Primary prevention implantable cardioverter-defibrillator and opportunities for sudden cardiac death risk assessment in non-ischaemic cardiomyopathy

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Sudden cardiac death (SCD) accounts for approximately one-third of all deaths among patients with non-ischaemic cardiomyopathy (NICM). Implantable cardioverter-defibrillator (ICD) therapy has been the primary intervention for managing individuals at high risk for SCD. However, individual ICD trials in the NICM population have failed to demonstrate a mortality benefit with prophylactic ICD implantation. Current guidelines recommend ICD implantation in NICM patients with symptomatic heart failure and a left ventricular ≤35% and are based on meta-analyses of multiple trials that span three decades and include the recent Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Heart Failure on Mortality (DANISH) trial. These pooled analyses report a significant reduction in all-cause mortality with ICD implantation compared with medical therapy alone. In addition, each of these trials has demonstrated consistently a reduction in the risk of SCD compared with medical therapy alone. As a result, a refined approach of risk stratification that selects patients at the highest risk for SCD may lead to a significant improvement in ICD efficacy. In this clinical review, we first discuss the evolution of clinical trials that have evaluated ICDs in the NICM population. We then highlight some key markers of arrhythmia risk that hold promise in personalizing risk stratification for SCD.

Introduction

Sudden cardiac death (SCD) is an important public health problem that accounts for 15–20% of the total annual mortality in industrialized nations.[1,2] Coronary heart disease has been implicated in the majority of SCD cases. In approximately 25% of SCDs, coronary artery disease (CAD) is absent, and either non-ischaemic cardiomyopathies (NICM) or primary electrical disorders are implicated as the causative factor.[2] Sudden cardiac death, which is a spontaneous condition often resulting from ventricular arrhythmias, accounts for ∼35% of all deaths among patients with NICM.[3,4] Implantable cardioverter-defibrillator (ICD) therapy has been the mainstay for managing individuals at risk of SCD. However, in the NICM population, individual ICD trials have failed to demonstrate

a mortality benefit with prophylactic ICD implantation. Recommendations for ICD implantation were initially based on the survival benefit observed in a mixed population of both ischaemic and non-ischaemic patients[5] and a meta-analysis of several non–ischaemic cohorts included in ICD clinical trials.[6] Given the limited data surrounding ICD benefit in the NICM population, the contemporary Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Heart Failure on Mortality (DANISH) was conducted. The DANISH study did not demonstrate a reduction in mortality with prophylactic ICD implantation; however, similar to other primary prevention trials in NICM populations,[3,4] ICDs reduce the risk of SCD. As a result, a refined approach of risk stratification that selects patients at the highest risk for SCD may lead to a significant improvement in ICD efficacy.

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In this clinical review, we first discuss the evolution of clinical trials that have evaluated ICDs in the NICM population. We will then highlight some key markers of arrhythmia risk that hold promise in personalizing risk stratification for SCD.

Evidence for primary prevention of sudden cardiac death in non-ischaemic cardiomyopathy

Multiple primary prevention trials have evaluated the benefit of ICDs in the NICM population. An overview and comparison of each trial's design, characteristics, and outcomes are provided in *Table 1* and *Figure 1*. Initial studies including the Cardiomyopathy Trial (CAT)[7] and the Amiodarone vs. Implantable Cardioverter-Defibrillator (AMIOVIRT) trial[8] each enrolled slightly more than 100 NICM participants with a LVEF ≤ 30–35% and randomized them to ICD vs. pharmacologic therapy. No mortality benefit was observed in either study. The larger Defibrillators in Non-ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) Study[3] then evaluated the impact of ICDs in 458 NICM participants with both non-sustained ventricular tachycardia (NSVT) and a LVEF ≤ 35%. Most individuals in this trial were treated with optimal medical therapy including beta-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Over a median follow-up period of 26 months, the total mortality was 6.2% in the medical only group, and there was a relative 35% decrease in overall mortality in the ICD group, a difference that did not achieve statistical significance. Because of an overestimation of the control group mortality and subsequent compromise in statistical power, none of these initial trials demonstrated a significant benefit to ICD therapy.

