

# Scar channels in cardiac magnetic resonance to predict appropriate therapies in primary prevention



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**BACKGROUND** Scar characteristics analyzed by late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) are related with ventricular arrhythmias. Current guidelines are based only on the left ventricular ejection fraction to recommend an implantable cardioverter-defibrillator (ICD) in primary prevention.

**OBJECTIVES** Our study aims to analyze the role of imaging to stratify arrhythmogenic risk in patients with ICD for primary prevention.

**METHODS** From 2006 to 2017, we included 200 patients with LGE-CMR before ICD implantation for primary prevention. The scar, border zone, core, and conducting channels (CCs) were automatically measured by a dedicated software.

**RESULTS** The mean age was  $60.9 \pm 10.9$  years; 81.5% (163) were men; 52% (104) had ischemic cardiomyopathy. The mean left ventricular ejection fraction was  $29\% \pm 10.1\%$ . After a follow-up of  $4.6 \pm 2$  years, 46 patients (22%) reached the primary end point (appropriate ICD therapy). Scar mass ( $36.2 \pm 19$  g vs  $21.7 \pm 10$  g;  $P < .001$ ), border zone mass ( $26.4 \pm 12.5$  g vs  $16.0 \pm 9.5$  g;  $P < .001$ ), core mass ( $9.9 \pm 8.6$  g vs  $5.5 \pm 5.7$  g;  $P < .001$ ), and CC

mass ( $3.0 \pm 2.6$  g vs  $1.6 \pm 2.3$  g;  $P < .001$ ) were associated with appropriate therapies. Scar mass  $> 10$  g (25.31% vs 5.26%; hazard ratio 4.74;  $P = .034$ ) and the presence of CCs (34.75% vs 8.93%; hazard ratio 4.07;  $P = .003$ ) were also strongly associated with the primary end point. However, patients without channels and with scar mass  $< 10$  g had a very low rate of appropriate therapies (2.8%).

**CONCLUSION** Scar characteristics analyzed by LGE-CMR are strong predictors of appropriate therapies in patients with ICD in primary prevention. The absence of channels and scar mass  $< 10$  g can identify patients at a very low risk of ventricular arrhythmias in this population.

**KEYWORDS** Ventricular tachycardia; Cardiac magnetic resonance; Scar; Border zone; Conducting channels

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## Introduction

In the last decades, cardiovascular mortality has decreased in developed countries because of the adoption of preventive measures to reduce the burden of ischemic heart disease and heart failure. Nevertheless, cardiovascular diseases are still the main cause of death in these countries and 25% of

them are related with sudden cardiac death (SCD). Currently, clinical practice guidelines for recommending an implantable cardioverter-defibrillator (ICD) for the primary prevention of SCD are based only on the left ventricular ejection fraction (LVEF). The European Society of Cardiology and American College of Cardiology/American Heart Association

Funding sources: This work was supported in part by Instituto de Salud Carlos III (ISCIII).CIBERCV16: CB16/11/00354 and grant number PI20/00693. Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR), Recognized Research Group: 2017-SGR-01548 and CERCA Programme/Generalitat de Catalunya. Disclosures: Dr Berruezo holds stock in ADAS3D and has received financial support from Siemens Healthcare. Dr Roca-Luque has served as a consultant for Boston Scientific and Abbott Medical. Dr Mont reports activities as consultants, lecturers, and advisory board members for Abbott Medical, Boston Scientific, Biosense Webster, Medtronic, and Biotronik. They are also shareholders in Galgo Medical, S.L. The rest of the authors report no conflicts of interest. **Address reprint requests and correspondence:** Dr Ivo Roca-Luque, Arrhythmia Unit, Institut Clinic Cardiovascular, Hospital Clínic, Universitat de Barcelona, Villarroel, 170, 08036 Barcelona, Spain. E-mail address: [iroca@clinic.cat](mailto:iroca@clinic.cat).

guidelines<sup>1,2</sup> recommend ICD implantation for the primary prevention of SCD in patients with heart failure and reduced LVEF on the basis of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II)<sup>3</sup> and the Sudden Cardiac Death in Heart Failure Trial.<sup>4</sup>

Although LVEF can identify a subgroup of patients at risk of SCD, appropriate ICD therapy is documented in only one-third of the patients,<sup>5</sup> so its use as the sole criterion for implanting an ICD implies overtreatment of a high number of patients. Thus, tools for improving the prediction of arrhythmic risk are needed.

Currently, it is well known that the presence of scar tissue is a substrate for malignant reentrant arrhythmias and several studies have shown that infarct size assessed by late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) is an independent predictor of arrhythmic events.<sup>6</sup> The aim of our study was to analyze the role of imaging to predict which patients with decreased LVEF are at risk of developing life-threatening arrhythmias and therefore would benefit from ICD implantation.

