

Incidence, risk assessment and prevention of sudden cardiac death in cardiomyopathies

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Cardiomyopathies are a significant contributor to cardiovascular morbidity and mortality, mainly due to the development of heart failure and increased risk of sudden cardiac death (SCD). Despite improvement in survival with contemporary treatment, SCD remains an important cause of mortality in cardiomyopathies. It occurs at a rate ranging between 0.15% and 0.7% per year (depending on the cardiomyopathy), which significantly surpasses SCD incidence in the age- and sex-matched general population. The risk of SCD is affected by multiple factors including the aetiology, genetic basis, age, sex, physical exertion, the extent of myocardial disease severity, conduction system abnormalities, and electrical instability, as measured by various metrics. Over the past decades, the knowledge on the mechanisms and risk factors for SCD has substantially improved, allowing for a better-informed risk stratification. However, unresolved issues still challenge the guidance of SCD prevention in patients with cardiomyopathies. In this review, we aim to provide an in-depth discussion of the contemporary concepts pertinent to understanding the burden, risk assessment and prevention of SCD in cardiomyopathies (dilated, non-dilated left ventricular, hypertrophic, arrhythmogenic right ventricular, and restrictive). The review first focuses on SCD incidence in cardiomyopathies and then summarizes established and emerging risk factors for life-threatening arrhythmias/SCD. Finally, it discusses validated approaches to the risk assessment and evidence-based measures for SCD prevention in cardiomyopathies, pointing to the gaps in evidence and areas of uncertainties that merit future clarification.

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Graphical Abstract

Sudden cardiac death	Incidence	Risk factors	Primary prevention ICD indications	Ancillary preventive measures
 Dilated cardiomyopathy Non-dilated LV cardiomyopathy	<ul style="list-style-type: none"> 0.15% per year ~33-48% of CV mortality Unclear in non-dilated LV cardiomyopathy 	<ul style="list-style-type: none"> LVEF, NYHA class Age Genotype LGE on CMR Syncope Positive PES 	<ul style="list-style-type: none"> LVEF <35%, NYHA class II-III, despite ≥3 months of OMT. LNMA mutation, estimated 5-year risk of SCD ≥10% and LVEF ≤50%, non-sustained VT, or AV block. LVEF ≤50% and ≥2 additional risk factors* 	<ul style="list-style-type: none"> GDMT for HFrEF CRT in eligible patients
 Hypertrophic cardiomyopathy	<ul style="list-style-type: none"> 0.5% per year Prevailing mode of death in younger HCM patients 	<ul style="list-style-type: none"> Age, family history, genotype LV structural and functional alterations NSVT Syncope LGE on CMR 	<ul style="list-style-type: none"> High estimated 5-year risk of SCD (≥6%, based on HCM Risk-SCD score) Intermediate (≥4% - <6%) or low (<4%) estimated 5-year risk of SCD (based on HCM Risk-SCD score) and ≥1 additional risk factor** 	<ul style="list-style-type: none"> Avoidance of high-intensity exercise in patients with high estimated risk of SCD
 Arrhythmogenic cardiomyopathy	<ul style="list-style-type: none"> 0.7% per year Prevailing mode of death 	<ul style="list-style-type: none"> Age, male sex RV and/or LV systolic dysfunction VT / NSVT Syncope Positive PES QRS fragmentation, T wave inversion 	<ul style="list-style-type: none"> Syncope Severe LV/RV systolic dysfunction Moderate LV/RV systolic dysfunction, NSVT/positive PES 	<ul style="list-style-type: none"> Beta-blockers Avoidance of high-intensity exercise
 Restrictive cardiomyopathy	<ul style="list-style-type: none"> Largely unknown due to heterogeneous aetiologies and clinical presentation 	<ul style="list-style-type: none"> Limited data 	<ul style="list-style-type: none"> Unclear In cardiac sarcoidosis: <ul style="list-style-type: none"> LVEF <35%, or LVEF 35-50%, extensive myocardial fibrosis, positive PES, or Pacemaker requirement. 	<ul style="list-style-type: none"> Unknown