These initial studies were followed by the large multicentre Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) that randomly assigned 2521 symptomatic individuals with either ischaemic (*n* = 1310) or non-ischaemic (*n* = 1211) heart failure and LVEF ≤ 35% to placebo, amiodarone, or ICD.[5] Compared with placebo, the ICD group was associated with a 23% relative risk reduction and an absolute decrease of 7.2% in all-cause mortality after 5 years of follow-up; however, this benefit was not statistically significant in the stratified analysis of NICM participants [hazard ratio (HR) 0.73, 95% confidence interval (95% CI) 0.50–1.07; *P* = 0.06]. In 2005, after the publication of SCD-HeFT, a pooled analysis of NICM participants from the primary prevention trials in *Table 1* demonstrated a statistically significant 31% reduction (*P* = 0.002) in all-cause mortality for ICD relative to medical therapy.[6] This analysis formed the basis for the European Society of Cardiology Guidelines' recommendation on prophylactic ICD implantation for symptomatic dilated cardiomyopathy patients with a LVEF ≤ 35%.[9]

The DANISH trial was conducted in response to the limited evidence surrounding ICD benefit in the chronic, NICM population. The trial enrolled individuals with New York Heart Association (NYHA) Class II or III heart failure symptoms with a LVEF ≤ 35% not due to CAD. In addition, it is the first ICD trial to require an elevated level of N-terminal pro-brain natriuretic peptide (NT-pro BNP) despite optimal medical therapy.[4] Randomization in this trial involved the assignment of 556 participants to ICD and 560 individuals to standard clinical care. In both the interventional and control groups, the
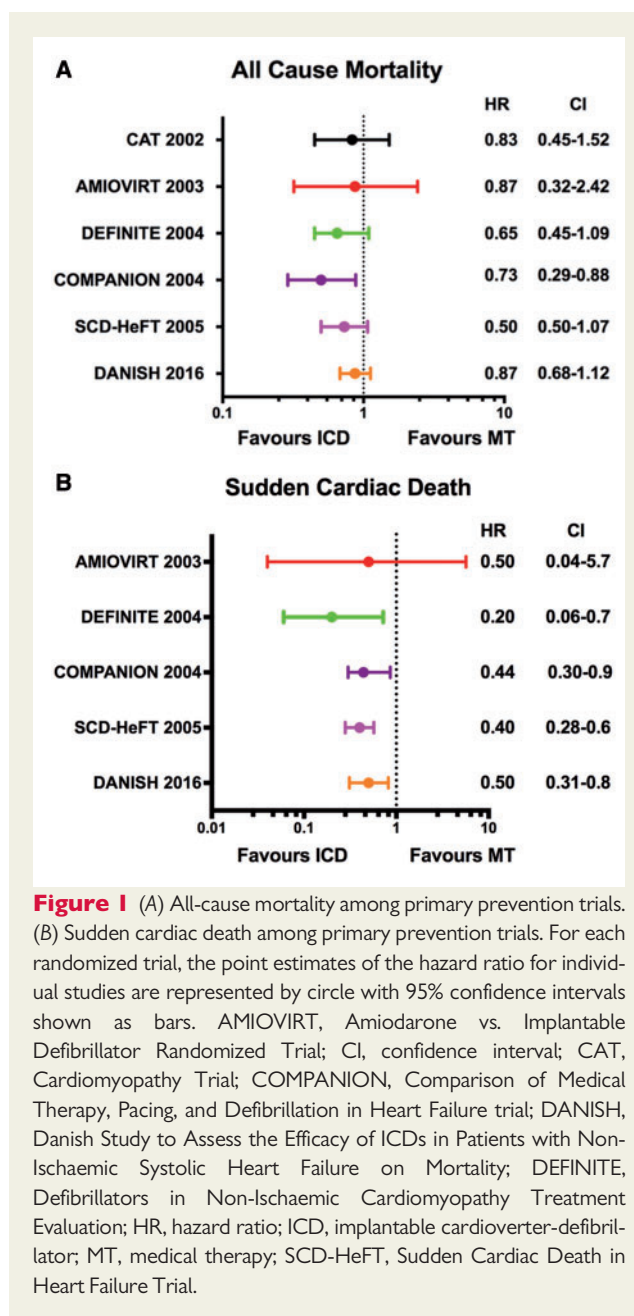

Figure 1 (*A*) All-cause mortality among primary prevention trials. (*B*) Sudden cardiac death among primary prevention trials. For each randomized trial, the point estimates of the hazard ratio for individual studies are represented by circle with 95% confidence intervals shown as bars. AMIOVIRT, Amiodarone vs. Implantable Defibrillator Randomized Trial; CI, confidence interval; CAT, Cardiomyopathy Trial; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial; DANISH, Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischaemic Systolic Heart Failure on Mortality; DEFINITE, Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MT, medical therapy; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

