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CLINICAL RESEARCH
Sudden death and ICDs

CarDiac magnEtic Resonance for prophylactic Implantable-cardioVerter defibrillAtor ThErapy in Non-Ischaemic dilated CardioMyopathy: an international Registry

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Aims The aim of this registry was to evaluate the additional prognostic value of a composite cardiac magnetic resonance (CMR)-based risk score over standard-of-care (SOC) evaluation in a large cohort of consecutive unselected non-ischaemic cardiomyopathy (NICM) patients.

Methods and results In the DERIVATE registry (www.clinicaltrials.gov/registration: RCT#NCT03352648), 1000 (derivation cohort) and 508 (validation cohort) NICM patients with chronic heart failure (HF) and left ventricular ejection fraction <50% were included. All-cause mortality and major adverse arrhythmic cardiac events (MAACE) were the primary and secondary endpoints, respectively. During a median follow-up of 959 days, all-cause mortality and MAACE occurred in 72 (7%) and 93 (9%) patients, respectively. Age and >3 segments with midwall fibrosis on late gadolinium enhancement (LGE) were the only independent predictors of all-cause mortality (HR: 1.036, 95% CI: 1.0117–1.056, $P < 0.001$ and HR: 2.077, 95% CI: 1.211–3.562, $P = 0.008$, respectively). For MAACE, the independent predictors were male gender, left ventricular end-diastolic volume index by CMR (CMR-LVEDVi), and >3 segments with midwall fibrosis on LGE (HR: 2.131, 95% CI: 1.231–3.690, $P = 0.007$; HR: 3.161, 95% CI: 1.750–5.709, $P < 0.001$; and HR: 1.693, 95% CI: 1.084–2.644, $P = 0.021$, respectively). A composite clinical and CMR-based risk score provided a net reclassification improvement of 63.7% ($P < 0.001$) for MAACE occurrence when added to the model based on SOC evaluation. These findings were confirmed in the validation cohort.

Conclusion In a large multicentre, multivendor cohort registry reflecting daily clinical practice in NICM work-up, a composite clinical and CMR-based risk score provides incremental prognostic value beyond SOC evaluation, which may have impact on the indication of implantable cardioverter-defibrillator implantation.

Keywords • Non-ischaemic dilated cardiomyopathy • Heart failure • Implantable cardioverter-defibrillator • Cardiac magnetic resonance • Primary prevention

What's new?

- In this large multicentre, multivendor setting, fibrosis assessment by late gadolinium enhancement (LGE)–cardiac magnetic resonance (CMR) in non-ischaemic cardiomyopathy (NICM) patients provides additional prognostic stratification for all-cause mortality and major adverse arrhythmic cardiac events (MACCE) predictions as compared to SOC evaluation recommended by current guidelines.
- At multivariate analyses, age and >3 segments with midwall fibrosis on LGE were showed as independent predictors for all-cause mortality while male gender, CMR-LVEDVi >120.5 mL/m^2, and presence of >3 segments with midwall fibrosis on LGE were independent predictors of MAACE.
- A CMR-based composite risk score identifies almost one-third of NICM patients fulfilling the current criteria for primary prevention ICD implantation as having low risk of MAACE.
- Randomized controlled study is warranted to test the cost-effectiveness of a CMR strategy when compared with SOC evaluation in NICM patient candidates for ICD implantation.

Introduction

Implantable cardioverter-defibrillator (ICD) therapy demonstrated to be the most effective sudden cardiac death (SCD) prophylactic strategy adopted for primary and secondary preventions in non-ischaemic dilated cardiomyopathy (NICM) patients.[1] To date, the standard-of-care (SOC) evaluation for primary prevention ICD therapy is based on left ventricular (LV) ejection fraction (EF) of 35% or less and New York Heart Association (NYHA) functional class II or III for both, NICM and ischaemic cardiomyopathy (ICM).[2] While easily applicable in a routine work-up, this strategy holds two major limitations. First, only a relatively small proportion of patients receiving ICD for SCD primary prevention benefits from this treatment. Secondly, SCD may also occur in patients with normal to moderately depressed left ventricular ejection fraction (LVEF). Therefore, novel prognostic stratification strategies are needed to improve the delivery of ICD therapy to patients, who may benefit from it while withholding device implantation in those at low SCD risk.[3] Recently, cardiac magnetic resonance (CMR) has emerged as the gold standard technique for LV volume and function assessment with the added benefit of providing tissue characterization.[4,5] Accordingly, the aim of the current registry was to validate a combined clinical and CMR-based prognostic risk score using a large cohort of NICM patients enrolled in several centres across Europe and the USA and using diverse CMR vendors. Specifically, the aim of the registry was to assess such a risk score not only in a population fulfilling current ICD implantation indication but also in patients not fulfilling these criteria, i.e. by including patients with no history of major cardiac arrhythmias and demonstrating an LVEF >35%. To increase the generalizability of the results, the CMR-based score derived from a large cohort of patients was re-tested in a large validation cohort.

Methods

Study design and target population

DERIVATE (http://www.clinicaltrials.gov: RCT#NCT03352648) is an international, multicentre, prospective, observational registry including

consecutive patients from 21 sites across Europe and the USA referred for heart failure (HF) work-up including transthoracic echocardiography (TTE) and CMR without a history of previous major ventricular arrhythmias. Inclusion criteria were (i) aged 18 or older, (ii) chronic HF according to the European Society of Cardiology Task force definition with >3 months from the last decompensated HF, and (iii) LV-EF < 50% at initial TTE. All patients underwent TTE and CMR within 3 months.[6] The registry workflow is shown in Supplementary material online, *Figure S1*. Briefly, patients with ICM, severe valvular heart diseases, primary or secondary cardiomyopathies other than NICM, and congenital heart disease were excluded. The institutional ethical committees of the participating centres approved the protocol and all patients gave written informed consent (see Supplementary material online, Methods).

Clinical patient assessment and data collection

The following clinical information was collected: (i) demographic characteristics; (ii) medical history (with particular regard to signs and symptoms of HF); (iii) cardiovascular risk factors; and (iv) medical and device therapy. All data were recorded in a standardized case report form.

Transthoracic echocardiography protocol and analysis

Transthoracic echocardiography was performed with patients in left lateral decubitus in the parasternal (long- and short-axis) and apical (four-, two-, and three-chamber) views. For each patient, the following measurements were acquired and collected: LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes. Left ventricular ejection fraction was calculated from Simpson method.[7]

Cardiac magnetic resonance protocol and analysis

After acquisition of localizers, breath-hold cine steady-state free precession sequences were used for functional analysis.[8] The CMR dataset was transferred and centrally evaluated by one observer (with >5 years of experience). Analysis of CMR was blinded to the patients' history. Volumetric and functional parameters were collected by using CMR4.2 software (Circle, Calgary, Canada). For late gadolinium enhancement (LGE), a qualitative analysis was performed defining the following variables: i) presence of LGE in a segment of the 17-segment model[9]; ii) LGE distribution pattern defined as midwall or subepicardial as previously described[10]; iii) LGE non-ischaemic pattern consisted of midwall, epicardial, and mixed distribution and iv) the number of segments with LGE counted using the standardized 17-segment model.[9] This type of standard CMR acquisition and analysis was chosen to be in agreement with current routine examinations[7,9] and to increase the applicability of the CMR procedures and the generalizability of the results (see Supplementary material online, Methods).

