Prognostic Benefit of Cardiac Magnetic Resonance Over Transthoracic Echocardiography for the Assessment of Ischemic and Nonischemic Dilated Cardiomyopathy Patients Referred for the Evaluation of Primary Prevention Implantable Cardioverter–Defibrillator Therapy

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Background—The aim of this study was to determine the prognostic benefit of cardiac magnetic resonance (CMR) over transthoracic echocardiography (TTE) in ischemic cardiomyopathy and nonischemic dilated cardiomyopathy patients evaluated for primary prevention implantable cardioverter–defibrillator therapy.

Methods and Results—We enrolled 409 consecutive ischemic and dilated cardiomyopathy patients (mean age: 64±12 years; 331 men). All patients underwent TTE and CMR, and left ventricle end-diastolic volume, left ventricle end-systolic volume, and left ventricle ejection fraction (LVEF) were evaluated. In addition, late gadolinium enhancement was also assessed. All patients were followed up for major adverse cardiac events (MACE) defined as a composite end point of long runs of nonsustained ventricular tachycardia, sustained ventricular tachycardia, aborted sudden cardiac death, or sudden cardiac death. The median follow-up was 545 days. CMR showed higher left ventricle end-diastolic volume (mean difference: 43±22.5 mL), higher left ventricle end-systolic volume (mean difference: 34±20.5 mL), and lower LVEF (mean difference: –4.9±10%) as compared to TTE (P<0.01). MACE occurred in 103 (25%) patients. Patients experiencing MACE showed higher left ventricle end-diastolic volume, higher left ventricle end-systolic volume, and lower LVEF with both imaging modalities and higher late gadolinium enhancement per-patient prevalence as compared to patients without MACE. At multivariable analysis, CMR-LVEF ≤35% (hazard ratio=2.18 [1.3–3.8]) and the presence of late gadolinium enhancement (hazard ratio=2.2 [1.4–3.6]) were independently associated with MACE (P<0.01). A model based on CMR-LVEF ≤35% or CMR-LVEF ≤35% plus late gadolinium enhancement detection showed a higher performance in the prediction of MACE as compared to TTE-LVEF resulting in net reclassification improvement of 0.468 (95% confidence interval, 0.283–0.654; P<0.001) and 0.413 (95% confidence interval, 0.23–0.63; P<0.001), respectively.

Conclusions—CMR provides additional prognostic stratification as compared to TTE, which may have direct impact on the indication of implantable cardioverter–defibrillator implantation. **(*Circ Cardiovasc Imaging*. 2016;9:e004956. DOI: 10.1161/CIRCIMAGING.115.004956.)**

Key Words: dilated cardiomyopathy ■ echocardiography ■ magnetic resonance ■ primary prevention ■ prognosis

Sudden cardiac death (SCD) is the most common cause of cardiovascular death in ischemic cardiomyopathy (ICM) and nonischemic dilated cardiomyopathy (NIDCM) patients, averaging 300 000 deaths in the United States annually.[1–6] Implantable cardioverter–defibrillator (ICD) demonstrated to be the most effective SCD prophylactic strategy adopted for both primary

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and secondary prevention in these patients.[7,8] Current guidelines provide indications for ICD therapy based on the left ventricular ejection fraction (LVEF) cut-off value and clinical conditions as classified by the New York Heart Association.[9] However, they also acknowledge that LVEF value may vary between different imaging modalities used for its determination. In this regard, 2-dimensional transthoracic echocardiography (TTE) is the most commonly used technique for evaluating patients with a clinical indication for primary prevention ICD implantation. Recently, cardiac magnetic resonance (CMR) imaging has emerged as the gold standard technique for left ventricle (LV) volume and function assessment, with the added benefit of providing tissue characterization. However, the clinical impact of using CMR versus TTE for risk stratification in patients eligible for ICD implantation is still unknown. Thus, the aim of our study was to evaluate the additional prognostic benefit of CMR over TTE for decision-making in consecutive ICM and NIDCM patients referred for the evaluation of primary prevention ICD implantation.

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Methods

Study Population

The study population consisted of 515 consecutive patients with a clinical history of chronic heart failure according to the Framingham Criteria[10] and referred to our hospital to be evaluated for potential indication of ICD implantation in primary prevention between January 2011 and December 2013. Among the 515 patients screened, the reasons for referral to the evaluation were low ejection fraction close or below the threshold used for ICD indication in 355 (69%) patients, mild LV dysfunction not meeting criteria but with a history of frequent premature ventricular beats and evaluation of wide-complex tachycardia in 103 (20%) patients, and undetermined syncope in 57 (11%) patients. The ischemic cause of LV dysfunction was defined as the 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. Patients without angiographic diagnosis of coronary artery disease were classified as having NIDCM.[11] Exclusion criteria were unstable angina (n=30), decompensated heart failure (n=28), acute myocarditis (n=3), severe claustrophobia (n=15), presence of an implantable device (n=11), estimated glomerular filtration rate ≤30 mL/min (n=12), and contraindication to gadolinium contrast agent (n=7). According to the exclusion criteria, the final study population comprised 409 patients (mean age: 64±12 year; 331 men). All patients gave written informed consent, and the institutional ethical committee approved the study protocol.

Screening Procedure and Enrollment

Site personnel screened consecutive ICM and NIDCM patients who were eligible for ICD implantation. Patients who did not meet inclusion and exclusion criteria were considered screening failures, whereas those meeting all criteria were enrolled. A structured interview to collect the clinical history was performed, and the following cardiac risk factors were assessed: (1) hypertension (blood pressure >140/90 mm Hg or use of antihypertensive agents), (2) current or previous smoking, (3) hyperlipidemia (low-density lipoprotein cholesterol >140 mg/dL), (4) diabetes mellitus (fasting glucose level >110 mg/dL or need for insulin or oral hypoglycemic drugs), (5) family history of coronary artery disease in first-degree relatives, and (6) home use of cardiovascular drugs.

