Arrhythmic risk stratification by cardiac magnetic resonance tissue characterization: disclosing the arrhythmic substrate within the heart muscle

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Abstract
Sudden cardiac death (SCD) is a pivotal health problem worldwide. The identification of subjects at increased risk of SCD is crucial for the accurate selection of candidates for implantable cardioverter defibrillator (ICD) therapy. Current strategies for arrhythmic stratification largely rely on left ventricular (LV) ejection fraction (EF), mostly measured by echocardiography, and New York Heart Association functional status for heart failure with reduced EF. For specific diseases, such as hypertrophic and arrhythmogenic cardiomyopathy, some risk scores have been proposed; however, these scores take into account some parameters that are a partial reflection of the global arrhythmic risk and show a suboptimal accuracy. Thanks to a more comprehensive evaluation, cardiac magnetic resonance (CMR) provides insights into the heart muscle (the so-called *tissue characterization*) identifying cardiac fibrosis as an arrhythmic substrate. Combining sequences before and after administration of contrast media and mapping techniques, CMR is able to characterize the myocardial tissue composition, shedding light on both intracellular and extracellular alterations. Over time, late gadolinium enhancement (LGE) emerged as solid prognostic marker, strongly associated with major arrhythmic events regardless of LVEF, adding incremental value over current strategy in ischemic heart disease and non-ischemic cardiomyopathies. The evidence on a potential prognostic role of mapping imaging is promising. However, mapping techniques require further investigation and standardization. Disclosing the arrhythmic substrate within the myocardium, CMR should be considered as part of a multiparametric approach to personalized arrhythmic stratification.

Keywords Sudden cardiac death · Arrhythmic stratification · Cardiac magnetic resonance · Late gadolinium enhancement · Mapping imaging · Cardiomyopathies

Introduction

Sudden cardiac death (SCD) is a significant cause of mortality worldwide, accounting for 50% of cardiovascular deaths and 20% of all natural deaths in Western societies [1], mainly due to malignant arrhythmias such as ventricular tachycardia (VT) or ventricular fibrillation (VF). Although occurring in every decade of life, SCD most frequently affects young and apparently healthy subjects, with a long life expectancy. Channelopathies and non-ischemic cardiomyopathies (NICMs) are the main conditions associated with SCD in subjects younger than 40 years [2], whereas ischemic heart disease (IHD) is a more frequent occurrence in the older population [3]. The improvement in SCD prevention achieved in recent years is due to the implementation of dedicated strategies, such as nationwide systematic cardiac screening programs succeeded in decreasing the incidence of SCD in young competitive athletes [4], the introduction of anti-neurohormonal medications promoting ventricular reverse remodeling or directly reducing the risk of SCD (beta-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid antagonists, and sacubitril/valsartan), particularly in patients with heart failure (HF) with reduced left ventricular (LV) ejection fraction (EF) [5], and the use of implantable cardioverter defibrillator (ICD).

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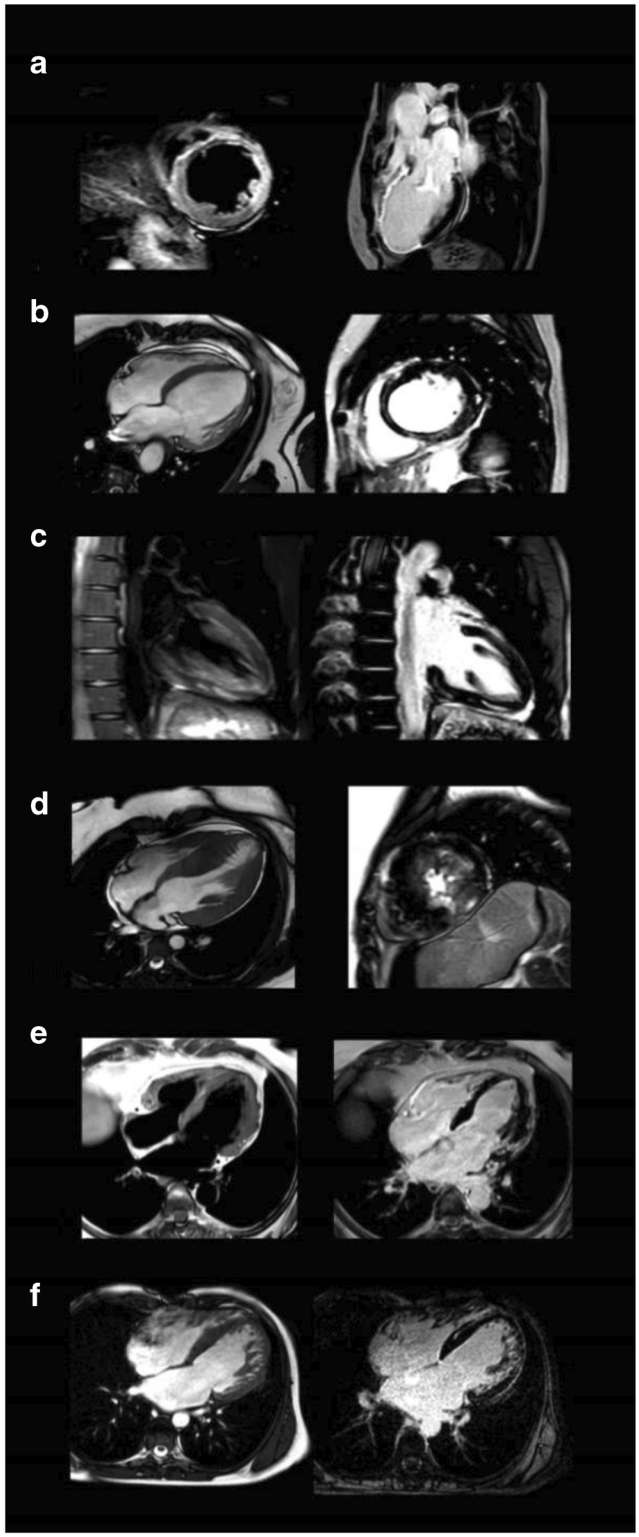
Over the years, ICD has proven to effectively prevent SCD. Although current recommendation for ICD implantation in secondary prevention are well-defined, the indications in the setting of primary prevention are more intricate because of the need to accurately estimate the SCD risk of patients who did not experience major arrhythmias previously.

Current strategies for arrhythmic stratification in heart failure with reduced EF (HFrEF) largely rely on LVEF and New York Heart Association (NYHA) functional class [5]. Arrhythmic risk estimation in specific cardiomyopathies, such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC), is based on multiparametric scores proposed by experts [6, 7]. However, based on these criteria, a significant number of patients would not be eligible for ICD implantation despite being at risk of SCD. Hence, arrhythmic risk assessment should be tailored on the individual patient rather than only upon data derived from study populations.

In this setting, cardiac magnetic resonance (CMR) is emerging in recent years as highly informative and reliable imaging technique, mostly because of its ability to provide tissue characterization. Although CMR evaluation is not included in current guidelines for SCD prediction, a growing evidence supports the incremental value of this technique for arrhythmic risk estimation. Furthermore, CMR accessibility is progressively increasing in clinical practice over the last years.

This review summarizes the value of CMR implemented in the multiparametric assessment of patients for arrhythmic stratification in the different scenarios encountered in clinical practice (Fig. 1).



Current strategies for arrhythmic stratification in heart failure

The risk of arrhythmic events generally increases with the progressive decline in LV systolic function, and, consequently, LVEF has been traditionally considered the most reliable predictor of long-term outcome in several cardiac diseases [8, 9]. Consequently, ICD implantation is largely based on the severity of LV systolic dysfunction along with functional capacity [2, 5].