Follow-up

Patient follow-up was performed by each local Institution by dedicated personnel. Event ascertainment was determined by (i) direct interviews during office visits or telephone contact with the patient or a close family member, (ii) contact of the patient's cardiologist or general physician in case of death, (iii) review of patient's medical records, (iv) device interrogation for patients who underwent device implantation, and (v) 24-h ECG-Holter monitoring for those patients who did not receive device implantation. Study monitoring was performed in accordance with ICH E6GCP and applicable local regulations. A Clinical Monitoring Plan including project-specific operational guidelines was provided to define responsibilities of the Site Management/Monitoring Team, which ensured the quality and integrity of data collection.

Endpoints

All-cause mortality was the primary endpoint. The secondary combined Endpoint consisted of major adverse arrhythmic cardiac events (MAACE), defined as combination of SCD, aborted SCD defined as appropriate ICD shock or anti-tachycardia pacing, and sustained ventricular tachycardia (VT lasting >30 s) and/or causing haemodynamic instability (haemodynamic collapse within <30 s).

Statistical method

Regarding sample size calculations, we want to refer the reader to reference.[6] The statistical analysis was performed by using Stata, version 14, and R version 3.3. The entire cohort of patients was randomly divided assigning 2/3 of the patients to the derivation cohort and the remaining 1/3 to the validation cohort (1000 and 508 patients, respectively) using a dedicated weblink (https://www.random.org/integers/? mode=advanced). Descriptive statistics was used to characterize the population and Student's independent *t*-test, Mann–Whitney tests, χ^2, or Fisher's exact test were used as appropriate to compare the distribution of continuous and categorical variables. Univariate Cox proportional hazard models were used to identify candidate predictors for the study endpoints. All variables with $P < 0.05$, after excluding collinear predictors on the basis of the variance inflation factor, were included in the final multivariable Cox proportional hazard model via stepwise bootstrap (considering 1000 replications). When TTE and CMR data were predictors at univariate analysis, relevant dummy variables were derived considering the optimal thresholds by Youden index from analyses of the area under receiver operating characteristic curves.

The multivariate model developed for the endpoints was used to generate a composite risk score assigning points on the basis of hazard ratio.

The discriminatory and risk reclassification ability of the developed multivariable models were compared to the model including TTE-LVEF (but no CMR parameters) by means of the net reclassification improvement (NRI) index. To our knowledge, definitions for high- and low-risk NICM patients are not available in guidelines. Therefore, in this registry, low and high risks were defined according to limits of the interquartile interval for the event rate in the population. In details, the 25th percentile (equal to 0.05 of total events during follow-up) of the event rate was used to define the low-risk group, while the 75th percentile (equal to 0.14) was used to define the high-risk group. By this definition, the event rate in the high-risk group is 5.2% per year, which is similar to high risk as defined for the hypertrophic CMP (which equals 6%/year). Values comprised between the 25th and 75th percentile were assumed to define the intermediate-risk group.

Event-free survival related to the study endpoints was estimated using the Kaplan–Meier method and survival curves were compared by means of the Log-Rank test.

The ability of the score of adequately predicting events was then evaluated in the validation cohort.

Results

Derivation cohort

According to the pre-specified inclusion and exclusion criteria, the derivation cohort consisted of 1000 subjects [mean age: 57 ± 14 years, male: 686 (68.6%)]. Patient baseline characteristics are listed in *Table 1*. Transthoracic echocardiography and CMR tests

Table 1 Baseline characteristics of non-ischaemic dilated cardiomyopathy patients with and without cardiac events in derivation cohort

	All patients (*n*: 1000)	Primary endpoint (−) (*n*: 928)	Primary endpoint (+) (*n*: 72)	*P*-value	Secondary endpoint (−) (*n*: 907)	Secondary endpoint (+) (*n*: 93)	*P*-value
Demographic characteristics							
Age (years)	56.7 ± 14.2	56.2 ± 11.4	63.4 ± 13.5	<0.001	56.7 ± 14.2	56.9 ± 13.9	0.907
Male	686 (68.6%)	635 (68.4%)	51 (70.8%)	0.672	609 (67.1%)	77 (82.8%)	0.002
BSA (m^2)	1.90 ± 0.24	1.90 ± 0.24	1.89 ± 0.26	0.797	1.90 ± 0.24	1.93 ± 0.20	0.254
Cardiovascular risk factor							
Family history	301 (30.1%)	282 (30.4%)	19 (26.4%)	0.476	274 (30.2%)	27 (29.0%)	0.814
Smoking history	338 (34.0%)	322 (34.9%)	16 (22.2%)	0.028	315 (35.0%)	23 (24.7%)	0.047
Hypertension	404 (40.7%)	373 (40.5%)	31 (43.1%)	0.676	404 (40.7%)	37 (39.8%)	0.846
Hyperlipidaemia	326 (32.6%)	307 (33.1%)	19 (26.4%)	0.243	298 (32.9%)	28 (30.1%)	0.590
Diabetes	147 (14.7%)	131 (14.1%)	16 (22.2%)	0.061	133 (14.7%)	14 (15.1%)	0.919
NYHA class							
I–II	808 (80.8%)	749 (80.7%)	59 (81.9%)	0.798	735 (81.0%)	73 (78.5%)	0.553
III–IV	192 (19.2%)	179 (19.3%)	13 (18.1%)		172 (19.0%)	20 (21.5%)	
Medical therapy							
β-Blockers	821 (82.1%)	765 (82.4%)	56 (77.8%)	0.321	732 (80.7%)	89 (95.7%)	<0.001
Ivabradine	51 (5.1%)	50 (5.4%)	1 (1.4%)	0.170	47 (5.2%)	4 (4.3%)	1.00
ACE-inhibitors/AT1 blockers	846 (84.6%)	787 (84.8%)	59 (81.9%)	0.517	763 (84.1%)	83 (89.3%)	0.192
Diuretics	632 (63.2%)	578 (62.3%)	54 (75.0%)	0.031	564 (62.2%)	68 (73.1%)	0.037
Calcium-blockers	37 (3.7%)	32 (3.5%)	5 (6.9%)	0.130	35 (3.9%)	2 (2.2%)	0.569
Anti-thrombotic agents	312 (17.4%)	290 (31.3%)	22 (30.6%)	0.902	289 (31.9%)	23 (24.7%)	0.157
Anticoagulant therapy	174 (20.3%)	156 (16.8%)	18 (25.0%)	0.077	155 (17.1%)	19 (20.4%)	0.418
Nitrates	61 (6.1%)	51 (5.5%)	10 (13.9%)	0.004	55 (6.1%)	6 (6.5%)	0.882
Statins	300 (30.0%)	277 (29.9%)	23 (31.9%)	0.709	270 (29.8%)	30 (32.3%)	0.618
Amiodarone/other antiarrhythmics	167 (16.7%)	152 (16.4%)	15 (20.8%)	0.329	145 (16.0%)	22 (23.7%)	0.059
Device implantation and treatment during the follow-up							
ICD/CRT-D implantation	321 (32.1%)	306 (33%)	15 (20.8%)	0.031	245 (27.1%)	76 (81.7%)	<0.001