TTE Protocol

TTE was performed with patients in left lateral decubitus using a commercially available system (IE33 system; Philips Medical System, Andover, MA) in the parasternal (long and short axis) and apical (2-, 3- and 4-chamber) views. Echocardiographic measurements were performed twice, according to the American Society of Echocardiography guidelines,[12] by an expert reader (with ≥8 years of clinical experience in TTE performance and analysis and certified by Italian Society of Echocardiography) blinded to patient clinical history. For each patient, LV end-diastolic volume and end-systolic volume were measured on apical 4- and 2-chamber views. LVEF was measured by Simpson method. Tricuspidal annular plane systolic excursion was measured by placing M-mode cursor line along the movement of the tricuspid annulus during an M-mode echocardiogram on an apical 4-chamber view. Right atrial pressure was approximated by inferior vena cava diameter and collapsibility during a sniff test. Through the application of the simplified Bernoulli equation, velocity of the tricuspidal regurgitant jet was used to calculate systolic pulmonary artery pressure according to the following equation: (4×[velocity of the tricuspid regurgitant jet]^2+right atrial pressure). Another expert reader (with ≥8 years of clinical experience in TTE performance and analysis and certified by Italian Society of Echocardiography) repeated TTE data evaluation to measure intraobserver and interobserver variability in all patients.

Cardiovascular Magnetic Resonance Protocol

All patients were studied with a 1.5-T scanner (Discovery MR450; GE Healthcare, Milwaukee, WI) within 30 days from TTE. After acquisition of localizer images of the heart, breath-hold steady state–free precession cine acquisitions were acquired using the following parameters: echo time 1.57 ms, 15 segments, repetition time 46 ms without view sharing, slice thickness 8 mm, field of view 350×263 mm, and pixel size 1.4×2.2 mm. To acquire cine planes, multiple short axis and 2-, 3-, and 4-chamber long axis of the LV were reached according to the guidelines of the Society of Cardiovascular Magnetic Resonance.[13] Then, 0.1 mmol/kg of Gadolinium-BOPTA (Multihence; Bracco, Milan, Italy) was administered at a flow rate of 3 mL/s followed by 20 mL of saline flush. Ten minutes after contrast injection, breath-hold, contrast-enhanced segmented T1-weighted inversion-recovery gradient-echo sequence was acquired with the same prescriptions for cine images to detect late gadolinium enhancement (LGE) as previously described.[14] The inversion time was individually adjusted to null normal myocardium.

Cardiovascular Magnetic Resonance Imaging Analysis

CMR data were transferred to a dedicated workstation and analyzed with dedicated cardiac software (Report Card 4.0; GE Healthcare, Milwaukee, WI). The following indexes were evaluated on cine images according to the recommendations of the Society of Cardiovascular Magnetic Resonance[13]: LV end-diastolic volume, LV end-systolic volume, LVEF, LV mass, right ventricle end-diastolic volume, right ventricle end-systolic volume, and right ventricle ejection fraction. Finally, detection of LGE was performed on T1-weighted inversion-recovery gradient-echo images. LGE was defined as a myocardial segment with a signal intensity increase >2 SD above the mean signal intensity of remote myocardium,[14] using the myocardial segmentation suggested by the American Heart Association/American College of Cardiology classification.[15] CMR data were evaluated twice by an expert reader (with ≥5 years of clinical experience in CMR performance and analysis and Level III certification by the European Association of Cardiovascular Imaging). The reader was blinded to the clinical history of the patients and TTE findings. Another expert reader (with ≥5 years of clinical experience in CMR performance and analysis and Level III certification by the European Association of Cardiovascular Imaging) repeated CMR data evaluation to measure intraobserver and interobserver variability in all patients.

Follow-Up and End Points

Patient follow-up was performed by trained physicians with office visits and 24-hour ECG-Holter monitoring for 6 months after enrollment and then once a year until the end of the study. ICD analysis was performed in patients receiving the device. If a patient missed

the follow-up visit, telephone contact, review of outpatient clinic or hospital records, and contact with the patient's primary care physician or cardiologist were performed. During follow-up, we recorded the following end points as previously described[16]: (1) long runs of nonsustained ventricular tachycardia defined as ≥10 consecutive ventricular premature beats at >120 bpm or sustained ventricular tachycardia, (2) aborted SCD, defined as an appropriate ICD intervention for ventricular arrhythmias excluding ATP, (3) SCD defined as unexpected death either within 1 hour of cardiac symptom onset in the absence of progressive deterioration, during sleep, or within 24 hours of last being seen alive, (4) hospitalization or cardiac death related to chronic heart failure because of unstable or progressive deterioration of LV function despite active therapy. Major adverse cardiac events (MACE) were defined as a composite end point of long runs of