According to latest guidelines [2], ICD implantation for primary prevention is recommended in symptomatic HF (NYHA classes II-III) with LVEF $\leq 35\%$ despite ≥ 3 months of optimal medical therapy (OMT). However, some cautions should be taken into account when risk-stratifying patients based on this approach. ICD therapy in patients with previous myocardial infarction (MI) is recommended after 40 days from the acute event (Level of evidence I, class A). However, due to ischemic instability and myocardial scarring, patients with recent MI could experience life-threatening arrhythmias early after MI. Prompt identification of these patients at higher arrhythmic risk is challenging but crucial, as they could be earlier considered for SCD prevention (Level of evidence IIb, class C) [5]. Furthermore, prophylactic ICD implantation is recommended in NICM patients with LVEF $\leq$ 35% (Level of evidence I, class B) [5], but its survival benefit

◀ **Fig. 1** CMR imaging in ischemic and non-ischemic cardiac disease. **a** Subacute myocardial infarction in the LAD territory. Left: myocardial edema of the anterior wall associated with no-reflow area of the septum, consistent with myocardial hemorrhage; Right: extensive subendocardial and transmural necrosis in the LAD territory. **b** Non-ischemic dilated cardiomyopathy. Left: severe LV dilatation and systolic dysfunction; Right: midwall LGE of interventricular septum extended to the inferior wall. **c** Acute myocarditis with infarct-like presentation. Left: extensive myocardial edema of the inferior wall; Right: non-ischemic LGE matching areas of edema. **d** Biventricular hypertrophic cardiomyopathy. Left: severe LV hypertrophy with apical aneurysm; Right: extensive LGE of hypertrophic segments. **e** Arrhythmogenic right ventricular cardiomyopathy with LV involvement. Left: areas of fatty infiltration of ventricles; Right: extensive LGE with predominant involvement of the right ventricular free-wall. **f** Left ventricular non-compaction cardiomyopathy. Left: pronounced trabeculation of the LV lateral and apical segments; right: septal midwall LGE. Legend: CMR cardiac magnetic resonance, LAD left anterior descending, LGE late gadolinium enhancement, LV left ventricular

has been recently challenged in the DANISH trial [10]. However, NICMs represent a heterogeneous group of cardiac diseases with different intrinsic arrhythmic risks. For this reason, the efficacy of ICD therapy could be underestimated in unselected populations of NICMs, regardless of the specific etiology [10].

LVEF is the cornerstone of HF classification [2] (preserved EF [HFpEF], midrange EF [HFmrEF], and HFrEF), current approach for arrhythmic stratification and clinical decision-making [5]. However, SCD in the presence of mildly to moderately reduced (HFmrEF) or preserved (HFpEF) systolic function represents the most important limitation of a LVEF-based strategy guiding ICD implantation. Hence, approximately 50% of SCD occurs in patients without severely reduced LVEF.

HFmrEF (LVEF in the range of 40–49%) represents a "gray area" including patients previously diagnosed with HFrEF and HFpEF. This HF category is dynamic in nature and should probably be considered as a transitional stage from other LVEF ranges rather than a specific HF subtype. Indeed, HFrEF can improve LVEF under evidence-based medical and device therapy and HFpEF can develop impaired systolic function due to the progression of underlying disease or occurrence of acute events. It has been recently reported that, although having an apparent better long-term evolution, up to 17% of patients with dilated cardiomyopathy (DCM) and HFmrEF will develop HFrEF despite medical therapy [11].

Finally, patients with HFpEF (LVEF > 50%) represent up to 50% of the whole HF population [12]. HFpEF includes a wide spectrum of cardiac diseases (i.e., hypertensive heart disease, HCM, cardiac amyloidosis, cardiac sarcoidosis, constrictive pericarditis) and is a condition at significant risk of SCD (about 25% of all deaths) [13]. In this HF group, arrhythmic stratification is particularly challenging and should be tailored on the specific patient.

These findings question the traditional concept of LVEF as cornerstone arrhythmic prognostic parameter [14]. LVEF indeed provides only a raw estimate of the severity of cardiac damage; it depends on loading conditions and represents only a single measure of arrhythmic risk [15]. Therefore, arrhythmic stratification should rely on other parameters in addition to LVEF. Providing tissue characterization and a more accurate quantification of LVEF compared to echocardiography [16], CMR represents a unique tool to characterize the arrhythmic substrate and to improve patient-tailored strategies for risk stratification.

Quantification of LVEF and clinical implications: the powerlessness of a number

As previously reported, LVEF below 35% identifies patients eligible for ICD implantation for primary prevention [5]. Evidence supporting current recommendations derives from randomized ICD trials using echocardiographic LVEF to guide prophylactic ICD implantation. However, systolic function can be measured by using multiple non-invasive imaging techniques and the reference modality is not specified in current guidelines. Furthermore, similar LVEF cutoff values for ICD eligibility are used for different imaging modalities.

Echocardiography is the widest used technique to estimate LVEF because of its diffuse availability in clinical practice. However, CMR is considered the gold standard technique for evaluation of systolic function. At present, no published ICD trial included LVEF assessed by CMR despite its high accuracy and reproducibility, particularly compared to echocardiography.

The issue of technique-dependent variability in measured LV parameters was investigated by many experts. In the study by Jerkins et al. [17], 2D and 3D echocardiographies underestimated LV volumes, while only contrast-enhancement 3D echocardiography resulted in LV volumes comparable to those measured by CMR. In addition, an absolute difference of 5% in LVEF was reported between non-contrast-enhanced 2D echocardiography and CMR.

Higher variability among different imaging modalities for assessment of systolic function has been recently reported with a mean absolute difference of 7.3% in LVEF values between echocardiography and CMR [18]. In patients with impaired LVEF, most studies demonstrate that echocardiography generally overestimates LVEF by 3–7% compared to CMR [19], resulting in a substantial reclassification of patients with regard to ICD implantation [20].

In a recent study by Pontone et al. [16], CMR showed 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 −4.9 ± 10%) compared to echocardiography ($P < 0.01$). Furthermore, the lower CMR-LVEF led to the reclassification of 47% of patients into a group at high risk of major adverse cardiovascular events (MACE) despite having an echocardiographic LVEF ≥ 35%.

Because of these differences, LVEF values should be considered with caution when measured by different imaging modalities, especially in the presence of LV dysfunction, as they cannot be directly interchanged. In addition, the accuracy of CMR parameters of LV dimensions and systolic function could be lower than expected in the peculiar settings of irregular R-R interval [21] (i.e., atrial fibrillation or frequent ectopic beats) and in the presence of dyssynchrony due to left bundle branch block [22]. Further investigation of modality-specific thresholds is required.

Cardiac magnetic resonance: new insights into cardiac muscle beyond LVEF

Along with a full morphological and functional cardiac assessment, CMR provides additional diagnostic and prognostic information due to the possibility of in vivo tissue characterization, which allows the evaluation of cardiac muscle composition, both at intracellular and extracellular levels, through semi-quantitative and quantitative parameters (Table 1).

