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ORIGINAL RESEARCH

Cardiac Magnetic Resonance for Prophylactic Implantable-Cardioverter Defibrillator Therapy in Ischemic Cardiomyopathy

The DERIVATE–ICM International Registry

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ABSTRACT

BACKGROUND Implantable cardioverter-defibrillator (ICD) therapy is the most effective prophylactic strategy against sudden cardiac death (SCD) in patients with ischemic cardiomyopathy (ICM) and left ventricle ejection fraction (LVEF) ≤35% as detected by transthoracic echocardiograpgy (TTE). This approach has been recently questioned because of the low rate of ICD interventions in patients who received implantation and the not-negligible percentage of patients who experienced SCD despite not fulfilling criteria for implantation.

OBJECTIVES The DERIVATE (CarDiac MagnEtic Resonance for Primary Prevention Implantable CardioVerter DebrillAtor ThErapy)-ICM registry (NCT03352648) is an international, multicenter, and multivendor study to assess the net reclassification improvement (NRI) for the indication of ICD implantation by the use of cardiac magnetic resonance (CMR) as compared to TTE in patients with ICM.

METHODS A total of 861 patients with ICM (mean age 65 ± 11 years, 86% male) with chronic heart failure and TTE-LVEF <50% participated. Major adverse arrhythmic cardiac events (MAACE) were the primary endpoints.

RESULTS During a median follow-up of 1,054 days, MAACE occurred in 88 (10.2%). Left ventricular end-diastolic volume index (HR: 1.007 [95% CI: 1.000-1.011]; $P = 0.05$), CMR-LVEF (HR: 0.972 [95% CI: 0.945-0.999]; $P = 0.045$) and late gadolinium enhancement (LGE) mass (HR: 1.010 [95% CI: 1.002-1.018]; $P = 0.015$) were independent predictors of MAACE. A multiparametric CMR weighted predictive derived score identifies subjects at high risk for MAACE compared with TTE-LVEF cutoff of 35% with a NRI of 31.7% ($P = 0.007$).

CONCLUSIONS The DERIVATE-ICM registry is a large multicenter registry showing the additional value of CMR to stratify the risk for MAACE in a large cohort of patients with ICM compared with standard of care.
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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ICD = implantable cardioverter-defibrillator

ICM = ischemic cardiomyopathy

LGE = late gadolinium enhancement

LVEF = left ventricular ejection fraction

MAACE = major arrhythmic adverse cardiac events

NICM = nonischemic cardiomyopathy

NRI = net reclassification index

RV = right ventricle

RVEF = right ventricular ejection fraction

SCD = sudden cardiac death

TTE = transthoracic echocardiography

Sudden cardiac death (SCD) is the most common event in patients with ischemic cardiomyopathy (ICM) and nonischemic dilated cardiomyopathy (NICM), averaging 300,000 deaths in the United States annually.[1] Implantable cardioverter-defibrillator (ICD) therapy was demonstrated to be the most effective prophylactic strategy adopted for primary and secondary prevention of SCD in these patients.[2,3] Yearly, 130,000 patients undergo ICD placement in the United States, although only 5% of those undergoing primary prevention ICD placement receive appropriate device intervention, and up to one-fourth experience inappropriate shocks.[4] To date, the standard-of-care evaluation for primary prevention ICD therapy is based on left ventricular ejection fraction (LVEF) ≤35% and New York Heart Association (NYHA) class II or III for both NICM and ICM.[5-8] Although easily applicable in a routine work-up, this strategy holds 2 major limitations. First, only a relatively small proportion of patients receiving ICD for primary prevention of SCD events benefits from this treatment, while still incurring a substantial risk of short and long-term device-related complications. This holds true, particularly in patients with NICM in whom ICD therapy has been recently questioned by the DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) trial results.[9] Second, SCD events may also occur in patients with normal to moderately depressed LVEF, which is particularly relevant, as it constitutes the most prevalent population of patients exposed to an increased risk of SCD.[10] 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 risk of SCD. Recently, cardiac magnetic resonance (CMR) has emerged as the gold-standard technique for assessment of left ventricular (LV) volume and function with the added benefit of providing tissue characterization in ICM.[11] Indeed, it is well known that fibrous tissue in the myocardium can induce re-entry circuits that are the anatomic substrates of life-threatening ventricular arrhythmias.[12] There is rapidly growing evidence from large single-center studies and meta-analyses showing the strong prognostic value of CMR-defined myocardial fibrosis in predicting outcomes in ICM.[13-16] However, to the best of our knowledge, there is a lack of evidence

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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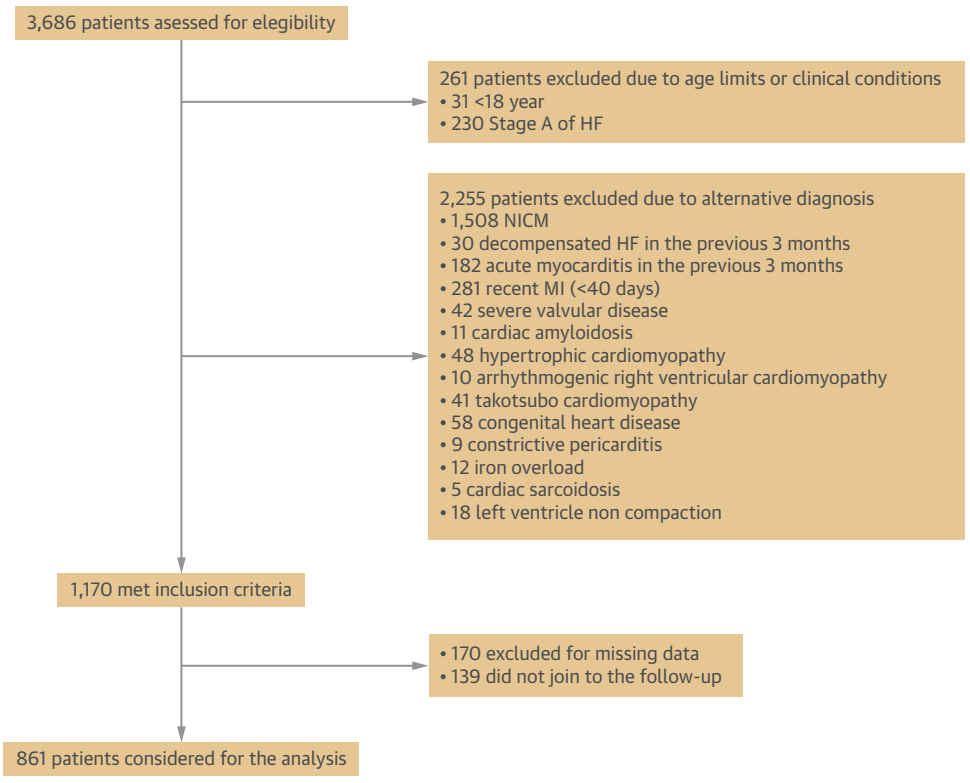
FIGURE 1 **Study Workflow of Study Population**



