Chapter 2
Risk Stratification Beyond Left Ventricular Ejection Fraction: Role of Cardiovascular Magnetic Resonance

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Introduction

In the United States, sudden cardiac death (SCD) affects 184,000–462,000 individuals per annum [1]. In Europe, annual incidence of SCD ranges between 50 and 100 per 100,000 population [2]. Although not all SCDs are due to ventricular tachyarrhythmias, up to 80% of out-of-hospital cardiac arrests are due to ventricular tachycardia (VT) or ventricular fibrillation (VF) [3, 4]. Whilst coronary heart disease accounts for most cases, around 20% are attributable to non-ischaemic causes or channelopathies.

Prominent amongst the purposes of risk stratification for SCD is the identification of patients who may benefit from implantable cardioverter defibrillator (ICD) therapy, the only life-saving therapy for patients at risk of SCD. In patient selection, clinical guidelines on primary prevention ICD therapy have adopted left ventricular ejection fraction (LVEF<30% or 40%) as the main criterion. Whilst randomized, controlled trials adopting a low LVEF as a risk stratifier have indeed shown a benefit from ICDs, it is well recognized that LVEF is a poor predictor of SCD in patients with or without cardiac disease. Moreover, most patients who succumb to a SCD fall outside the LVEF cut-offs recommended for primary prevention ICD implantation. In addition, most patients who actually receive an ICD do not develop ventricular arrhythmias (VAs) requiring ICD therapy [5].

Some authors have proposed that the myocardial phenotype could be a better predictor of ventricular arrhythmias (VAs) than LVEF [6]. Cardiovascular magnetic resonance (CMR) is now the gold standard for the characterization of myocardial phenotypes. By means of late gadolinium enhancement, CMR can inform on the quantity and patterns of myocardial scar. This review focuses on how CMR can

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J. S. Steinberg, A. E. Epstein (eds.), *Clinical Controversies in Device Therapy for Cardiac Arrhythmias*, https://doi.org/10.1007/978-3-030-22882-8_2

contribute to the arrhythmic risk stratification of patients with ischaemic (ICM) and non-ischaemic (NICM) cardiomyopathy and how it may help in selecting patients for an ICD.

What Is 'High Risk' of SCD?

There is no consensus as to what constitutes a 'high risk' of SCD in patients with ICM or NICM. There is, however, consensus in patients with hypertrophic cardiomyopathy. In the latter, an estimated 6% over 5 years, which equates to an annual risk of 1.2%, is considered high enough to recommend ICD therapy. However, the annual risk of SCD in ICM and NICM is as high as 2.6% (Fig. 2.1). On this basis, one could propose that a patient with ICM or NICM with an estimated 6% risk of SCD over 5 years should be considered for an ICD.

Definition of Cardiomyopathy

In the ACC/AHA/HRS 2006 Key Data Elements and Definitions for Electrophysiological Studies and Procedures, idiopathic cardiomyopathy is defined as 'heart failure and reduced systolic function without evidence of other cardiomyopathies, including toxic cardiomyopathy, inflammatory myocarditis, valvular heart disease, tachyarrhythmia-induced cardiomyopathy, hypertrophic cardiomyopathy, cardiomyopathies associated with neuromuscular disorders and arrhythmogenic right ventricular cardiomyopathy'. Outside this definition, however, there will be patients who do not have clinical signs of heart failure, who may have reduced LV

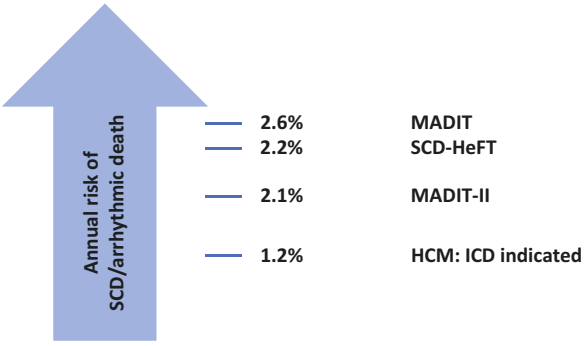


Fig. 2.1 SCD risk**.** Annual risk of sudden cardiac death (SCD) in the control (no ICD) arms of the Multicentre Automatic Defibrillator Implantation Trials (MADIT) and the Sudden Cardiac Death in Heart Failure Trials (SCD-HeFT) in relation to the level of risk for which an ICD is recommended for patients with hypertrophic cardiomyopathy (HCM)

function but a non-dilated LV or a myocardial scar but without LV dilation or LV dysfunction. Moreover, this definition does not specify cut-offs of LVEF or LV volumes, nor does it refer to the size or pattern of myocardial scar. To confound matters, the popular term 'NICM', referred to in device trials, is usually defined as LV dysfunction in the absence of coronary heart disease. In interpreting the findings of studies presented herein, the reader is advised to take into account variations in the definition of cardiomyopathy.