## Methods

### Patients

We performed a prospective registry of 224 consecutive patients with ischemic and nonischemic systolic dysfunction (LVEF  $\leq 35\%$ ) who underwent LGE-CMR between 2011 and 2017 before ICD implantation for primary prevention. Coronary disease was diagnosed by coronary angiography or computed tomography angiography. Incomplete revascularization was considered when  $\geq 1$  vessels with severe lesions were not revascularized percutaneously or surgically or when there was chronic total occlusion. The study was approved by the institutional ethics committee. We analyzed this registry retrospectively.

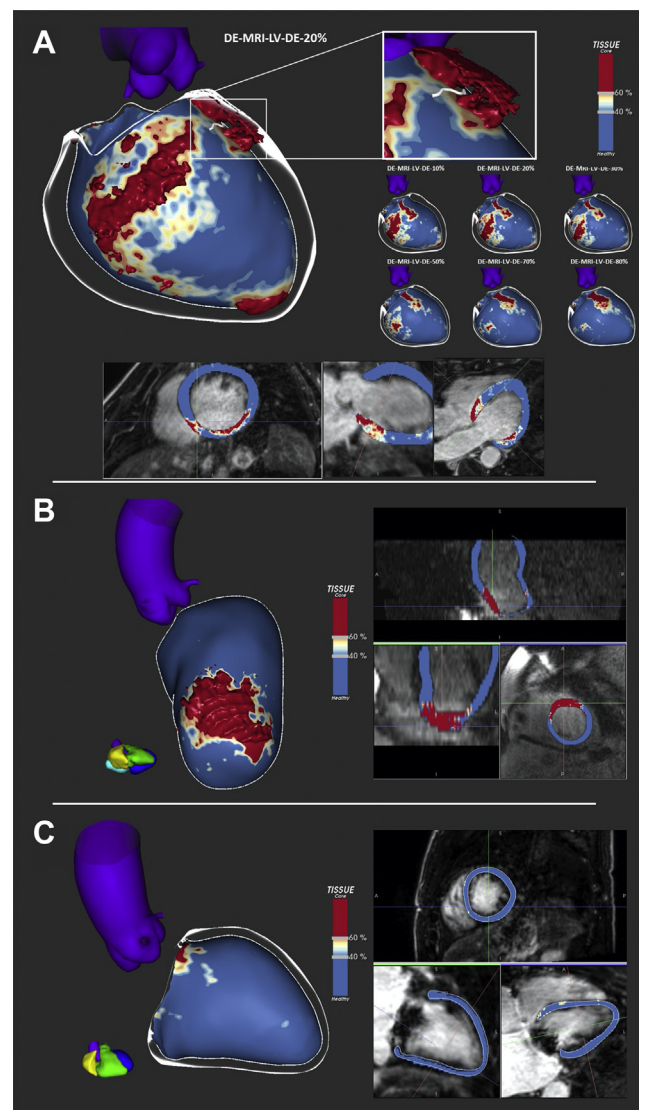
### LGE-CMR acquisition and processing

All CMR studies were performed with a 3T MAGNETOM Trio scanner (Siemens Healthcare, Erlangen, Germany), and the images were processed with ADAS 3D software (ADAS3D Medical S.L., Barcelona, Spain) following a previously described protocol.<sup>7–9</sup> Briefly, 2 independent investigators analyzed the CMR images and a third observer was available in case of discrepancies. Full left ventricular volume was reconstructed in the axial orientation, and the resulting images were processed with ADAS3D software. After semiautomatically delineating the endocardium and epicardium, 9 concentric layers were created automatically from the endocardium to the epicardium at 10%–90% of the left ventricular wall thickness. A 3-dimensional shell was obtained for each layer. Pixel signal intensity maps were obtained from LGE-CMR images and projected to each of the shells following a trilinear interpolation algorithm and were color coded (core scar in red, border zone [BZ] in light yellow, and healthy tissue in blue). A pixel signal intensity–based algorithm was applied to characterize the hyperenhanced area as scar core or BZ by using  $40\% \pm 5\%$  (healthy tissue) and  $60\%$

$\pm 5\%$  (core scar) of the maximum intensity signal as thresholds. A *conducting channel* (CC) in LGE-CMR reconstruction was defined as a corridor of the BZ between 2 core areas or between a core area and a valve annulus (Figure 1).

### ICD implantation and follow-up

After implantation, 2 detection zones were programmed: ventricular tachycardia (VT) zone from 170 to 220 beats/min and ventricular fibrillation (VF) zone at a detection rate of  $>220$  beats/min (as per protocol for primary prevention in our institution). In all patients, shocks were programmed in the VF zone. The VT zone therapy was



**Figure 1** A: LGE-CMR reconstruction of the LV with a posteroseptal scar (core in red, BZ in white, and healthy myocardium in blue). A white line is drawn over the surface, representing a conducting channel. We can see the substrate evolution through different layers, from the endocardium (10%–30%) to the epicardium (70%–90%), with a defined channel in different layers. B: LGE-CMR reconstruction of the LV with an anterior scar. In this case the scar is very homogeneous (mainly composed of core tissue) compared with the scar in panel A and it has no conducting channels. C: LGE-CMR reconstruction of the LV without scar. BZ = border zone; LGE-CMR = late gadolinium enhanced cardiac magnetic resonance; LV = left ventricle.

antitachycardia pacing at 91% and 81% of the tachycardia cycle length with 10-ms scan followed by shocks. Device follow-up was performed in our device clinic every 8 months (12 months if patients had remote monitoring). Interrogation was stored in the computer system and was analyzed by the study investigators.