NT-pro BNP levels were markedly elevated (median value 1244 pg/mL in the ICD group and 1110 pg/mL in the medical group), and the majority of participants received cardiac resynchronization therapy (CRT). After a median follow-up of 67.6 months, all-cause mortality had occurred in 21.6% of the ICD group and 23.4% in the control group (HR 0.87, 95% CI 0.68–1.12; *P* = 0.28). In a pre-specified analysis from DANISH, survival benefit from ICD implantation was seen only in individuals ≤70 years of age.[10] Participants ≤70 years had a 30% reduction in total mortality in the ICD arm compared with standard medical therapy. Among individuals >70 years of age, the rate of non-sudden deaths was nearly twice as high compared with the younger population, and no mortality benefit was seen with ICD implantation. As a result of this age interaction, the widespread use of cardioprotective therapies including CRT, and overall lack of

Table 1 Study details of clinical trials evaluating implantable cardioverter-defibrillator use in non-ischaemic cardiomyopathy

	CAT	AMIOVIRT	DEFINITE	SCD-HeFT	COMPANION	DANISH
No. of patients randomized	104	103	458	2521	1520	1116
No. of patients with NICM (%)	104 (100)	103 (100)	458 (100)	792 (47.3)	682 (44.0)	1116 (100)
Year of publication	2002	2003	2004	2005	2004	2016
Trial details						
Design	ICD vs. OMT	ICD vs. OMT	ICD vs. amiodarone	ICD vs. amiodarone vs. placebo	OMT vs. CRT-P vs. CRT-D	ICD vs. OMT
Inclusion criteria	LVEF ≤ 30%, NYHA II–III	LVEF ≤ 35%; DCM; NSVT; NYHA I–III	LVEF ≤ 35%; DCM; NSVT or PVCs; NYHA I–III	LVEF ≤ 35%; NYHA II–III	NYHA III–IV; QRS duration ≥120 ms	LVEF ≤ 35%; NT-pro-BNP >200 pg/mL; NYHA II–IV
Duration of follow-up (months)	66 ± 26.4 (mean)	24 ± 14.4 (mean)	29 ± 14.4 (mean)	45.5 (median)	14.8–16.0 (median)	67.6 (median)
Primary endpoint	All-cause mortality	All-cause mortality	All-cause mortality	All-cause mortality	All-cause mortality/ hospitalization	All-cause mortality
Baseline characteristics						
Mean age (years)	52	59	58	60	67	64
Male (%)	86	71	71	77	68	73
HTN (%)	n/a	63	n/a	56	n/a	32
Diabetes (%)	n/a	34	23	31	41	19
Medication						
Beta-blocker (%)	4	51.5	86	69	67	92
ACE inhibitor/ARB (%)	94%	85	97	94	89	96
MRA (%)	n/a	20	NR	20	55	59
Number with CRT (%)	0	0	0	0	100%	58
Main result						
	ICD therapy did not reduce mortality, $P = 0.55$	ICD therapy did not reduce mortality, $P = 0.80$	ICD therapy resulted in 35% RR reduction, $P = 0.08$	ICD therapy resulted in 23% RR reduction in all-cause mortality, $P = 0.007$	CRT-D therapy resulted in a 36% RR reduction in mortality $P = 0.001$	ICD therapy did not reduce mortality $P = 0.28$

ACEI, angiotensin-converting enzyme inhibitor; AMIOVIRT, Amiodarone vs. Implantable Defibrillator Randomized Trial; ARB, angiotensin receptor blocker; CAT, Cardiomyopathy Trial; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial; CRT, cardiac resynchronization therapy; DANISH, Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischaemic Systolic Heart Failure on Mortality; DEFINITE, Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation; HTN, Hypertension; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist, n/a, not available; NICM, non-ischaemic cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; OMT, optimal medical therapy; PVCs, premature ventricular contractions; RR, relative risk; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; Y, Year.

mortality benefit to prophylactic ICD implantation, clinicians are evaluating critically the evolution of heart failure management, ICD implantation, and SCD risk stratification in NICM.

The advent of CRT has resulted not only in improved morbidity from heart failure but also a reduction in mortality events. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial (COMPANION), both CRT with pacemaker function only (CRT-P) and CRT with defibrillator (CRT-D) demonstrated similar reductions in mortality risk.[11,12] Further, the Cardiac Resynchronization-Heart Failure (CARE-HF) study also demonstrated that CRT pacing alone reduced mortality in NICM patients when compared with medical therapy only.[13] These findings have been supported by a recent, multicentre, observational study of 5307 European patients, who had an indication for CRT. The addition of primary prevention, defibrillator therapy over CRT pacing only is beneficial in well-selected patients with ischaemic cardiomyopathy but does not convey a significant survival benefit in NICM patients.[14] Understanding how best to leverage defibrillator therapy in the selected patients with CRT pacing remains an important area for investigation.

