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# Imaging for sudden cardiac death risk stratification: Current perspective and future directions☆

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ABSTRACT

Sudden cardiac death (SCD) accounts for one fifth of global deaths, and occurs when a trigger (e.g. myocardial ischemia, premature ventricular contraction) interacts with an arrhythmic substrate (e.g. myocardial scar, dilated cardiomyopathy). Multimodality imaging (echocardiographic, cardiac magnetic resonance and nuclear techniques) can potentially visualize many predisposing substrates and triggers. Implantable cardioverter-defibrillator (ICD) is the most effective approach to primary prevention of SCD, and current guidelines regarding ICD implantation are based on a left ventricular ejection fraction (LVEF) ≤35%. This practice is limited by a low sensitivity and specificity, and has limited value when applied to different etiologies. In this review, the role of multimodality imaging in SCD risk-stratification and the limitations of an LVEF-based approach, are discussed. Additional randomized, prospective data are eagerly awaited to inform on the role of imaging in SCD risk-stratification, and ongoing/ planned trials are subsequently discussed.



**Contents**



Globally, more than four million deaths per year can be attributed to sudden cardiac death (SCD), which is usually defined as "a non-traumatic, unexpected, fatal event occurring within one hour of the onset of symptoms in an apparently healthy subject".[1] Although causes are varied (including cardiomyopathies, valvulopathies, myocarditis and primary electrical disorders) coronary artery disease (CAD)

*Abbreviations and acronyms:* CAD, Coronary artery disease; CMR, Cardiac magnetic resonance; CVD, Cardiovascular disease; ECV, Extracellular volume; HF, Heart failure; ICD, Implantable cardioverter-defibrillator; ICM, Ischemic cardiomyopathy; LGE, Late gadolinium enhancement; LV, Left ventricular; LVEF, Left ventricular ejection fraction; LVMD, Left ventricular mechanical dispersion; MI, Myocardial infarction; MOLLI, Modified Look-Locker Inversion Recovery; NICM, Non-ischemic cardiomyopathy; PET, Positron emission tomography; SCD, Sudden cardiac death; STEMI, ST-segment elevation myocardial infarction; VA, Ventricular arrhythmia.

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**Table 1**
**Summary of cardiac imaging techniques employed for risk-stratification of sudden cardiac death, with clinical examples.** Only examples which are specifically relevant to target groups discussed in the section on Future Directions, are listed here.

| Substrate | Imaging modality | Technique | Clinical example |
|---|---|---|---|
| Fibrosis (direct) | CMR | LGE | HCM |
| | | Grey zone | ICM |
| | | $T_1$ mapping | NICM |
| | | ECV | NICM |
| | | Strain | NICM |
| Fibrosis (indirect) | Echocardiography | MD | ICM |
| | | Strain | ICM |
| | | LVMD | ICM |
| Denervation | Nuclear imaging | $^{123}$I-MIBG SPECT | NICM |
| Inflammation | | $^{18}$F-FDG PET | Sarcoidosis |
| Perfusion | | $^{82}$Rb PET | Sarcoidosis |

CMR: cardiac magnetic resonance imaging; ECV: extracellular volume; $^{18}$F-FDG PET: $^{18}$F-labeled fluorodeoxyglucose positron emission tomography; HCM: hypertrophic cardiomyopathy; ICM: ischemic cardiomyopathy; $^{123}$I-MIBG SPECT: iodine-123 metaiodobenzylguanidine single photon emission computed tomography; LGE: late gadolinium enhancement; LVMD: left ventricular mechanical dispersion; NICM: non-ischemic cardiomyopathy; $^{82}$Rb: rubidium-82.

remains the most frequent etiology.[1] The pathophysiology of SCD may include a predisposing substrate (anatomical e.g. bundles of collagen interspersed with viable myocytes after a myocardial infarction (MI) or functional, e.g. a channelopathy in long QT syndrome) upon which a trigger (e.g. ischemia, premature ventricular contraction) acts, leading to a lethal ventricular arrhythmia (VA; ventricular tachycardia or ventricular fibrillation).[1] Both primary and secondary prevention are best achieved with an implantable cardioverter-defibrillator (ICD).[1] Currently, left ventricular (LV) ejection fraction (LVEF) is the main criterion to select patients for ICD implantation as primary prevention. However, various cardiac imaging modalities [echocardiography, cardiac magnetic resonance (CMR) and nuclear techniques] have shown superiority to LVEF in risk-stratifying patients for SCD by both the ability to predict outcome and the accuracy of measurement (e.g. CMR), and to guide ICD implantation for primary prevention. In addition, these imaging modalities have provided new insights on how to visualize the pathophysiological mechanisms of VAs in patients who survived SCD.