LVEF as a Risk Stratifier

LVEF is the most widely used imaging parameter in routine cardiology practice. Despite its limitations, elegantly discussed by Marwick [7], LVEF deserves credence in clinical decision-making, from the treatment for patients with MI to heart failure valvular heart disease and arrhythmias.

Few studies have explored LVEF in relation to SCD in the general population. In the Oregon Sudden Unexpected Death Study, a community-based study comprising 660,486 individuals, a retrospective assessment revealed that out of 121 SCD cases, LVEF before the SCD or aborted SCD was ≤35% in 17%, 36–54% in 22% and ≥55% in 48% [8]. The ability of LVEF to predict SCD in these patients, however, was poor (C-statistic, 0.57) (Fig. 2.2) [9]. In the Maastricht Circulatory Arrest

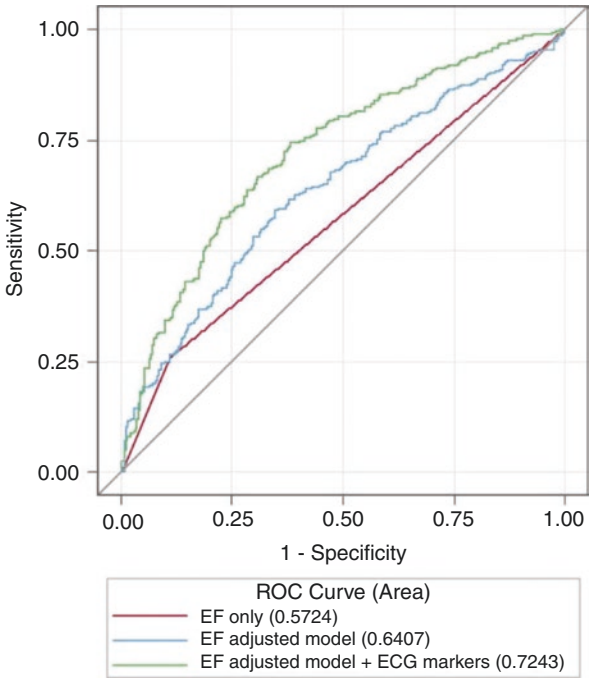


Fig. 2.2 LVEF as a predictor of SCD. Receiver operating characteristic curves for LVEF in relation to SCD. As shown, LVEF alone had poorest performance. Adjustment for age, gender, diabetes and hypertension improved performance. The adjusted model with LVEF plus ECG risk markers provided the best performance (C-statistic 0.72 vs. 0.64; $p < 0.0001$). (Reproduced with permission from Reinier et al. [9])

Registry, the predictive value of LVEF was not explored, but 51% of persons suffering a cardiac arrest had an LVEF≥50% prior to the event [10].

In the context of coronary heart disease, the first evidence in support of LVEF as a high-risk prognostic marker after a MI was provided by the Multicenter Postinfarction Research Group in the 1980s [11]. In the subsequent Canadian Assessment of Myocardial Infarction (CAMI) study, the odds ratio for 1-year mortality after MI was 9.48 for patients with LVEF≤30% and 2.94 for patients with an LVEF 30–40%, compared with patients with an LVEF>50% [12]. A similar trend was observed in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, in which cardiac mortality after MI was 7.3 higher in patients with an LVEF<35%, compared to patients with an LVEF>50% [13]. These studies showed that patients in the different LVEF categories have varying risks, but this does not equate to proof of predictive utility. This was illustrated by the Risk Estimation Following Infarction Noninvasive Evaluation (REFINE) study, in which multiple variables were considered as potential predictors of cardiac death or aborted SCD [14]. It showed that whilst patients with an LVEF≤30% had a 3.3 times higher risk of the endpoint, the receiver operating characteristic (ROC) curve was only 0.62. In the ISAR-Risk, comprising 2343 MI survivors, an LVEF≤30% emerged as a predictor of SCD at 5 years, but with a poor sensitivity (22.1%), specificity (95.4%) and positive predictive value (12.0%) [15].