Recently, the Heart Rhythm Society guidelines have continued to recommend prophylactic ICD implantation in patients with NICM,
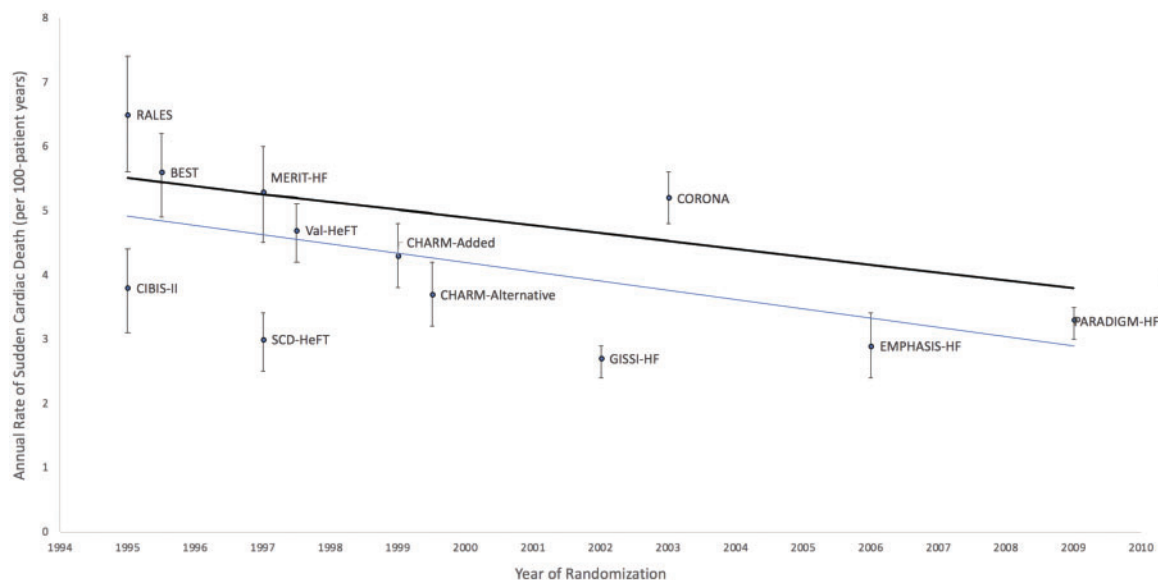
Figure 2 Declining rates of sudden cardiac death in heart failure trials. The black line reflects the unadjusted rates of sudden cardiac death. The blue line is based on the linear regression of the annualized rate of sudden cardiac death in each trial group with the randomization year and group as covariates.[9] BEST, Beta-Blocker Evaluation of Survival Trial; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity; CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure Trial; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; PARADIGM-HF, Prospective Comparison of Angiotensin-Neprilysin Inhibition with ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES, Randomized Aldactone Evaluation Study; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; Val-HeFT, Valsartan Heart Failure Trial.

LVEF ≤35%, and NYHA Class II–III heart failure despite optimal medical therapy.[15] Partial justification for recommending prophylactic ICD implantation in NICM is provided by multiple meta-analyses, which span three decades and now include the DANISH study. These studies report a significant reduction in all-cause mortality with ICD implantation compared with medical therapy alone.[16–19] Regardless of whether DANISH was evaluated in context of the five other primary prevention ICD trials from *Table 1* or only those trials that did not include CRT, the pooled analyses demonstrate that prophylactic ICD implantation in NICM results in an ∼25% relative risk reduction in all-cause mortality compared with standard therapies only. These pooled analyses, however, do not account adequately for the evolution and benefit of heart failure therapies. The annualized mortality rate in the control arm of DANISH was ∼4.2% compared with 7–8% in the other NICM, ICD trials. Similarly, in a recent analysis of 12 heart failure clinical trials spanning nearly two decades and comprising over 40 000 participants, investigators have demonstrated a 44% reduction in SCD rates (*Figure 2*).[20] Annual SCD rates decreased from 6.5% in the earliest trials to 3.3% in one of the most recent heart failure trials, Prospective Comparison of Angiotensin-Neprilysin Inhibition with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF). This decline paralleled the increasing use of evidence-based pharmacotherapies such as beta-blockers, ACE inhibitors, ARBs, mineralocorticoid receptor blockers, and CRT.[21,22] Further, the proportion of SCD relative to overall mortality did not change across trials indicating that the falling rates of SCD were in line with the downward trend

in the overall death rates. Overall improvements in heart failure therapeutics and the recent DANISH study should force clinicians to consider how these data may affect decision-making for prophylactic ICD implantation in a NICM patient.