In particular, gadolinium-based contrast agents provide detection and quantification of myocardial fibrosis, which is considered an arrhythmic substrate and the final pathway of irreversible cardiac injury [23]. In a recent, large meta-analysis [24], late gadolinium enhancement (LGE) was demonstrated to provide more accurate arrhythmic stratification in contrast to LVEF. LGE is strongly associated with major arrhythmic end points such as SCD, sustained VT, or appropriate ICD therapy in the context of LVEF < 35% as well as LVEF > 35% [24]. Furthermore, the association between LGE and life-threatening arrhythmias is observed in both IHD and NICM [23, 25, 26]. However, LGE, in the chronic setting, identifies fibrotic scars and might fail to detect the presence of interstitial fibrosis underlying myocardial impairment in advanced HF or progressive cardiomyopathies [27].

In recent years, parametric mapping emerged as useful technique to overcome this limitation, providing quantitative information on magnetic tissue properties of cardiac muscle through the measurement of relaxation times (T1, T2, and T2*) and extracellular volume (ECV) quantification [28]. The main advantage of this technique consists in the evaluation of the pathological process regardless of its extent (localized or diffuse). Furthermore, changes in these parameters provide identification of specific disease pathways affecting myocardial tissue composition and could detect early myocardial injuries, potentially reversible under treatment [28].

Myocardial edema results from an acute cardiac injury and leads to prolongation of T1 and, especially, T2 relaxation times. Prolongation of myocardial T1 relaxation time is not specific for acute cardiac damage, being associated also with presence of fibrosis [29]. Providing direct measurement of the prolongation of myocardial T2 relaxation time, T2 mapping can detect and quantify myocardial edema more accurately than traditional T2 sequences [30]. In addition, T2 mapping combined with T1 mapping could allow better assessment of cardiac muscle and, potentially, differentiation between acute (increased T1 and T2 values) and/or healed (increased T1 values and normal T2 values) processes.

ECV is measured from native and post-contrast T1 relaxation time of the myocardium and the blood, combined with patients' hematocrit. It provides direct measurement of the myocardial interstitium and is considered a marker of myocardial tissue fibrosis [31]. Recent evidences demonstrate that

Table 1 Cardiac magnetic resonance parameters for tissue characterization

Parameter	Purpose	Normal heart	AMI	AM	DCM	HCM	CA	Anderson-Fabry	Iron overload
Cine	Myocardial function and wall thickness	Normal LVEF	Low LVEF	Normal/low LVEF	Low LVEF	Normal/low LVEF	Normal/low LVEF	Normal LVEF	Normal/low LVEF
T2-STIR	Edema	–	+++	++	±	±	–	–	–
LGE	Fibrosis	–	+++	+/++	−/+	−/+	+++	+	–
Native T1	Edema, fibrosis		++	+++	+/++	+/++	+++	–	–
Native T2	Edema		++	++	+/−	+/−	–	–	+
ECV	Interstitial space		++	+++	+/++	+/++	+++	+/−	+/−
T2*	Iron		+/−	–	–	–	–	–	+++

+ increased, − reduced, *AM* acute myocarditis, *AMI* acute myocardial infarction, *CA* cardiac amyloidosis, *CMR* cardiac magnetic resonance, *ECV* extracellular volume, *HCM* hypertrophic cardiomyopathy, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *STIR* short tau inversion recovery, *T1* time of relaxation 1, *T2* time of relaxation 2, *T2** T2 star

ECV offers prognostication toward HF outcomes incremental to LGE or native T1 mapping [32]. In detail, ECV was significantly associated with MACE in any anatomical location of the LV (with highest association in the anteroseptal location), and, for every 10% increase, mean ECV portended to a 2.8-fold increase risk to MACE [32]. Increased ECV values are mostly found in areas of high collagen deposition as reported by histological studies demonstrating ECV to be associated with collagen volume fraction [33, 34]. However, ECV results from the sum of interstitial fibrosis and myocardial edema in acute processes, given the ability of tissue edema to expand myocardial interstitium. Hence, ECV reliably reflects diffuse myocardial fibrosis only in the absence of significant myocardial inflammation [31].

CMR with tissue characterization significantly improves the identification of patients at high arrhythmic risk that would be otherwise missed across the full LVEF range, especially in those without severely reduced LV systolic function (Fig. 2). LGE is currently the most robust and largely accepted parameter in clinical practice, whereas mapping techniques (i.e., T1 and T2 mapping) are less diffuse, being routinely used within few CMR laboratories, mainly for research purposes. This is mostly related to several technical issues and lack of standardization, with the need of center-specific normal values.

Although a consistent body of literature has gathered in recent years, whether a CMR-guided strategy for ICD implantation based on the presence of myocardial fibrosis is superior to the current strategy for SCD prevention is still debate, given the absence of large published clinical trials. The ongoing CMR-GUIDE trial [35] enrolling HF patients, including IHD and NICM, with mild-to-moderate systolic dysfunction and LGE positivity is going to answer this question, but results are expected in August 2023.

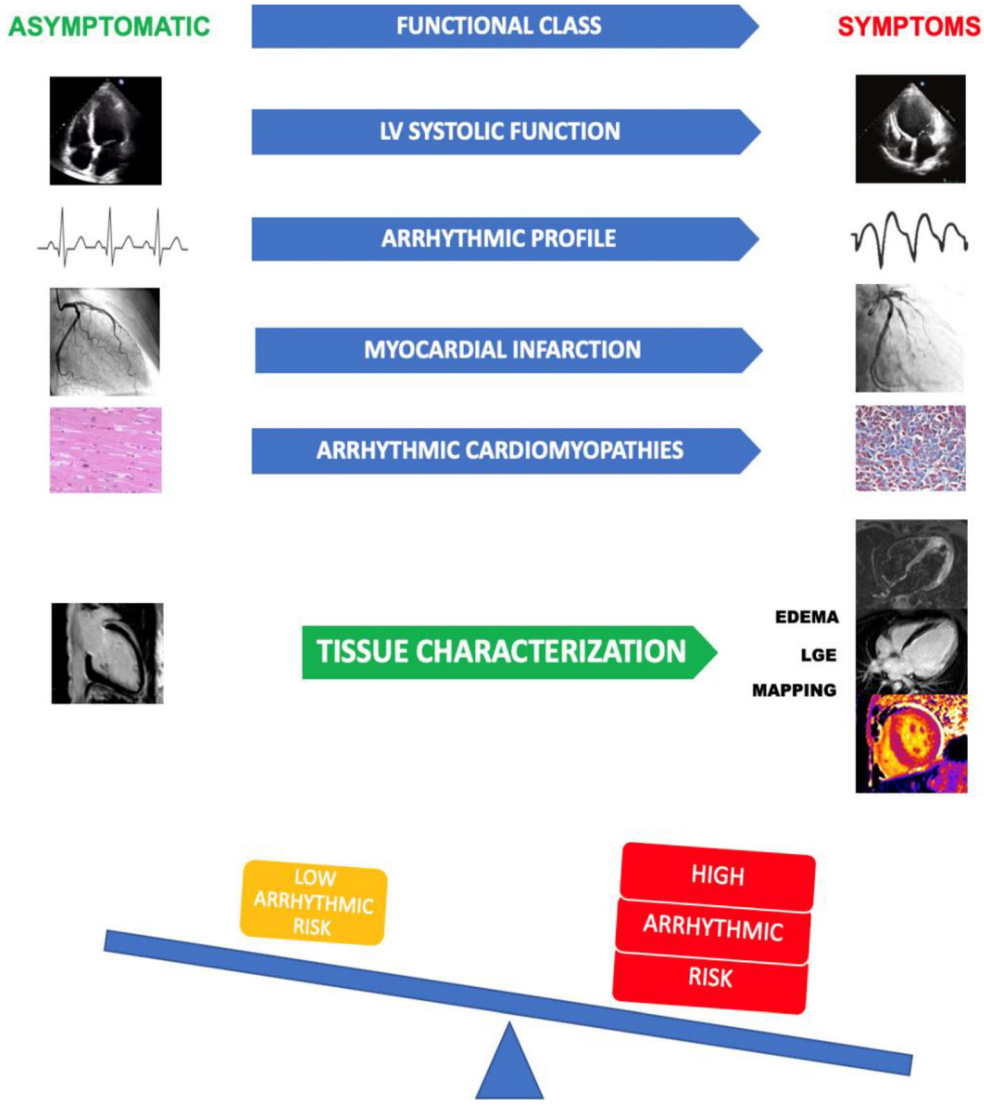


Fig. 2 The additional value of CMR assessment in combination with current parameters for arrhythmic risk stratification. Legend: CMR cardiac magnetic resonance, LGE late gadolinium enhancement, LV left ventricular