HF = heart failure; MI = myocardial infarction; NICM = nonischemic cardiomyopathy.

regarding the additional prognostic value of CMR compared with standard of care in ICM to identify low-risk patients for SCD events in the setting of patients with LVEF ≤35% and, on the other side, to identify high-risk patients for SCD events in the setting of LVEF >35%. Accordingly, the DERIVATE (CarDiac MagnEtic Resonance for Primary Prevention Implantable CardioVerter DebrillAtor ThErapy NCT03352648) registry (NCT03352648) has the aim to evaluate the net reclassification improvement (NRI) for the indication of ICD implantation by the use of CMR compared with standard of care based on transthoracic echocardiography (TTE) LVEF evaluation in consecutive patients with ICM enrolled in several centers across Europe and the United States and using diverse CMR machine vendors.

METHODS

STUDY DESIGN AND TARGET POPULATION. DERIVATE is an international, multicenter, prospective, observational registry including consecutive patients with heart failure caused by ICM from 21 sites across Europe and the United States.[17] Inclusion criteria were: 1) age 18 years or older; 2) chronic heart failure (>3 months from the last decompensated heart failure) with reduced LVEF <50% as measured at initial TTE; and 3) ischemic etiology of LV dysfunction, defined as the presence of 1 of the following criteria: a) previous percutaneous coronary intervention or coronary artery bypass grafting; b) angiographic evidence of coronary artery disease with ≥70% stenosis in ≥1 epicardial vessel or a significant lesion of the left main coronary artery or proximal left anterior descending coronary artery; c) evidence of ischemic scar at late gadolinium enhancement (LGE) imaging in a specific coronary perfusion territory involving at least 2 contiguous myocardial segments according to American Heart Association LV segmentation.[18] Exclusion criteria were severe valvular diseases, primary or secondary cardiomyopathies other than ICM, acute coronary syndromes within 40 days of admission, and congenital heart diseases. According to the inclusion

and exclusion criteria, 861 patients with ICM were enrolled in this study (Figure 1). The study conforms to the principles of the Declaration of Helsinki. Dr Gianluca Pontone and Dr Andrea I. Guaricci had access to all data and final responsibility for the submission of the manuscript. The authors from each participating center guarantee the integrity of data from their institution and had approval from a local ethics committee-internal review board. All investigators have agreed to the manuscript as written.

CLINICAL PATIENT ASSESSMENT AND DATA COLLECTION. The following clinical information was collected: demographic characteristics; medical history, with particular regard to signs and symptoms of heart failure; cardiovascular risk factors; and medical therapy. Standardized definitions for cardiovascular risk factors were used as follows: 1) family history of coronary artery disease in first-degree relatives; 2) current or previous smoking; 3) hyperlipidemia (low-density lipoprotein cholesterol >40 mg/dL); 4) diabetes mellitus (fasting glucose level >110 mg/dL or need for insulin or oral hypoglycemic drugs); and 5) hypertension (blood pressure >140/90 mm Hg or use of antihypertensive agents). All data were recorded in a standardized case report form.

TTE PROTOCOL PERFORMANCE AND ANALYSIS. TTE was performed with patients in left lateral decubitus in the parasternal (long- and short-axis) and apical (4-, 2-, and 3-chamber) views. For each patient the following measurements were acquired and collected: left ventricle end-diastolic and end-systolic volumes, LVEF calculated from the Simpson method, diastolic function, tricuspid annular plane systolic excursion, and pulmonary artery systolic pressure.[19]

CMR PROTOCOL PERFORMANCE AND ANALYSIS. After the acquisition of localizers, breath-hold cine steady-state free precession (SSFP) sequences were used for functional analysis with the following minimum requirements: in-plane spatial resolution of <2.0 mm × <2.0 mm, slice thickness ≤8 mm, gap 0-2 mm, and temporal resolution 35-50 ms. Cine-SSFP were acquired in long-axis views, and a base-to-apex stack of short axis images was used to quantify LV volumes, mass, and LVEF. Ten-to-fifteen minutes after an intravenous bolus of 0.1-0.2 mmol/kg gadolinium-based contrast agent according to the local acquisition protocol, late gadolinium enhancement (LGE) was acquired according to each center's protocol, using segmented phase-sensitive gradient-echo inversion-recovery sequences. LGE imaging was carried out in the same orientation as the cine-SSFP images, and the inversion time was adjusted on magnitude images to null normal myocardium.[20] The CMR data set was transferred to the core laboratory and centrally evaluated by 1 certified expert reader with more than 5 years of experience. Analysis of CMR was blinded to the patients' history, demographic data, echocardiographic data, and outcome as previously described.[21,22] The following parameters were collected employing a segmentation process using CVI 4.2 (5.11.2) software (Circle Software) by using automatic segmentation followed by manual correction: 1) standard left ventricle (LV) and right ventricular (RV) volumetric parameters: LV end-diastolic volume, LV end-systolic volume, LV stroke volume, LVEF, LV mass, RV end-diastolic volume, RV end-systolic volume, RV stroke volume, and RVEF; and 2) for LGE, the analysis was performed defining hyperenhanced myocardium as any myocardial segment with a signal intensity increase >5 SD above the mean signal intensity of remote myocardium. According to the definition, the number of myocardial segments with LGE and absolute LGE mass were calculated as previously described.[16,22] For each patient, the number of myocardial segments involved by LGE was counted according to the American Heart Association myocardial segments classification.[18]

FOLLOW-UP AND CLINICAL OUTCOME. Patient follow-up was performed at each local institution, by dedicated personnel. The combined endpoint consisted of major adverse arrhythmic cardiac events (MAACE), defined as the combination of SCD, aborted SCD event, and sustained ventricular tachycardia. In patients with devices and history of ICD shock, electrograms were reviewed to determine arrhythmias and to decide whether delivered shocks were appropriate or inappropriate.