Table 1. Baseline Characteristics of Patients With and Without MACE

Variables	All (n=409)	Patients Without MACE (n=306)	Patients With MACE (n=103)	*P* Value
Demographic characteristics				
Age, y	66 (56–73)	66 (55–73)	67 (59–73)	0.118
Male, n (%)	331 (81)	249 (81)	82 (80)	0.694
BMI, kg/m^2	26.4±4.0	26.3±4.0	26.5±3.9	0.707
Family history of CAD, n (%)	96 (24)	68 (22)	28 (77)	0.304
Smoking, n (%)	65 (16)	48 (15)	17 (16)	0.84
Hypertension, n (%)	213 (52)	160 (52)	53 (51)	0.88
Hyperlipemia, n (%)	226 (55)	174 (57)	52 (52)	0.283
Diabetes mellitus, n (%)	97 (24)	71 (23)	26 (25)	0.67
Ischemic cause, n (%)	212 (52)	157 (51)	55 (53)	0.71
Medications				
β-blockers, n (%)	340 (83)	253 (82)	87 (84)	0.67
Ivabradine, n (%)	32 (8)	20 (6)	12 (11)	0.09
ACEi/ARBs, n (%)	332 (81)	251 (82)	81 (78)	0.44
Diuretics, n (%)	284 (69)	204 (66)	80 (77)	0.04
Antithrombotic, n (%)	284 (69)	211 (68)	73 (71)	0.71
Anticoagulant, n (%)	103 (25)	78 (25)	25 (24)	0.80
Nitrates, n (%)	84 (21)	58 (19)	26 (25)	0.17
Statins, n (%)	220 (54)	164 (53)	56 (54)	0.89
Amiodarone, n (%)	139 (34)	87 (28)	52 (50)	<0.001
TTE				
LVEDVi, mL/m^2	80 (67–102)	78 (63–98)	87 (70–118)	<0.001
LVESVi, mL/m^2	51 (39–70)	48 (38–66)	61 (43–81)	<0.001
LVEF, %	35.7±10.0	36.7±9.8	32.7±10.2	0.001
TAPSE, mm	20.4±5.1	20.7±5.0	19.4±5.0	0.037
PAP, mm Hg	31 (26–39)	31 (25–37)	33 (28–42)	0.010
CMR				
LVEDVi, mL/m^2	122 (102–151)	118 (101–145)	135 (111–160)	<0.001
LVESVi, mL/m^2	82 (64–109)	78 (62–100)	98 (74–126)	<0.001
LVEF, %	32 (25–38)	33 (27–40)	26 (21–34)	<0.001
RVEF, %	55 (47–63)	56 (48–63)	51 (41–63)	0.042
LGE, n (%)	247 (60)	169 (55)	78 (76)	<0.001
LGE, no. of segments	4.5±4.1	3.6±4.0	5.1±4.1	0.001
ICD implantation, n (%)	138 (34)	85 (28)	53 (51)	<0.001

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II inhibitor; BMI, body mass index; CAD, coronary artery disease; CMR, cardiac magnetic resonance; ICD, implantable cardioverter–defibrillator; LGE, late gadolinium enhancement; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MACE, major adverse cardiac events; PAP, pulmonary artery pressure; RVEF, right ventricle ejection fraction; TAPSE, tricuspidal annular plane systolic excursion; and TTE, transthoracic echocardiography.

nonsustained ventricular tachycardia, sustained ventricular tachycardia, aborted SCD, or SCD.

Statistical Analysis

Statistical analysis was performed with the SPSS, version 17.0 software (SPSS Inc, Chicago, IL) and R version 2.15.2. Continuous variables were expressed as mean±SD or median (25th–75th percentile) as appropriate and discrete variables as absolute numbers and percentages. Student independent *t* or Mann–Whitney tests were used as appropriate to compare continuous variables between patients with and without MACE. Comparisons between groups of discrete variables were performed by χ^2 or Fisher exact test if the expected cell count was <5. The Spearman correlation and Bland–Altman analysis were used for comparing CMR to TTE values. Intraobserver and interobserver variability for the evaluation of TTE and CMR variables was defined by the coefficient of variation. Survival curves were obtained by Kaplan–Meier analysis and compared by Log-rank test. Univariable Cox proportional hazard models were used to assess the association between baseline covariates and the composite end point (results presented as hazard ratio and 95% confidence interval [CI]). Variables with $P<0.10$ at univariable analysis were then included as covariates in multivariable Cox proportional hazard models to test which variables were independently associated with the composite end point analyzing TTE-LVEF and CMR-LVEF separately. The discriminative ability of TTE-LVEF ≤35% and CMR-LVEF ≤35%, the presence of LGE, and the combination of CMR-LVEF ≤35% plus LGE to diagnose MACE were evaluated by means of time-dependent receiver operating curve analysis. For each variable accuracy, sensitivity, specificity, negative predictive value, and positive predictive value at 2 years were obtained; 95% CI and pairwise comparison between accuracy values were also calculated. Time-dependent areas under receiver operating characteristic curves for censored event times with competing risks were estimated and compared. Finally, the incremental value in predicting composite end point by stepwise inclusion of TTE-LVEF, CMR-LVEF, and the presence of LGE in addition to clinical data was assessed by the χ^2 using Omnibus test of model coefficients. Reclassification of patients was determined using net reclassification improvement analysis for MACE and obtained by adding CMR-LVEF and LGE status to the model based on clinical history and TTE-LVEF. Because no conventional cut-off values exist for the onset of MACE in such population, risk categories were determined on the basis of mean event rate at 2 years of follow-up, and, therefore, a threshold of 20% was used to stratify patients into low-risk (<20%) and high-risk (≥20%) categories. Categorical and continuous net reclassification improvements were computed together with integrated discrimination improvement. All tests were 2-tailed, and *P* value of <0.05 was considered statistically significant.

Results

Overall, 514 patients were screened, and 105 were excluded according to the exclusion criteria. Therefore, 409 patients were finally included in the study population. Both the imaging tests were performed successfully in all patients. There was a median of 2 (1–4) days between TTE and CMR studies for both patients with and without MACE. Median follow-up time was 545 (270–924) days. No patient was lost to follow-up. Patient baseline characteristics are listed in Table 1. Two-hundred twelve (52%) patients showed an ischemic cause. Long runs of nonsustained ventricular tachycardia or sustained ventricular tachycardia, aborted SCD, and SCD occurred in 37 (19%), 10 (5%), and 7 (4%) and 26 (12%), 9 (4%), and 14 (7%) in NIDCM and ICM patients, respectively. Finally, 25 (13%) and 30 (14%) of NIDCM and ICM patients, respectively, experienced an event related to chronic