Future directions: potential markers and approach for arrhythmia risk stratification

Non-ischaemic cardiomyopathies remain a heterogeneous set of conditions, and optimal ICD use will rely on identifying individuals who have an increase in SCD risk without a concomitant rise in the risk for non-arrhythmic death. Implantable cardioverter-defibrillators have consistently demonstrated a reduction in SCD.[3,4,19,23] However, the current approach of utilizing a low LVEF for ICD decision-making has poor sensitivity and specificity for identifying a group at increased SCD risk.[24–27] In ICD patients who had a LVEF ≤ 35% and dilated cardiomyopathy, 80% did not have any interventions for VT/VF during a 5-year follow-up period.[5,28] In addition, a decision based on LVEF only does not account for the competing risk of non-sudden cardiac death and non-cardiac death. Various risk stratification approaches such as the Seattle Heart Failure Model, which has been validated in multiple cohorts, have attempted to differentiate arrhythmic risk in order to maximize the benefit of ICD therapy.[29] In particular, the Seattle Heart Failure Model is a multivariable risk score that incorporates routine clinical variables including age, gender,
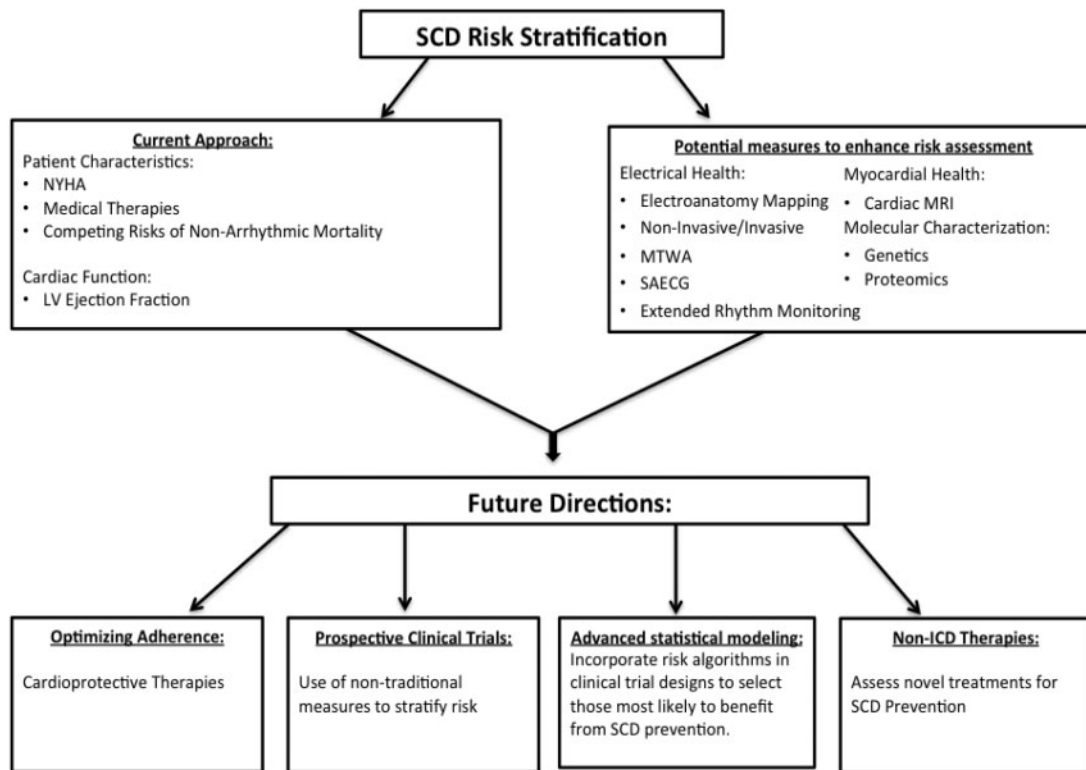
Figure 3 Future model for sudden cardiac death risk stratification. ICD, implantable cardioverter-defibrillator; LV, left ventricular; MRI, magnetic resonance imaging; MTWA, microvolt T-wave alternans; NYHA, New York Heart Association; SAECG, signal-averaged electrocardiogram; SCD, sudden cardiac death.

NYHA class, weight, ejection fraction, and specific laboratory parameters to predict both all-cause and cause-specific mortality in heart failure patients. As a result, the model can identify patient groups who have different levels of benefit from ICD therapy.[29] This score can also predict the mode of death including either SCD vs. pump failure.[30] Individuals with demographic and clinical factors corresponding to male sex, younger age, and the absence of several other comorbid conditions had a disproportionate likelihood of dying suddenly than by other modes of death such as pump failure.

In addition to more sophisticated approaches to SCD risk modelling, advances in cardiac imaging, biologic markers, and non-invasive electrophysiologic testing have the potential to provide insight into arrhythmia risk stratification (*Figure 3*). Future studies that incorporate traditional measures of risk stratification with novel ones have the potential to enhance the benefits of prophylactic ICD implantation.