NYHA, New York Heart Association; ICD, implantable cardioverter-defibrillator.

were performed successfully in all patients with a median interval of 3 days (25th–75th: 2–5 days) between TTE and CMR. The median follow-up time was 959 days (25th–75th: 559.5–1590). Implantable cardioverter-defibrillator implantation was observed in 321 patients (32%) and of these 153 patients (15%) received cardiac resynchronization therapy (CRT). Mortality and MAACE occurred in 72 (7%) and 93 (9%) patients, respectively. Cardiovascular death, SCD, aborted SCD, and sustained VT occurred in 33 (3%), 8 (0.8%), 67 (7%), and 75 (8%), respectively. The sum of events exceeds the overall number of MAACE because several events could occur in the same patients but just the first event was counted.

Characteristics of the population according to the events

Patients who died by all-cause were older as compared to the patients still alive, while patients who experienced MAACE were predominantly male. No differences were found in terms of TTE and CMR parameters between dead and alive patients with the only exception for reduced RVEF and higher prevalence of subjects with midwall LGE pattern in the all-cause mortality group (*Table 2*).

Patients who experienced MAACE had higher LVEDV, higher LVESV ($P < 0.001$), and lower LVEF ($P = 0.001$) when compared with patients without MAACE irrespective of the imaging modality used. Major adverse arrhythmic cardiac events patients had higher prevalence and extent of LGE than patients without MAACE ($P < 0.001$) (*Table 2*).

Predictors of all-cause mortality and major adverse arrhythmic cardiac events

Univariate and multivariate analyses for all-cause mortality and MAACE prediction are shown in *Tables 3 and 4*, respectively. At multivariate analyses for all-cause mortality, only age and the presence of the midwall LGE pattern in >3 segments were independent predictors.

In the univariate analyses for MAACE, together with male gender all functional parameters by TTE and CMR were highly predictive for outcome, which is in line with general knowledge. In the univariate analyses, also several drug classes (β-blockers, diuretics, and antiarrhythmics) and several tissue characteristics measured by CMR were significant predictors. However, in the multivariate analyses, all functional TTE and CMR parameters were too weak to remain in the

Table 2 Transthoracic echocardiography and CMR characteristics of non-ischaemic dilated cardiomyopathy patients with and without cardiac events in the derivation cohort

	All patients (*n*: 1000)	Primary endpoint (−) (*n*: 928)	Primary endpoint (+) (*n*: 72)	*P*-value	Secondary endpoint (−) (*n*: 907)	Secondary endpoint (+) (*n*: 93)	*P*-value
TTE							
LVEDVi (mL/m^2)	101.3 ± 36.1	101.4 ± 36.1	100.0 ± 37.0	0.789	99.4 ± 35.9	118.2 ± 34.2	<0.001
LVESVi (mL/m^2)	68.2 ± 31.0	68.2 ± 31.0	67.5 ± 30.3	0.872	66.6 ± 30.7	82.1 ± 29.6	<0.001
LVEF (%)	33.4 ± 10.9	33.4 ± 11.0	33.7 ± 10.5	0.813	33.8 ± 11.1	29.7 ± 8.2	0.001
LVEF <35%	539 (54.3%)	499 (54.1%)	40 (56.3%)	0.718	472 (52.4%)	67 (72.8%)	<0.001
CMR functional evaluation							
LVEDVi (mL/m^2)	128.6 ± 39.6	128.5 ± 39.4	129.4 ± 42.6	0.853	126.1 ± 38.2	152.7 ± 44.7	<0.001
LVESVi (mL/m^2)	88.6 ± 39.1	88.4 ± 38.8	90.9 ± 43.3	0.598	86.1 ± 37.8	112.7 ± 43.4	<0.001
LV mass (g/m^2)	81.8 ± 26.1	81.7 ± 25.9	82.4 ± 28.5	0.828	81.5 ± 25.7	84.2 ± 29.4	0.366
LVSV, mL)	75.3 ± 46.3	75.2 ± 46.4	75.6 ± 47.7	0.953	75.0 ± 46.1	77.6 ± 50.0	0.614
LVEF (%)	33.0 ± 11.2	33.0 ± 11.1	32.8 ± 13.1	0.877	33.4 ± 11.3	28.4 ± 9.3	<0.001
LVEF <30%	393 (39.3%)	361 (38.9%)	32 (44.4%)	0.357	341 (37.6%)	52 (55.9%)	0.001
RVEDVi (mL/m^2)	78.4 ± 30.1	78.2 ± 30.2	82.1 ± 28.7	0.325	78.2 ± 30.6	80.6 ± 25.6	0.469
RVESVi (mL/m^2)	35 (25–47)	35 (25–47)	40 (25.2–56.7)	0.098	35 (25–47)	38.2 (26–50)	0.224
RVSV (mL)	66 (49–85)	66 (49–85)	63.7 (46–84)	0.773	66 (49–85)	64.6 (46.8–79.5)	0.295
RVEF (%)	51.0 ± 13.3	51.3 ± 13.2	47.8 ± 14.2	0.049	51.1 ± 13.2	50.4 ± 14.0	0.634
CMR LGE evaluation							
Prevalence of LGE positive patients	457 (46.0%)	418 (45.3%)	39 (54.9%)	0.116	391 (43.4%)	66 (71.0%)	<0.001
No. of segments with LGE	0 (0–3)	0 (0–3)	1 (0–4)	0.088	0 (0–3)	2 (0–5)	<0.001
Presence of midwall LGE pattern	341 (33.8%)	310 (33.2%)	29 (42%)	0.235	291 (32%)	50 (52.8%)	<0.001
Presence of epicardial LGE pattern	53 (5.3%)	49 (5.2%)	5 (7.3%)	0.547	49 (5.4%)	4 (4.5%)	0.650
Prevalence of mixed LGE pattern	63 (6.2%)	59 (6.4%)	3 (4.4%)	0.457	51 (5.6%)	12 (12.4%)	0.006
Number of segments with epicardial LGE pattern	0 (0–0)	0 (0–0)	0 (0–0)	0.980	0 (0–0)	0 (0–0)	0.101
Number of segments with midwall LGE pattern	0 (0–2)	0 (0–2)	0 (0–4)	0.094	0 (0–2)	0 (0–4)	<0.001
Presence of midwall LGE > 2 myocardial segments	213 (21.3%)	188 (20.3%)	25 (34.7%)	0.004	175 (19.3%)	38 (40.9%)	<0.001
Presence of midwall LGE pattern > 3 segments	173 (17.3%)	153 (16.5%)	20 (27.8%)	0.015	142 (15.7%)	31 (33.3%)	<0.001

All continuous variables were expressed as mean ± SD or median and interquartile range. All discrete variables were expressed as absolute number and percentage or as minimum and maximum value.