### Definition of end points

The primary end point was appropriate ICD therapy (antitachycardia pacing or shock) for VT or VF. The secondary end point was all-cause mortality.

### Statistical analysis

Continuous data are reported as mean  $\pm$  SD, and comparisons between groups were performed using the Student *t* test or the Mann-Whitney *U* test, as appropriate. Categorical variables are presented as frequency (percentage) and were compared using the  $\chi^2$  test or Fisher exact method. Receiver operating characteristic curves were calculated to estimate the predictive value of scar variables and to identify cutoff points of interest. For the competing risk analysis, we tabulated the number of patients with each of the 2 outcomes of interest (appropriate ICD therapy and death). Because of the presence of competing risks, to analyze the effect of baseline predictors on the primary end point (appropriate ICD therapy), we used regression modeling of the subdistribution functions to analyze competing risk survival data. Variables selected in the univariable analyses ( $P < .05$ ) were entered into multivariable subdistribution hazards models to estimate the independent effect of the scar tissue characteristics on event-free survival for both end points. The scar-related variables were included separately in the multivariable analysis because they were strongly related. For all tests, a *P* value of  $<.05$  was considered statistically significant. Analysis was performed using SPSS 17.0 software (IBM, Armonk, NY) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Clinical and demographic data

A total of 226 patients who underwent CMR before ICD implantation for primary prevention were included. Twenty-six patients were excluded because of insufficient CMR image quality, and finally a total of 200 patients were evaluated. Baseline characteristics are listed in Table 1. The mean age of the study population was  $60.9 \pm 10.9$  years; 81.5% (163) were men; and 52% (104) had ischemic cardiomyopathy (ICM). A combined cardiac resynchronization therapy-defibrillator device was implanted in 101 patients (50.5%). Of the 200 patients, 34 did not have LGE in CMR, and of these 34 patients, 30 had nonischemic cardiomyopathy (NICM) and 4 had ICM.

### Predictors of appropriate therapies and SCD

During a median follow-up of  $4.6 \pm 2$  years, 43 patients (21.5%) reached the primary end point. From those 43

**Table 1** Baseline characteristics of the study population (N = 200)

Characteristic	Value
Age (y)	60 $\pm$ 10.9
Male sex	81.5 (163)
Ischemic cardiomyopathy	52 (104)
Smoker	20 (40)
Hypertension	71 (142)
Diabetes	34.5 (69)
Dyslipidemia	61 (122)
eGFR (mL/min)	65.5 $\pm$ 56
NYHA class	
I	19.1
II	52.5
III	27.9
IV	0.5
Complete revascularization	62.5 (125)
$\beta$ -Blocker therapy	90.5 (181)
Amiodarone therapy	10.5 (21)
Echocardiographic parameters	
LVEF (%)	29 $\pm$ 10.1
LVEDD (mm)	63.06 $\pm$ 12
LVESD (mm)	49.3 $\pm$ 12
CMR parameters	
LVEF (%)	26.2 $\pm$ 9.8
LVEDV (mL)	294.4 $\pm$ 100
LVESV (mL)	220.4 $\pm$ 97

Values are presented as mean  $\pm$  SD or percentage and (n).

CMR = cardiac magnetic resonance; eGFR = estimated glomerular filtration rate; LVEDD = left ventricle end-diastolic diameter; LVEDV = left ventricle end-diastolic volume; LVEF = left ventricle ejection fraction; LVESD = left ventricle end-systolic diameter; NYHA = New York Heart Association.

patients who reached the primary end point, 23 patients (53.5%) presented ventricular arrhythmias (VAs) detected in the VT zone, 8 patients (18.6%) in the VF zone, and 12 patients (27.9%) presented VAs in both zones. Only shocks in the VF zone were delivered to 8 patients (18.6%), 16 patients (37.2%) received only antitachycardia pacing in the VT zone, and 19 patients (44.2%) received a combination therapy of antitachycardia pacing plus shocks. The event rate was not different in patients with ICM (26%) from that in patients with NICM (16.7%) ( $P = .2$ ) and neither in patients with and without resynchronization therapy ( $P = .3$ ).

Competing risk analysis with cumulative incidence plots of appropriate ICD therapy with death as the competing event was performed. The clinical characteristics and CMR parameters for the prediction of appropriate ICD therapy are listed in Table 2. Neither LVEF and ventricular diameters assessed by echocardiography and neither the presence of comorbidities as hypertension and diabetes were not associated with appropriate therapies.

According to the clinical parameters, patients who received appropriate therapy were younger (hazard ratio [HR] 0.96; 95% confidence interval [CI] 0.93–0.96;  $P = .003$ ) and less likely to have complete revascularization (HR 0.52; 95% CI 0.29–0.95;  $P = .03$ ).