## Cardiac imaging techniques: linking arrhythmogenic substrate to SCD risk by direct visualization of pathologic substrate

Cardiac multimodality imaging can be utilized to either directly or indirectly visualize arrhythmogenic substrates, and thereby risk-stratify patients for SCD (Table 1). With the exception of inherited VA syndromes, the other causes of SCD are characterized by changes in the extracellular matrix that predispose to re-entrant VAs. Type I collagen is the main constituent of the myocardial extracellular space (in the absence of edema or amyloid) and accumulates in a focal or diffuse manner, which can be identified on CMR by late gadolinium enhancement (LGE), which may however, also represent non-collagenous substrates, e.g. edema, amyloid or myocyte disarray. Gadolinium-based contrast agents accumulate in the enlarged extracellular space, which can be visualised by delayed (10–20 min after gadolinium contrast medium administration) CMR acquisitions.[2] Delineation of LGE is achieved by nulling of normal myocardium by an inversion recovery sequence, while the grey zone can be differentiated from a more dense area of scar ("core") by using specific signal intensity thresholds (Fig 1A).[2] While electrically inert, scar is surrounded by a so-called "grey zone", containing a mix of normal myocardium and fibrotic scar (Fig 1B). Impulse conduction is delayed in the grey zone, leading to re-entry and VAs.[2] LGE is firmly linked to VAs in both ischemic cardiomyopathies (ICM) and non-ischemic cardiomyopathies (NICM),[3–6] which is conventionally defined as the absence of CAD, valvular disease, hypertension or congenital heart disease. Both the presence and extent (expressed as absolute mass or percentage of volume/mass) of LGE is associated with VAs and SCD in ICM and NICM.[2–6] The presence of LGE was independently associated with a composite endpoint including VAs and ICD discharge (hazard ratio (HR), 5.98; 95% CI 2.68–13.30; $P < 0.0001$) in 195 patients with suspected CAD.[7] In a study of 66 patients with

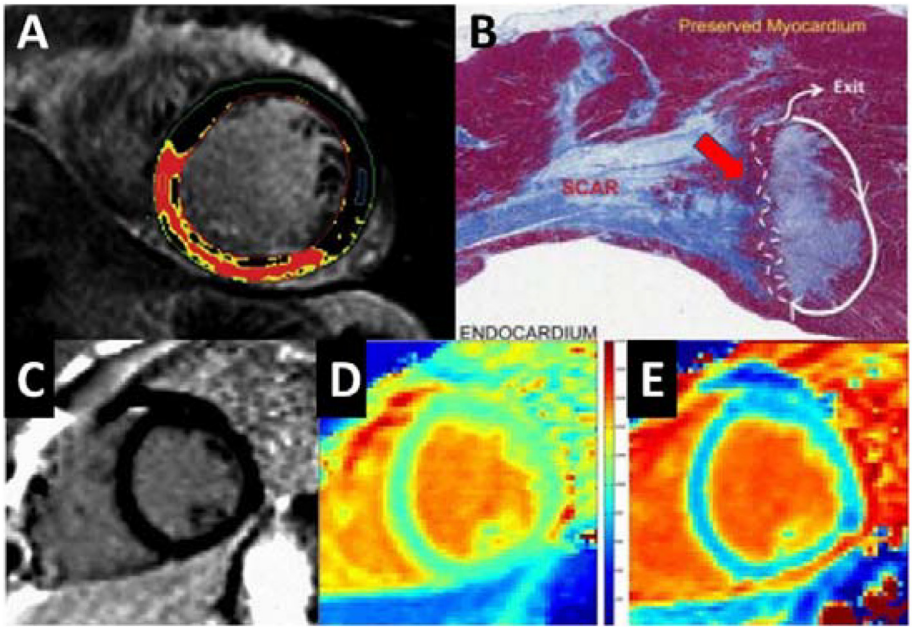


**Fig 1. Linking arrhythmogenic substrate to sudden cardiac death risk with cardiac magnetic resonance (CMR) imaging.** CMR of infarct core and peri-infarct grey zone (A). Infarct core is displayed in red and grey zone in yellow, in a short axis view of the left ventricle in a patient with an infero-posterior myocardial infarct. The full-width half-maximum thresholding technique was applied to differentiate between infarct core and grey zone. Histological section of myocardium, demonstrating dense scar (core) in blue (Masson trichrome stain) and peri-infarct grey zone (red arrow), where a re-entry circuit can be established (depicted by white arrows) (B). Short axis image of the left ventricle in a patient with Duchenne muscular dystrophy and cardiac involvement, demonstrating absence of late gadolinium enhancement (C). $T_1$ map with elevated values (D) and an extracellular volume map depicting an expanded extracellular space (E) in the same patient as in (C), suggesting the presence of diffuse myocardial fibrosis. (A) reproduced from Robbers et al.[25] with permission, and (B) adapted from Wu et al.[58] with permission. (C-D) reproduced from Soslow et al.[15] with permission.