LGE, late gadolinium enhancement; LV, left ventricle; LVEDVi, left ventricle end-diastolic volume index; LVEF, left ventricle ejection fraction; LVESVi, left ventricle end-systolic volume index; NYHA, New York Heart Association; PAP, pulmonary artery pressure; RVEDVi, right ventricle end-diastolic volume index; RVEF, right ventricle ejection fraction; RVESVi, left ventricle end-systolic volume index; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography.

model and the only independent predictors for MAACE were male gender, left ventricular end-diastolic volume index (LVEDVi) by CMR, and the presence of >3 segments with midwall LGE.

Composite risk score, table of reclassification, and survival curve

Based on the multivariate analysis, a composite risk score for MAACE prediction was created comprising seven points with two points assigned to male gender, three points to CMR LVEDVi >120.5 mL/m^2, and two points to the presence of >3 segments with midwall fibrosis on LGE. When comparing this composite risk score for MAACE with the SOC risk model including TTE-LVEF, a significant re-classification improvement was observed resulting in a continuous NRI of 63.7% (95% CI: 44.7–82.8%, $P < 0.001$) (*Figure 1*). In order to estimate the performance of the composite risk score for MAACE, which integrates clinical, functional, and tissue characteristics, Kaplan–Meier survival curves were built-up on the basis of tertiles of this composite risk score showing significantly different event-free rates ($P < 0.001$) (*Figure 1*). The re-distribution of the event rate (per 100 person-years) according to

Table 3 Univariable predictors of primary and secondary endpoint in the derivation cohort

	Primary endpoint		Secondary endpoint	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Demographic characteristics				
Age (years) (per 1 year)	1.037 (1.017–1.057)	<0.001	1.004 (0.988–1.019)	0.655
Male	1.204 (0.717–2.022)	0.482	2.589 (1.499–4.472)	0.001
Cardiovascular risk factor				
Family history	0.816 (0.413–1.611)	0.558	0.848 (0.513–1.402)	0.521
Smoking history	0.626 (0.355–1.105)	0.106	0.967 (0.593–1.577)	0.892
Hypertension	1.11 (0.689–1.79)	0.668	1.059 (0.694–1.615)	0.792
Hyperlipidaemia	0.659 (0.385–1.129)	0.129	0.928 (0.591–1.458)	0.746
Diabetes	1.511 (0.852–2.68)	0.158	1.239 (0.693–2.217)	0.469
NYHA class (I–II vs. III–IV)	1.02 (0.547–1.901)	0.951	1.532 (0.91–2.578)	0.108
Medication				
β-Blockers	0.799 (0.439–1.454)	0.463	3.759 (1.349–10.476)	0.011
Ivabradine	0.501 (0.681–3.687)	0.497	1.253 (0.447–3.511)	0.668
ACE-inhibitors/AT1 blockers	0.785 (0.402–1.530)	0.477	1.104 (0.557–2.189)	0.778
Diuretics	1.756 (1.012–3.046)	0.045	1.800 (1.126–2.877)	0.014
Calcium-blockers	2.087 (0.809–5.381)	0.128	0.711 (0.168–3.006)	0.643
Anti-thrombotic agents	1.029 (0.598–1.771)	0.919	0.731 (0.447–1.196)	0.212
Anticoagulant therapy	1.637 (0.946–2.834)	0.078	1.354 (0.809–2.267)	0.249
Nitrates	2.898 (1.399–6.003)	0.004	0.933 (0.400–2.175)	0.873
Statins	0.866 (0.503–1.491)	0.604	1.467 (0.931–2.311)	0.098
Amiodarone/other antiarrhythmics	1.569 (0.770–3.196)	0.215	2.355 (1.416–3.918)	0.001
Device treatment				
ICD/CRT-D	0.444 (0.246–0.800)	0.007	7.610 (4.428–13.080)	<0.001
TTE				
LVEDVi (mL/m^2) (per 1 mL/m^2)	0.999 (0.99–1.008)	0.761	1.011 (1.005–1.018)	0.001
LVESVi (mL/m^2) (per 1 mL/m^2)	0.998 (0.989–1.008)	0.707	1.012 (1.005–1.018)	0.001
LVEF (per point %)	1.010 (0.988–1.032)	0.383	0.965 (0.944–0.987)	0.002
LVEF <35%	0.863 (0.533–1.397)	0.548	2.165 (1.349–3.476)	<0.001
CMR functional evaluation				
LVEDVi (mL/m^2) (per 1 mL/m^2)	1.001 (0.995–1.007)	0.809	1.012 (1.008–1.016)	<0.001
LVESVi (mL/m^2) (per 1 mL/m^2)	1.001 (0.995–1.008)	0.637	1.013 (1.008–1.017)	<0.001
LV mass (g/m^2) (per 1 g/m^2)	1.003 (0.992–1.015)	0.571	1.006 (0.997–1.015)	0.214
LVSV (mL) (per 1 mL)	0.996 (0.989–1.004)	0.325	1.003 (0.998–1.008)	0.194
LVEF (per point %)	1.003 (0.982–1.025)	0.769	0.961 (0.942–0.981)	<0.001
LVEF <30%	1.168 (0.728–1.876)	0.520	1.958 (1.293–2.965)	0.002
RVEDVi (mL/m^2) (per 1 mL/m^2)	1.004 (0.993–1.014)	0.521	1.010 (1.001–1.019)	0.037
RVESVi (mL/m^2) (per 1 mL/m^2)	1.006 (0.995–1.018)	0.292	1.015 (1.005–1.025)	0.002
RVSV (mL) (per 1 mL)	0.996 (0.986–1.006)	0.439	1.000 (0.991–1.009)	0.999
RVEF (per point %)	0.988 (0.968–1.008)	0.223	0.979 (0.964–0.995)	0.011
RVEF <51%	1.476 (0.886–2.458)	0.135	1.669 (1.086–2.564)	0.019
CMR LGE evaluation				
Prevalence of LGE positive patients	1.557 (0.936–2.592)	0.088	2.905 (1.802–4.686)	<0.001
No. of segments with LGE	1.065 (0.997–1.138)	0.061	1.099 (1.048–1.152)	<0.001
Presence of midwall LGE pattern	1.515 (0.877–2.617)	0.136	2.898 (1.750–4.798)	<0.001
Presence of epicardial LGE pattern	1.987 (0.744–5.305)	0.170	1.700 (0.583–4.952)	0.331
Presence of mixed LGE pattern	1.046 (0.306–3.58)	0.943	3.408 (1.615–7.192)	0.001
No. of segments with epicardial LGE (per 1 segment)	1.021 (0.894–1.167)	0.755	1.06 (0.971–1.158)	0.195
No. of segments with midwall LGE (per 1 segment)	1.088 (1.007–1.175)	0.033	1.123 (1.062–1.187)	<0.001
Presence of midwall LGE > 2 myocardial segments	1.711 (1.015–2.885)	0.044	2.314 (1.503–3.564)	<0.001
Presence of midwall LGE > 3 myocardial segments	2.103 (1.226–3.610)	0.007	2.252 (1.448–3.501)	<0.001