According to the CMR parameters, the volumes and all scar parameters were significantly associated with the primary end point: left ventricular end-diastolic volume

**Table 2** Univariable analysis for the primary end point (appropriate ICD therapies) (N = 200)

Variable	No appropriate therapy (n=157)	Appropriate therapy (n=43)	HR	95% CI	P
Male sex	79.6	88.4	0.62	0.24–1.59	.32
Age (y)	62 ± 10	56.8 ± 12.8	0.96	0.93–0.96	<b>.003</b>
Ischemic cardiomyopathy	49	62.8	1.49	0.81–2.76	.2
Smoker	16.6	32.6	0.86	0.63–1.19	.37
Hypertension	71.3	69.8	0.87	0.45–1.68	.68
Diabetes	35.7	30.2	0.80	0.42–1.53	.49
Dyslipidemia	60.5	62.8	1.12	0.61–2.07	.72
eGFR mL/(min·1.73 m <sup>2</sup> )	66 ± 20	63.9 ± 19.3	1.00	0.98–1.01	.81
CVA	10.2	11.6	1.08	0.46–2.54	.86
NYHA class III–IV	27.2	33.3	1.22	0.61–2.43	.58
Complete revascularization	65.6	51.2	0.52	0.29–0.95	<b>.03</b>
β-Blocker therapy	91.1	88.4	0.85	0.34–2.13	.73
Amiodarone therapy	10.8	9.3	0.78	0.29–2.11	.62
Echocardiographic parameters					
LVEF (%)	29.1 ± 10.3	28.6 ± 9.1	1	0.97–1.03	.83
LVEDD (mm)	62.9 ± 12.3	63.8 ± 10.6	1.01	0.98–1.03	.54
LVESD (mm)	48.9 ± 12.6	50.9 ± 11.1	1.01	0.99–1.04	.31
CMR parameters					
LVEF (%)	26.6 ± 10	23.9 ± 8.7	0.97	0.94–1.01	.16
LVEDV (mL)	282.2 ± 96.6	352.2 ± 110	1	1–1.01	<b>.003</b>
LVESV (mL)	211.8 ± 92.8	252 ± 107.3	1	1–1.01	<b>.004</b>
Presence of LGE	78.9	97.7	10	1.34–74.8	<b>.025</b>
Scar mass (g)	21.7 ± 10	36.2 ± 19	1.04	1.03–1.05	<.001
Scar mass > 10 g	77.07	95.3	4.74	1.12–20	<b>.034</b>
BZ mass (g)	16 ± 9.5	26.4 ± 12.5	1.06	1.04–1.07	<.001
Core mass (g)	5.5 ± 5.7	9.9 ± 8.6	1.06	1.04–1.09	<.001
Presence of channels	58.6	88.3	4.07	1.59–10.4	<b>.003</b>
Channel mass (g)	1.6 ± 2.3	3.0 ± 2.6	1.15	1.06–1.25	<b>.001</b>
Number of channels	1.2 ± 1.4	11.3 ± 2.6	1.25	1.11–1.4	<.001

Values are presented as mean ± SD or percentage and absolute value unless stated otherwise.

Bold values are statistically significant.

BZ = border zone; CVA = cerebrovascular accident; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; other abbreviations as in Table 1.

(352.2 ± 110 mL vs 282.2 ± 96.6 mL;  $P = .003$ ), left ventricular end-systolic volume (252.0 ± 107.3 mL vs 211.8 ± 92.8 mL;  $P = .004$ ), scar mass (36.2 ± 19 g vs 21.7 ± 10 g;  $P < .001$ ), BZ mass (26.4 ± 12.5 g vs 16.0 ± 9.5 g;  $P < .001$ ), core mass (9.9 ± 8.6 g vs 5.5 ± 5.7 g;  $P < .001$ ), and CCs mass (3.0 ± 2.6 g vs 1.6 ± 2.3 g;  $P < .001$ ), as shown in Figure 2. Likewise having scar mass > 10 g was a strong predictor of appropriate therapies (25.31 vs 5.26%; HR 4.74; 95% CI 1.12–20;  $P = .034$ ).