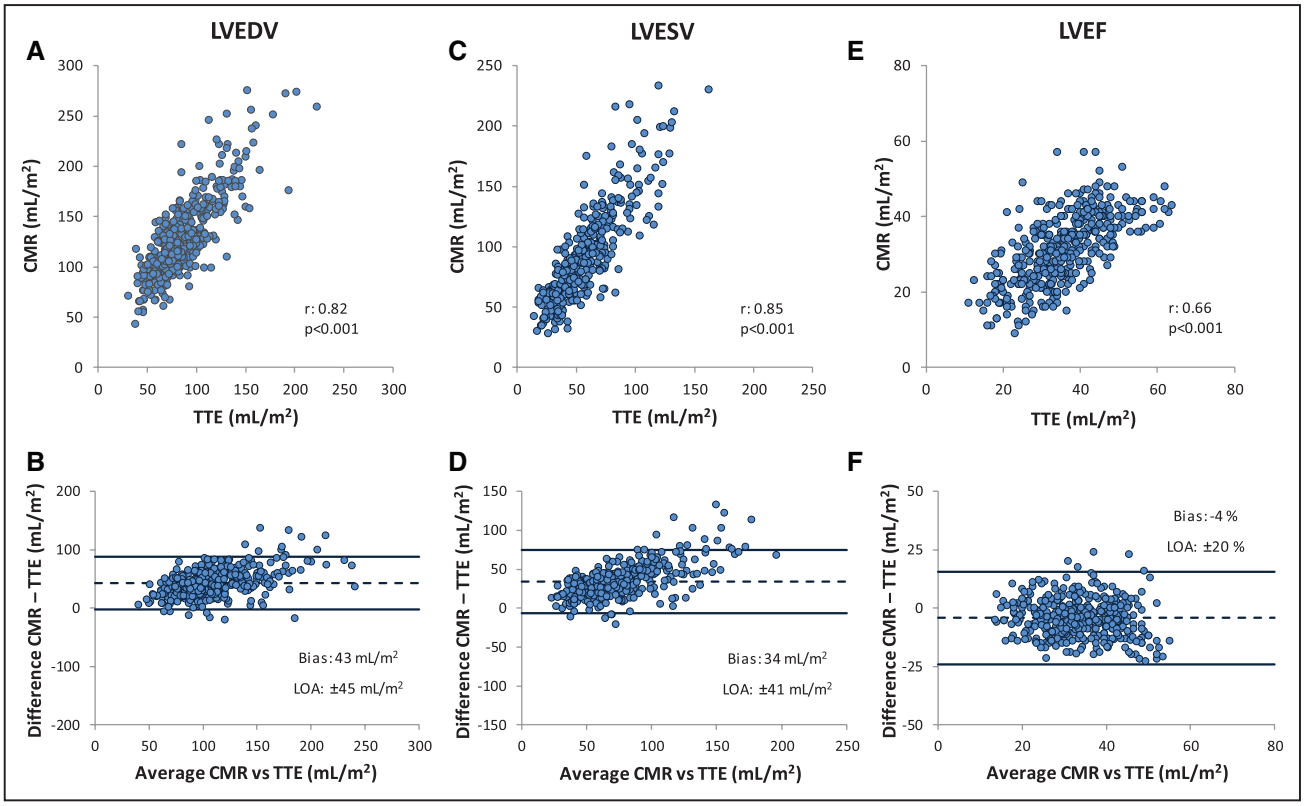

Figure 1. Pearson correlation and Bland–Altman analysis between cardiac magnetic resonance (CMR) and transthoracic echocardiography (TTE) assessment of left ventricle end-diastolic volume (LVEDV; **A and B**), left ventricle end-systolic volume (LVESV; **C and D**), and left ventricle ejection fraction (LVEF; **E and F**). LOA indicates limits of agreement.

heart failure. According to the definition of primary combined end point, MACE occurred in 103 (25%) patients. No differences were found in terms of demographic characteristics and cardiovascular risk factors between patients with and without MACE. On the contrary, patients experiencing MACE showed higher LV end-diastolic volume, higher LV end-systolic volume, and lower LVEF irrespective of the imaging modality used. They also had higher per-segment and per-patient prevalence of LGE as compared to patients without MACE (Table 1). Patients who experienced MACE received more ICD implantation as compared to patients who did not experience MACE during follow-up (51% versus 28%, respectively, $P<0.001$).

Higher LV end-diastolic volume (mean difference: 43±22.5 mL), higher LV end-systolic volume (mean difference: 34±20.5 mL), and lower LVEF (mean difference: −4±10%) were found with CMR as compared to TTE ($P<0.001$; Figure 1). CMR showed also better intraobserver and interobserver variability for LVEF evaluation when compared with TTE (κ: 0.97 and 0.96 versus 0.81 and 0.78, respectively, $P<0.01$).

Kaplan–Meier survival curves showed different event-free rates with respect to TTE-LVEF (Figure 2A), CMR-LVEF (Figure 2B), LGE detection (Figure 2C), and combination of CMR-LVEF plus LGE (Figure 2D). The univariable and multivariable analyses (Table 2) showed that CMR-LVEF ≤35% and LGE were independently associated with MACE ($P<0.01$). Sensitivity, specificity, negative predictive value, positive predictive value, and accuracy for CMR-LVEF, LGE, TTE-LVEF, and CMR-LVEF plus LGE evaluated at 2 years are shown in Table 3. The combined evaluation of CMR-LVEF and LGE showed a higher accuracy as compared to TTE-LVEF ($P=0.003$) and CMR-LVEF