Event ascertainment was determined by direct interview during office visits or telephone contact with the patient or a close family member, patient's cardiologist, or general physician in case of death. Moreover, referral physician or cardiologist and review of the patient's medical records represented further means of information (eg, ICD interrogation and 24-hour electrocardiogram [ECG]-Holter monitoring). A monitoring plan was applied for the processing and quality control of all data recorded in the case report forms.

STATISTICAL METHOD. Statistical analysis was performed using SPSS 25 (SPSS Inc), R version 3.3 and Stata version 14 (StataCorp LLC). Continuous variables were expressed as mean ± SD or median (25th-75th percentile) as appropriate and discrete variables as absolute numbers and percentages. Student's *t*-test or Mann-Whitney tests were used as appropriate to compare continuous variables between

patients with and without MAACE. Comparisons between groups of discrete variables were performed by chi-square or Fisher exact test if the expected cell count was <5. Univariate Cox proportional hazard models were used to identify predictors for study endpoints. All TTE and CMR variables with $P < 0.05$ at univariate analysis were considered for inclusion in multivariate Cox proportional hazard models after excluding collinear predictors based on the variance inflation factor. According to the Cox proportional hazard models TTE and CMR weighted scores were calculated. The discriminatory and risk reclassification ability of the developed CMR multivariable model was compared with the standard of care model including the TTE-LVEF cutoff of 35% and the developed TTE multivariable model using the NRI index, respectively. Finally, the Kaplan-Meier method and survival curves estimated event-free survival related to the study endpoints. All results were considered significant with values of $P < 0.05$.

RESULTS

The study cohort consisted of 861 subjects (mean age: 65 ± 11 years; male: 739 [86%]). Patient baseline characteristics are listed in Table 1. TTE and CMR tests were performed successfully in all patients with a median interval of 3 days (25th-75th percentile: 2-5 days), and TTE and CMR baseline characteristics are listed in Table 2. The median follow-up time was 1,054 days (25th-75th percentile: 562-1,583 days). MAACE occurred in 88 (10.2%) patients, respectively. Cardiovascular death, SCD event, aborted SCD event, and sustained ventricular tachycardia occurred in 77 (9%), 10 (1%), 16 (6%), and 63 (7%), respectively. The sum of events exceeded the overall number of MAACE because several events could occur in the same patients but only the first one was counted for MAACE.

Patients who experienced MAACE showed a higher use of angiotensin-converting enzyme (ACE) inhibitors-AT1 blockade and antiarrhythmic therapy and a lower use of antithrombotic agents compared with patients who did not experience MAACE (Table 1). Moreover, higher LV end-diastolic volume index ($P < 0.01$), LV end-systolic volume index ($P < 0.01$), and lower LVEF ($P < 0.01$) was observed in patients with MAACE compared with patients without MAACE, regardless of the imaging modality used (Table 2). Finally, patients who experienced MAACE showed a higher number of myocardial segments with LGE ($P = 0.026$) and higher LGE mass ($P < 0.001$) compared with patients without MAACE, respectively (Table 2).

TABLE 1 Baseline Characteristics

	All Patients (n = 861)	No MAACE (n = 773)	MAACE (n = 88)	*P* Value
Demographic characteristics				
Age, y	65 ± 11	65 ± 11	67 ± 10	0.189
Male	739 (86)	663 (86)	76 (86)	0.880
BSA, m^2	1.91 ± 0.21	1.91 ± 0.20	1.93 ± 0.22	0.317
Cardiovascular risk factor				
Family history	279 (32)	250 (32)	29 (34)	0.907
Smoking history	405 (47)	369 (48)	36 (40)	0.224
Hypertension	562 (65)	500 (65)	62 (71)	0.281
Hyperlipemia	531 (62)	482 (62)	49 (56)	0.223
Diabetes	275 (32)	249 (32)	26 (30)	0.611
NYHA functional class				0.190
I-II	637 (74)	577 (75)	60 (68)	
III-IV	224 (26)	196 (25)	28 (30)	
Medical therapy				
Beta-blockade	761 (88)	683 (88)	78 (89)	0.938
Ivabradine	72 (8)	67 (9)	5 (6)	0.338
ACE inhibitors/AT1 blockade	714 (83)	634 (82)	80 (91)	**0.036**
Diuretic agents	625 (73)	558 (72)	67 (76)	0.431
Calcium blockade	74 (9)	68 (9)	6 (7)	0.530
Antithrombotic agents	728 (85)	661 (86)	67 (76)	**0.021**
Anticoagulant therapy	227 (26)	197 (26)	30 (34)	0.083
Nitrates	135 (16)	117 (15)	18 (21)	0.194
Statins	666 (77)	601 (78)	65 (74)	0.409
Amiodarone/other antiarrhythmics	195 (23)	165 (21)	30 (34)	**0.007**

Values are mean ± SD or n (%). **Bold** indicates *P*-value <0.05.

ACE = angiotensin-converting enzyme; BSA = body surface area; MAACE = major adverse arrhythmic cardiac events; NYHA = New York Heart Association.

Univariable analysis for MAACE prediction is shown in Table 3. LV end-diastolic volume index, LV end-systolic volume index, and LVEF were all predictors of MAACE ($P < 0.01$) for both TTE and CMR imaging modalities. In addition, both the number of myocardial segments with LGE ($P = 0.05$) and LGE mass ($P = 0.001$) were predictors of MAACE, as well. Multivariable analysis for MAACE prediction is shown in Table 4. For the TTE model, both LVEDVI ($P = 0.045$) and LVEF ($P = 0.023$) were associated with MAACE. Similar to the TTE model, both LVEDVI ($P = 0.05$) and LVEF ($P = 0.045$) as detected by CMR were independent predictors of MAACE. In addition, LGE mass ($P = 0.015$) was associated with MAACE. Based on the multivariable analysis, TTE and CMR weighted risk scores were developed according to the following equation: 0.007 × EDV/body surface area (BSA) (mL/m^2) − 0.032 × LVEF (%) and 0.005 × EDV/BSA (mL/m^2) − 0.029 × LVEF (%) + 0.010 × LGE scar mass (g) for TTE and CMR, respectively.

Based on these results, the study population was divided for both TTE and CMR scores into 4 quartiles by considering low-, intermediate- and high-risk patients who fell into the first (Q1), second to third (Q2-Q3), and fourth quartiles (Q4), respectively.