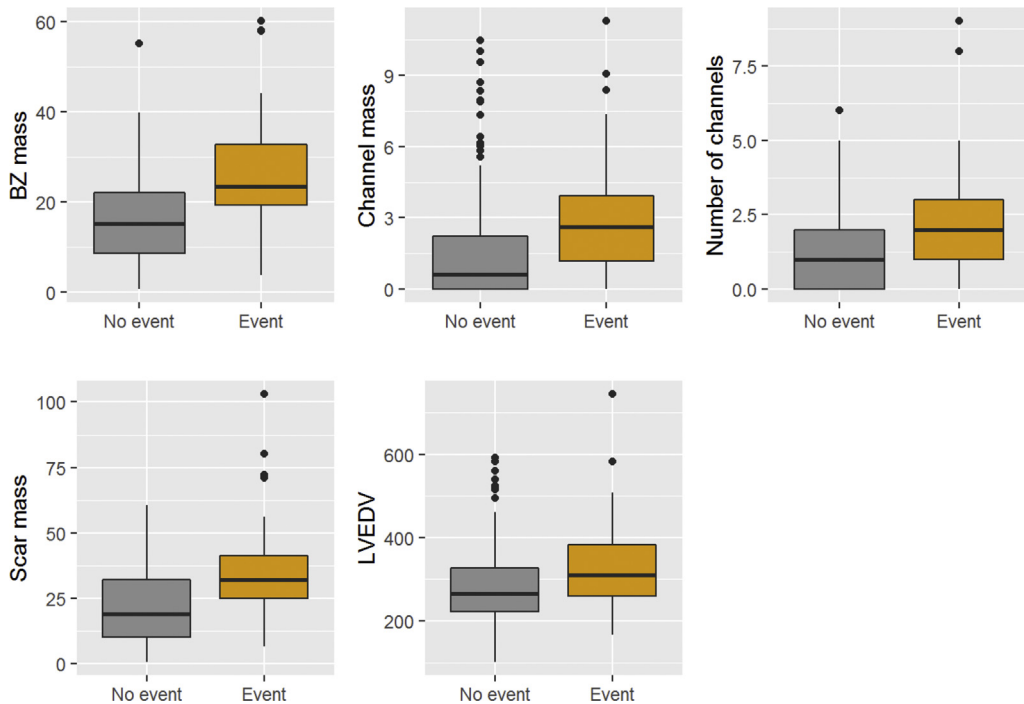
Additionally, at 6-year follow-up, 34.75% of patients with CCs reached the primary end point compared with 8.93% without CC (34.72% vs 8.93%; HR 4.07; 95% CI 1.59–10.4;  $P = .003$ ) (Figure 3).

An additional analysis has been performed differentiating patients with VT from patients with only VF during follow-up. In patients with VT, all scar-related parameters were related with the primary end point (scar mass: HR 1.04; 95% CI 1.03–1.06;  $P < .001$ ; BZ mass: HR 1.06; 95% CI 1.04–1.09;  $P < .001$ ; core mass: HR 1.08; 95% CI 1.05–1.1;  $P < .001$ ; channel mass: HR 1.2; 95% CI 1.1–1.3;  $P < .001$ ; presence of channels: HR 5.69; 95% CI 1.75–18.8;  $P = .004$ ; and scar mass > 10 g: HR 7.82; 95% CI 1.06–57.8;  $P = .04$ ). In patients with VF, only scar mass (HR 1.03; 95% CI 1.03–1.04;  $P < .001$ ), BZ mass (HR 1.04;

95% CI 1.01–1.07;  $P = .002$ ), and core mass (HR 1.06; 95% CI 1.03–1.1;  $P < .001$ ) were related with primary end point. However, channel mass (HR 1.12; 95% CI 0.99–1.26;  $P = .07$ ), the presence of channels (HR 3.02; 95% CI 0.88–10.4;  $P = .08$ ), and scar mass > 10 g (HR 4.38; 95% CI 0.58–33.2;  $P = .15$ ) did not reach statistical significance, probably owing to the low number of patients with VF.

Multivariable Cox regression analysis was performed using the covariables age, complete revascularization, left ventricular end-diastolic volume, BZ mass, and the presence of CCs. All of them were independent predictors of the primary end point (Table 3). In addition, 4 different multivariable analysis models including MADIT risk score<sup>10</sup> and different CMR scar parameters were used. In all models, scar parameters were independent predictors of the primary end point.

Finally, following a previous study in patients of our group who underwent cardiac resynchronization therapy (CRT),<sup>11</sup> we developed an algorithm on the basis of the amount of scar tissue and the presence or absence of CCs to identify patients predicted to receive appropriate therapies. As we can see in Figure 4, those patients with scar mass < 10 g and without CCs had very low risk of having VA during follow-up with respect to those with scar mass > 10 g and



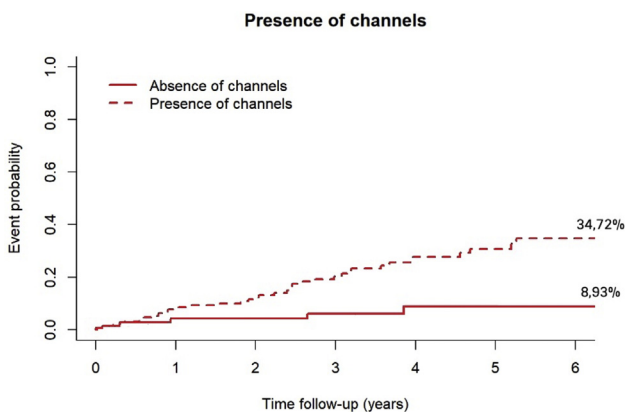
**Figure 2** Plot showing the distribution of border zone mass, channel mass, number of channels, scar mass, and LVEDV in patients with and without appropriate therapy for ventricular arrhythmias. LVEDV = left ventricle end-diastolic volume; other abbreviation as in Figure 1.