CMR: differential diagnosis and prognostic stratification in selected cardiac diseases

Ischemic heart disease

Myocardial scar resulting from necrosis of cardiomyocytes acts as substrate for ventricular arrhythmias (VA) and can be detected by subendocardial or transmural LGE, mirroring a specific coronary distribution [36, 37]. The extent of LGE provides incremental prognostic value over LVEF in IHD (Table 2). In a recent meta-analysis [25] on 2850 patients with chronic IHD and NICM, the extent of LGE was a powerful predictor of VT. Patients with greater LGE extent met the composite arrhythmic end point (SCD, aborted SCD, VT/VF, appropriate ICD therapy) more frequently than LGE negative patients (23.9% vs 4.9%, respectively).

The complex architecture of MI is characterized by an area surrounding LGE, known as "border zone" (BZ), which includes viable and non-viable myocytes separated by fibrotic tissue of the scar region. This heterogeneous area provides a substrate for reentrant forms of VA [38], and its extent was demonstrated to predict VT inducibility on electrophysiological study (EPS) [39], appropriate ICD therapy [40], and mortality [38]. In detail, the BZ was reported to be strongly associated with all-cause mortality, life-threatening arrhythmias, and appropriate ICD shock regardless of LVEF, particularly in patients with mild-to-moderate LV dysfunction [41]. Moreover, patients with LVEF > 35% and a high degree of infarct heterogeneity at CMR experienced similar mortality, compared with those with LVEF < 35% [41]. In the recent multicenter prospective GAUDI-CRT study [42], enrolling patients with class I indication to CRT, scar characterization at pre-procedural CMR was able to predict the arrhythmic outcomes. In detail, the presence of an infarct mass > 10 g and a BZ-mass > 5.3 g was associated with an additional arrhythmic risk, predicting appropriate ICD therapy and SCD in CRT patients during follow-up [42]. In addition, besides LGE and BZ, abnormal T1 mapping was found to predict appropriate ICD therapy or sustained VT in IHD [43]. Although promising, more studies and a consensus on the methodology of BZ quantification are required.

Evidence is growing about the potential long-term prognostic information of LGE assessed in the acute phase. In the PROSPECT study [44], 209 patients with acute MI underwent CMR evaluation after successful primary percutaneous coronary intervention (PCI). A weighted CMR score was created to predict the risk of major adverse cardiovascular (CV) events, including ICD implantation, CV death/aborted SCD. This score was demonstrated to provide incremental prognostic stratification compared with GRACE score and LVEF [44]. In addition, infarct size assessed by CMR at a median time of 4 days from primary PCI was found a strong independent predictor of all-cause mortality and HF hospitalization within 1 year [45]. In a promising investigation by Izquierdo et al. [46] involving 440 patients undergoing CMR within the first week from acute MI, the combination

Table 2 Selected studies on late gadolinium enhancement in ischemic heart disease

Study	Patients (*n*)	Study design	Mean age (years)	Mean LVEF (%)	Median follow-up (months)	End Point	Results
Jablonowski, 2017 [40]	74	Retrospective cohort	64	21	63	Appropriate ICD therapy	BZ predicted ICD therapy: HR 1.23; 95% CI 1.01–1.49; $P < 0.05$
Zeidan-Shwiri, 2015 [135]	43	Prospective cohort	64	27	30	Appropriate ICD therapy (shock and ATP)	Gray zone: OR 2.09; 95% CI, 1.14–3.85 in multivariate analysis; $P = 0.018$; MI core: OR 1.21; 95% CI 1.05–1.38; $P = 0.007$
Alexandre, 2013 [136]	66	Retrospective cohort	62	22	41	Appropriate ICD therapy	Each 1 g extra scar mass: HR, 3–.15; 95% CI, 1.35–7.33 in multivariate analysis; $P < 0.001$
Krittayaphong, 2011 [137]	1148	Prospective cohort	64	71	32	Cardiac death, life-threatening arrhythmia and other MACE	Presence of LGE: HR, 3.92; 95% CI, 1.98–7.76 in multivariate analysis; $P < 0.001$
Scott, 2011 [138]	64	Retrospective cohort	67	30	19	Appropriate ICD therapy	Each 10% increase in Percent scar: HR,1.75; 95% CI, 1.09–2.81; $P = 0.02$ Number of transmural scar segments: HR per segment,1.40; 95% CI, 1.15–1.70; $P = 0.001$
Kwon, 2009 [139]	349	Prospective cohort	65	24	29	All-cause mortality, HTx	Each 1% increase in LV scar: HR,1.02; 95% CI, 1.003–1.03; $P = 0.004$

AM acute myocarditis, *AMI* acute myocardial infarction, *ATP* anti-tachycardia pacing, *BZ* border zone, *CI* confidence interval, *CMR* cardiac magnetic resonance, *HR* hazard ratio, *HTx* heart transplantation, *ICD* implantable cardioverter defibrillator, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *OR* odds ratio

of LVEF < 35% and LV acute MI size > 31% predicted adverse arrhythmic cardiac events at a medium follow-up of 2 years.

Parametric mapping in the acute setting could offer additional prognostic information. Infarct core native T1 values were reported to inversely correlate with end points associated with arrhythmic risk as adverse LV remodeling and all-cause mortality [47]. Furthermore, acute MI ECV has been demonstrated to predict adverse LV recovery in reperfused acute MI, regardless of transmural extent of infarction [48].

These findings suggest that CMR could contribute to prognostic stratification in IHD, providing more accurate estimation of patients' arrhythmic risk and potentially leading to a reclassification into a higher as well as lower SCD risk class. The evaluation of LGE along with mapping parameters could have consequences on patients' clinical management. For instance, patients with IHD and LVEF of 35% could carry a higher than expected risk of arrhythmic events in the presence of large LGE extent and abnormal mapping parameters.

Finally, lipomatous metaplasia (LM), resulting from progressive infiltration of infarcted myocardium by adipose cells, might represent a further element to consider [49]. The infarcted myocardium displays abnormal metabolism with reduced uptake of fatty acids that may partially explain the pathogenesis of this process, which is not clearly understood [49, 50]. However, locally impairing myocardial conduction, LM might provide a substrate for re-entrant tachycardia, predisposing to increased risk of VA and SCD, as suggested elsewhere [49, 51]. In a recent prospective study enrolling patients with prior MI (> 6 months) [50], LM was found in up to 24% of cases and was associated with more adverse remodeling and older and more extensive infarcts. Furthermore, the presence of LM was a stronger predictor of hard events (all-cause mortality, sustained VA, and HF hospitalization) than infarct size alone, even when adjusting for LV volumes and LVEF [50]. Therefore, LM could provide additional prognostic value in IHD along with LGE, but further studies are needed.