Myocardial substrate

The remodelling process in NICM patients is characterized by fibrosis, and the presence of myocardial scar results in tissue heterogeneity that can provide a substrate for ventricular arrhythmias (*Figure 4*).[31–33] Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) reflects myocardial fibrosis[34] and correlates closely with histopathological scar. Multiple studies have demonstrated strong associations between the presence and degree of myocardial scar and arrhythmic events.[35–39] A meta-analysis of 9 studies that included 1488 NICM patients with a mean LVEF of 37% reported that LGE was present in 38% of patients.[40] Patients with LGE had increased risk of SCD or ventricular arrhythmias (odds ratio 5.32; $P < 0.00001$) compared with those without LGE. Specifically, the annualized event rates for SCD/aborted SCD were 6.0% in those with LGE vs. 1.2% in those without. These data may lead to clinical trials that incorporate cardiac MRI into additional risk stratification approaches for identifying not only those at the highest risk for SCD but also a subset of NICM patients with a LVEF ≤ 35%, who are unlikely to benefit from ICD implantation. Cardiac MRI may also provide an opportunity to identify high risk, non-ischaemic patients, who do not meet indication for ICD implantation based on LVEF alone. Recently, the presence of mid-wall LGE on cardiac MRI in 399 non-ischaemic cardiomyopathy patients with an LVEF ≥ 40% was associated with a nine-fold increased risk of SCD/aborted SCD.[41] Over a median follow-up period of 4.6 years, the risk of SCD/aborted SCD in those with mid-wall LGE was 17.8% compared with 2.3% in those without LGE. The rate of SCD in this population with mild left ventricular dysfunction and LGE compares to the SCD rate observed in ICD trials with LVEF ≤ 35% and provides additional rationale for the CMR-Guide (ClinicalTrials.gov identifier no. NCT01918215) randomized trial, which aims to evaluate the efficacy of ICD therapy in patients with more mild to moderate reductions in LVEF and LGE. In clinical practice, current guidelines support the use of cardiac MRI
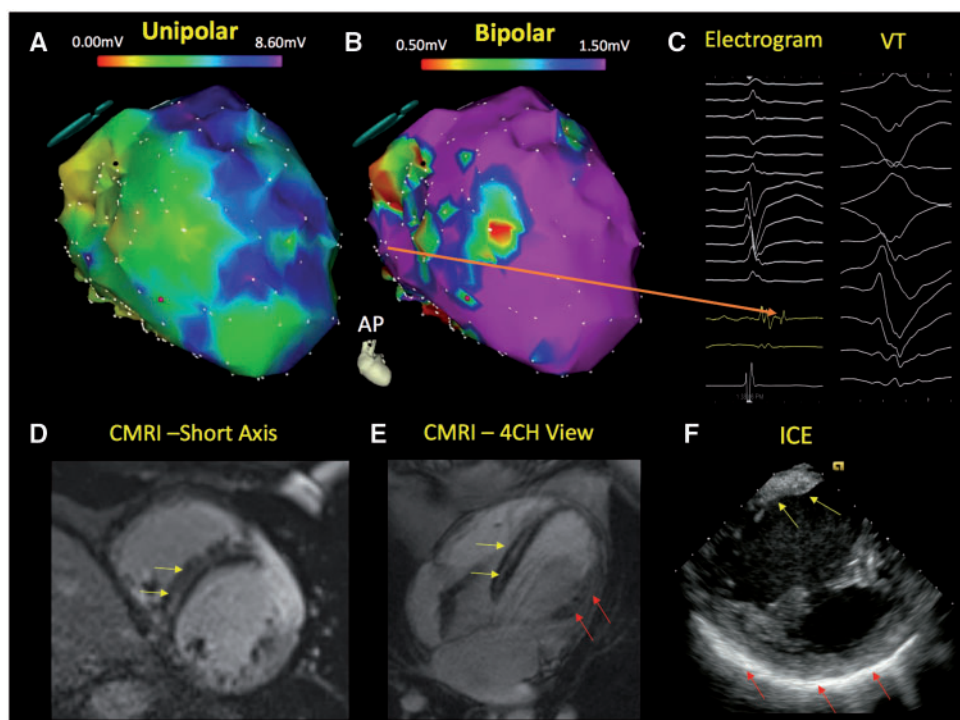
Figure 4 Electrophysiologic imaging of a non-ischaemic cardiomyopathy patient with ventricular tachycardia. The electroanatomical map of the left ventricle demonstrates a significantly abnormal endocardial unipolar voltage map (*A*—modified antero-posterior view) and a limited bipolar abnormality (*B*) in the septum. The unipolar electroanatomic map can provide insight regarding the presence of intramyocardial scar when the bipolar voltage map is relatively normal. Late potentials are also observed in this region during sinus rhythm (*C*—orange arrow). Cardiac magnetic resonance imaging demonstrates mid myocardial septal scar (yellow arrow) in the short axis (*D*) and four-chamber view (*E*). The patient's intracardiac echocardiography (*F*) depicts regions of brightness in the septum (yellow arrow) and lateral wall (red arrow). CMRI, cardiac magnetic resonance imaging; ICE, intracardiac echocardiography; VT, ventricular tachycardia.