In primary prevention ICD trials, there is no doubt that patients selected on the basis of LVEF derive a benefit from ICDs. In the Multicentre Automatic Defibrillator Implantation Trial II (MADIT-II) of 1232 post-MI patients with an LVEF ≤30% randomized to ICD or conventional medical therapy, mortality was lower with ICDs (14.2% vs. 19.8%) [16]. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) of patients with ICM or NICM, ICD therapy was associated with a 23% reduction in mortality, compared to amiodarone [17].

Whilst a low LVEF denotes a 'high-risk' group of patients who can benefit from ICD therapy, this does not equate to LVEF being a reliable predictor of SCD. For a prognostic biomarker to be useful, it must be able to predict clinical outcomes or treatment effect, regardless of other clinical features or biomarkers. The limited specificity of LVEF in the risk stratification for SCD relates to the fact that it is a measure of pump function, rather than arrhythmic substrates. Patients with a low LVEF may therefore succumb to pump failure rather than VAs, which amounts to a competing risk. We should also consider that predicting SCD in non-ICD recipients is not the same as predicting the effectiveness of ICD therapy. In this context, the National Heart, Lung, and Blood Institute and Heart Rhythm Society report on SCD prediction and prevention has recognized the limitations of LVEF in predicting SCD [18].

Myocardial Scar and Arrhythmias: The Paradigm

Myocardial scar is a fibroblastic response to necrosis. Whilst the core of scar is electrically inert, the surrounding tissue, which consists of a borderzone of viable

cardiomyocytes and fibrotic bundles [19, 20], is electrically active [21]. In the melting pot of the borderzone of scar, isthmuses with slow and fast conduction are the seat of VAs [22, 23]. Electrically, these substrates can be identified by abnormal electrograms, re-entry circuits and late potentials [24].

Myocardial Scar and Arrhythmias: Clinical Evidence

By virtue of its unparalleled ability to identify myocardial, CMR is the gold standard for the characterization of myocardial phenotypes (Fig. 2.3). Several identifiable 'imaging substrates' have been shown to relate to VAs, namely, the total amount of scar core or 'scar burden', the total amount of borderzone of scar and 'channels' within and between borderzones of scar.

Scar Core The obvious question is whether the total amount of scar, or scar 'burden', relates to poor outcomes. In this respect, scar burden certainly relates to poor outcomes after revascularization [25–28] and pharmacologic therapy [29]. Numerous studies have also linked total scar (scar core) with SCD and VAs. In ICM, a prospective cohort study on 137 patients referred for ICD implantation showed that a scar size >5% of the LV mass adds to the prognostic value of LVEF in predicting death or appropriate ICD therapy for VAs [30] (Fig. 2.4). In a substudy of the Multicentre Automatic Defibrillator Implantation Trial II (MADIT-II), the size of myocardial perfusion defects at rest on nuclear imaging emerged as a predictor of VAs [31]. Whilst not all studies have found a link between scar burden and arrhythmic events in ICM [32] or inducibility on electrophysiological testing [33], meta-analyses do support a link [34].

The association between scar and SCD/VAs also appears to hold in NICM. Using LGE-CMR study of 65 patients with NICM undergoing ICD therapy, Wu et al. found that the endpoint of SCD or appropriate ICD shock was reached in 22% patients with CMR evidence of scar versus 8% of patients without scar [35]. In a meta-analysis of 1488 patients with NICM from nine studies, Kuruvilla et al. showed that total myocardial scar was associated with a higher risk of SCD/aborted SCD patients (6.0% versus 1.2% in patients with no scar) [36] (Fig. 2.5). In a corroborative meta-analysis, Ganesan et al. also found that presence of scar (versus absence) was associated with hazard ratio of 4.25 for SCD or ventricular arrhythmia [34]. Importantly, this association was observed in both NICM and ICM and in patients with LVEF≥35% and LVEF>35%.