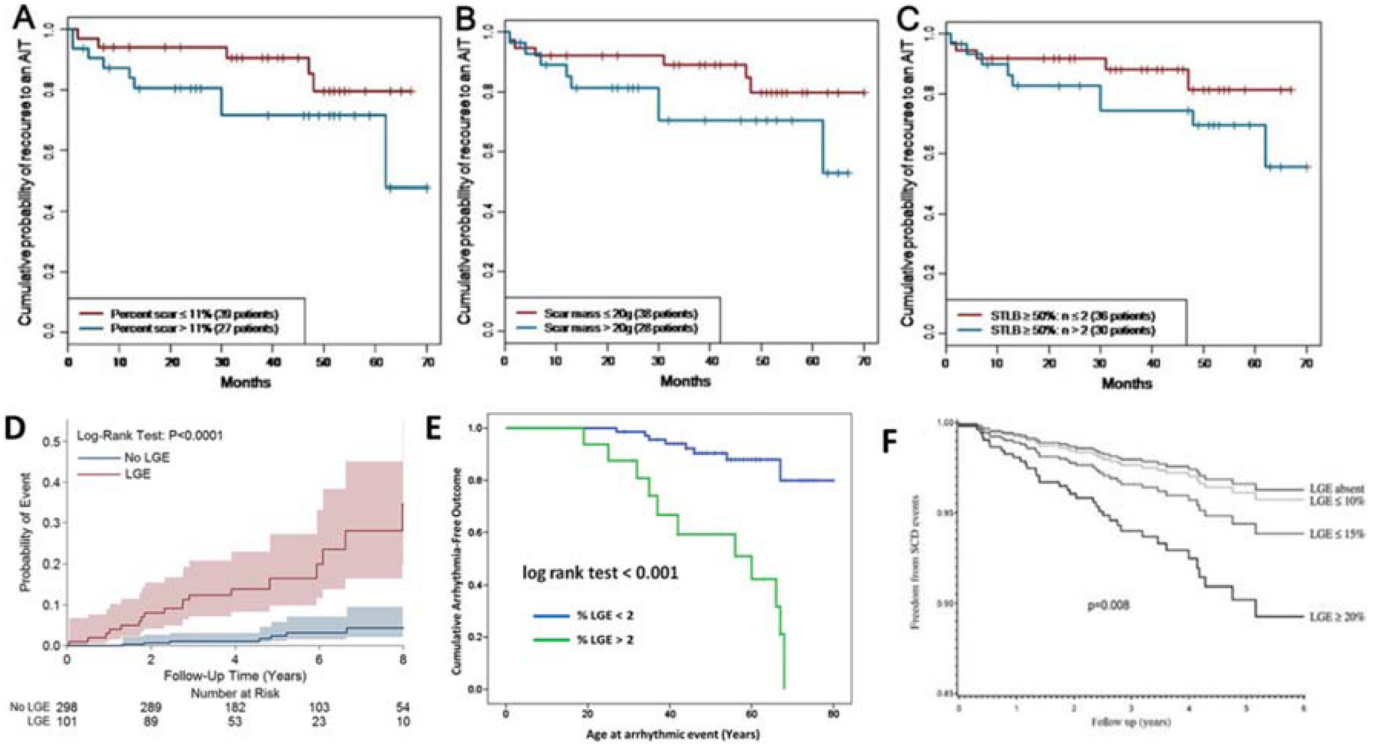


**Fig 2. Linking arrhythmogenic substrate to sudden cardiac death risk with cardiac magnetic resonance (CMR) imaging in various conditions.** Kaplan-Meier curves for freedom from appropriate implantable-cardioverter therapy in patients with coronary artery disease, stratified according to the burden of late gadolinium enhancement (LGE) on CMR imaging, expressed as a percentage of total myocardial volume (A), scar mass (B) and percentage of scar transmurality (C). Kaplan-Meier curves for freedom from sudden cardiac death (SCD), stratified according to the presence of LGE on CMR imaging in patients with non-ischemic dilated cardiomyopathy (D). Kaplan-Meier curves for freedom from ventricular arrhythmias, stratified according to the presence of LGE on CMR imaging, expressed as a threshold percentage of myocardial volume, in patients with hypertrophic cardiomyopathy (E). Kaplan-Meier curves for freedom from SCD, stratified according to the burden of LGE on CMR imaging, expressed as a percentage of myocardial volume, in patients with hypertrophic cardiomyopathy (F). Patients with LGE, as well as a higher burden of LGE, experienced worse outcomes. Reproduced from Alexandre et al.[8] (A-C), Halliday et al.[6] (D), Haland et al.[12] (E) and Chan et al.[44] (F) with permission.