CMR, cardiac magnetic resonance; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; LVEDVi, left ventricle end-diastolic volume index; LVEF, left ventricle ejection fraction; LVESVi, left ventricle end-systolic volume index; NYHA, New York Heart Association; RVEDVi, right ventricle end-diastolic volume index; RVEF, right ventricle ejection fraction; RVESVi, left ventricle end-systolic volume index; TTE, transthoracic echocardiography.

Table 4 Multivariable predictors of primary and secondary endpoint in the derivation cohort

	Primary endpoint		Secondary endpoint	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Demographic characteristics				
Age (years) (per 1 year)	1.036 (1.017–1.056)	<0.001	–	–
Male	–	–	2.131 (1.231–3.690)	0.007
TTE				
LVEF <35%	–	–	1.336 (0.806–2.215)	0.261
CMR functional evaluation				
LVEDVi > 120.5 mL/m^2	–	–	3.161 (1.750–5.709)	<0.001
CMR LGE evaluation				
Prevalence of midwall LGE in >3 segments	2.077 (1.211–3.562)	0.008	1.693 (1.084–2.644)	0.021

CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; LVESVi, left ventricle end-systolic volume index; TTE, transthoracic echocardiography.

the composite risk score tertiles is represented in *Figure 2*. *Figure 3* depicts two clinical cases.

Analysis of the validation cohort

The validation cohort consisted of 508 NICM patients (Supplementary material online, *Tables S1* and *S2*) with baseline characteristics comparable to those of the derivation cohort. The rate of events in the validation cohort is listed in Supplementary material online, *Table S3*. As for the derivation cohort, the composite risk score was compared with the SOC-based risk score resulting in a continuous NRI for MAACE of 31.3% (95% CI: 4.6–58.0%, $P = 0.022$) (*Figure 4*). Kaplan–Meier survival curves were built-up on the basis of tertiles of the composite risk score showing again significantly different event-free rates ($P = 0.001$) (*Figure 4*).

Discussion

The present multicentre, multivendor observational registry of a large population of NICM patients provides information on how the clinical use of CMR imaging may alter the decision-making of primary prevention ICD implantation. The main findings are the following: (i) age and myocardial fibrosis by CMR were the only independent predictors for all-cause mortality in NICM patients; (ii) gender, LVEDVi, and fibrosis by CMR were the only independent predictors of MAACE in NICM patients; (iii) LVEF, measured either by TTE or CMR, lost its prognostic value when CMR LGE, i.e. fibrosis data, were introduced in the multivariate model; and (iv) a composite risk score for MAACE including gender and CMR data had an incremental prognostic value as compared to SOC-based risk stratification.

Previous randomized trials had failed to show a significant reduction in all-cause mortality with ICD therapy in patients with NICM and an LVEF ≤35%, and current International Recommendations on this topic stem mainly from *post hoc* analyses.[11] Subsequently, the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure on Mortality (DANISH) trial *per se* mitigated the survival benefit of ICD therapy for primary prevention in NICM patients, thus, challenging the approach of ICD implantation based on LVEF alone.[12] Recently, the association between myocardial fibrosis and cardiac events has been demonstrated in patients with DCM, i.e. in patients with severely reduced LVEF, but excluded patients with mildly reduced LVEF.[13,14] In contrast to the above studies, the present international, multicentre registry included a population of NICM patients with a lower risk for mortality and MAACE by targeting patients with a broader range of LV dysfunction. Moreover, the registry cohort was large enough to provide sufficient events for multivariate analyses and it allowed the additional confirmation in a validation cohort.

The current results show that age and both, the presence and extent of midwall fibrosis, are associated with an increased likelihood of all-cause mortality in NICM patients. Of note, age predicted all-cause mortality in the multivariable analysis but did not have any weight in MAACE, i.e. in arrhythmic outcomes. This is not surprising as increasing age is likely to come with an increasing risk of death from all causes, whilst arrhythmic manifestations per se do not seem to correlate with this parameter. According to the current results, midwall LGE is a strong prognostic determinant for both, all-cause mortality and MAACE. The reason why midwall LGE pattern in NICM shows a strong association with MAACE is not yet delucidated in the literature. Notably, previous studies provide us with insight into histopathological changes of myocardial substrate in this subset of patients showing that the myocardial remodelling can be associated with an increased collagen volume fraction and that the extent of fibrosis increases from epicardium to endocardium in transmural LV-free wall sections and from the right to the left side of the septum.[15,16] Likely, the major rearrangement in the mid part of ventricular wall may promote the well-known arrhythmogenic mechanism of macro-reentry.

In addition, it emerges from this registry that a composite risk score, which includes midwall fibrosis, is able to correctly reclassify the risk of the patients with respect to MAACE. In the derivation cohort (1000 patients), for example, the composite risk score yielded 81 correct net re-classifications in the NO MAACE group and 8 correct net re-classifications in the MAACE group yielding an overall categorical NRI of 17.5%. Importantly, the re-distribution of the event rate (per 100 person-years) according to the composite risk score