Even within the positive studies showing a link between scar burden and SCD/VAs, there is no validated cut-off of myocardial scar that one could adopt as a predictor of SCD in clinical practice. Therefore, scar burden should not, by itself, be used as a predictor SCD or as indication for an ICD.

Borderzone of Scar As discussed above, the borderzone of scar constitutes the arrhythmic substrate. Intuitively, therefore, the borderzone of scar should be a better

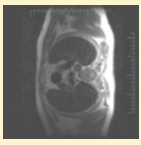
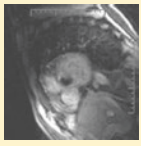
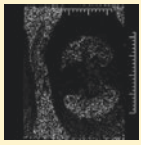
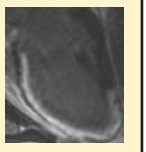
IMAGES	FOCUS	SEQUENCES	COMMENTS
	**STRUCTURE**	T1-weighted, contiguous slices from lung apices to diaphragm	Static 'black blood' images delineate cardiac structure
	**WALL MOTION**	Cine steady-state-in free precession imaging (25 phases per cardiac cycle) from mitral valve place to apex	'White blood' cine images provide information on global and segmental wall motion. In post-processing, segmentation of short axis stack is used to quantify LV volumes and LVEF. Signal loss within 'white blood' indicates high velocity or turbulence
	**PERFUSION**	Saturation-recovery imaging with gradient echo-echo planar, or steady-state-in free precession imaging 2 min after contrast administration	Perfusion defects are seen as myocardial signal loss within 2 min of gadolinium contrast administration. This can be combined with stress agents, such as adenosine.
	**HEMODYNAMICS**	Phase contrast imaging for assessment of velocity and volumes across valves.	In post-processing, velocity can be measured to assess valvular gradients.
	**VIABILITY**	Phase-sensitive inversion recovery gradient echo in short axis and long axis planes to cover entire LV, 10 min after contrast administration	In this 'white blood scan', myocardial scar appears white and viable myocardium appears 'black' after appropriate 'nulling' of viable myocardium. Signal intensity thresholds are used to define normal myocardium (≤30%), scar core (≥50%) and borderzoneof scar (30% to 50%).

Fig. 2.3 A CMR scan. Brief description and interpretation of a basic gadolinium enhancement CMR scan

predictor of VAs than the scar core. In an early study, Schmidt et al. found that borderzone of scar predicted inducibility for VT on electrophysiological testing, whilst neither scar burden (core) nor LVEF emerged as predictors [33]. In a study of 91 patients with a previous MI, Roes et al. found that borderzone of scar, but not scar core, predicted VAs requiring ICD therapy (Fig. 2.6) [32]. Jablonowski et al.