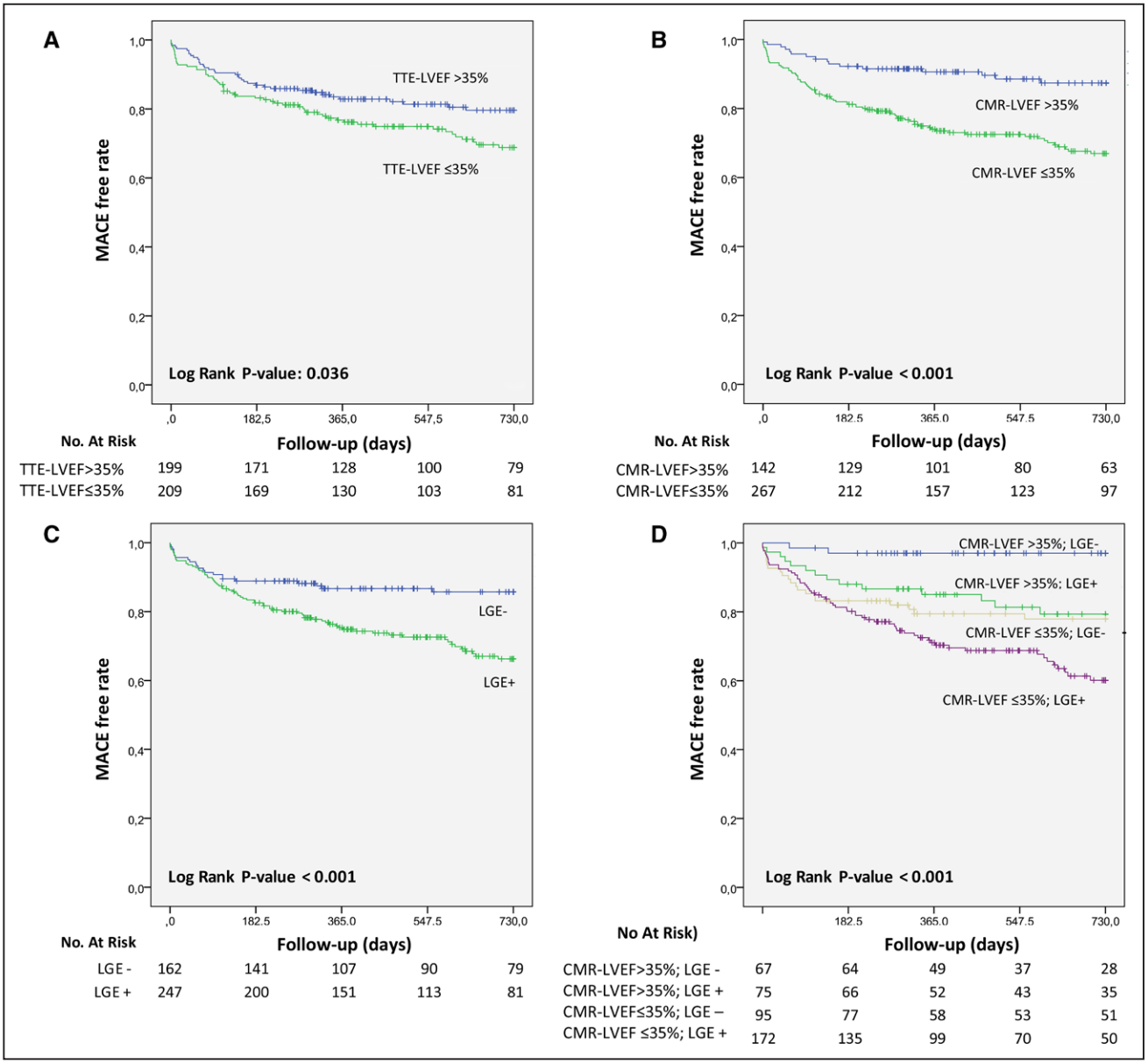

Figure 2. Kaplan–Meier curves for major adverse cardiac events (MACE) based on transthoracic echocardiography (TTE)-left ventricle ejection fraction (LVEF; **A**), cardiac magnetic resonance (CMR)-LVEF (**B**), late gadolinium enhancement (LGE) detection (**C**), and the combination of CMR-LVEF plus LGE detection (**D**).

Table 2. Univariable and Multivariable Predictors of MACE

	Univariable Analysis		Multivariable Analysis, Including TTE-LVEF		Multivariable Analysis, Including CMR-LVEF and LGE	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Demographic characteristics						
Age	1.017 (1.001–1.035)	0.049	1.013 (0.994–1.031)	0.187	1.007 (0.988–1.026)	0.499
Male	0.911 (0.564–1.471)	0.703	…	…	…	…
BMI	0.998 (0.952–1.046)	0.931	…	…	…	…
Family history of CAD	1.284 (0.831–1.984)	0.259	…	…	…	…
Smoking	1.170 (0.692–1.978)	0.559	…	…	…	…
Hypertension	0.973 (0.659–1.434)	0.888	…	…	…	…
Hyperlipemia	0.745 (0.504–1.101)	0.140	…	…	…	…
Diabetes mellitus	1.121 (0.718–1.749)	0.617	…	…	…	…
Ischemic cause	1.091 (0.741–1.607)	0.660	…	…	…	…
Medications						
β-blockers	1.050 (0.616–1.790)	0.857	…	…	…	…
Ivabradine	1.557 (0.853–2.842)	0.150	…	…	…	…
ACEi/ARBs	0.780 (0.487–1.250)	0.303	…	…	…	…
Diuretics	1.726 (1.085–2.745)	0.021	1.398 (0.994–1.031)	0.190	1.351 (0.822–2.221)	0.236
Antithrombotic	1.100 (0.719–1.682)	0.661	…	…	…	…
Anticoagulant	1.003 (0.639–1.573)	0.991	…	…	…	…
Nitrates	1.228 (0.786–1.916)	0.367	…	…	…	…
Statins	1.023 (0.694–1.508)	0.908	…	…	…	…
Amiodarone	2.325 (1.580–3.422)	<0.001	2.137 (1.408–3.242)	<0.001	2.142 (1.422–3.226)	<0.001
TTE						
LVEDVi	1.012 (1.006–1.018)	<0.001	…	…	…	…
LVESVi	1.016 (1.009–1.023)	<0.001	…	…	…	…
LVEF≤35%	1.491 (1.005–2.212)	0.047	1.225 (0.797–1.882)	0.355	…	…
TAPSE	0.952 (0.913–0.993)	0.022	…	…	…	…
PAP	1.023 (1.006–1.041)	0.009	…	…	…	…
CMR						
LVEDVi	1.008 (1.004–1.012)	<0.001	…	…	…	…
LVESVi	1.010 (1.005–1.014)	<0.001	…	…	…	…
LVEF≤35%	2.803 (1.686–4.662)	<0.001	…	…	2.176 (1.250–3.790)	0.006
RVEF	0.981 (0.966–0.995)	0.009	…	…	…	…
LGE, presence	2.250 (1.433–3.534)	<0.001	…	…	2.201 (1.356–3.571)	0.001
LGE, no. of segments	1.086 (1.034–1.140)	0.001	…	…	…	…