NICM

In the last years, a progressive decline in SCD is characterizing the natural history of NICM due to better diagnostic accuracy, prognostic stratification and therapies, and increasing overall survival [52]. In particular, left ventricular reverse remodeling, defined as an improvement in LV dimensions and LVEF, has been reported in about 40% of DCM patients receiving OMT and associated with favorable long-term outcome [53, 54]. NICM patients with LVEF ≤ 35% at presentation could experience recovery of systolic function over time and an observational period of 3 to 6 months is advisable to identify optimal candidates for ICD implantation. About two-thirds of patients eligible for ICD therapy at baseline do not fulfill indications for implantation 6 months after initiation of OMT [55]. However, approximately 2% of patients die suddenly due to SCD/VT/VF within the first 6 months after diagnosis, bringing out a major knowledge-gap in prognostic stratification [56].

Recent data suggest the use of CMR in this setting could improve current strategies for SCD prediction among a wide range of LVEF values. There is plenty of published literature [24, 25, 57, 58] supporting the ability of LGE to predict major arrhythmic events and all-cause mortality in NICM, even after adjustment for LVEF (Table 3). In an elegant paper by Iles et al. [59] comparing patients with IHD and NICM who underwent ICD implantation in primary prevention (mean NYHA 2; mean LVEF 26 ± 9%), LGE predicted appropriate ICD therapy. In particular, NICM patients without LGE experienced no ICD discharges compared with a 29% discharge rate in those with LGE positivity ($P < 0.01$). The value of LGE presence and distribution in the setting of mild-to-moderate LV systolic dysfunction has been investigated in a prospective study on 399 patients with NICM and LVEF > 40% [60]. The presence of midwall LGE predicted the occurrence of SCD and aborted SCD and the combined end point at a median follow-up of 4.6 years [60]. These results are in line with previous electrophysiological studies reporting midwall LGE positivity in association with sites of VT inducibility [61] and matching between midwall LGE positive areas and critical VT sites [62]. Furthermore, the combination of LGE positivity and wide QRS was reported to add more precise arrhythmic stratification, predicting overall mortality and SCD even in NICM with LVEF≤ 35% [63].

In a recently published Danish-MRI study [64] enrolling patients with NICM and moderate-to-severe systolic dysfunction (mean LVEF 35%), the presence of LGE predicted all-cause mortality and the arrhythmic end point, after adjusting for known cardiovascular risk factors. However, ICD implantation did not reduce all-cause mortality, for patients either with or without LGE [64]. Nevertheless, some limitations should be underlined. This analysis was a non-randomized single-center substudy of the DANISH trial [65]. Furthermore, the primary end point included only all-cause mortality, which resulted unaffected by ICD implantation also in the DANISH trial [10], where a significant reduction of SCD was demonstrated in ICD patients. Moreover, each of the four subgroups stratified by LGE and ICD status had very limited number of patients, making the study underpowered to assess the primary end point [65]. Finally, several monocentric investigations [65, 66] enrolling smaller, but well-characterized cohorts, showed different results, suggesting the need of future research.

Unlike LGE positivity and localization, the pattern and quantification of LGE did not offer significant advantages for SCD risk estimation [67]. In NICM, LGE frequently is found as linear *stria* in the midwall of the septum, despite various distributions that can be observed. Subepicardial

Table 3 Selected studies on late gadolinium enhancement in dilated cardiomyopathy

Study	Patients (*N*)	Study design	Population	Mean age (years)	Mean LVEF (%)	LGE location	Follow-up (median) (months)	Arrhythmic end point	Association of LGE with MVAs/SCD
Halliday, 2017 [60]	399	Prospective cohort	NICM	50	50	Midwall, subepicardial	16	SCD and aborted SCD (excluding ATP)	LGE positivity: HR, 9.3; 95% CI, 3.9–22.3; $P < 0.0001$
Di Marco, 2017 [24]	2948	Meta-analysis	DCM	46–66	20–43	Various	36		Presence of LGE: OR, 4.9; 95% CI, 3.3–7.3; $P < .001$ Extent of LGE: OR, 3.4; 95% CI, 1.6–7.7; $P < .002$
Piers, 2015 [140]	87	Prospective observational	NICM, primary or secondary prevention ICD	56	29	Basal, nonbasal	45		Presence of LGE: $P < .001$ (no HR; all events in LGE group) Extent of LGE: HR, 1.90; 95% CI, 1.35–2.67; $P < 0.001$
Masci, 2014 [141]	228	Prospective observational	DCM, no history of HF	50	43	Midwall	23	Aborted SCD (including ATP)	Presence of LGE: HR, 8.31 (95% CI, 1.66–41.55; $P = 0.01$)
Gulati, 2013 [57]	472	Prospective cohort	NICM, no subendocardial LGE	51	37	Midwall	64	SCD and aborted SCD (excluding ATP)	Presence of LGE: HR, 4.61; 95% CI, 2.75–7.74; $P < 0.001$ Extent of LGE: HR, 1.10; 95% CI, 1.05–1.16; $P < 0.001$
Assomull, 2006 [142]	101	Prospective cohort	NICM	51	35	Midwall	22	SCD and sustained VT	Presence of LGE: HR, 5.2; 95% CI, 1.0–26.9; $P = 0.03$

% percentage, *ATP* anti-tachycardia pacing, *CI* confidence interval, *DCM* dilated cardiomyopathy, *HR* hazard ratio, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *MVAs* major ventricular arrhythmias, *NICM* non-ischemic cardiomyopathy, *OR* odds ratio, *SCD* sudden cardiac death, *VT* ventricular tachycardia

and patchy LGE as well as subendocardial LGE (the latter up to 10% of cases) [36] could be found. The limited incremental value of LGE extension could be a consequence of the great heterogeneity fibrosis distribution which is a typical feature of this cardiomyopathy. Myocardial fibrosis in NICM is indeed characterized by complex mechanisms including inflammation along with genetic predisposition and could occur in a diffuse form, not accurately depicted by LGE. Similarly to replacement fibrosis seen by LGE, diffuse fibrosis has been recently associated with life-threatening arrhythmias and all-cause mortality in NICM [68]. In particular, NICM patients with a history of complex arrhythmias showed increased global native T1 values compared with age-matched NICM patients without any documented ventricular arrhythmia, even after adjusting for LV function and LGE [69].

Although T1 mapping could detect diffuse fibrosis [43, 68, 70], more studies are required to derive solid information as this methodology suffers from several technical limitations.

For the abovementioned reasons, a multiparametric approach is required when managing arrhythmic stratification in patients with NICM, including current evidence-based clinical-echocardiographic evaluation, full structural and functional CMR assessment, and genetic testing, when indicated [71].

Acute myocarditis

Acute myocarditis (AM) is a polymorphic disease characterized by great variability in clinical presentation and evolution [72]. The diagnosis of AM is challenging and could be missed with potential adverse prognostic implications as patients with prior AM could progress toward post-inflammatory DCM in up to 9–16% of cases [73]. Although definitive diagnosis may only be achieved with endomyocardial biopsy (EMB), CMR evaluation allows non-invasive diagnosis in the presence of Lake Louise Criteria (LLC) [74]. Besides its diagnostic value among other LLC, LGE has been identified as useful prognostic parameter for SCD risk estimation in AM,

independently from LVEF (Table 4). In 222 patients with biopsy-proven viral AM, LGE was the best predictor of cardiac mortality, including SCD (mean follow-up 4.7 ± 1.2 years) [75]. In addition to LGE positivity, LGE distribution and extent could add prognostic information in AM. Midwall septal LGE was recently reported as the most malignant localization in AM with normal LVEF, doubling the risk of adverse cardiac events [76]. In a recent study on AM patients with preserved LVEF, the presence of antero-septal LGE positivity was associated with a worse prognosis compared with other LGE distributions [77].