TABLE 2 TTE and CMR Baseline Characteristics

	All Patients (N = 861)	No MAACE (n = 773)	MAACE (n = 88)	*P* Value
TTE				
LVEDVI, mL/m^2	91 ± 32	90 ± 32	101 ± 33	**0.006**
LVESVI, mL/m^2	61 ± 27	60 ± 26	71 ± 28	**0.001**
LVEF, %	34 ± 10	34 ± 10	31 ± 10	**0.001**
LVEF<35%	500/861 (58)	438/773 (57)	62/88 (70)	**0.012**
CMR				
LVEDVI, mL/m^2	124 ± 43	122 ± 41	143 ± 50	**<0.001**
LVESVI, mL/m^2	91 ± 39	89 ±37	111 ± 46	**<0.001**
LVEF, %	28 ± 10	29 ± 10	24 ± 10	**<0.001**
LVEF<21%	241/861 (28)	199/773 (26)	42/88 (48)	**<0.001**
LVSV, mL	33 ± 12	33 ± 12	32 ± 12	0.370
LV mass/BSA, g/m^2	75 ± 25	74 ± 25	81 ± 25	**0.011**
RVEDVI, mL/m^2	69 ± 31	69 ± 31	69 ± 27	0.947
RVESVI, mL/m^2	40 ± 25	40 ± 25	41 ± 25	0.683
RVEF, %	44 ± 16	44 ± 16	43 ± 16	0.518
RVSV, mL	52 ± 22	52 ± 22	52 ± 21	0.943
LGE, n° of segments	7.2 ± 4.0	7.1 ± 4.0	8.2 ± 3.4	**0.026**
LGE mass, gr	27.4 ± 20.8	26.5 ± 19.9	35.0 ± 26.0	**0.001**

Values are mean ± SD or n (%). **Bold** indicates *P*-value <0.05.

CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LV = left ventricle; LVEDVI = left ventricle end diastolic volume indexed; LVEF = left ventricle ejection fraction; LVESVI = left ventricle end systolic volume indexed; PAP = pulmonary artery pressure; RVEDVI = right ventricle end diastolic volume indexed; RVEF = right ventricle ejection fraction; RVESVI = right ventricle end systolic volume indexed; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography; other abbreviation as in Table 1.

Figures 2 and 3 show the comparison between the CMR risk score vs the model based on a TTE-LVEF cutoff of 35% and CMR risk score vs TTE risk score with a NRI of 31.7% and 29.6%, respectively.

The redistribution of the event rate (per 100 person-years) according to the CMR predictive model is represented in Figure 4, with evidence of how the CMR predictive model can estimate the prevalence of MAACE independently of the value of TTE-LVEF. Figure 5 shows 2 case examples.

DISCUSSION

The main results of our study are as follows: TTE and CMR parameters were the only independent predictors of MAACE over clinical data in patients with ICM; LGE quantification was an independent predictor of MAACE beyond LVEF; a multiparametric CMR weighted predictive derived score including LVEDV, CMR-LVEF; and the amount of LGE identifies subjects at high risk for MAACE compared with TTE-LVEF cutoff of 35% with a NRI of 31.7% ($P = 0.007$).

Initially, following consistent evidence, LVEF has been considered the strongest independent predictor of SCD events with values below the cutoff of 30% to 35%, indicating a high-risk condition.[2,3,23-25] Theoretically, this implies that ICD placement in patients with low LVEF would lead to the prevention of both SCD events and all-cause mortality and, on the opposite, that patients with moderate-to-high LVEF would not need ICD implantation because they are at very low risk. However, more recent analysis showed that this simple and linear equation is not representative of the real world. Indeed, LVEF represents a global estimation of LV systolic function but is poorly related to the myocardial substrate underlying malignant ventricular tachyarrhythmias. To date, the standard of care evaluation for primary prevention ICD therapy is based on LVEF ≤35% and NYHA functional class II or III class for both NICM and ICM.[5-7] Although widely applied in a routine work-up, this strategy holds 2 major limitations. First, only a relatively small proportion of patients receiving ICD for primary prevention of SCD events benefit from this treatment, while still incurring a substantial risk of short- and long-term device-related complications. In this regard, a post hoc analysis of the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) showed that only 30% of ICD recipients has benefit from appropriate therapy within 3 years of follow-up after implantation, and a European registry demonstrated that among almost 5,000 patients who underwent primary-prevention ICD therapy, two-thirds died without any beneficial intervention from the device.[26] Moreover, up to one-fourth of patients with ICD experience inappropriate shocks, which significantly affects quality of life and is a cause of morbidity and mortality.[4] In addition, most patients will need at least 1 ICD replacement over their lifetimes, with 40% requiring 2 replacements, with consequent additional complications and costs.[27] Second, SCD events may also occur in patients with normal to moderately depressed LVEF, which is particularly relevant, as it represents the most prevalent population of patients exposed to increased risks of SCD events.[10] 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 risk of SCD events.

CMR imaging is a standardized technique that represents the reference standard for LV volumes and LVEF measurement due to its high spatial resolution and independence from geometrical assumptions.[28,29] In particular, several studies

TABLE 3 Univariable Analysis of MAACE

	Univariate Analysis	
	HR (95% CI)	*P* Value
Demographic characteristics		
Age, y	1.017 (0.996-1.037)	0.106
Male	1.115 (0.606-2.051)	0.726
BSA, m^2	1.710 (0.596-4.907)	0.318
Cardiovascular risk factor		
Family history	1.152 (0.738-1.799)	0.534
Smoking history	0.745 (0.486-1.142)	0.177
Hypertension	1.374 (0.869-2.174)	0.174
Hyperlipemia	0.715 (0.469-1.09)	0.118
Diabetes	0.951 (0.601-1.504)	0.831
NYHA functional class III-IV	1.49 (0.950-2.338)	0.083
TTE		
LVEDVI, mL/m^2	1.009 (1.003-1.015)	**0.002**
LVESVI, mL/m^2	1.013 (1.006-1.020)	**<0.001**
LVEF, %	0.964 (0.942-0.986)	**0.002**
LVEF <35%	1.930 (1.204-3.093)	**0.006**
CMR		
LVEDVI, mL/m^2	1.009 (1.005-1.014)	**<0.001**
LVESVI, mL/m^2	1.011 (1.007-1.016)	**<0.001**
LVEF, %	0.954 (0.931-0.977)	**<0.001**
LVSV, mL	0.990 (0.972-1.009)	0.309
LV mass/BSA, g/m^2	1.009 (1.001-1.016)	**0.024**
RVEDVI, mL/m^2	1.001 (0.994-1.008)	0.723
RVESVI, mL/m^2	1.003 (0.995-1.011)	0.433
RVEF, %	0.994 (0.981-1.007)	0.390
RVSV, mL	1.000 (0.990-1.010)	0.996
LGE, n° of segments	1.057 (1.000-1.117)	**0.050**
LGE mass, g	1.014 (1.006-1.022)	**0.001**