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II inhibitor; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CMR, cardiac magnetic resonance; HR, hazard ratio; LGE, late gadolinium enhancement; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end-systolic volume; MACE, major adverse cardiac events; PAP, pulmonary artery pressure; RVEF, right ventricle ejection fraction; TAPSE, tricuspidal annular plane systolic excursion; and TTE, transthoracic echocardiography.

alone (*P*=0.028; Figure 3). Finally, adding CMR-LVEF in the presence of LGE to the model, including only clinical data and TTE-LVEF, provided a significant improvement in outcome prediction (Figure 4) with a net reclassification improvement of 0.468 (95% CI, 0.283–0.654; *P*<0.001) and 0.413 (95% CI, 0.229–0.634; *P*<0.001), respectively (Table 4). It is noteworthy that in the subset of patients in which TTE-LVEF falls in the gray zone (30%–40%), the addition of CMR-LVEF in the presence of LGE to the model, including only clinical data and TTE-LVEF, still provided a significant improvement in outcome prediction with a net reclassification improvement of 0.484 (95% CI, 0.215–0.752; *P*<0.001) and 0.419 (95% CI, 0.177–0.660; *P*<0.001), respectively.

Table 3. Discriminatory Ability (Evaluated at 2 Years) of TTE-LVEF, CMR-LVEF, and LGE for the Prediction of MACE

	Sensitivity, %	Specificity, %	NPV, %	PPV, %	AUC (95% CI)
TTE-LVEF≤35%	62.0	49.4	78.7	30.1	55.7 (49.4–62.0)*
CMR-LVEF≤35%	83.2	39.4	87.0	32.5	61.3 (59.9–66.7)*
LGE+	78.3	49.4	86.6	35.2	63.8 (58.2–69.5)
CMR-LVEF≤35% plus LGE+	63.4	71.3	84.7	43.6	67.3 (61.3–73.3)

AUC indicates area under the curve; CI, confidence interval; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; MACE: major adverse cardiac event; NPV, negative predictive value; PPV, positive predictive value; and TTE, transthoracic echocardiography.

*P<0.05 vs CMR-LVEF ≤35% plus LGE+.

Discussion

The main results of our study are the following: (1) the combined evaluation of CMR-LVEF and LGE is a better independent predictor of MACE in ICM and NIDCM patients as compared to TTE-LVEF assessment, and (2) CMR allows reclassification of a relevant number of patients at high risk for MACE as compared to a model, including TTE-LVEF beyond the baseline clinical characteristics of the patients. In the past 2 decades, primary prevention ICD implantation in patients with severe LV dysfunction demonstrated a survival benefit in terms of a significant reduction in SCD, initially in those with ICM[17] and then also in those with NIDCM.[18] Taking into account the New York Heart Association class, current guidelines recommend ICD implantation in heart failure patients with LVEF lower than 30% to 35%.[9] Although LVEF has been considered as the strongest independent predictor of SCD among traditional risk factors and, therefore, poses the patient in a high-risk condition,[19] its use in decision-making has shown limitations in terms of sensitivity and specificity. On one hand, post hoc analysis of the MADIT (Multicenter Automatic Defibrillator Implantation Trial) II study demonstrated that only one third of ICD recipients received appropriate therapy within 3 years of follow-up after implantation.[20] On the other hand, several patients who had aborted SCD did not meet LVEF cut-off values for ICD implantation eligibility. Indeed, Stecker et al[21] reported that, among patients who experienced cardiac arrest, ≈65% of patients would not have qualified for a primary prevention ICD therapy. The issue is worsened further by the inadequate reproducibility and accuracy of TTE.[22,23] CMR imaging is a standardized technique that, thanks to high spatial resolution and independence from geometric assumptions, represents the reference standard for LV volumes and LVEF measurement.[24,25] Indeed, a significant discrepancy between CMR and TTE has been demonstrated, ranging from 7% LVEF overestimation to 4% underestimation with the latter imaging technique[26,27] with the majority of studies indicating an overestimation of LVEF assessment by TTE.[21] In addition, CMR has proven to have high diagnostic