chronic CAD, the burden of LGE was independently associated with appropriate ICD therapy (HR, 3.15; 95% CI 1.35–7.33; $P < 0.001$) (Fig 2A-C).[8] The size of the peri-infarct grey zone however, remains independently associated with VAs and all-cause mortality, even when corrected for scar burden (i.e. core zone, quantified with LGE).[9,10] Quantification of the grey zone therefore has incremental prognostic value over the extent of the scar core, and is probably a better reflection of the arrhythmogenic substrate.[1] Both the presence (odds ratio (OR), 4.9; 95% confidence interval (CI) 3.3–7.3; $P < 0.001$) and extent (OR, 3.4; 95% CI 1.6–7.7; $P < 0.002$) of LGE was independently associated with VAs and appropriate ICD therapy in a meta-analysis of 2948 patients with NICM (Fig 2D).[5,6] In a meta-analysis which included 2993 patients with hypertrophic cardiomyopathy (HCM), the presence of LGE was associated with an increased risk for SCD (OR, 3.41; 95% CI 1.97–5.94; $P < 0.001$), all-cause mortality (OR, 1.80; 95% CI 1.21–2.69; $P = 0.004$) and cardiovascular disease (CVD) mortality (OR, 2.93; 95% CI 1.53–5.61; $P = 0.001$) (Fig 2E).[11,12] In the same study, the extent of LGE was associated with an increased risk of SCD (HR, 1.56/10% LGE; 95% CI 1.33–1.82; $P < 0.0001$), heart failure (HF) death (HR, 1.61/10% LGE; 95% CI 1.21–2.13; $P = 0.001$), all-cause mortality (HR, 1.29/10% LGE; 95% CI 1.09–1.51; $P = 0.002$) and CVD mortality (HR, 1.57/10% LGE; 95% CI 1.30–1.89; $P < 0.001$).[11] In a meta-analysis of 760 patients with cardiac sarcoidosis,

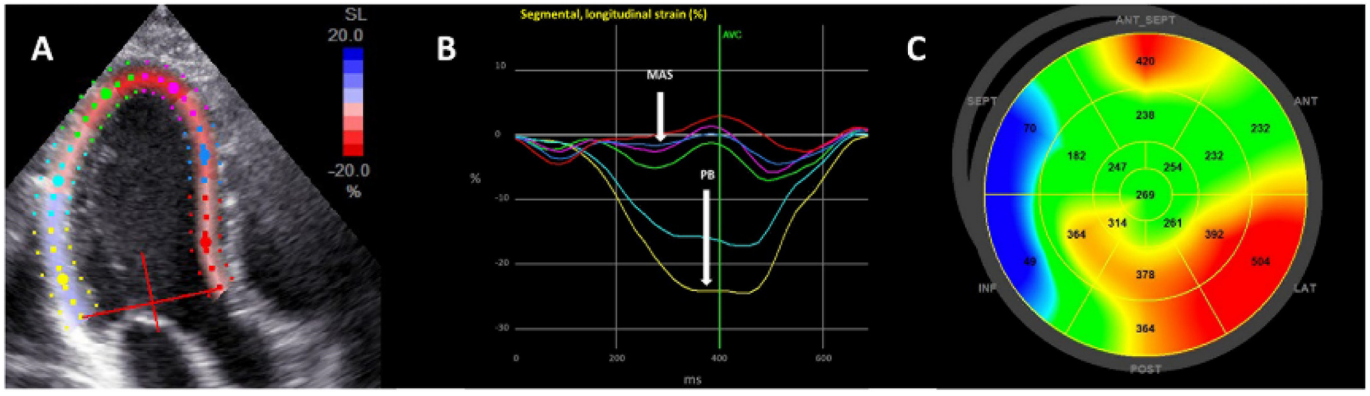


**Fig 3. Speckle tracking echocardiography to assess the risk of ventricular arrhythmias.** Panels A & B: Impaired anteroseptal strain in the territory of a left anterior descending coronary artery infarct. Longitudinal strain is measured with 2-dimensional speckle-tracking echocardiography in the apical 3-chamber view (A). Different colors represent different segments, e.g. the mid-anterior segment in dark blue and the posterobasal segment in yellow. The mid-anterior segment demonstrates impaired peak longitudinal strain, while the posterobasal segment shows evidence of compensatory hypercontractility (B). AVC: aortic valve closure; SL: longitudinal strain. Panel C: Mechanical dispersion of the left ventricle, displayed as a parametric map in a patient with ischemic cardiomyopathy. Late activation of the posterolateral segments (orange/red) results in an abnormally elevated mechanical dispersion of 121 ms.

the presence of LGE increased the risk for a composite endpoint of all-cause mortality, VAs and SCD (OR, 10.74; 95% CI 4.12–27.90; $P < 0.00001$).[13]

Myocardial fibrous tissue may also occur in a more diffuse, non-focal distribution (i.e. not as a "core" with surrounding "grey zone") especially in NICM.[14] The mechanism of VAs in such diffuse fibrosis is less well understood than in the case of focal scar tissue, but is nevertheless believed to be re-entrant in nature.[14] Conventional LGE imaging is unable to clearly image diffuse, non-focal fibrosis.[14] Since non-focal fibrosis is also a substrate for VAs, novel techniques are being developed for its visualization and quantification. CMR $T_1$ mapping is an emerging technique, which can depict diffuse myocardial fibrosis, even in the absence of LGE (Fig 1C-D).[2,15] In $T_1$ mapping, the time constant of longitudinal spin relaxation is represented on a pixel-by-pixel basis by means of a pre- or post-contrast $T_1$ map, which is generated with special CMR sequences, e.g. Modified Look-Locker Inversion Recovery (MOLLI) or shortened MOLLI.[2] Longitudinal spin relaxation values are therefore displayed in their anatomical location pixelwise, constituting a $T_1$ map (Fig 1C-D).