AM presenting with life-threatening arrhythmias represents a peculiar and demanding subgroup for both clinical management in the acute phase and long-term prognostic stratification [78]. As AM is a form of inflammatory cardiomyopathy, the arrhythmic phenotype could regress after the acute phase or specific medical therapy initiation. LGE could provide incremental value for arrhythmic risk prediction in AM with arrhythmic presentation, even strengthening the decision to implant an ICD [79, 80]. However, few data are available in this field and future studies on large populations focused on this issue are needed.

LLC accuracy is higher in patients with infarct-like presentation compared with arrhythmic or HF presentations [81]. On this basis, LLC have been recently reviewed and novel diagnostic criteria, combining T1- and T2-based criteria, were proposed to increase the specificity of detecting acute myocardial inflammation [82]. Solid data about mapping imaging for the prediction of major arrhythmic events are lacking, but some initial evidence is gathering on the potential value of these parameters for patients' stratification in NICM and AM. T1 mapping imaging has been recently demonstrated to add prognostic information incremental to LVEF and LGE for the prediction of all-cause mortality, HF mortality, and hospitalization [68]. In addition, abnormal T2 values at presentation were reported to predict a combined end point of cardiac death, heart transplantation (HTx), and ventricular assist device implantation as well as re-hospitalization at median follow-up of 11 ± 7 months in AM [83]. In a small investigation on 24 suspected AM patients studied with repetitive CMR evaluations at three time frames (2–3, 4–8, and > 8 weeks) [84], ongoing symptoms and persistent LV impairment were associated with increased T2 values. In addition, AM patients showing progressive and consistent decrease in T2 values during the follow-up, indicating the resolution of myocardial edema, exhibited improved LV function.

These findings suggest that myocardial edema, identifying reversible cardiac injury, might predict LV functional

Table 4 Selected studies on late gadolinium enhancement in acute myocarditis

Study	Patients (*N*)	Study design	Population	Mean age (years)	Mean LVEF (%)	LGE location	Follow-up (median) (months)	Arrhythmic end point	Association of LGE with MVAs/SCD
Imazio, 2018 [143]	71	Retrospective cohort	AM with normal and impaired LVEF	47	51	Septal	61	Cardiovascular mortality, SVT	Septal LGE is not associated with adverse cardiovascular events ($P = 0.576$)
Aquaro, 2017 [77]	386	Retrospective	AM with normal LVEF	35	61	Midwall of the AS myocardial segment	52	Cardiac death, appropriate ICD shock, resuscitated cardiac arrest	Presence of LGE at AS location: OR, 2.73; 95% CI, 1.2–5.9; $P < 0.01$
Gräni, 2017 [76]	670	Retrospective observational	AM with normal and impaired LVEF	48	50	Midwall, septal	45	SVT as part of composite end point	Presence of LGE: HR, 1.72; 95% CI, 1.08–2.76; $P = 0.023$; Each 10% increase in LGE extent conferred 79% increase in the risk of MACE
Grun, 2012 [75]	222	Prospective observational	EMB-proven AM with normal and impaired LVEF	52	45	Subepicardial, Midwall	56	All-cause mortality, cardiac mortality, SCD either as composite end point or in isolation	Presence of LGE: HR, 8.4 ($P = 0.004$) for all-cause mortality, and, HR, 12.8 for cardiac mortality ($P < 0.01$)

% percentage, *AM* acute myocarditis, *AS* anterior septum, *CI* confidence interval, *EMB* endomyocardial biopsy, *HR* hazard ratio, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *MACE* major adverse cardiovascular events, *MVAs* major ventricular arrhythmias, *N* number, *OR* odds ratio, *SCD* sudden cardiac death, *SVT* sustained ventricular tachycardia

recovery. As LV derangement is the main prognostic parameter in AM [85], T2 mapping could indeed provide incremental value for outcome prediction.

In a recent CMR investigation [86], ECV was reported to improve risk stratification in suspected AM, incremental to LGE and LVEF. In this study, in a mixed cohort of 179 patients with suspected AM (mean LVEF 48 ± 16%), ECV > 35% was found to predict major adverse cardiac events (all-cause death, hospitalization for HF, HTx, sustained VT, recurrent AM) at a median follow-up of 4.1 years, even after adjustment to LVEF and LGE [86]. In particular, a significant improvement in outcome was reported in LGE negative suspected AM with ECV < 35%. ECV might be a useful tool for prognostic stratification and should be considered when evaluating AM patients. Furthermore, ECV has been proposed to estimate the amount of myocardial fibrosis and/or inflammation not accurately characterized by LGE in AM [87]. However, these findings require validation in future studies.

CMR examination should be performed as early as possible in suspected AM, mostly considering that CMR parameters show significant alterations at initial stage, myocardial edema is a transient phenomenon, and the optimal time window to perform parametric mapping imaging is largely unknown. In addition, repetitive CMR imaging is useful to monitor the healing process and to detect persistent cardiac inflammation, potentially identifying a subgroup of patients who may benefit from short-term follow-up examinations or further investigations [88].

Specific etiologies such as eosinophilic myocarditis, giant cell myocarditis, and cardiac sarcoidosis (CS) are peculiar high-risk conditions [78]. The decision to prevent SCD in these patients should be considered on an individual basis and rely on a multiparametric approach including the presence of ventricular derangement (akinetic segments, regional aneurysms, ventricular remodeling, LGE), histopathologic substrate, and response to medical therapy [78]. Notably, in light of the patchy cardiac involvement, CS may not behave similarly to other cardiomyopathies with regard to the arrhythmic risk and patients may benefit from ICD implantation even in the presence of LVEF > 35% [89]. The presence of progressive fibrosis in the basal segments of the infero-septum could exert a progressive effect of compression on the atrioventricular node, leading to bradyarrhythmias such as advanced blocks, a major clinical issue of the disease.

Hypertrophic cardiomyopathy

The risk of SCD in HCM can be estimated using the validated risk prediction model of the European Society of Cardiology (ESC), including anamnestic, clinical, and echocardiographic parameters [6]. However, it does not include any CMR parameter. Careful LV wall thickness assessment is pivotal in HCM as the risk of VA has been reported to increase along with maximum wall thickness [6] and with global LV mass [90]. In this regard, CMR evaluation has proven to be more accurate compared to echocardiography, leading to reclassification into a lower risk class in about 10% of patients with HCM [91]. In particular, CMR enables to assess the presence of cardiac hypertrophy in segments difficult to image by echocardiography (i.e., the posterior wall and the apex of the LV) as well as to identify muscle bundles close to other cardiac structures (i.e., interventricular septum), preventing inaccurate wall thickness measurement. In addition, CMR allows detection of specific phenotypes as apical HCM, apical aneurisms, or biventricular HCM, otherwise missed. LV apical aneurisms can be accurately identified in approximately 2% of patients and are associated with adverse clinical events, including SCD [92]. Furthermore, biventricular HCM has been reported at poorer clinical outcome [93] compared to isolated LV HCM.