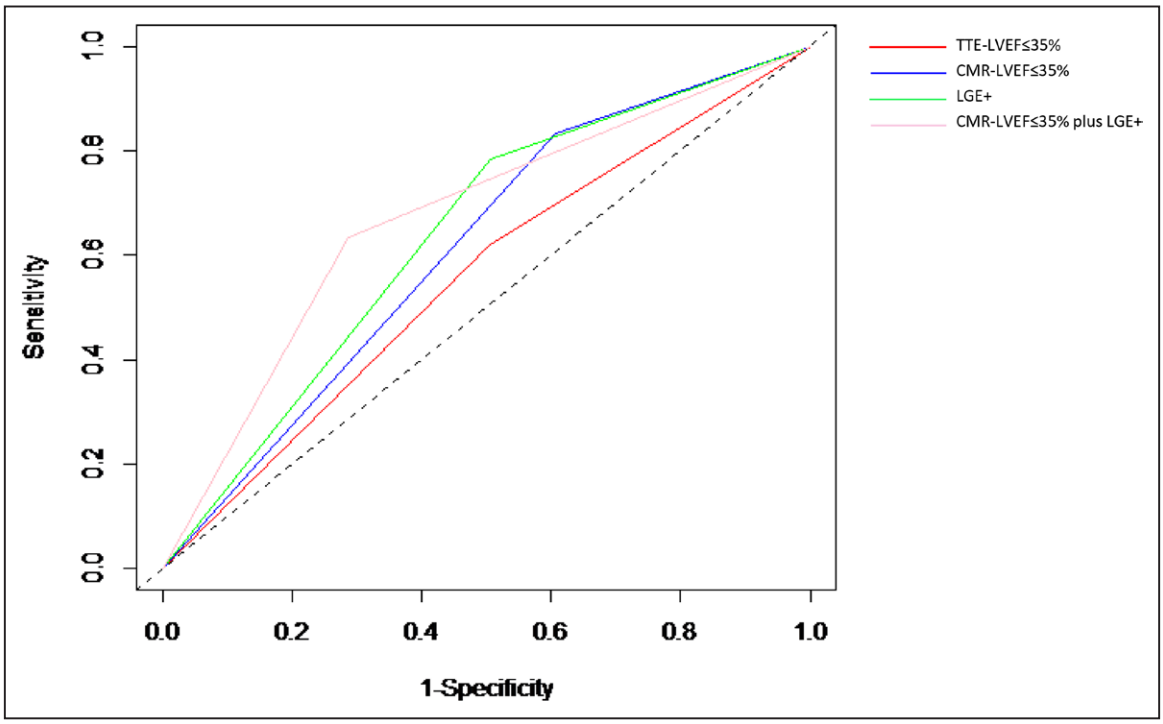

Figure 3. Receiver operating curves for the detection of major adverse cardiac events. CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; and TTE, transthoracic echocardiography.

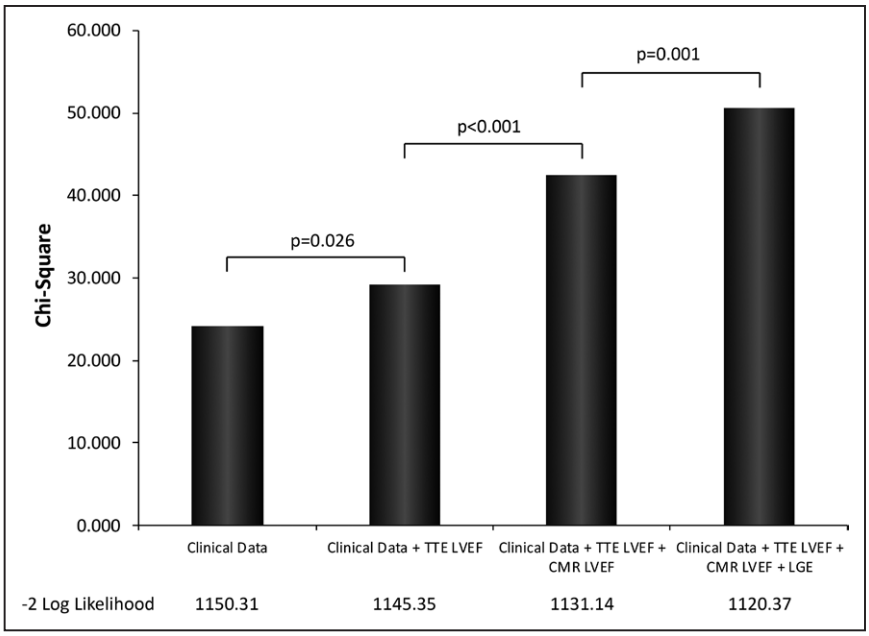

Figure 4. Incremental value of cardiac magnetic resonance (CMR)-left ventricle ejection fraction (LVEF) and late gadolinium enhancement (LGE) in predicting outcome when compared with models, including clinical data alone or in combination with transthoracic echocardiography (TTE)-LVEF.

and prognostic value in cardiomyopathy evaluation apart from the pure LVEF estimation, thanks to LGE technique.[28–33] In this regard, Boyé et al[31] prospectively studied 52 patients with a previous myocardial infarction who were referred for primary prevention ICD implantation according to the MADIT Study criteria and demonstrated that the extent of fibrosis was a predictor of the composite end point of life-threatening arrhythmias and cardiac death. Similarly, Scott et al[33] showed a significant association between LGE and appropriate ICD discharge in patients with ICM undergoing ICD implantation, although no correlation was observed with all-cause mortality. Accordingly, they concluded that fibrosis burden, as quantified by LGE, was not a reliable forecaster of all-cause death but could be a specific predictor of SCD instead. Along the same lines, a study by Gao et al[34] showed that myocardial fibrosis was a robust, independent predictor of appropriate ICD therapy, aborted SCD, and SCD in consecutive ICM and NIDCM patients. Moreover, among the SCD anatomic substrates, growing research interest has been aroused by the region at the margins of LGE zone, the so-called border zone because of an alleged correlation with ventricular arrhythmias, appropriate ICD discharge, and cardiovascular mortality.[4,35,36] Our findings about CMR and TTE evaluation of LVEF are in keeping with previous research, showing that TTE provides a systematic overestimation of LVEF and that CMR has less intraobserver and interobserver variability than TTE. This implies that the 2 imaging modalities are not interchangeable in this patient population and that the discrepancy may significantly affect clinical decisions for individual patients in terms of eligibility for device therapy. The true novelty of our study is that, thanks to the better observer variability and the multiparametric nature of CMR, including LVEF and LGE

Table 4. NRI With the Addition of TTE-LVEF to Models, Including Clinical Data (Age and Medical Therapy With Diuretics and Amiodarone)

Categorical NRI: −0.028 (−0.098 to 0.041), *P*=0.424; Continuous NRI: 0.256 (0.031 to 0.481), *P*=0.026; IDI: 0.002 (−0.003 to 0.008); *P*=0.455					Categorical NRI: 0.054 (−0.034 to 0.145), *P*=0.2553; Continuous NRI: 0.468 (0.283 to 0.654), *P*<0.001; IDI: 0.029 (0.013 to 0.044), *P*<0.001					Categorical NRI: 0.097 (0.022 to 0.173), *P*=0.012; Continuous NRI: 0.431 (0.229 to 0.634), *P*<0.001; IDI: 0.026 (0.006 to 0.046), *P*=0.009				
Predicted Risk With Clinical Data, %	Predicted Risk With Clinical Data and TTE-LVEF, %				Predicted Risk With Clinical Data and TTE-LVEF, %	Predicted Risk With Clinical Data, TTE-LVEF, and CMR-LVEF, %				Predicted Risk With Clinical Data, TTE-LVE,F and CMR-LVEF, %	Predicted Risk With Clinical Data, TTE-LVEF, CMR-LVEF, and LGE, %			
	<20	≥20	Total	Reclassified		<20	≥20	Total	Reclassified		<20	≥20	Total	Reclassified
MACE absent					MACE absent					MACE absent				
<20	115	13	128	10	<20	94	35	129	27	<20	113	13	126	10
≥20	14	171	185	8	≥20	32	152	184	17	≥20	50	137	187	27
MACE present					MACE present					MACE present				
<20	15	3	18	17	<20	11	10	21	48	<20	12	3	15	20
≥20	6	71	77	8	≥20	4	70	74	5	≥20	5	75	80	6