Since type I collagen accumulates mainly in the extracellular space, thereby increasing its volume, it may be useful to quantify the extracellular volume fraction (ECV) itself. Calculation of the ECV, which reflects the arrhythmogenic substrate (diffuse myocardial fibrosis) and is also displayed as an ECV map, can be performed using pre- and post-contrast $T_1$ values of the blood pool and myocardium, and also requires a hematocrit value.[2]

Pre-contrast $T_1$ mapping has been shown to be independently associated with VAs in both ICM and NICM, even when correcting for LGE burden.[14,16] $T_1$-based quantification of diffuse myocardial fibrosis therefore appears to be of incremental prognostic benefit, beyond the extent of dense/focal fibrosis (depicted by LGE).[14]

## Cardiac imaging techniques: linking arrhythmogenic substrate to SCD risk by indirect visualization of pathologic substrate

Demonstration of abnormal myocardial deformation (strain) indirectly reflects myocardial fibrosis (focal and diffuse) and can be measured in various directions (longitudinal, circumferential and radial) with echocardiography or CMR. Impaired longitudinal and circumferential myocardial strain are associated with VAs and SCD when measured by CMR techniques (tagging or feature tracking).[2] Due to its ease of application and higher temporal resolution than CMR, myocardial strain is more commonly assessed with echocardiography (Fig 3A-B). Impaired LV global longitudinal strain, measured with speckle tracking strain echocardiography is linked to VAs and SCD in ICM and NICM.[1] Arrhythmogenic substrates also frequently lead to electromechanical heterogeneity of LV contraction, which can be quantified with LV mechanical dispersion (LVMD), defined as the standard deviation of the time from the onset of the QRS complex on the triggered ECG, to the peak longitudinal myocardial strain (on speckle tracking strain echocardiography) in a 17-segment model of the LV (Fig 3C).[17] LVMD analysis has also been applied to CMR feature tracking, and was associated with VA risk.[2]

## Cardiac imaging techniques: linking arrhythmogenic triggers to SCD risk

Furthermore, cardiac sympathetic denervation (pathological decrease of sympathetic innervation) is a trigger for VAs and SCD, and can be imaged with nuclear techniques, e.g. Iodine-123 ($^{123}$I) metaiodobenzylguanidine single photon emission computed tomography, which is an analogue of noradrenaline.[1] Myocardial denervation is a risk factor for VAs and SCD in both ICM and NICM.[1] Nuclear techniques (perfusion-metabolic imaging with rubidium-82 ($^{82}$Rb) and $^{18}$F-labeled fluorodeoxyglucose (FDG)) positron emission tomography (PET) have the ability to reveal active myocardial inflammation (e.g. in cardiac sarcoidosis) which is related to the development of VAs (Fig 4).[18]

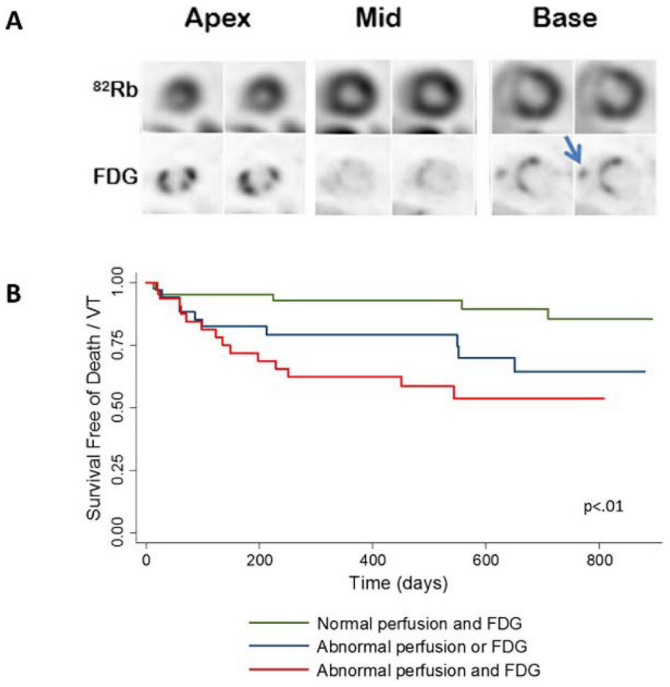


**Fig 4. Positron emission tomography (PET) imaging in cardiac sarcoidosis.** A) Short axis perfusion (rubidium-82, $^{82}$Rb) and metabolic (fluorodeoxyglucose, FDG) images in a patient with a left ventricular, septobasal perfusion and metabolic abnormality (i.e. abnormal perfusion and FDG in fig. B). The blue arrow indicates abnormal right ventricular FDG uptake. B) Kaplan-Meier curves for freedom from death and ventricular tachycardia (VT), stratified according to PET perfusion and FDG uptake. Patients with both myocardial perfusion abnormalities and inflammation (FDG uptake) experienced a worse outcome than those with either perfusion or inflammation alone. Reproduced from Blankstein et al.[18] with permission.