Sudden cardiac death in cardiomyopathies: incidence, risk factors and prevention. AV, atrioventricular; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; CV, cardiovascular; FLNC, filamin C; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LMNA, lamin A/C; LV, left ventricular; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; OMT, optimal medical therapy; PES, programmed electrical stimulation; PLN, phospholamban; RBM20, RNA-binding motif protein 20; RV, right ventricular; SCD, sudden cardiac death; VT, ventricular tachycardia. *Syncope, LGE on CMR, inducible sustained VT at PES, pathogenic mutations in LMNA, PLN, FLNC, and RBM20. **Significant LGE at CMR; LVEF <50%; abnormal blood pressure response during exercise test; LV apical aneurysm; high-risk genotype.

Keywords

Dilated cardiomyopathy • Non-dilated left ventricular cardiomyopathy • Hypertrophic cardiomyopathy • Arrhythmogenic right ventricular cardiomyopathy • Restrictive cardiomyopathy • Sudden cardiac death • Arrhythmia • Incidence • Risk stratification • Primary prevention

Introduction

Cardiomyopathies, including dilated (DCM), non-dilated left ventricular (NDLVC), hypertrophic (HCM), arrhythmogenic right ventricular (ARVC) and restrictive (RCM) cardiomyopathy, represent a heterogeneous group of disorders, sometimes with overlapping phenotypes.¹ Over the past decades, the management of cardiomyopathies has significantly improved, including earlier diagnosis, detailed aetiologic assessment and provision of evidence-based medical and device treatments, which now include a growing array of aetiology-specific therapies (e.g. bromocriptine in peripartum cardiomyopathy, mavacamten in obstructive HCM, tafamidis in transthyretin cardiac amyloidosis, etc.).² Although these advancements have secured improvement in patient outcomes, cardiomyopathies remain a significant contributor to cardiovascular hospitalization and mortality. In addition to being an important cause of heart failure (HF), they entail an increased, and often unrecognized risk of sudden cardiac death (SCD).³ SCD is defined as death of a cardiac cause occurring within 1 h of symptom onset in witnessed cases, or within 24 h of last being seen alive in unwitnessed cases and includes unexpected death of unknown or cardiac cause in autopsied cases.⁴ Ventricular

fibrillation (VF) is the most common mechanism of SCD in cardiomyopathies, but asystole or pulseless electrical activity may also occur.^{3,5}

This review first summarizes the incidence of SCD in cardiomyopathies and then focuses on the established and emerging risk factors for malignant arrhythmias/SCD. Finally, it discusses validated approaches to SCD risk assessment and prevention in different types of cardiomyopathies, emphasizing the gaps in evidence and areas of uncertainties that deserve future prospective evaluation.

Dilated cardiomyopathy

Incidence and risk factors for sudden cardiac death

Temporal trends suggest a stable decline in the incidence of SCD and its proportional contribution to cardiovascular mortality in DCM, attributable to the improvements in management.^{6,7} Accordingly, the incidence of SCD in a large registry of unselected patients with DCM has decreased from 2% per year in the period

before the widespread use of modern therapies, to 0.15% per year in the latest period.⁸