CMR indicates cardiac magnetic resonance; IDI, integrated discrimination improvement; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; MACE, major adverse cardiac events; NRI, net reclassification improvement; and TTE, transthoracic echocardiography.

assessment, the necessity for a new multimodality imaging approach to improve the prediction of patients who should receive greater beneficial effects of device therapy compared with TTE evaluation alone is emerging. Indeed, patients with TTE-LVEF estimation around the cut-off usually used for ICD implantation, such as our study population, are in a gray zone in which several missed-ICD implantations fall. Our results demonstrate that volumetric LVEF assessment and LGE detection by CMR may provide additional discriminatory value to the evaluation of LV function by TTE alone. In this regard, the lower LVEF value measured by CMR led to the reclassification of 47% of patients into a group at high risk of MACE despite that their LVEF by TTE was ≥35%. Moreover, if we add the LGE detection to the model, a further reclassification of 41% was observed. However, some limitations of CMR needs to be taken into account. CMR scanners may not be widely available, particularly at community imaging centers. Also, the examination requires a long scan time, and it is not feasible in patients who have previously implanted electronic devices or with a history of claustrophobia. However, these limitations should be weighed against the capability of CMR to avoid missed ICD implantations as a consequence of using the sole TTE-LVEF criterion. In this regard, a potential use of CMR in patients with ICM or NIDCM could be when the patients' LVEF detection by TTE is in a gray zone.

Limitations

Some limitations are present in this study. First, TTE and CMR were not necessarily performed on the same day, and although patients were clinically stable between the 2 examinations, subclinical changes may have occurred. However, despite the inclusion criteria requiring a maximum delay between the 2 imaging modalities of 30 days, the median of 2-day delay (interquartile range 1–4) either for patients without or with MACE should have minimized a potential bias. Second, referring physicians referred the enrolled patients for potential ICD implantation, and this might have introduced a selection bias. Moreover, considering that decompensated patients with heart failure could be referred to acute care units and definitively not referred to CMR evaluations, a further potential referral inclusion bias could be present and justify a mean LVEF around the cut-off for the indication of ICD implantation. Therefore, despite our study population having similar demographic characteristics, medication usage, and disease severity profile compared with those reported in previous experience of patients with NIDCM available in the literature, our findings could not be generalized to the entire spectrum of ICM and NIDCM populations. Third, we have not included in our analysis the impact of different LGE patterns and the LGE border zone on the risk classification. However, some studies[36] have showed that the LGE border zone assessed by CMR was not superior to the total fibrosis size in identifying those in whom ventricular arrhythmias occurred. Finally, despite the methods we used to assess the ability of the model to predict MACE, the observational nature of the data requires caution in generalizing findings from this study. Validation of the proposed model to estimate the risk of MACE will be performed in the near future to have better understanding of the strength of the study.

Conclusions

This study confirms that TTE is limited by a systematic overestimation of LVEF and lack of information about myocardial tissue characterization as compared to CMR in ICM and NIDCM patients. This may affect clinical decision-making for ICD therapy, suggesting that patient assessment with volumetric CMR-LVEF and LGE detection may be superior to TTE-LVEF for risk stratification. Indeed, CMR imaging may identify a subgroup of patients in which ICD implantation is still indicated despite TTE-LVEF higher than 35%. However, the potential additional clinical use of CMR as compared to echocardiographic evaluation in the risk stratification of patients with NIDCM requires further prospective randomized trials comparing ICD therapy guided by TTE alone versus CMR alone versus a sequential decisional workflow based on TTE followed by CMR.

Disclosures

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CLINICAL PERSPECTIVE

Implantable cardioverter–defibrillator implantation reduces mortality in ischemic cardiomyopathy and nonischemic dilated cardiomyopathy patients and reduced left ventricular ejection fraction (LVEF <35%). Transthoracic echocardiography (TTE) is the imaging modality of choice for LVEF assessment. However, cardiac magnetic resonance (CMR) is now considered the gold standard technique for LVEF evaluation and provides prognostic information with late gadolinium enhancement detection. The aim of this study was to determine the prognostic benefit of CMR over TTE in ischemic cardiomyopathy and dilated cardiomyopathy patients evaluated for primary prevention implantable cardioverter–defibrillator therapy. We demonstrated in 409 consecutive ischemic cardiomyopathy and dilated cardiomyopathy patients (median age: 66 [56–73]; 331 men) that CMR-LVEF ≤35% and the presence of late gadolinium enhancement were independently associated with major adverse cardiac events (P<0.01). A model based on CMR-LVEF ≤35% plus late gadolinium enhancement detection showed a higher performance in the prediction of major adverse cardiac events as compared to TTE-LVEF (area under the curve 0.67 versus 0.56, respectively; P<0.05), resulting in net reclassification improvement of 0.468 (95% confidence interval, 0.283–0.654; P<0.001) and 0.431 (95% confidence interval, 0.229–0.634; P<0.001), respectively. These findings may have a clinical implication to avoid the number of missed implantable cardioverter–defibrillator implantations as a consequence of using the sole TTE-LVEF criterion when CMR is introduced in the clinical decision-making process, suggesting the use of CMR in ischemic cardiomyopathy or dilated cardiomyopathy patients with TTE-LVEF falling in the border zone area for the indication of implantable cardioverter–defibrillator implantation in primary prevention.