CCs (HR 9.31; 95% CI 1.25–69.3;  $P = .029$ ). Moreover, from those 36 patients with scar mass  $< 10$  g and without CCs, only 1 reached the primary end point (negative predictive value 97.2%). In contrast, from those 164 patients who had scar mass  $> 10$  g and/or CCs, 42 patients reached the primary end point (positive predictive value 25.6%).

### Predictors of all-cause mortality

Among patients in this cohort, 30 patients (15%) died. Non-cardiovascular death was reported in 10 patients (5%), and cardiovascular death was reported in 20 (10%) (heart failure, recurrent myocardial infarction, or arrhythmic storm).

In the univariable Cox regression analysis (Table 4), advanced age (HR 1.06; 95% CI 1.01–1.19;  $P = .009$ ), lower estimated glomerular filtration rate (eGFR) (HR 0.97; 95% CI 0.95–0.99;  $P = .001$ ), diabetes (HR 3.1; 95% CI 1.44–6.7;  $P = .004$ ), prior cerebrovascular accident (CVA) (HR 2.95; 95% CI 1.25–6.98;  $P = .03$ ), and higher New York Heart Association (NYHA) class (HR 2.96; 95% CI 1.32–6.66;  $P = .008$ ) were associated with all-cause mortality. None of the echocardiographic parameters except LVESD ( $54.53 \pm 11.07$  mm vs  $48.46 \pm 12.31$  mm;  $P = .01$ ) were associated with the secondary end point. The presence or absence of LGE was not associated with all-cause mortality, nor were any of the scar parameters except the presence of CCs (HR 2.88; 95% CI 1.00–8.35;  $P = .04$ ). Nevertheless, when multivariable Cox regression analysis was performed using the covariables age, diabetes, eGFR, NYHA class, prior CVA, LVESD measured by echocardiography, and the presence of CCs, only the clinical parameters eGFR, NYHA class III–IV, and prior CVA were associated with all-cause mortality (Table 3).



**Figure 3** Primary end point cumulative incidence. Cumulative incidence functions for the primary end point appropriate therapies depending on the presence or absence of channels. At 6-year follow-up, 34.72% of patients with channels reached the primary end point compared with 8.93% of patients without channels.

## Discussion

### Main findings

The presence of LGE and CCs, scar mass, BZ mass, and CCs mass were strong predictors of appropriate ICD therapies in patients with ICM and NICM who received an ICD for primary prevention. Even more important from our point of view, patients without CCs and with scar mass  $< 10$  g were at very low risk of having appropriate therapies, with a high negative predictive value.

**Table 3** Multivariable competing risk regression analysis for the primary and secondary end points and for the association between the MADIT risk score and the CMR parameters and the study end point of ICD therapies

Variable	HR (95% CI)	P
Multivariable competing risk regression analysis for the primary and secondary end points		
<i>Appropriate ICD therapies</i>		
Age	0.95 (0.92–0.98)	<b>&lt;.001</b>
Complete revascularization	0.53 (0.30–0.97)	<b>&lt;.001</b>
LVEDV	1.003 (1.00–1.01)	<b>&lt;.001</b>
BZ mass	1.045 (1.03–1.07)	<b>&lt;.001</b>
Presence of channels	2.849 (1.06–7.70)	<b>.039</b>
<i>Mortality</i>		
Age	1.00 (0.94–1.06)	.99
Diabetes	2.71 (1.08–6.8)	.16
eGFR (mL/min)	0.97 (0.95–0.99)	<b>.005</b>
CVA	3.03 (1.04–8.83)	<b>.04</b>
NYHA class III–IV	2.19 (1.13–4.25)	<b>.02</b>
Presence of channels	2.16 (0.73–6.40)	.16
Multivariable analysis for the association between MADIT risk score and CMR parameters to predict appropriate ICD therapies		
<i>Model 1</i>		
MADIT score	1.10 (0.96–1.25)	.17
Scar mass	1.03 (1.02–1.05)	<b>&lt;.001</b>
<i>Model 2</i>		
MADIT score	1.11 (0.98–1.27)	.11
Border zone mass	1.05 (1.03–1.07)	<b>&lt;.001</b>
<i>Model 3</i>		
MADIT score	1.12 (0.98–1.27)	.09
Core mass	1.06 (1.03–1.08)	<b>&lt;.001</b>
<i>Model 4</i>		
MADIT score	1.18 (1.03–1.34)	<b>.01</b>
Channel mass	1.15 (1.05–1.25)	<b>&lt;.01</b>

Bold values are statistically significant.

MADIT = Multicenter Automatic Defibrillator Implantation Trial; other abbreviations as in Tables 1 and 2.