Bold indicates *P*-value <0.05.
Abbreviations as in Table 2.

demonstrated an overestimation of LVEF assessment by TTE compared with CMR, mainly when an automatic myocardial segmentation is used.[16,30] A strength of CMR consists in the possibility to evaluate the tissue characterization of the myocardium, thanks to its ability to identify edema, interstitial fibrosis, and irreversible myocardial scar by LGE imaging. It is well known that the fibrous tissue may result from the healing process after myocardial infarction or inflammatory processes and can induce re-entry phenomena.[12,13] In keeping with this cause-and-effect mechanism, the evidence of LGE through the use of CMR could correlate with patient mortality and, in particular, with arrhythmic major cardiac events, opening a new scenario in the evaluation of patients for prophylactic ICD therapy. In particular, Pontone et al[16] have concluded a study on 409 consecutive patients with ICM and dilated cardiomyopathy with chronic heart failure referred for evaluation of prophylactic ICD placement. The study demonstrated that the addition of the presence of LGE to the model including clinical data, TTE-LVEF, and CMR-LVEF provided a significant improvement in the outcome prediction. The current analysis reinforces the strength of previous reports regarding the importance of employing a multiparametric imaging approach able to provide information on tissue characterization, together with precise functional assessment. Notwithstanding, the dichotomic presence or absence of LGE misses the possibility of estimating the risk prediction according to quantitative data and topographic and structural features of fibrosis itself. Moreover, the limited number of patients and the methods of the study did not allow us to make prognostic considerations related to the pathogenetic nature of the cardiomyopathy.

TABLE 4 Multivariate TTE and CMR Analysis of MAACE

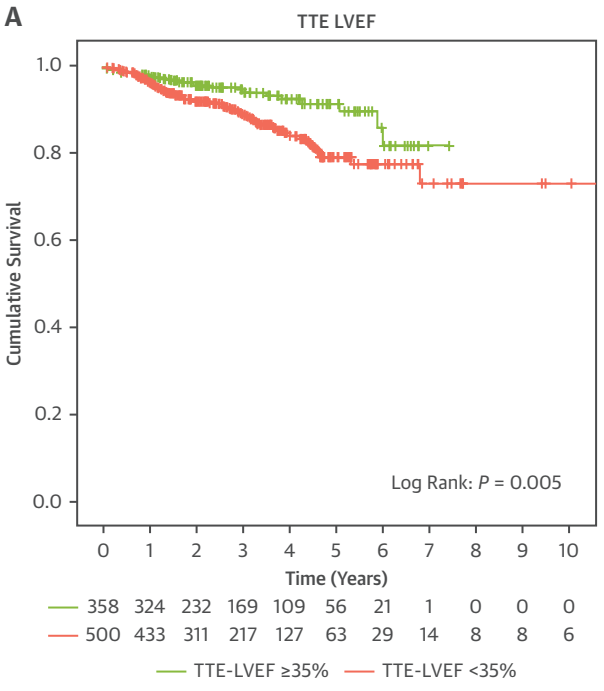
	Multivariate Analysis	
	HR (95% CI)	*P* Value
TTE model		
LVEDVI, mL/m^2	1.007 (1.000-1.013)	**0.045**
LVEF, %	0.968 (0.942-0.996)	**0.023**
CMR model		
LVEDVI, mL/m^2	1.005 (1.000-1.011)	**0.050**
LVEF, %	0.972 (0.945-0.999)	**0.045**
LGE mass, g	1.010 (1.002-1.018)	**0.015**

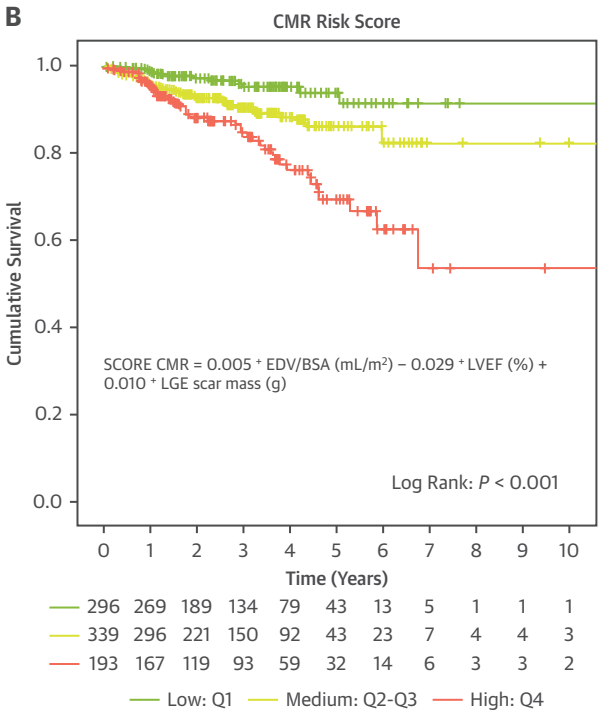
Bold indicates *P*-value <0.05.
Abbreviations as in Table 2.

Of note, RV parameters did not predict outcome as previously reported.[31] However, some reasons could explain this apparent discrepancy. First, only ischemic ICM was included in our registry compared with previous reports including idiopathic cardiomyopathy. Indeed, it is well known from the published reports that RV dysfunction is more associated with heart failure death rather than with arrhythmic events. Second, in the majority of studies, all-cause mortality was used as endpoint, whereas, in our paper, only adverse arrhythmic cardiac events were considered. Finally, the mean RVEF of our study population was 44%, suggesting a population with mild reduction of RV function.

In contrast to the previous studies, the current international, multicenter, observational study included a population of patients with ICM and a broad range of LV dysfunction (LVEF <50%) and highlights the value of a multiparametric approach in decision making about ICD therapy.