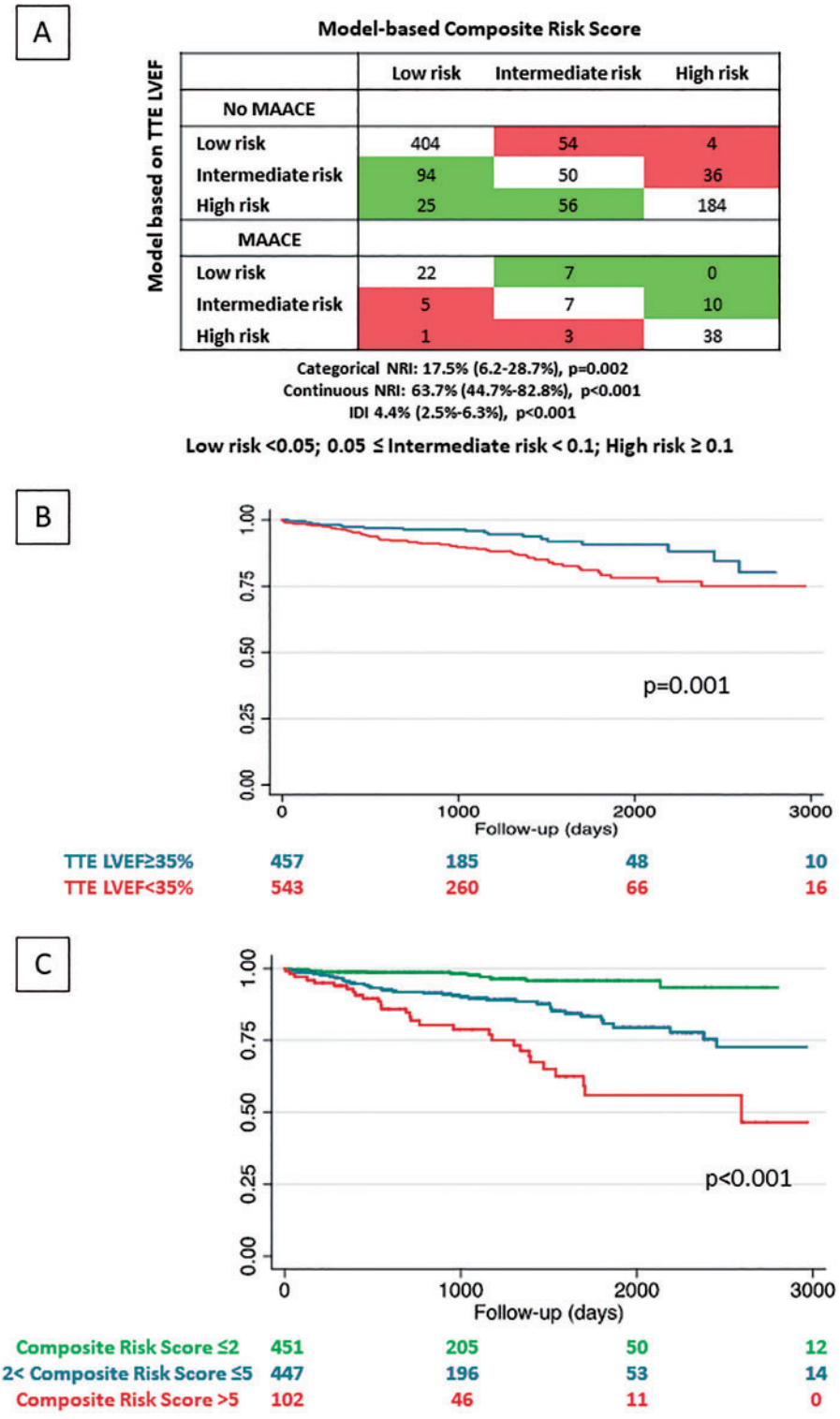

Figure 1 Derivate score for MAACE in the derivation cohort. (*A*) Table of reclassification of the composite risk score integrating clinical, functional, and tissue characteristics (assessed by CMR) compared to the model applying current guidelines criteria (TTE-LVEF ≤35% model and NYHA functional Classes II and III). Green and red colours indicate correct and incorrect reclassification, respectively. (*B*) Kaplan–Meier curves according to the TTE-LVEF model. (*C*) Kaplan–Meier curves according to composite risk score. CMR, cardiac magnetic resonance; IDI, integrated discrimination index; MAACE, major adverse arrhythmic cardiac events; NRI, net reclassification improvement; NYHA, New York Heart Association; TTE-LVEF, transthoracic echocardiography-left ventricle ejection fraction.