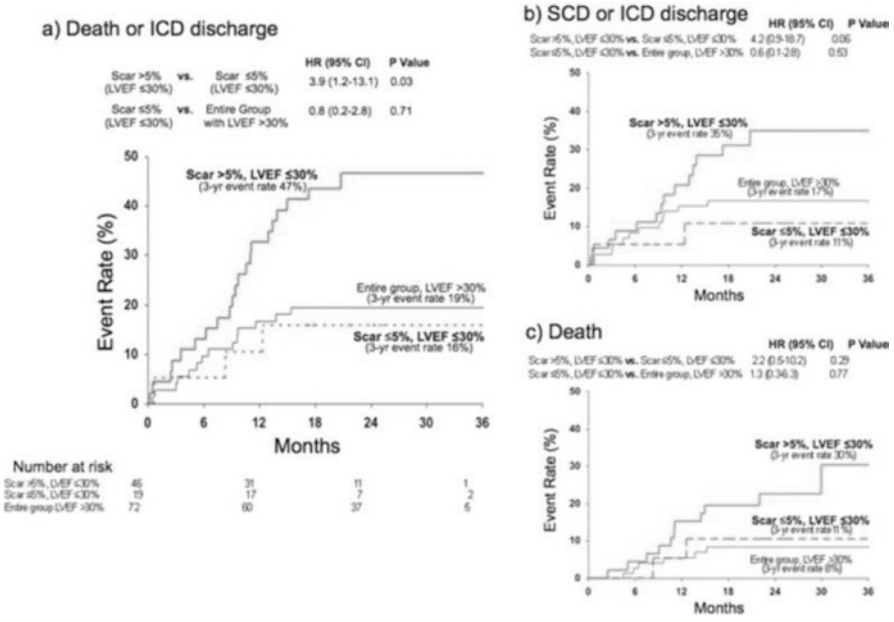


Fig. 2.4 Myocardial scar and LVEF in relation to outcomes in patients with ischaemic cardiomyopathy. Kaplan–Meier estimates of patient outcomes according to LVEF and scar burden. As shown, patients with LVEF ≤30% and myocardial scar>5% of LV mass had a higher event rate than those with myocardial scar (≤5%) for both the primary (panel **a**) and the two secondary endpoints (panels **b**, **c**). Patients with LVEF ≤30% and minimal or no scarring had similar event rate to the entire group of patients with LVEF>30%

also explored the predictive utility of different post-processing algorithms in risk stratification of patients with ICM or NICM [37]. They found that in ICM, border-zone measured by various methods consistently predicted ICD therapy (negative predictive value of 92%) in ICM. In NICM, however, only total scar and not border-zone emerged as a predictor.

Scar Patterns Myocardial scar patterns depend on and are a marker of etiology. In coronary heart disease, ischaemia resulting from coronary artery occlusion initially leads to injury of the subendocardium. With increasing ischaemia, injury involves the mid-myocardium and ultimately the epicardium. Consequently, myocardial scar in ICM runs from the subendocardium and becomes transmural, within coronary artery territories. In contrast, myocardial injury in NICM scar is typically patchy, usually in a mid-myocardial or epicardial distribution that does not follow coronary artery territories [38].

In an early study of the relationship between scar transmurality and arrhythmogenesis, Nazarian et al. found that scar with a transmurality of 26–75% was predictive of inducible ventricular tachycardia (odds ratio, 9.125; $P = 0.020$), independent of LVEF [39]. More recent studies have shown that midwall scar, which is found in