FIGURE 2 Comparison Between CMR Risk Score vs Model Based on a TTE-LVEF Cutoff of 35%





C

Model Based on Composite CMR Risk Score

Model Based on TTE LVEF	Low Risk	High Risk	% Reclassified
No MAACE			
Low Risk	271	22	8
High Risk	245	154	61
MAACE			
Low Risk	18	4	18
High Risk	24	33	42

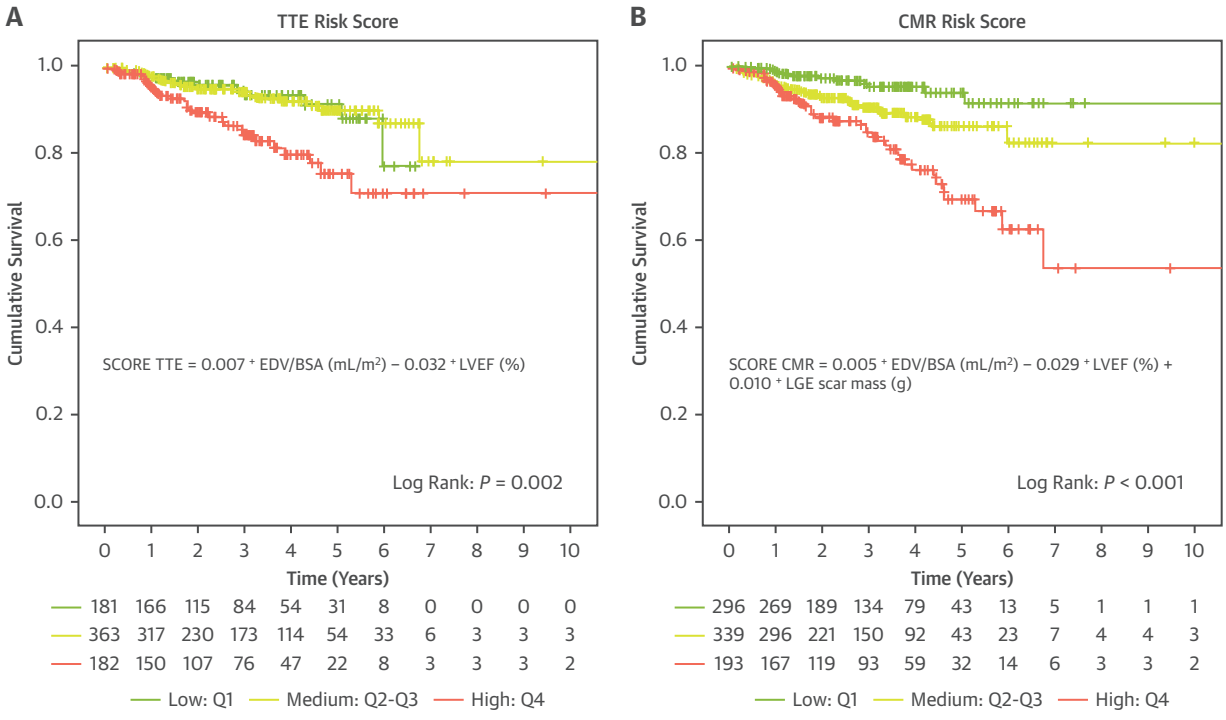
Continuous NRI: 31.7% (8.6%-54.8%), *P* = 0.007
IDI 2.1% (1.0%-3.3%), *P* < 0.001

Low risk <8%; High risk ≥8%

(A) Kaplan-Meier curves according to the guidelines-based TTE-LVEF model. **(B)** Kaplan-Meier curves according to the CMR weighted score as derived from multivariate analysis. **(C)** Table of reclassification of the CMR vs TTE predictive model. CMR = cardiac magnetic resonance; IDI = integrated discrimination index; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end diastolic volume indexed; NRI = net reclassification index; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; TTE = transthoracic echocardiography.

Further data will be generated by the PROFID (Implementation of Personalised Risk Prediction and Prevention of Sudden Cardiac Death After Myocardial Infarction) project[32] funded by the European Union in the setting of Horizon 2020 program. This project consists of 2 steps: 1) analysis of existing evidence from a large variety of different data sources, including national registries of postinfarction patients, registries of primary prevention ICD placement, electronic health records, and claims databases

FIGURE 3 **Comparison Between CMR Risk Score vs TTE Risk Score**



C

Model Based on CMR Risk Score

Model Based on TTE Risk Score	Low Risk	High Risk	% Reclassified
No MAACE			
Low Risk	358	60	14
High Risk	83	90	48
MAACE			
Low Risk	25	6	19
High Risk	10	22	31

Continuous NRI: 29.6% (3.8%-55.3%), *P* = 0.025
IDI 1.7% (0.4%-3.0%), *P* = 0.011

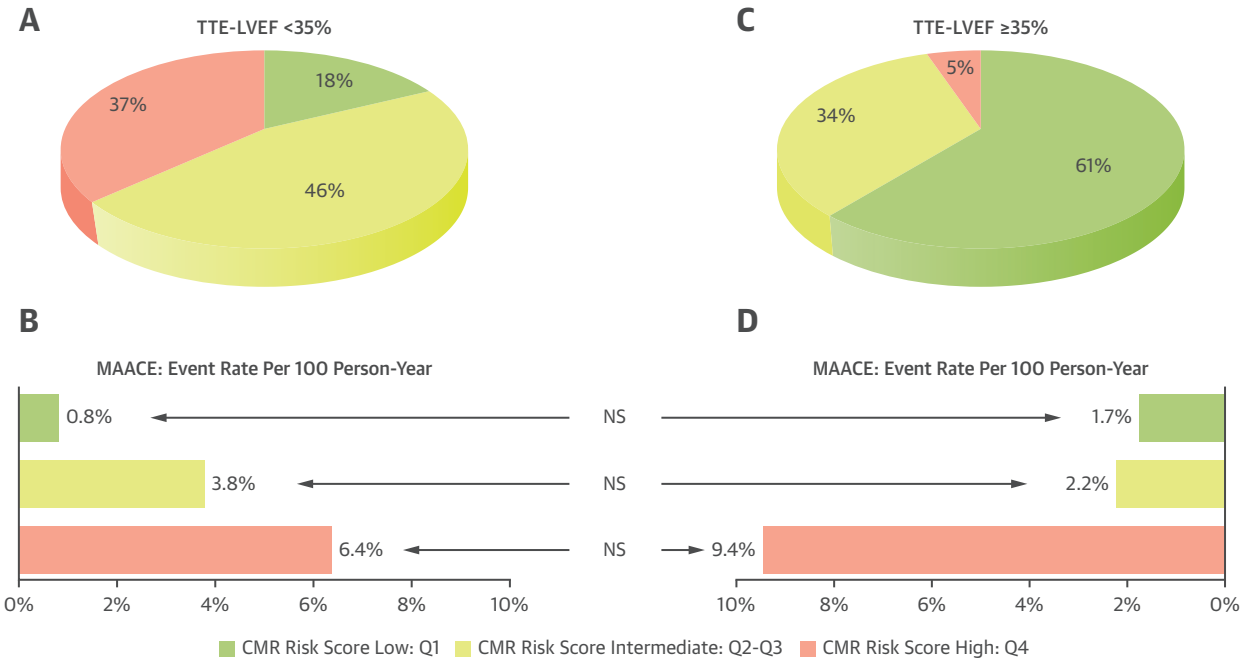
Low risk <8%; High risk ≥8%

(A) Kaplan-Meier curves according to the TTE weighted score as derived from multivariate analysis. **(B)** Kaplan-Meier curves according to the CMR weighted score as derived from multivariate analysis. **(C)** Table of reclassification of the CMR vs TTE predictive model. Abbreviations as in Figure 2.

by a combination of traditional statistical methods and machine-learning techniques to develop an individual risk predictive model for SCD events; and 2) this model will be applied to large randomized clinical trials in patients with lower than and higher than 35% LVEF.