## Cardiac imaging techniques in the prevention of SCD: current practice and limitations

Despite a wealth of data linking different echocardiographic, CMR and nuclear imaging parameters (representing direct or indirect evidence of focal or diffuse myocardial fibrosis) to the risk of SCD, contemporary clinical practice for the selection of primary prevention ICD candidates still relies on echocardiography-derived LVEF.[2] This is due to prospective evidence for ICD efficacy in primary (and secondary) SCD prevention which originates from trials employing echocardiography-measured LVEF, e.g. the Multicenter Automatic Defibrillator Trial (MADIT II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[19,20] An LVEF ≤35% is currently a class IA indication for ICD implantation.[21] Since the presence of an arrhythmogenic substrate does not consistently lead to an LVEF <35%, and conversely an LVEF ≤35% may exist without a high risk of SCD, this is neither a sensitive nor a specific approach to ICD candidate selection.[1] Less than a third of ICD recipients with LVEF ≤35% ever receive appropriate therapy, while being exposed to potential complications (e.g. lead failure and inappropriate ICD therapy) and even fewer individuals (<25%) who experience SCD have an LVEF ≤35%.[1]

## Future directions

In order to capitalize on the potential of multimodality imaging in overcoming the limitations of an LVEF-based approach for SCD risk-stratification, more prospective data are required (Table 2). Elucidation of the interaction between LVEF and HF etiology is also required. In the following section, the limitations of using LVEF for SCD risk-stratification in ICM, NICM, HCM and cardiac sarcoidosis will be discussed, as well as the evidence for non-LVEF based imaging techniques and ongoing/future studies.

**Table 2**
**Summary of ongoing, prospective trials for cardiac imaging in sudden cardiac death risk stratification.** Only studies and outcomes which are specifically relevant to the target groups discussed, are listed here.

| Study & NCT Identifier | Estimated no. of patients | Imaging technique | Target group | Relevant outcome(s) |
|---|---|---|---|---|
| PROTECT-ICD[22]<br>*NCT03588286* | 1058 | CMR | **ICM**<br>Acute myocardial infarct & LVEF ≤40% | ▪ SCD<br>▪ Ventricular arrhythmias (nonfatal)<br>▪ All-cause mortality<br>▪ Non-sudden cardiovascular death<br>▪ Non-fatal, repeat MI<br>▪ Heart failure<br>▪ Inappropriate ICD denial<br>▪ Appropriate ICD activations<br>▪ Inappropriate ICD activations<br>▪ Complications of rehospitalization |
| CMR-GUIDE[31]<br>*NCT01918215* | 1055 | CMR | **ICM**<br>Chronic with LVEF >35% | ▪ SCD<br>▪ Ventricular arrhythmias<br>▪ All-cause mortality<br>▪ Change in symptomatic status<br>▪ Heart failure hospitalizations<br>▪ Cost analysis |
| NICMR<br>*NCT02657967* | 1950 | CMR | **NICM**<br>LVEF <40% | ▪ SCD<br>▪ Appropriate ICD therapy<br>▪ All-cause mortality |
| *NCT01076660* | 400 | CMR | **NICM**<br>LVEF ≤35% | ▪ SCD<br>▪ Appropriate ICD therapy<br>▪ Ventricular arrhythmias<br>▪ Cardiac mortality<br>▪ Heart transplantation<br>▪ Left ventricular assist device placement<br>▪ Hospitalization for heart failure<br>▪ Atrial fibrillation<br>▪ Stroke |
| HCMR[51]<br>*NCT01915615* | 2750 | CMR | **HCM** | ▪ Ventricular arrhythmias<br>▪ Atrial fibrillation |
| HCM-PET<br>*NCT03278457* | 25 | PET | **HCM** | Adverse events, including prognostic markers |
| *NCT03356756* | 60 | PET & CMR | **Sarcoidosis** | ▪ Ventricular arrhythmias<br>▪ All-cause mortality<br>▪ Cardiac mortality<br>▪ Heart failure hospitalization<br>▪ Atrial fibrillation burden<br>▪ Percentage ventricular pacing |
| CHASM-CS<br>*NCT01477359* | 1500 | PET & CMR | **Sarcoidosis** | |

CMR: cardiac magnetic resonance; HCM: hypertrophic cardiomyopathy; HCMR: hypertrophic cardiomyopathy registry; ICD: implantable cardioverter defibrillator; ICM: ischemic cardiomyopathies; LVEF: left ventricular ejection fraction; MI: myocardial infarct; NCT: national clinical trial; NICM: non-ischemic cardiomyopathies; NICMR: non-ischemic cardiomyopathy registry; PET: positron emission tomography; SCD: sudden cardiac death.