to guide ICD decision-making for non-ischaemic conditions such as cardiac sarcoidosis.[15] Conduction abnormalities and ventricular arrhythmias can occur in sarcoid patients with relatively normal left ventricular function, and prophylactic ICD implantation is recommended for those who have evidence of myocardial scar by MRI even when the LVEF > 35%.

Electroanatomic mapping (EAM) has also expanded our knowledge regarding the distribution of myocardial scarring seen in NICM (*Figure 4*). Electroanatomic mapping assesses the intrinsic myocardial health by measuring local electrical properties. Abnormalities on endocardial EAM are strongly associated with regions of scar detected through LGE-CMR. In contrast to ischaemic cardiomyopathies, NICM have different scar patterns that are often represented as patchy areas and commonly involve the epicardial and mid-myocardial layers of the heart.[42–45] Identification of the underlying substrate with EAM can provide prognostic insight in patients with newly diagnosed NICM.[46,47] Greater scar percentage and wider native QRS duration are strong predictors of mortality in NICM patients.[32,48–51] Ongoing and future studies will assess whether electrophysiologic phenotyping utilizing EAM can enhance risk stratification beyond LVEF and possibly even CMR. This area holds potential promise as non-invasive methods for EAM are utilizing body surface mapping, which can be performed with minimal risk to patients.[52–56]

Biologic markers

The identification of an arrhythmogenic substrate is particularly meaningful in situations where fatal arrhythmias occur before myocardial dysfunction. Genetic mutations that are associated with a loss of integrity in the sarcolemma, cytoskeleton, sarcomere or intercellular links could disrupt ion channel function, and result in cardiac arrhythmias. More than 60 genes have been implicated in contributing to dilated cardiomyopathy, and some of these are strongly associated with the added risk of fatal arrhythmias (*Table 2*).[57–64] Recent HRS guidelines have highlighted how genetic information can be combined with clinical features for risk stratification and ICD decision-making.[15] In particular, *Lamin A/C* mutations, which have been implicated in familial cardiomyopathies and subtypes of muscular dystrophy, are also associated with cardiac conduction disease and SCD. Implantable cardioverter-defibrillator implantation is recommended in mutation carriers who also have at least two of the following features: NSVT, LVEF <45%, non-missense mutation, and male sex. Further, although not traditionally categorized as a dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC) is a commonly inherited NICM. At least eight genes have been implicated in ARVC, and mutations in many of these genes result in impaired desmosomal function. Approximately 35% of mutation positive individuals ultimately develop progressive disease expression

Table 2   Genetic mutations associated with dilated cardiomyopathy and cardiac arrhythmias

Gene	Function	Findings/Notes
Lamin A/C (*LMNA*)	Encodes structural proteins that provide stability to the nuclear envelope.	Mutations are involved in 8% of familial and 2% of sporadic DCM. They are associated with cardiac conduction disease.[57,58] In one small study, *LMNA* mutation carriers, who had cardiac conduction disease requiring permanent pacemaker, had a high risk for ventricular arrhythmias and benefitted from ICD implantation.[59]
Phospholamban (*PLN*)	Transmembrane protein in the sarcoplasmic reticulum that plays a key role in calcium homeostasis.	In 403 mutation carriers, 20% of individuals had incident ventricular arrhythmias after a median follow-up of 42 months.[60]
Desmin (*DES*)	Intermediate filament protein that is expressed in skeletal, cardiac, and smooth muscle and helps to form the cytoskeletal network.	The majority of mutation carriers are reported to have cardiac conduction disease and/or arrhythmias.[61] The most common abnormality reported was high degree atrioventricular block.
SCN5A	Cardiac sodium channel gene that is responsible for the fast depolarization of the myocardium and maintenance of impulse conduction in the heart.	Mutations found in 1.7% of DCM families.[62] Two-thirds of these *SCN5A* mutations localized to the highly conserved, transmembrane segments suggesting a shared mechanism of disruption of the voltage-sensing mechanism of this channel and DCM.