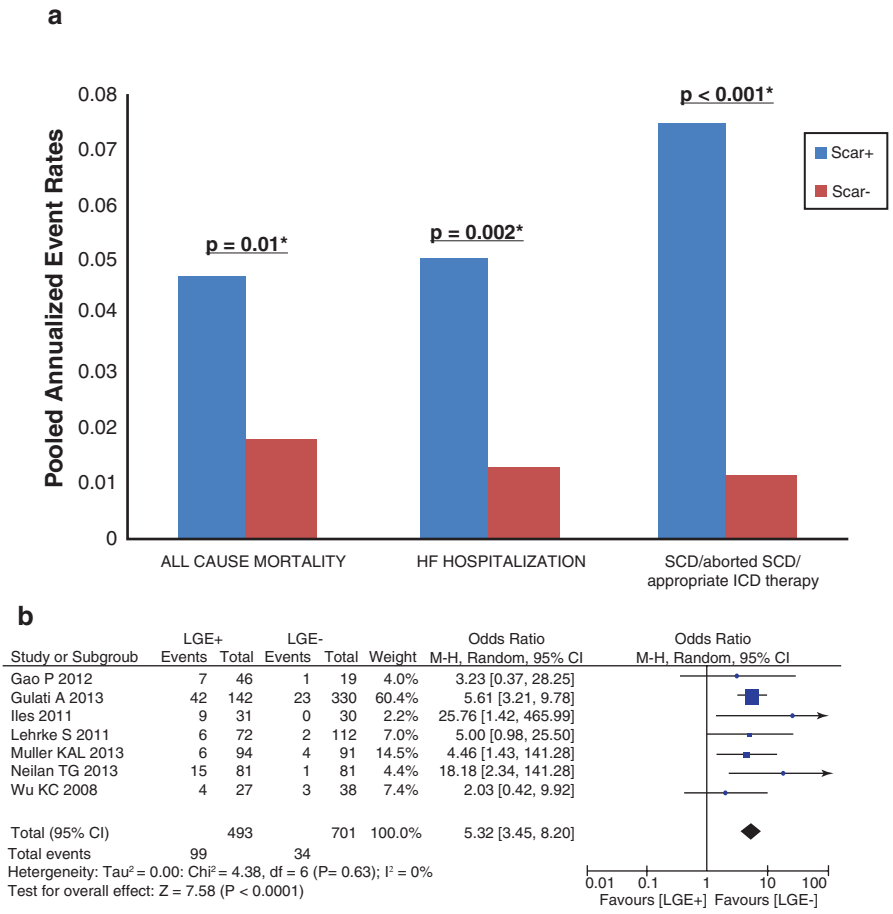


Fig. 2.5 Myocardial scar and SCD. Panel A shows weighted mean annualized event rates of cardiovascular outcomes according to the presence (+) or absence (−) of myocardial scar on late gadolinium enhancement (LGE) CMR (p values refer to scar+ and scar- groups). Panel B shows individual and pooled risk of cardiovascular outcomes for LGE CMR as well as a forest plot comparing clinical outcomes of patients with known or suspected NICM with positive LGE+ and LGE-. CI indicates confidence interval. (Adapted from Kuruvilla et al. [36])

approximately 30% of patients with idiopathic dilated cardiomyopathy, also relates to SCD and VAs. In a study of 472 patients with dilated cardiomyopathy, Gulati et al. showed that midwall scar was associated with SCD (adjusted HR, 4.61, compared to patients with no midwall scar) [40] (Fig. 2.7). In patients undergoing CRT-P, Leyva et al. found that midwall scar was associated with an 18.5-fold risk of death from cardiovascular causes [41]. In a further study from this group, cardiac resynchronization therapy with defibrillation (CRT-D) was superior to CRT pacing in patients with NICM and midwall scar, but not in patients without midwall scar (Fig. 2.8) [42].

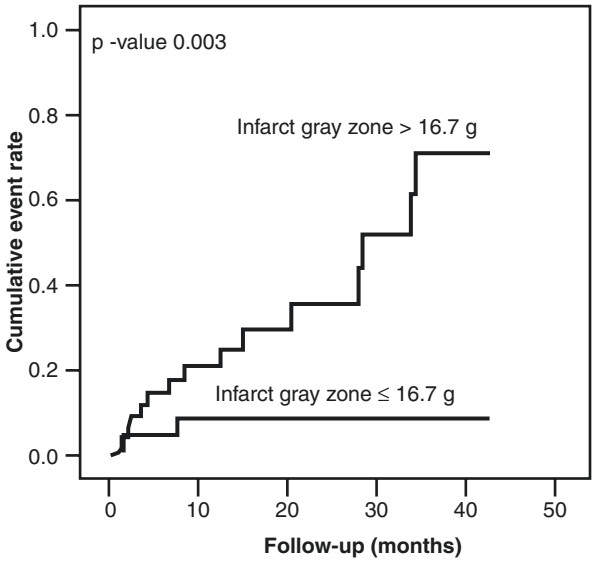


Fig. 2.6 Borderzone of scar and outcomes. Kaplan–Meier curve analysis rate of appropriate ICD therapy when ICD recipients are stratified according to the median value of infarct borderzone (grey zone). (Reproduced with permission from Roes et al. [32])

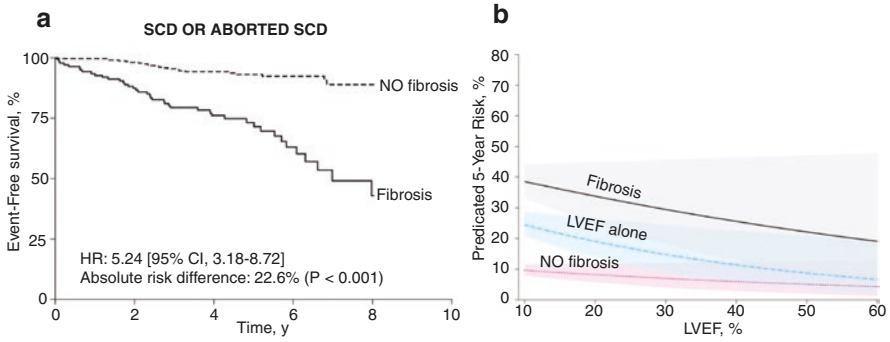


Fig. 2.7 Myocardial scar and SCD in NICM. Panel (**a**) shows Kaplan–Meier estimates of survival (left) in 472 patients with NICM patients with dilated cardiomyopathy, according to the presence or absence of myocardial scar on CMR. Panel (**b**) shows predicted 5-year risk of all-cause mortality (upper graphs) and sudden cardiac death (SCD)/aborted SCD according to LVEF. Shaded areas represent 95% confidence intervals. (Adapted with permission from Gulati, et al. [40])

