium enhancement technique using contrast-enhanced cardiovascular magnetic resonance in a cohort of patients with NICM without history of CHF. Among 765 patients with NICM studied with cardiovascular magnetic resonance, 228 patients without history of CHF were enrolled in the study and prospectively followed up (median, 23 months) for the composite end point of cardiac death, onset of CHF, and aborted sudden cardiac death. Myocardial fibrosis was detected in 61 (27%) patients. Thirty-one of 61 (51%) patients with fibrosis reached combined end point when compared with 18 of 167 (11%) patients without fibrosis (hazard ratio, 5.10 [2.78–9.36]; $P<0.001$). Multivariable analysis showed that fibrosis was associated with high likelihood of composite end point independent of other prognostic determinants, including age; duration of cardiomyopathy; and left ventricular volumes, mass, and ejection fraction (hazard ratio, 4.02 [2.08–7.76]; $P<0.001$). Moreover, addition of LGE to age and left ventricular ejection fraction improved risk stratification for composite end point (net reclassification improvement, 29.6%) and onset of CHF (net reclassification improvement, 25.4%; both $P<0.001$). We have shown that in patients with NICM without history of CHF myocardial fibrosis is a strong and independent predictor of outcome, providing incremental prognostic information and improvement in risk stratification beyond clinical data and degree of left ventricular dysfunction.

SUPPLEMENTAL MATERIAL

Supplemental Methods

Parameters of CMR sequences used by diverse 1.5 T scanners in the 3 Centers.

	Cine b-steady state free precession	T1-weighted fast gradient-echo Inversion-recovery
Discovery MR, GE	FOV: 380-400 mm; TR/ TE: 3.2/1.4ms; α: 50°; matrix: 256x224; ST: 8 mm; no interslice gap	FOV: 380-400 mm; TR/TE: 6.7/1.6ms α: 20°, matrix: 256x192, ST:8mm; no interslice gap
Intera CV, Philips	FOV: 350-400 mm; TR/ TE: 3.6/1.8 ms; α: 60°; matrix: 256x160; ST: 8 mm; no interslice gap	FOV: 350-400 mm; TR/TE: 4.5/1.3ms α: 15°, matrix: 256x128, ST:5mm; no interslice gap;
CVi, GE	FOV: 350-400 mm, TR/TE: 3.2/1.6 ms, α: 60°, matrix: 256x256, ST: 8 mm; no interslice gap	FOV: 380-420 mm; TR/TE: 4.6/1.3ms α: 20°; matrix: 256x192; ST: 8 mm; no interslice gap ST: 8 mm; no interslice gap

Table Legend: α : flip angle; FOV: field of view; ST: slice thickness; TE: echo time; TR: repetition time.