STUDY LIMITATIONS. This study is based on a prospective registry; therefore, unlike randomized control trials (RCTs), the current study is subject to referring biases (which are not corrected by randomization), and, consequently, it cannot, for example, explore disease pathomechanisms, and it cannot

FIGURE 4 Event Rate Redistribution According to the CMR Risk Score



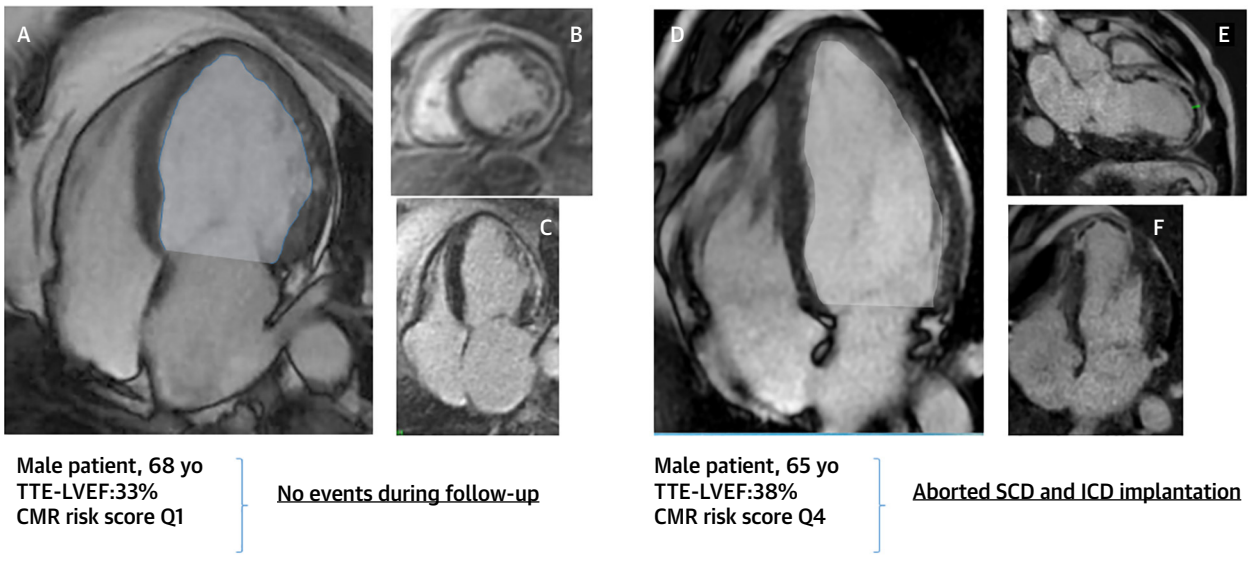
(A) Distribution of CMR predictive score in patients with TTE-LVEF ≤35%. **(B)** MAACE rate per 100 person-years according to the CMR predictive model in patients with TTE-LVEF ≤35%. **(C)** Distribution of CMR predictive score in patients with TTE-LVEF >35%. **(D)** MAACE rate per 100 person-years according to the CMR predictive model in patients with TTE-LVEF >35%. MAACE = major arrhythmic adverse cardiac events; NS = not significant; other abbreviations as in Figure 2.

compare with a control group. However, the large registry structure allows for assessing the impact of CMR on risk stratification in a real-world routine situation involving multiple centers and multiple CMR protocols and magnetic resonance imaging machine vendors. Despite this variability, a strong prognostic power is documented for LGE-CMR in our large study population, which should further increase the generalizability of the result.[33] In this context, the judgment of authoritative published reports—stating that there is no significant difference between the estimates provided by RCTs vs well-conducted observational studies—is important to consider. Accordingly, the adoption of CMR-derived information by international recommendations for ICD placement in patients with ICM should not be avoided despite the lack of RCT results. Second, physicians referred the enrolled patients for potential ICD placement, and this might have introduced a selection bias. In this regard, given both TTE and CMR were done clinically on all patients, and their results were not blinded, the effects of association with outcomes likely is a mixture of the diagnostic values of both tests, and their impact cannot be easily separated, as they are not independent strategies. However, this approach reflects the real-word experience in which the interaction of different imaging modalities is the standard in the clinical decision-making process.

Third, our reference model based on LVEF cutoff as detected by TTE could be considered too simplistic. However, this kind of reference is still considered a unique criterion for primary prevention ICD therapy. Therefore, we have decided to calculate the additional value of a CMR-based model on top of reference according to actual guidelines. However, a head-to-head comparison between both TTE and CMR weighted derived score was also performed to overcome this potential bias, confirming a CMR additional value.

Fourth, in this wide registry, a relatively low rate of MAACE was observed. By purpose, the registry also included patients with LVEF up to 50%: ie, also patients with LVEF higher than 35% to test whether a novel risk prediction model can identify high-risk patients in the population with LVEF ≥35% in the

FIGURE 5 Clinical Cases



(A to C) Patient with TTE-LVEF of 33% (ie, fulfilling current guidelines criteria for ICD implantation) showing a Q1 CMR risk score according to LVEDVI **(A)** and LGE extent inversion recovery CMR images **(B to C)**. According to the CMR predictive model the patient does not satisfy any CMR criteria suggestive of high risk for SCD event and indeed no events were recorded during the follow-up. **(D to F)** Patient with TTE-LVEF of 38% (ie, not fulfilling current guidelines criteria for ICD placement), showing a Q4 CMR risk score according to LVEDVI **(D)** and LGE extent **(E to F)**. According to the CMR predictive model, the patient satisfies criteria suggestive of high risk for SCD event, and, indeed, aborted SCD event after ICD placement was recorded during the follow-up. Abbreviations as in Figure 2.

population currently not fulfilling the guideline-based criteria for ICD placement. Along this line, also patients without history of ventricular arrhythmias were enrolled, which is likely to affect the rate of arrhythmic outcomes.