Some evidence supports the potential value of T2-weighted short-tau inversion recovery (STIR) sequences in identifying HCM patients at higher arrhythmic risk. In a recent study [94] enrolling 65 well-characterized HCM patients, myocardial T2-hyperintensity (HyT2), consistent with presence of edema, was associated with disease progression and arrhythmogenesis. In detail, myocardial edema was detected in 42% of cases, with the midwall layer of hypertrophic segments being the predominant localization. This population showed higher LV mass, lower LVEF and greater LGE extent as well as a higher arrhythmic risk score and more frequent non-sustained VT at 24-h Holter recordings [94].

The relation between myocardial HyT2 on STIR sequences and myocardial edema remains incompletely understood. Some authors hypothesize T2 abnormalities in HCM to be associated with myocardial ischemia caused by microvascular dysfunction, impaired ventricular relaxation, and mismatch between capillary density, cardiac mass, and interstitial fibrosis [95]. These hypotheses seem to find confirmation in positron emission tomography studies [96].

In a recent validation study [97], the ESC HCM Risk-SCD score was demonstrated to accurately discriminate high- from low-risk patients but to overestimate the arrhythmic risk in intermediate-risk patients (i.e., 5-year event rate 4–6%) that represent the vast majority of HCM population. In this setting, CMR could offer a more detailed characterization. LGE is a strong marker of arrhythmic risk in HCM (Table 5), and, over time, it has been associated to an increased risk of SCD [98], cardiac mortality, and all-cause mortality [99]. However, LGE can be found in up to 50–70% of HCM patients, involving on average 10% of global LV mass [100]. For this reason, the extent of LGE rather than the dichotomous approach (presence vs absence of LGE) seems related to the arrhythmic risk and is expected to worsen along with disease progression. The prognostic role of LGE extent (%LGE) as strong independent predictor of SCD was demonstrated in recent multicenter large

Table 5 Selected studies on late gadolinium enhancement in hypertrophic cardiomyopathy

Study	Patients (*N*)	Study design	Population	Mean age (years)	Mean LVEF (%)	LGE location	Follow-up (median) (months)	Arrhythmic end point	Association of LGE with MVAs/SCD
Todiere, 2019 [102]	354	Prospective cohort	HCM, ESC SCD score < 6%, LVOT obstruction (22%)	54	69	Extension of LGE	40	SCD, resuscitated cardiac arrest, appropriate ICD shock, SVT.	LGE ≥ 10%: HR, 8.8; 95% CI, 2.03–37.8; $P < 0.0001$.
Mentias, 2018 [101]	1423	Meta-analysis	HCM, ESC SCD score < 6%, LVOT obstruction (68%), myectomy during follow-up (48%).	66	62	Extension of LGE	56	SCD, appropriate ICD shock	Extent of LGE ≥ 15%: HR, 2.84; 95% CI, 1.27–6.34; $P = 0.01$ in non-obstructive HCM; HR, 3.04; 95% CI, 1.48–6.10; $P = 0.01$ in obstructive HCM
Weng, 2016 [100]	2993	Meta-analysis	HCM	55	69	–	37	SCD, aborted SCD	Presence of LGE: OR 3.41; 95% CI, 1.97–5.94; $P < 0.001$ Each 10% increase in LGE: $HR_{adjusted}$, 1.36; 95% CI, 1.10–1.69; $P = 0.005$
Briasoulis, 2015 [99]	3067	Meta-analysis	HCM	60	–	–	37	SCD, aborted SCD	Presence of LGE: OR, 2.52; 95% CI, 1.44–4.4; $P = 0.01$
Chan, 2014 [98]	1293	Prospective cohort	HCM, LVOT obstruction (23%)	46	67	–	40	SCD, appropriate ICD shock, aborted SCD (excluding ATP)	Presence of LGE: $HR_{adjusted}$, 2.56; 95% CI, 1.44–4.4; $P = 0.02$ Each 10% increase in LGE: HR, 1.46; 95% CI, 1.12–1.92; $P = 0.002$
Maron, 2008 [144]	202	Prospective cohort	HCM, LVOT obstruction (24%), no previous myectomy and MI	42	≥ 60% (90-%)	Midwall	23	Composite: SCD, appropriate ICD shock, progressive HF symptoms	Presence of LGE: HR, 1.45; 95% CI, 0.45–4.97; $P = 0.5$

ATP anti-tachycardia pacing, *CI* confidence interval, *ESC* European Society of Cardiology, *HCM* hypertrophic cardiomyopathy, *HF* heart failure, *HR* hazard ratio, *ICD* implantable cardioverter defibrillator, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *MVAs* major ventricular arrhythmias, *N* number, *OR* odds ratio, *SCD* sudden cardiac death, *SVT* sustained ventricular tachycardia

studies [98, 100, 101]. %LGE ≥ 15% of the LV mass was associated with a significant increase in major arrhythmic events at mid-term (i.e., 3 to 5 years). Furthermore, a linear relation between %LGE and SCD risk was found, highlighting the value of LGE assessment beyond a stringent cutoff.

In the latest multicenter, prospective investigation by Todiere et al. [102] on 354 consecutive HCM patients with an ESC Risk-HCM score < 6%, %LGE ≥ 10% was an independent predictor of malignant arrhythmic events (SCD, appropriate ICD shock, resuscitated cardiac arrest, sustained VT) and mortality, during a median follow-up of 3.3 years. Unlike previous studies, the low-intermediate risk HCM population enrolled in this study is a more accurate reflection of real-world patients (mean age 54 years, 22% obstructive HCM, 85% patients at low SCD risk < 4%). Moreover, %LGE was calculated using the conventional ≥ 6 SD grayscale threshold compared with the visual grayscale threshold adopted by Chan et al. [98], more dependent upon operator's expertise.

Some studies investigated the value of parametric mapping imaging in HCM [103, 104]. Native T1 values were reported to be increased in both LGE negative and LGE positive

segments in HCM [105], suggesting the ability to reveal diffuse cardiac fibrosis not well characterized by LGE. However, the prognostic significance of parametric mapping remains to be established. T1 mapping has been included as exploratory parameter in the ongoing Hypertrophic Cardiomyopathy Registry [106], and its potential association with adverse outcome in HCM will be investigated.

In conclusion, CMR should be systematically considered early in the arrhythmic stratification of HCM, particularly if at low-to-intermediate ESC risk score, where additional information is required to guide ICD therapy. Although %LGE might be more useful than LGE positivity/absence to predict adverse events, this parameter is variable depending on which grayscale threshold is chosen. Standardization is required before translation of this measure to clinical practice.

ARVC/AC

ARVC is a genetically determined heart muscle disease predisposing to VA and SCD. Sustained VT is a recognized major cause of SCD in this cardiomyopathy, mainly in young individuals and athletes [107]. In recent years, the approach to ARVC has evolved from a phenotypic to a morpho-functional model. Hence, the fundamental characteristic of ARVC is the intrinsic arrhythmogenicity and the increased risk of life-threatening arrhythmias. In addition, phenotypic variants with associated or isolated LV involvement have been characterized, leading to the definition of arrhythmogenic cardiomyopathy (AC), rather than ARVC [7].

Although most AC patients with prior sustained VTs or aborted SCD benefit from secondary prevention ICD therapy, the identification of high-risk patients who could be candidates for primary prevention of SCD is an issue. In this setting, CMR characterizes morpho-functional abnormalities of both ventricles providing identification of biventricular or left-dominant forms of AC [108], RV dilatation with global or regional dysfunction [109]. As shown by Aquaro et al. [110], the presence of any CMR abnormalities including either RV and/or LV fat infiltration identifies patients at higher risk of arrhythmic events and is associated with worse prognosis.