## Ischemic cardiomyopathy

Although improved survival with ICD implantation in primary and secondary prevention of SCD is well-established for ICM (e.g. the MADIT II and SCD-HeFT trials) this benefit does not appear to extend to the immediate post-infarct period.[1,19,20] In the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), patients with LVEF ≤35% did not gain an advantage in terms of all-cause mortality reduction when an ICD was implanted in the first 40 days post-infarct - even though such patients remain at high risk of SCD.[22,23] There are very limited data for the use of non-invasive imaging in the immediate post-infarct context. The Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator Implantation to Prevent Tachyarrhythmias following Acute Myocardial Infarction (PROTECT-ICD) trial (NCT03588286) will provide new insight into the role of CMR to select patients who will benefit from ICD implantation.[22] The study will randomize post-MI patients [with an ST-segment elevation MI (STEMI) or non-STEMI MI] with LVEF ≤40% to an invasive, electrophysiology-guided ICD implantation group and a control arm (ICD insertion guided by LVEF after 40 days) in a 1:1 fashion. A proportion of both groups will receive a CMR study, assessing LV size and function, myocardial edema, infarct size (LGE), $T_1$ mapping and ECV quantification.[22] Participants will be followed-up for the occurrence of non-fatal VAs and SCD (Table 2).[22]

In the Oregon Sudden Unexpected Death Study (including 2093 patients with SCD; primarily ICM) only 20.5% had an LVEF ≤35%. The majority of patients who suffered SCD therefore had only mild or moderate LV dysfunction. This represents a target group of patients where non-invasive imaging may aid in risk-stratification. CMR-LGE (presence, extent and grey zone, Fig 1) has been firmly linked to SCD and VAs in the immediate aftermath of an acute coronary syndrome and in chronic ICM, when the LVEF is >30–35%.[7,24–26] LVMD calculated from peak circumferential strain measured with CMR feature tracking was independently associated with SCD and VAs in STEMI patients with LVEF >35% in the first week post-infarct.[27] In a prospective, observational study of 988 patients with acute MI and LVEF >35%, impaired echocardiographic LV global longitudinal strain (GLS;Fig 3A & B) and increased LVMD (Fig 3C) in the first 48 h of hospital admission, remained prognostic for VAs and SCD after multivariate adjustment.[28,29] In patients with previous MI and LVEF >35%, the HR for VAs increased by 1.12 for every 10 ms increment in LVMD (95% CI, 1.07–1.18; $P < 0.001$).[30] A prospective, multicenter trial (Cardiovascular Magnetic Resonance Guided Management of Mild-Moderate Left Ventricular Systolic Dysfunction (CMR-GUIDE), NCT01918215) is enrolling patients with ICM and NICM who have an LVEF of 36–50%, and who would not be eligible for primary ICD implantation according to current guidelines.[31] Participants with myocardial LGE will be randomized to receive either a primary prevention ICD or a loop recorder and will be followed up for hemodynamically-significant VAs and SCD (Table 2).[31]

## Non-ischemic cardiomyopathy

The benefits of ICD in patients with NICM and LVEF ≤35% were demonstrated in three randomized, prospective trials.[20,32,33] While current

guidelines are primarily based on results of the SCD-HeFT trial, they have been challenged by the more recently published Danish Study to Assess the Efficacy of ICDs in Patients With Non-Ischemic Systolic Heart Failure on Mortality (DANISH) study. None of these trials specifically assessed the role of CMR in risk-stratification.

Observational studies support a role for non-invasive imaging in risk-stratification of NICM patients. In an observational trial of 228 NICM patients, the presence of CMR-LGE was associated with SCD (HR, 4.02; 95% CI 2.08–7.76; $P < 0.001$) independently of LVEF.[34] Similarly, in a prospective study of 65 NICM patients with LVEF ≤35%, LGE was associated with a higher risk of SCD and VAs.[35] More recently, 452 patients with NICM and an LVEF ≤35% were followed up for all-cause mortality.[36] Only in those with LV scar, demonstrated by CMR-LGE, did ICD implantation independently lead to decreased mortality (HR, 0.45; 95% CI 0.26–0.77; $P = 0.003$).[36] In a community-based study of 900 individuals without HF, including random participants and patients with diabetes mellitus, LGE-fibrosis was associated with all-cause mortality and HF hospitalizations in NICM patients.[37] Furthermore, Chen et al. demonstrated that every 10 ms increase in native $T_1$ increased the HR for VAs by a factor of 1.1 (95% CI, 1.04–1.16; $P = 0.0001$).[16] In a CMR feature tracking study, a subgroup analysis of 210 NICM patients demonstrated that LV GLS was associated with SCD in those patients with LVEF ≤35%.[38] An ongoing large, multicenter registry (Development of an Evidenced-Based Tool for Prediction of Sudden Cardiac Death in Patients With Non-Ischemic Cardiomyopathy Registry; NCT02657967) is enrolling patients with NICM and LVEF <40% to investigate the use of LGE-CMR in predicting SCD and VAs (Table 2).