Fifth, in our predictive model, the LGE quantification plays a pivotal role. However, the detection of absolute amount of LGE is strongly dependent on many factors such as the type of contrast agent, the absolute injected dose, and the administration regimen. Unfortunately, all this information were not collected in detail in this registry, and therefore the impact of contrast agent injection protocol on our model cannot be evaluated

Finally, no validation cohort was included in this registry. Therefore, further studies are required to confirm our findings in an independent cohort of patients with similar baseline characteristics.

CONCLUSIONS

In this large multicenter multivendor setting, we showed that a CMR risk score identifies over the TTE parameters, a subset of patients with TTE-LVEF <35% at low risk of SCD events, and, on the other side, it identifies a subset of patients who are at high risk of MAACE despite TTE-LVEF ≥35%. The incremental value of this score is mainly related to the integration of LGE quantification in a model including LV volume and function that is a unique prerogative of CMR (Central Illustration). Further randomized trials to test a CMR-guided strategy for ICD implantation vs standard of care are now needed.

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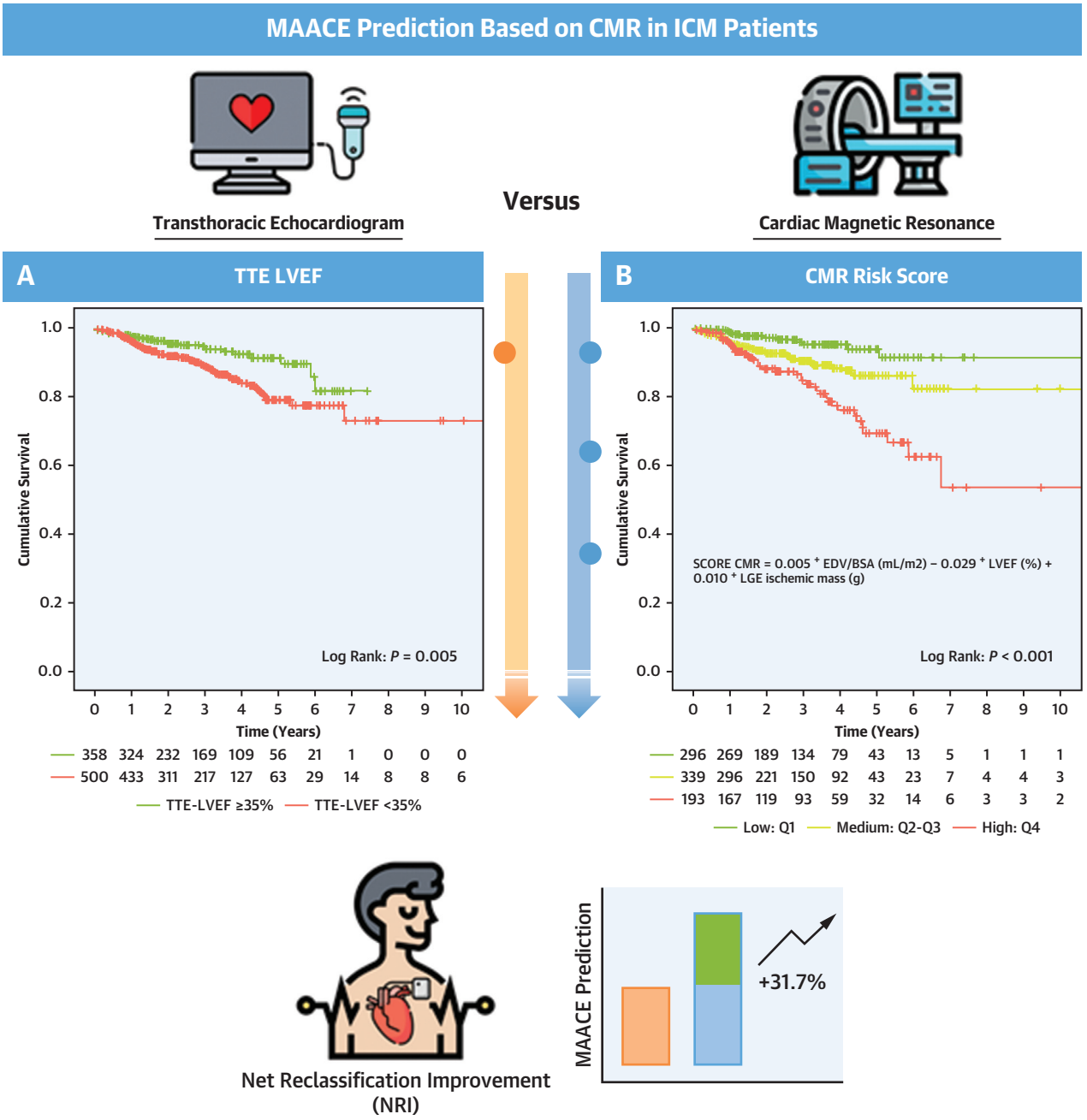
CENTRAL ILLUSTRATION **MAACE Prediction Based on CMR in ICM Patients**



Pontone G, et al. J Am Coll Cardiol Img. 2023;■(■):■-■.

A multiparametric CMR predictive model identify subjects at high risk for MAACE, regardless of the TTE-LVEF with a NRI of 31.7%. BSA = body surface area; CMR = cardiac magnetic resonance; EDV = end diastolic volume; ICM = ischemic cardiomyopathy; LGE = late gadolinium enhancement; LVEF = left ventricle ejection fraction; MAACE = major arrhythmic adverse cardiac events; NRI = net reclassification index; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; TTE = transthoracic echocardiography.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: ICD in primary prevention has been demonstrated to reduce the rate of sudden cardiac deaths in ICM.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The prediction of arrhythmic risk is suboptimal because of the absence of appropriate interventions after ICD placement and of the exclusion of patients incorrectly considered to be at low risk with current methods.

TRANSLATIONAL OUTLOOK: By comparing the standard of care evaluation vs a CMR-guided strategy for ICD therapy, the DERIVATE-ICM registry shows a better stratification of arrhythmic risk, especially in the population that currently does not fulfil the implantation criteria.

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KEY WORDS **cardiac magnetic resonance, heart failure, implantable cardioverter-defibrillator, ischemic dilated cardiomyopathy, primary prevention**