Clinical characteristics

It has long been recognized that left ventricular (LV) ejection fraction (LVEF) and functional status represent key determinants of SCD risk in DCM.^{9,10} An earlier analysis suggested a 2.3-fold increase in the relative risk of SCD per 10% decrease in LVEF in DCM.¹⁰ Among out-of-hospital SCD victims without coronary heart disease, most individuals had an LVEF <30%.⁹ However, the severity of functional impairment in DCM (as determined by the New York Heart Association [NYHA] functional class) also bears on the risk of SCD. Although the annual mortality rates increase significantly with worsening functional status, SCD is considerably more prevalent among patients with NYHA class I–II (50–60%) compared with only 20–30% of those in NYHA class III–IV, most of whom succumb to progressive HF.¹¹ It has been hypothesized that the mechanism of SCD may differ between patients with moderate LV dysfunction (predominantly VF), compared to patients with severe LV dysfunction and extensive fibrosis (predominantly asystole or pulseless electrical activity).^{3,5} This observation is supported by a meta-analysis of four primary prevention implantable cardioverter-defibrillator (ICD) trials, demonstrating attenuation of survival benefit with ICD in patients with the more advanced HF with reduced ejection fraction (HFrEF) and worse functional impairment (NYHA class III).¹² The impact of the severity of HF (as measured by natriuretic peptide levels) on SCD risk in patients with non-ischaemic HFrEF (76% idiopathic DCM) was also observed in the DANISH trial (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality).¹³ A sub-analysis of this trial indicated that patients with higher levels of natriuretic peptides (N-terminal pro-B-type natriuretic peptide >1177 pg/ml), despite having a trend towards higher rates of SCD, had a lower efficacy of ICD in SCD prevention and in reduction of all-cause mortality, compared with patients with lower levels of natriuretic peptides.¹³

Age and comorbidities appear to modify the risk for SCD in DCM. As evidenced by a prespecified analysis of the DANISH trial, age was a major determinant of a heterogeneity in ICD effect on all-cause mortality.¹⁴ The analysis demonstrated that individuals ≤70 years old had a higher incidence of SCD and a significantly greater proportion of all deaths attributable to SCD, compared with individuals >70 years.¹⁵ This conferred a significant 30% risk reduction in total mortality with ICD in patients ≤70 years old.¹⁵ In individuals >70 years, the proportion of non-sudden deaths was twice as high as in younger patients, and the competing risk of non-sudden death reduced the benefit of ICD on overall mortality.¹⁵

Besides age, the risk of death from non-sudden causes may be higher in patients with a greater burden of comorbidities. A meta-analysis of patient-level data from three primary prevention ICD trials, suggested attenuation of an overall survival benefit with ICD with declining glomerular filtration rate in individuals with HFrEF, including DCM.¹⁶ Likewise, a post hoc analysis of the SCD-HeFT trial (Sudden Cardiac Death in Heart Failure

Trial) indicated that patients with type 2 diabetes, despite having a higher risk of SCD compared with non-diabetic patients, did not experience a reduction in SCD or all-cause mortality with ICD, regardless of HFrEF aetiology (ischaemic or non-ischaemic).¹⁷ These observations need to be regarded as hypothesis generating, and a potential impact of comorbidities on the arrhythmic substrate in DCM merits further exploration.

Several multiparametric risk assessment models (e.g. the Seattle HF Model and Seattle Proportional Risk Model), which incorporate the presence of comorbidities, have shown the ability to reliably discriminate between the risk of SCD and death due to progressive HF in patients with HFrEF, including DCM.^{18,19} However, their utility in predicting potential benefit of ICD implantation has not yet been clinically fully understood.

Genetic background

A growing body of evidence indicates that certain pathogenic gene variants portend a significantly increased arrhythmic risk, which may be beyond or independent of phenotypic characterization (i.e. SCD may occur in the absence of a significant LV dysfunction/dilatation) or symptoms and severity of HF. Sometimes there may be an overlap with other types of cardiomyopathies, which share a profound propensity for arrhythmic events.²⁰ The best studied gene variants and their association with the clinical phenotype and the risk of SCD are presented in *Table 1*,^{21–26} whilst an overlapping genetic background of different types of cardiomyopathies is presented in *Figure 1*. Genetic testing and counselling should be offered to all patients with DCM (and other cardiomyopathies) as it can aid in diagnosis, risk assessment, prognostication and reproductive decisions, and serve to initiate cascade genetic screening of the relatives.²⁷

Currently there is a paucity of validated risk stratification schemes for SCD which include the knowledge of a pathogenic gene variant. A notable exception is a SCD risk prediction score for the highly penetrant LMNA gene mutations associated with premature conduction abnormalities, a high risk of SCD and progression to advanced HF (<https://lmna-riskvta.fr/>).²⁸ Recently, a similar risk prediction model has been developed for carriers of PLN p.Arg14del mutation (https://plnriskcalculator.shinyapps.io/final_shiny), which awaits further validation.²⁹ Some data suggest that, in patients with truncating TTN mutations (the most common genetic variant in DCM), the occurrence of malignant ventricular arrhythmias is most commonly observed in individuals with severely impaired LVEF.³⁰