Channels Continuity of borderzone of scar creates 'channels' that can potentially harbour re-entry circuits. Berruezo's group has devised a method for identifying channels using CMR (Fig. 2.9). In a study of 21 patients with MI and VT, they used a three-dimensional high-resolution 3 Tesla acquisition to explore the relationship of channels of borderzone and critical isthmuses, identified using electroanatomic mapping (CARTO). They found that CMR-defined borderzone channels identified 74% of the critical isthmus of clinical VTs and 50% of all the channels identified by electroanatomic mapping [43]. In a study of 217 patients (39.6% ischaemic), this group also showed that among patients with scar (57.6%), those with ICD therapies

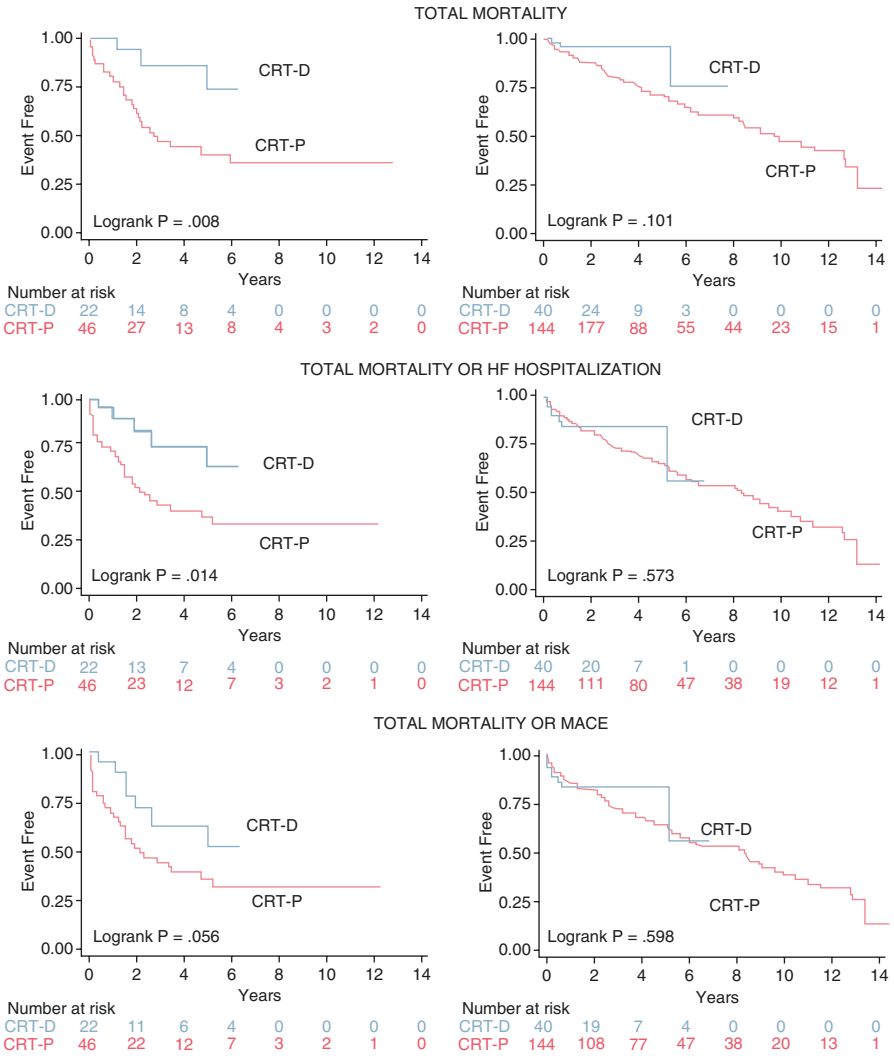


Fig. 2.8 Outcomes of CRT in patients with NICM and midwall scar. Kaplan–Meier survival curves for outcomes after CRT with (CRT-D) and without (CRT-P) defibrillation in patients with NICM, according to presence or absence of midwall scar. (Adapted with permission from Leyva et al. [42])

or SCD had the highest borderzone channel mass [44]. An algorithm based on scar mass and absence of borderzone channels identified 68.2% of patients without ICD therapy or SCD during follow-up with a 100% negative predictive value. Whilst this work provides proof of concept that CMR is able to identify the electrical substrate for VAs, it is far from providing a validated diagnostic technique that can be used in SCD risk stratification. Moreover, these findings require external validation.