LGE is associated with fibro-fatty changes at histopathology and predicts inducible VT on EPS [111]. Furthermore, LV involvement at CMR is considered a strong independent predictor of cardiac events and has an additive prognostic role [110, 112, 113].

In 2010, an International Task Force proposed new diagnostic criteria for ARVC including quantitative CMR parameters but not tissue characterization [109]. However in a recent investigation, a CMR-based strategy with evaluation of LGE and fat infiltration provided an improvement in diagnostic accuracy, potentially adding information for arrhythmic risk stratification [114].

LVNC cardiomyopathy

Left ventricular non-compaction (LVNC) is a rare cardiomyopathy characterized by pronounced ventricular trabeculation, due to abnormal compaction process of myocardial walls during development, clinically associated with thromboembolic events, HF, VA, and SCD [115]. Differential diagnosis with hypertrabeculation due to volume overload conditions and other myocardial diseases is challenging [115, 116].

CMR is an essential tool for both diagnosis and prognostic implications (Table 6). Several diagnostic criteria have been proposed, considering the extent and complexity of distribution of the non-compacted (NC) myocardium [117–120]. However, these morphological criteria do not have an absolute sensitivity and specificity, with the risk of overdiagnosis [115, 121].

Several studies showed the prognostic value of CMR findings in LVNC. In a contribution by Nucifora et al. [122], LV systolic dysfunction was present in about half of 42 cases and LGE was present in 55% of patients, mainly with midwall distribution. The presence and extent of LGE were significantly related to clinical disease severity. Moreover, LGE was the only independent predictor of LV systolic dysfunction. Two subsequent small studies reported a significant association between LGE and the risk of HF and VA [123, 124].

In a prospective multicenter study by Andreini et al. [125], cardiac events occurred in 36 (32%) patients (16 HF hospitalizations, 10 VA, 5 cardiac deaths, 5 thromboembolic events) during a mean follow-up of 48 ± 24 months. LGE was a strong independent predictor of events. Moreover, a higher rate of cardiac events was observed in patients with LV dilatation and dysfunction (DCM-like phenotype). Interestingly, hypertrabeculation according to LVNC diagnostic criteria had no significant impact on prognosis, as confirmed in a large study by Ivanov et al. [126].

A recent meta-analysis [127] focused on the prognostic role of LGE and global systolic impairment in LVNC. Four studies with 574 patients were considered. Average follow-up duration was 5.2 years. LGE was independently associated with the combined end point (cardiac death, SCD, appropriate ICD intervention, resuscitated cardiac arrest, HTx, assist device implantation) and cardiac death. Furthermore, LGE was associated with MACE also in patients with preserved LVEF. Conversely, no MACE were observed in patients with LVNC, preserved LVEF and negative LGE.

Limited data about the usefulness of parametric mapping in LVNC are available. Zhou et al. [128] reported higher native T1 in LVNC patients compared to normal controls, also in LGE negative subgroup. This finding was confirmed by Araujo-Filho et al. [129]. In their study [129], the authors also reported an expanded ECV in LV segments without LGE, suggesting an extracellular expansion by diffuse fibrosis.

Table 6 Selected studies on late gadolinium enhancement in left ventricular non-compaction cardiomyopathy

Study	Patients (*n*)	Study design	Mean age (years)	Mean LVEF (%)	LGE prevalence (%)	LGE location	Median follow-up (months)	End Point	Results
Grigoratos, 2019 [127]	574	Meta-analysis of prospective cohorts	33–60	25–51	28	–	62	Cardiac death, SCD, appropriate ICD shock, resuscitated CA, HTx, assist device implantation	LGE predicted combined end point (pooled OR 4.9, 95%IC 1.63–14.6; *P* 0.005) and cardiac death (pooled OR 9.8, 95% CI 2.44–39.5; $P < 0.001$)
Ivanov, 2017 [126]	700	Single center, prospective cohort	70	51	32	–	84	Ischemic stroke, VT/VF, and HF hospitalization.	The diagnosis of LVNC was not associated with the primary outcome
Andreini, 2016 [125]	113	Multicenter prospective cohort	44	45	10	Mainly mid-wall	48	Thromboembolism, HF hospitalizations, VAs, and cardiac death	LGE predicted cardiac events (HR, 4.2; 95% CI, 1.7–10.6; $P = 0.002$)
Nucifora, 2011 [122]	42	Retrospective cohort	46	50	55	Mainly mid-wall	–	–	LGE associated with clinical status and LVEF

% percentage, *CA* cardiac arrest, *CI* confidence interval, *HF* heart failure, *HR* hazard ratio, *HTx* heart transplantation, *ICD* implantable cardioverter defibrillator, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *LVNC* left ventricular non-compaction, *OR* odds ratio, *VAs* major ventricular arrhythmias, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *SCD* sudden cardiac death

Furthermore, ECV was associated with LVEF and VA, but not with the amount of NC myocardium.

CMR in prognostic stratification

Over the last years, CMR has become a valuable tool for both diagnostic and prognostic purposes. However, parameters currently used in clinical practice, mostly LGE, represent only a part of potential applications of CMR. Refinements and advances in new applications will provide additional clinically relevant information in the next future, turning CMR into a fundamental technique for global and arrhythmic risk estimation. This information needs to be integrated in a multiparametric evaluation, considering traditional as well as novel prognostic indexes. NYHA class, ECG, LVEF, right ventricular function [130], diastolic function [131], mitral regurgitation [132], deformation imaging [133], and serum biomarkers (i.e., NTpro-BNP) are fundamental instruments to stratify the risk of events as they reflect the functional status of patients, the degree of biventricular derangement, the hemodynamic impairment, and the magnitude of neurohumoral activation. The change of these indicators over time along with the ventricular arrhythmic burden is an additional element to consider [134]. A comprehensive multiparametric evaluation may result in a significant reclassification of patients' risk of events. Future studies in large populations will allow CMR to be integrated in clinically applicable prognostic scores.

Limitations of CMR

CMR evaluation is not currently recommended in official guidelines to support ICD implantation. Although very informative and characterized by lower interobserver variability compared with other imaging techniques, CMR suffers from several limitations such as high costs, limited availability, and poor image quality in the presence of difficult hold-breathing or arrhythmias and presence of CMR non-compatible devices. In addition, CMR requires a significant learning curve to be mastered. Gadolinium contrast agent administration should be avoided in the presence of reduced renal function, especially when dealing with severely impaired glomerular filtration rate. Novel quantitative techniques such as native T1 and T2 allow a direct tissue characterization without administration of contrast agents, but they lack standardization.

Conclusion

CMR enables a comprehensive morphological and functional cardiac evaluation. The combination of LGE, T1 and T2 mapping, and ECV provides crucial insights into myocardial tissue composition, incremental to LVEF. For these reasons, CMR

discloses the arrhythmic substrate within the myocardium of the specific patient, taking a major step forward toward "precision medicine." LGE is a recognized strong parameter for arrhythmic stratification in many cardiomyopathies. Although promising, the use of parametric mapping is restricted by several technical limitations. This technique requires standardization and further evidence before clinical translation. In addition, the use of CMR parameters to guide ICD implantation needs to be tested in randomized clinical trials.

CMR represents a pivotal tool in the identification of patients at increased SCD risk in whom ICD implantation may be most beneficial and should be systematically considered as part of a multiparametric approach to arrhythmic stratification.

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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