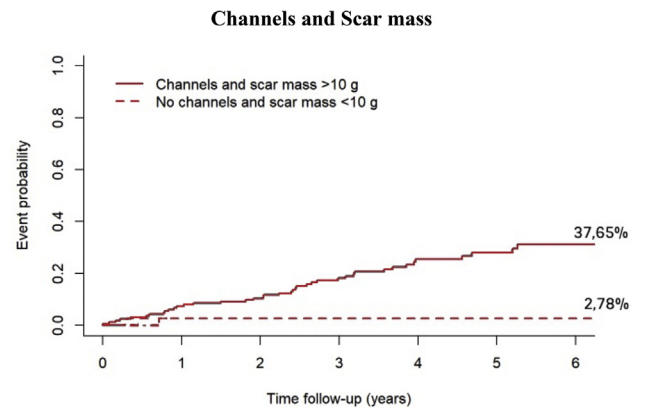
**Scar and VA**

There is a general consensus that current LVEF criteria for identifying patients at high risk of SCD is far from ideal.<sup>12</sup> Given the well-established relation between fibrosis and VA,<sup>13</sup> there is an increasing interest in analyzing the role of CMR in stratifying the risk and in deciding the need for an ICD. Nevertheless, we are still far from the end of the road, and further effort to better stratify the risk of SCD is needed.

In our population, the majority of patients had LGE in CMR images (83%), but, despite this high prevalence of LGE, only 21.55% of them received therapies in follow-up. Therefore, the presence or absence of LGE in CMR alone is probably not sufficient and a better characterization of the scar could improve risk stratification.

In a previous study in patients who underwent CRT,<sup>11</sup> it was already demonstrated that both fibrosis and the BZ mass and CC mass were related to arrhythmic events. However, many patients in that study were carrying CRT pacemakers without defibrillator capacity, so some VAs could have not been detected.

Our study confirms those results in patients with and without CRT and, in addition to the amount of scar tissue, is, to our knowledge, the first to analyze the relation between



**Figure 4** Cumulative incidence functions for the primary end point appropriate therapies depending on scar mass > 10 g and the presence of channels. At 6-year follow-up, 37.65% of patients with channels and scar mass > 10 g reached the primary end point compared with 2.78% of patients without channels and scar mass < 10 g.

CCs and arrhythmic events in a population with ICD. Actually, the CCs of BZ tissue are the main substrate for reentrant VTs, and CMR has been shown to be able to detect these CCs.<sup>14</sup> If confirmed by other studies, the presence of CCs, in addition to the presence of LGE itself, would be helpful for evaluating the risk of SCD in patients with decreased LVEF.

In our population, as shown in Figure 4, the risk of arrhythmic events at 6-year follow-up in patients with a small scar (<10 g) and without CCs was very low as compared with the risk in patients with scar mass > 10 g and CCs (2.8% vs 31.2%).

Furthermore, the negative predictive value for patients with no CCs and scar mass < 10 g (who represent the 18% of our cohort) was very high (97.2%). If results are confirmed with larger trials, the benefit of ICD implantation for primary prevention in this group of patients should be discussed.

Among the clinical factors analyzed, incomplete revascularization was shown to be a predictor of the primary end point in addition to scar parameters. Incomplete revascularization (untreated severe lesions or chronic total occlusion) has been related with VAs<sup>15</sup> and with appropriate ICD therapy in primary prevention.<sup>16</sup> Although the mechanism is not clear, incomplete revascularization could be linked to ischemia, which could potentially act as a trigger of VA. Younger age as a predictor for ICD therapy, already suggested by other studies,<sup>17</sup> could be the result of competing events. In addition, a multivariable analysis was performed to check the value of CMR against MADIT risk score,<sup>10</sup> and in all models, scar-related CMR parameters were independent predictors of appropriate therapies.

Finally, in our population, ICM was not a predictor of appropriate therapy compared with those having NICM. However, the study probably lacked sufficient power to analyze the differences between patients with ICM and those with NICM. Indeed, from our cohort, only 34 patients (16.5%) did not have LGE in CMR (30 patients with NICM and 4 with ICM). Therefore, this supports the