Markers of electrical instability

Electrocardiographic changes in DCM are frequent and non-specific; however certain patterns of abnormalities may serve as 'red flags' potentially pointing to clinical phenotypes associated with a higher risk of SCD (e.g. atrioventricular block and other conduction abnormalities and/or presence of atrial fibrillation in young patients; low QRS voltages, prolonged QRS duration, frequent ventricular premature complexes, non-sustained ventricular tachycardia [NSVT]).³¹ Several other markers of electrical inhomogeneity/instability (e.g. QRS fragmentation, T-wave alternans,

Table 1 Common genetic background in dilated cardiomyopathy and associated phenotypes^a

Gene/protein location	Protein function	Estimated prevalence	Age of phenotypic expression	Phenotypes	Distinctive features and diagnostic red flags	Risk of SCD
Nuclear membrane LMNA (lamin A/C)	Nuclear membrane; participates in mitosis, nuclear stability and gene expression	4–6% in DCM (up to 30% in patients with conduction abnormalities)	Third–fourth decade. High penetrance	DCM, overlap with NDLVC or ARVC (rare) Emery–Dreifuss muscular dystrophy Lipodystrophy Progeria	Conduction abnormalities (first, second, third degree AV block, sinus bradycardia, sinus node arrest, bundle branch block) often precede overt cardiomyopathy Atrial fibrillation Ventricular arrhythmias Progressive HF Midwall (septal) LGE on CMR preceding overt DCM	Very high
TMEM43 (transmembrane protein 43)	Maintains nuclear envelope structure and signalling	Rare in RCM/ARVC Higher in the Netherlands	Variable, third–fourth decade. High penetrance	Overlap with NDLVC or ARVC	High penetrance, progressive cardiomyopathy	Very high
Sarcomere TTN (titin)	Facilitates myocyte contraction and relaxation	Up to 25% of DCM patients	Fifth–sixth decade Variable penetrance	Isolated DCM	Similar to idiopathic DCM May be associated with atrial fibrillation and/or ventricular arrhythmias No specific LGE pattern on CMR	Variable (may be increased)
MYH7 (β-myosin heavy chain) MYH6 (α-myosin heavy chain) TNNT2 (cardiac muscle troponin T) TPM1 (α-tropomyosin) Cytoskeleton Z-disk DES (desmin)	Contribution to myocyte contraction Myofibrillar protein	4–10% in DCM 4% in DCM 2–3% in DCM 0.5–1% in DCM	Variable (adolescence though fifth decade)	Isolated DCM or overlap with HCM	Presentation variable depending on the site of genetic mutation Progressive HF	Increased with some mutations
		1–2% in DCM	Variable Penetrance up to 50%	DCM; may be associated with muscular dystrophy Overlap with NDLVC, RCM, or ARVC	Conduction disorders (often AV block + RBBB) Atrial fibrillation common Ventricular arrhythmias Progressive HF Basal lateral subepicardial ring-like LGE on CMR	High

Table 1 (Continued)