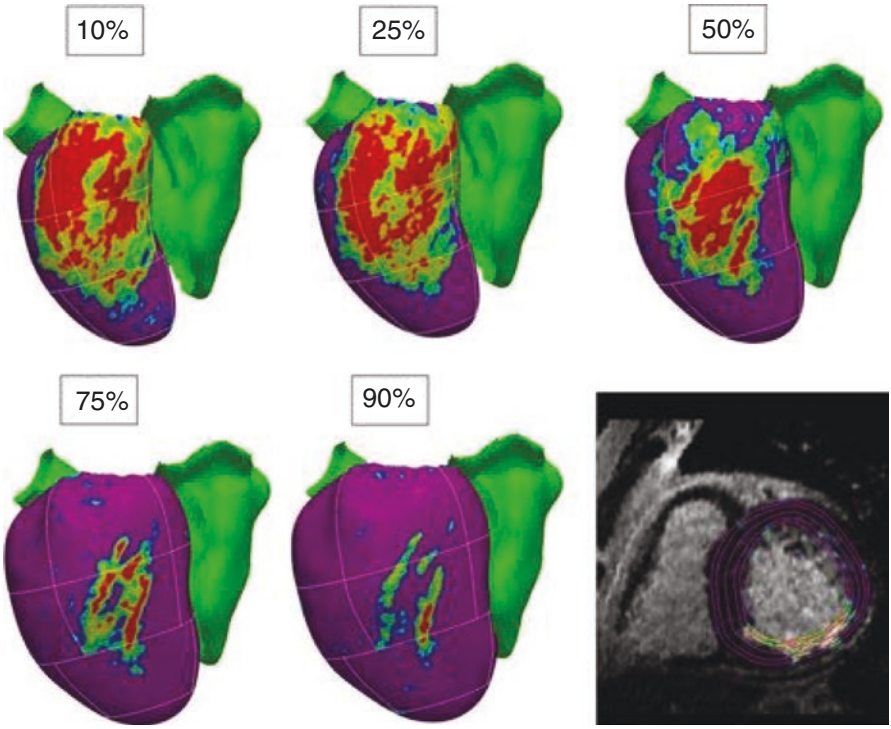


Fig. 2.9 Mapping arrhythmogenic channels with CMR. In mapping borderzone channels with CMR, concentric surface layers are created using varying cut-offs of myocardial thickness (10–90%). A three-dimensional shell is then obtained for each layer, from endocardium to epicardium. In the figure, normal myocardium is coded in purple, scar core in red and borderzone in blue, green and yellow. (Reproduced with permission from Fernandez-Armenta et al. [43])

The Future

Despite the promise of CMR in the selection of patients for ICD therapy, no randomized, controlled trials have emerged. Such trials need to test the intention-to-treat principle as to whether risk stratification on the basis of CMR is superior to echocardiographic LVEF in improving patient outcomes. The Defibrillators To Reduce Risk By Magnetic Resonance Imaging Evaluation (DETERMINE) trial, which set out to randomize 1500 patients, was discontinued because of poor recruitment [45]. The current CMR Guide Trial (NCT01918215), which includes patients with an LVEF 36–50%, may throw light on the value of CMR in selecting patients for ICDs.

Conclusions

There is no doubt that using LVEF to select patients for ICD therapy improves survival in patients at risk of SCD. Importantly, however, LVEF is ultimately a measure

of pump function that is opaque to the myocardial phenotype and the arrhythmic substrate. We are currently at a juncture in deciding whether the 'imaging substrates' of VAs characterized by CMR can aid or even replace LVEF as a criterion for deciding on ICD therapy. So far, however, no scar measure or cut-off thereof has been externally validated as a predictor of SCD or benefitted from ICDs. The future of delivering the right treatment for the right patient in the field of defibrillation must surely rest on the best measures of cardiac function and myocardial phenotype that we have available. In this regard, CMR holds the most promise.

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