DCM, dilated cardiomyopathy.

characterized by either a major arrhythmic event such as SCD or heart failure.[65,66] As such, electrocardiographic and MRI screening are recommended in mutation carriers to identify patients at early, subclinical stages of the disease process.[15]

Circulating cardiac biomarkers offer another potential opportunity to assess arrhythmia risk. At present, only selected candidate biomarkers that reflect inflammation, neurohormonal activation, and cardiac injury have been evaluated as predictors of ventricular arrhythmias and sudden cardiac death. In the Prospective Observation Study of Implantable Cardioverter Defibrillators (PROSe-ICD), which is a cohort of 1189 patients with systolic dysfunction who underwent primary prevention ICD implantation, elevations in N-terminal pro-brain natriuretic peptide, C reactive protein, and troponin T performed poorly in predicting the likelihood of an appropriate ICD shock.[67] These markers, however, enhanced identification of individuals that had an increased risk of non-SCD. Similarly, in a population-based analysis from the Cardiovascular Health Study, the addition of these three biomarkers to a 12-variable clinical risk score did not enhance the prediction of SCD.[68] Based in part on these studies, the candidate biomarker approach is unlikely to capture the complexity of SCD. Instead, recent developments in large-scale proteomics have provided a less biased approach to identifying important biomarkers that may be important in various diseases.[69–71] Protein expression integrates the effects of genetics with environmental influences such as lifestyle habits, comorbidities and medications. This type of agnostic approach has demonstrated improvements in the risk prediction of a global cardiovascular endpoint[69] and should be assessed rigorously for the risk of ventricular arrhythmias in NICM.

Non-invasive electrophysiologic parameters

Non-sustained ventricular tachycardia
Multiple studies have evaluated the independent association between NSVT on cardiac monitoring and total mortality.[72,73] Limited studies,

however, have evaluated rigorously the presence of NSVT and arrhythmic death. The GESICA study, which evaluated the effect of low-dose amiodarone on mortality in patients with advanced heart failure, contained a stratified randomization procedure in which all participants underwent Holter monitoring prior to randomization.[74] The study, which included a majority of NICM patients, demonstrated a higher incidence of SCD in the NSVT group (relative risk 2.77, 95% CI 1.78–4.44) compared to those without NSVT.[75] The subsequent higher risk of total mortality in the NSVT group was driven by this higher risk of SCD and was independent of amiodarone use.

Signal-averaged electrocardiogram
Delayed activation in small regions of the ventricle can be detected using signal-averaged electrocardiogram (SAECG). These abnormalities are common findings in regions of scar since the parallel orientation of myocardial fibres are disrupted and lead to areas of slow ventricular conduction.[76] In sinus rhythm, delayed ventricular activation or the presence of late potentials are detectable at more cardiac sites in patients with sustained VT compared to those without VT.[77] Abnormalities in the SAECG are also associated with increased mortality and an increased risk of arrhythmic events.[78,79] In prospective analyses, investigators have demonstrated that patients with abnormal SAECG had a higher likelihood of having either sustained VT or cardiac arrest.[80,81] These studies also demonstrated that dilated cardiomyopathy patients with a normal SAECG have an excellent prognosis with adverse outcomes related to progressive HF and not arrhythmic complications.

Microvolt T-wave alternans
Microvolt T-wave alternans (MTWA) or significant fluctuations in the T-wave amplitude at high heart rates reflect abnormalities in repolarization and are associated with ventricular arrhythmias.[82] Multiple clinical studies and meta-analyses have evaluated MTWA as a

predictor of arrhythmic events in non-ischaemic populations.[83–85] The findings across these studies are consistent and summary estimates suggest a positive predictive value of only 21% and a negative predictive value of 95% after approximately 20 months of follow-up. Clinically, this NPV could classify a patient with absent MTWA as low arrhythmic risk; however, it is unlikely for MTWA to identify those who would benefit the most from ICD therapy.

Conclusions

Complications from ventricular arrhythmias are a critical issue in patients with NICM, and the ICD remains the primary intervention for SCD prevention. The recent DANISH study has challenged the efficacy of ICD implantation; however, multiple meta-analyses of primary prevention trials of ICD use in the NICM population have demonstrated clinical efficacy. It is interesting to consider whether risk stratification beyond LVEF and heart failure symptoms will help to identify patients who are either eligible or can be safely excluded from prophylactic ICD implantation. The current lack of prospective data will rightfully limit a more widespread approach that incorporates risk stratification beyond LVEF in the NICM population. Although observational studies and subgroup analyses of large clinical trials suggest the benefits of refining the 'at risk' population, the application of advanced statistical methods and novel risk markers will require clinicians, biostatisticians, and government and industry stakeholders to partner on the thoughtful design of future clinical trials. Only then are we likely to enhance and implement methods for both arrhythmia risk stratification and SCD prevention.

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