**Table 4** Univariable analysis for the secondary end point (mortality) (N = 200)

Variable	Alive	All-cause mortality	HR	95% CI	P
Male sex	80.6	86.7	0.78	0.27–2.25	.63
Age (y)	59.8 ± 10.6	66.4 ± 11.1	1.06	1.01–1.19	<b>.009</b>
Ischemic cardiomyopathy	51.2	56.7	0.91	0.43–1.91	.80
Smoker	20.6	16.7	0.83	0.29–2.4	.93
Hypertension	69.4	80	1.94	0.77–4.87	.13
Diabetes	31.3	53.3	3.1	1.44–6.7	<b>.004</b>
Dyslipidemia	58.8	73.3	1.78	0.79–4.03	.15
eGFR (mL/min)	68.15 ± 19.1	50.3 ± 16.9	0.97	0.95–0.99	<b>.001</b>
CVA	8.2	23.3	2.95	1.25–6.98	<b>.026</b>
NYHA class III–IV	24.1	56	2.96	1.32–6.66	<b>.008</b>
Complete revascularization	65.9	43.3	0.47	0.22–1.01	.055
β-Blocker therapy	92.4	80	0.6	0.23–1.55	.314
Amiodarone therapy	10.6	10	0.85	0.26–2.84	.792
Echocardiographic parameters					
LVEF (%)	29.4 ± 10.6	26.8 ± 6.1	0.96	0.91–1.01	.071
LVEDD (mm)	62.4 ± 12.2	66.9 ± 9.5	1.03	0.99–1.08	.067
LVESD (mm)	48.4 ± 12.3	54.5 ± 11.1	1.04	1.01–1.08	.01
CMR parameters					
LVEF (%)	26.5 ± 10	23.3 ± 7.5	0.97	0.92–1.01	.135
LVEDV (mL)	287.8 ± 97.4	311 ± 118.6	1.00	1–1.01	.197
LVESV (mL)	217 ± 97.3	239 ± 106.8	1	1–1.01	.217
Presence of LGE	82.4	86.6	1.22	0.42–3.51	.71
Scar mass (g)	24.1 ± 16.1	29 ± 16.3	1.01	0.99–1.04	.2
BZ mass (g)	17.7 ± 10.9	21.3 ± 11.6	1.02	0.99–1.05	.2
Core mass (g)	6.4 ± 6.7	7.7 ± 5.9	1.03	0.98–1.08	.34
Presence of channels	61.2	86.7	2.88	1.0–8.34	<b>.04</b>
Channel mass (g)	1.9 ± 2.5	2.3 ± 2.5	1.04	0.9–1.2	.59
Number of channels	1.39 ± 1.5	2.3 ± 2.5	1.04	0.9–1.2	.76

Values are presented as mean ± SD or percentage and absolute value unless stated otherwise.

Bold values are statistically significant.

CI = confidence interval; LGE = late gadolinium enhancement; other abbreviations as in Tables 1 and 2.

usefulness of CMR to assess the risk of VA in patients with NICM, providing additional prognostic information beyond LVEF (because what truly matters is the presence of LGE, CCs, and the amount of scar).

### Scar parameters and mortality

The scar parameters were not related to mortality in our study, which was not designed to detect a beneficial effect on the survival of patients with ICD and depressed LVEF, as everybody received an ICD. In this sense, it can be hypothesized that the ICD prevented an important number of deaths—the arrhythmia-related death that is the main cause of death related with the scar parameters. As the population was young (61 years), it can be assumed that the risk of non-arrhythmic death in this group is lower than in older populations. This could explain, at least partially, why the amount of scar tissue has not been shown to be a predictor of total death, as everybody was protected by an ICD, supporting the benefit of ICD implantation.

In the multivariable Cox regression analysis, only having a lower eGFR, prior CVA, and NYHA class III–IV were predictors of mortality. LVEF also tended to be worse in those patients who died, but this association did not reach statistical significance. Because the inclusion criterion was LVEF < 35%, the study could also be insufficiently powered to find significant differences in LVEF between groups.

The survival benefit of primary prevention ICD implantation is better established in patients with ICM. However, there are controversies regarding this benefit in patients with NICM. In the DANISH-MRI trial,<sup>18</sup> fibrosis was shown to be an independent predictor of all-cause mortality and arrhythmic events. Nevertheless, no benefit of ICD was observed in relation to the presence or absence of fibrosis. In this setting, an observational study conducted by Gutman et al<sup>19</sup> demonstrated a survival benefit associated with the implantation of an ICD for primary prevention in NICM only for patients with scar tissue on CMR whereas no benefit was shown in patients without scar. Given these controversial results, the risk stratification of SCD based on CMR in NICM requires additional larger randomized studies.

To conclude, we strongly believe in the utility of scar characterization with CMR for the risk stratification of VA and SCD in both ICM and NICM, with a relevant role of CC. A small scar mass (<10 g) and the absence of CCs, if validated by other studies, could identify patients without clear benefit of ICD in primary prevention.

### Limitations

The study was performed in a cohort from a single center, so it could be susceptible to selection bias. Other limitation of this study is the low incidence of the primary and secondary end points (although they are similar to those reported in

previous studies). Furthermore, the sample size was not sufficient for performing more detailed subgroup analyses, for example, according to the type of arrhythmic event. In this sense, very few women were enrolled (only 18.5%); therefore, these results could not be applicable to women. Finally, patients with moderate to severe renal failure were not included in the study as CMR was contraindicated.

Finally, another important limitation is that as in previous ICD trials, shocks were considered a surrogate for SCD; nevertheless, it is not clear that the number of shocks is equivalent to the mortality.

## Conclusion

Scar mass, BZ mass, and CCs mass are predictors of appropriate therapy in patients eligible to receive an ICD for primary prevention. A combined algorithm with scar mass (with 10 g as a cutoff) and the presence or absence of CCs could improve the risk stratification of SCD with a very high negative predictive value. Scar assessment and scar characterization are likely superior to LVEF for the risk stratification of SCD, but to support this recommendation, further research is needed.

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