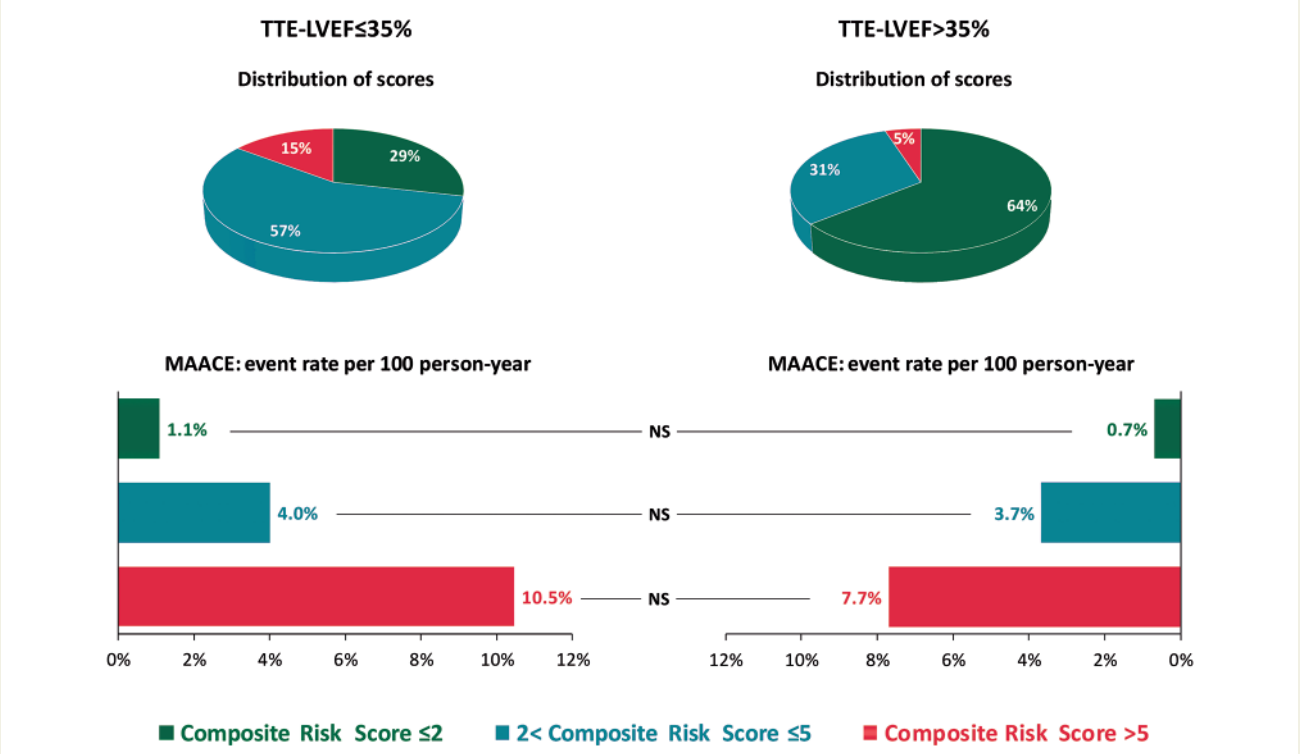

Figure 2 Event rate in the derivation cohort. Pie charts: percentages represent subgroups of patients in TTE-LVEF ≤35% (i.e. fulfilling current guidelines criteria for ICD implantation) and TTE-LVEF >35% population (i.e. not fulfilling current guidelines criteria for ICD implantation) in the derivation cohort according to the composite risk score tertiles. Composite risk score ≤2 (dark green), >2 to ≤5 (bluelight green), and >5 (red) represent low, intermediate, and high event risk, respectively. Bar graphs: event rate (MAACE) per 100 person-years according to the composite risk score in the TTE-LVEF ≤35% and TTE-LVEF >35% populations. Dark Green bars (composite risk score ≤2): 1.1% and 0.7% represent the event rates per 100 person-years in TTE-LVEF ≤35% and TTE-LVEF >35% groups, respectively. There is no difference in event rates between these two subgroups suggesting that the patients included in this category (low risk of events) do not benefit from ICD implantation and this irrespective of their LVEF. Light GreenBlue bars (risk score >2 to ≤5): 4.0% and 3.7% represent the event rates per 100 person-years in TTE-LVEF ≤35% and TTE-LVEF >35% populations, respectively. Red bars (composite risk score >5): 10.5% and 7.7% represent the event rates per 100 person-years in TTE-LVEF ≤35% and TTE-LVEF >35% populations, respectively. There is no difference in event rates between red groups suggesting that the patients included in this category (high risk of events) could potentially benefit from ICD implantation and this irrespective of their LVEF. ICD, implantable cardioverter-defibrillator; MAACE, major adverse arrhythmic cardiac events; TTE-LVEF, transthoracic echocardiography-left ventricle ejection fraction.

tertiles may lead to a better therapeutic choice regarding ICD implantation. For instance, in the group qualifying for ICD implantation according current guidelines (patients with TTE-LVEF ≤35%), a low composite risk score (≤2, green bar) identifies 29% of the NICM derivation cohort as being at low risk. Thus, the observed low MAACE rate in this subgroup of patients could exclude them from the need of an ICD implantation. On the other hand, 5% of patients with TTE-LVEF >35%, thus, not qualifying for ICD implantation, have a high composite risk score (>5, red bar) and an observed high MAACE rate, which could favour the ICD implantation in these patients.

From the current registry, interesting data emerge about the role of gender in risk estimation of arrhythmic events. In the presence of CMR-LVEDVi >120.5 mL/m^2 and >3 segments with midwall fibrosis on LGE, male gender maximally increases the composite risk score for MAACE and thus, substantially increases the predicted risk for MAACE. This is in line with a previous meta-analysis of fives studies that analysed 7229 patients showing that the benefit of ICD therapy on mortality was higher in men (HR 0.67, 95% CI: 0.58–0.78, *P*<0.001), but did not reach statistical significance in women.[17] Despite a clear and indisputable lack of data on mechanisms underlying sex differences, different gene expression and hormonal status could play a role. Indeed, some preclinical models identified sex-dependent transcriptome variability and different epigenetic regulation between sexes that could be associated with MAACE.[18]

Regarding the association between MAACE and LVEDVi, Phan *et al.*[19] found that eccentric LV hypertrophy was independently associated with increased risk of SCD by over two-fold in subjects with LV dysfunction. Similarly, an analysis among patients with LVEF ≤30% enrolled in the MADIT-CRT study found the magnitude of eccentric remodelling to be predictive of risk of recurrent ventricular arrhythmias.[20] A potential explanation could be that adverse myocardial interstitial remodelling could have a role in increasing arrhythmic risk in eccentric hypertrophy due to increased interstitial collagen.[21] Nevertheless, these observations would partly justify the association between increased LV volumes and arrhythmias observed in our

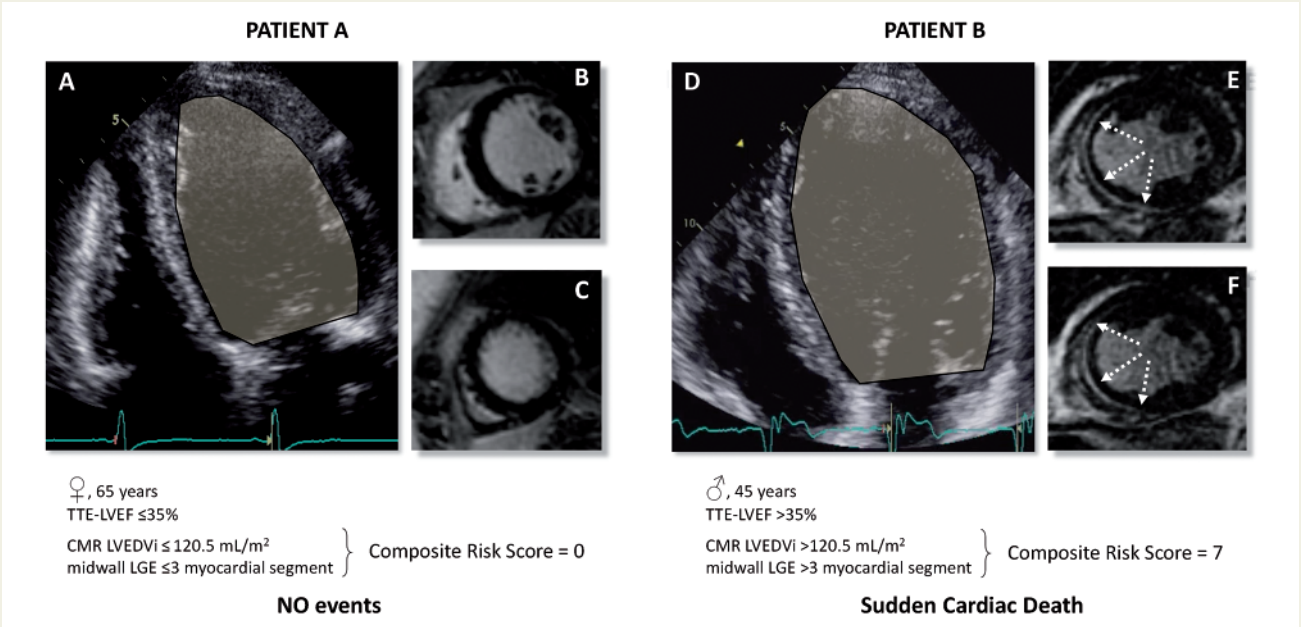

Figure 3 Clinical cases: (A and D): LV apical 4-chamber view TTE images. (B, C, E, and F): LV short-axis CMR-LGE images; the arrows show mid-wall fibrosis as hyperenhancement streaks. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEDi: left ventricle end-diastolic index; LV, left ventricularLVEF: left ventricle ejection fraction; TTE, transthoracic echocardiography.

registry since LVEDVi does not totally demonstrate eccentric LV hypertrophy.