The evidence for echocardiographic risk-stratification in NICM patients is more limited than for CMR: in a study by Haugaa et al. of 94 NICM patients LVMD was associated with SCD and VA's, independent of LVEF.[39] The importance of diastolic dysfunction in SCD was highlighted by Negishi et al., where measurement of the mitral A-wave demonstrated incremental prognostic value over LVMD and GLS as a predictor of VAs in a group of 124 NICM patients with mean LVEF ≤35%.[40]

Finally, the role of innervation imaging with nuclear imaging was assessed in the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study, where cardiac denervation (imaged with $^{123}$I-MIBG SPECT) was a significant contributor to VAs in a large cohort of HF patients, one third of them being NICM patients.[41] Similar results were obtained in studies of patients with LVEF ≤35% by Kioka et al. and Tamaki et al., where half the patients had NICM.[42,43]

## Hypertrophic cardiomyopathy

An LVEF-based approach to SCD risk stratification cannot be applied to HCM, since the LVEF is usually >35%, unless adverse remodeling supervenes (which occurs only in 2%).[44] There is a need for improved risk-stratification of HCM, due to the insensitivity of current approaches.[45,46] Multimodality imaging techniques may be very useful in refining selection for ICD implantation in HCM patients. Multiple studies have linked the presence and extent of LGE on CMR with VAs and SCD in patients with HCM.[2,11] The use of LGE as a an “arbitrator” in decision-making for primary ICD implantation in HCM patients with an intermediate or ambiguous risk, has been included in the American College of Cardiology/American Heart Association HCM guidelines.[47] Impaired LV GLS and elevated LVMD on echocardiography, have also been associated with SCD and VAs in HCM.[12,48–50] A large multinational registry (NCT01915615) is currently recruiting patients to further define the role of CMR (as well as clinical and genetic) markers for predicting SCD risk in HCM (Table 2).[51] An advanced nuclear imaging (PET) study (HCM PET; NCT03278457) will also assess the risk of VAs in HCM with perfusion ($^{15}$O-labeled water, $^{15}$O-$H_2O$) and denervation ($^{11}$C-labeled hydroxyephedrine, $^{11}$C-HED) PET imaging (Table 2).

## Cardiac sarcoidosis

In a large, multicenter trial of ICD therapy for cardiac sarcoidosis, most patients who experienced appropriate therapy had an impaired LVEF, although still >35%.[52] Using a threshold of LVEF ≤35% may therefore not be appropriate in the SCD risk-stratification of cardiac sarcoidosis. Data have accumulated on the role of cardiac imaging in this context, e.g. the presence and burden of LGE which is linked to the risk for VAs in cardiac sarcoidosis patients with LVEF >35%.[53–56] Impaired echocardiographic LV GLS in a cohort of sarcoidosis patients with LVEF >35% was independently associated (HR, 1.4; 95% CI, 1.1–1.7; $P = 0.006$) with a composite endpoint: VAs, all-cause mortality, HF hospitalizations, device implantations and future development of cardiac sarcoidosis.[57] Active myocardial inflammation (demonstrated by perfusion-metabolic imaging with $^{82}$Rb and $^{18}$F-FDG PET) is pathophysiologically and clinically related to the risk of VAs in cardiac sarcoidosis patients with LVEF >35% (Fig 4).[18] Two prospective trials (NCT03356756 and Cardiac Sarcoidosis Multi-Center Prospective Cohort (CHASM-CS; NCT01477359)) are currently enrolling patients with suspected or confirmed cardiac sarcoidosis for combined $^{18}$F-FDG PET and CMR imaging, and both will evaluate the imaging findings' prognostic significance (Table 2).

## Conclusions

Various SCD etiologies converge on a final common pathway of an arrhythmogenic substrate and a trigger, which interact to cause a fatal VA. Primary prevention is best achieved by ICD implantation which is indicated when LVEF ≤35%. This approach however, is hampered by both a low sensitivity and specificity, leading to as many as two thirds of patients experiencing SCD not receiving an ICD, and < 25% of those that do receive an ICD, ever benefiting from appropriate therapy. Accumulating experience with novel, multimodality cardiac imaging techniques supports a role in SCD risk-stratification. The results of several ongoing and future trials, which will collect prospective data and address areas of uncertainty (e.g. patients with LVEF >35%), are eagerly awaited.

## Conflict of interest

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