Limitations

Firstly, the current results, unlike randomized controlled trial, are possibly affected by referring biases. However, the sites included in the registry represent referral centres, where the addition of CMR on top of TTE is part of the usual care. Moreover, the large registry structure allowed to assess the impact of CMR on risk stratification in a real-world routine situation even when investigating a lower risk population with fewer events. Due to the large patient number, a strong prognostic power is documented for LGE-CMR and this finding was confirmed in a large validation cohort, which should further increase the generalizability of the results. In this registry, a relatively low MAACE rate was observed. Different from most previous studies on this topic, which enrolled cohorts of NICM patients with low EF, this registry also included patients with LVEF up to 50% and without a history of ventricular arrhythmias, which was done by intention to investigate the prognostic yield of CMR in a lower risk population. In addition, prior studies often reported on 'mixed' cohorts of NICM patients, while the present registry adopted more strict exclusion criteria (i.e. excluding hypertrophic cardiomyopathy, ARVD), which may have led to a NICM population at lower risk of arrhythmic events.[22–24] The TTE-LVEF ≤ 35% model was used to identify the patients fulfilling current ICD implantation criteria. As patients without a history of ventricular arrhythmias were allowed to enter the study, a lower risk profile may be found in the population meeting the ICD implantation criteria. Nevertheless, it should be noted that current ICD implantation guidelines do not include a positive history of ventricular arrhythmias. Another point worth to be raised is that the dynamic changes of the myocardial substrate and the influence of others factors (e.g. chronic myocarditis, muscular dystrophies, and laminopathies) make a precise point in the timeline from diagnosis to fibrosis in LGE-CMR very difficult in clinical practice, this way influencing the practicability of the study registry. Moreover, this study did not take into account relative effects of CRT. At the time of analysis, the use of CRT was not widespread in several of the participating centres, and therefore, conclusion regarding this treatment modality could not be adequately deduced. Finally, we did not include biomarkers, such as brain natriuretic peptide or novel CMR techniques such as quantitative T1 mapping (due to the limited availability of T1 mapping in several study centres). It was the aim of the study to investigate the prognostic power of a CMR-based score that could be readily applied in general cardiology routine. Whether the presented score would provide additional prognostic information compared with these biomarkers or novel quantitative CMR parameters like T1 is of interest and further studies in this area are warranted.

Conclusions

In this large multicentre, multivendor setting, fibrosis assessment by LGE-CMR in NICM patients provides additional prognostic stratification for all-cause mortality and MACCE predictions as compared to SOC evaluation recommended by current guidelines. A composite risk score for MAACE including gender and CMR data is useful to stratify the event risk in NICM patients with a wide range of LV dysfunction and its performance was demonstrated in both, the derivation and validation cohort. The re-distribution of the event rate according to the composite risk score tertiles indicates the potential to alter the decision on ICD implantation in a substantial portion of

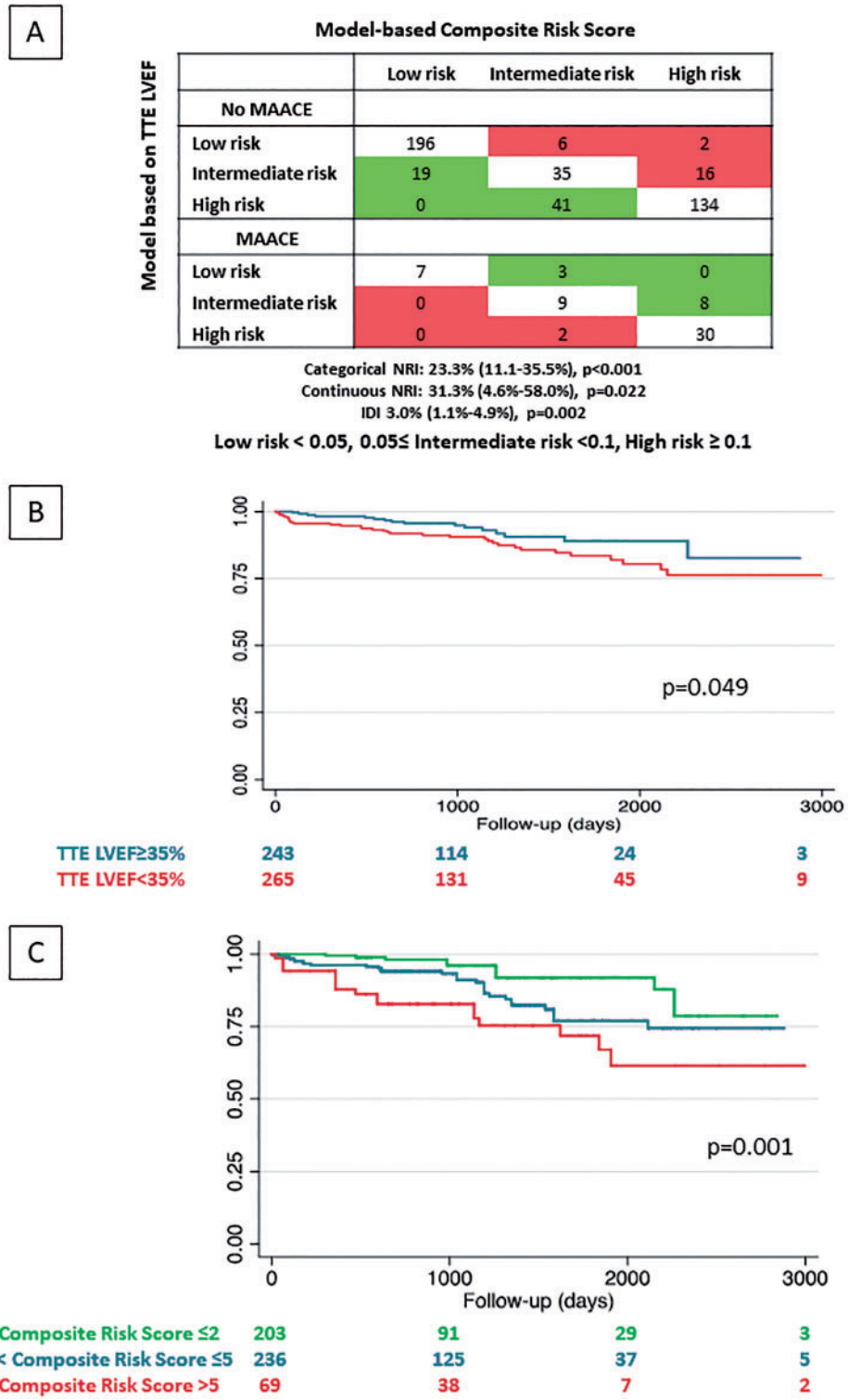

Figure 4 Derivate score for MAACE in the Validation Cohort. For explanation and abbreviations see *Figure 1* legend.

NICM patients. These results warrant further confirmation in prospective randomized controlled trials.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

All data are available.

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