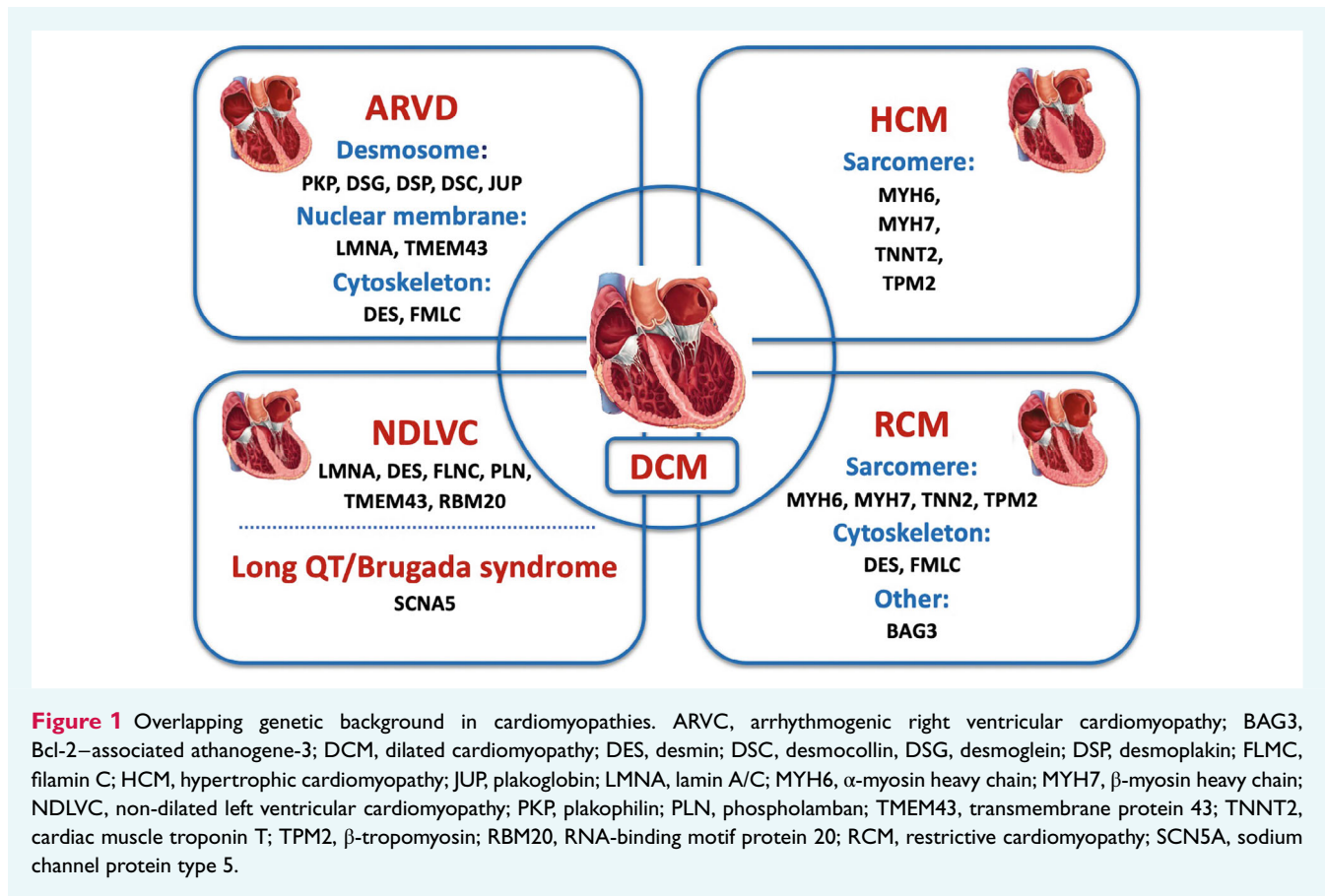
Gene/protein location	Protein function	Estimated prevalence	Age of phenotypic expression	Phenotypes	Distinctive features and diagnostic red flags	Risk of SCD
FLMC (filamin C)	Cross links between Z-disk and sarcolemma	4% in DCM	Variable	DCM, overlap with NDLCV or ARVC (rare)	Low QRS voltages T-wave inversion in inferolateral leads Ventricular arrhythmias Basal lateral subepicardial ring-like LGE on CMR	Very high
Desmosome PKP2 (plakophilin-2)	Maintenance of structural stability and communication between cells	34–74% in ARVC	Variable, usually third to fifth decade	Classic ARVC	Low QRS voltages in precordial leads T-wave inversion in precordial leads Epsilon waves	High
DSG2 (desmoglein-2)	Same as above	5–26% in ARVC		Frequent LV involvement, overlap with DCM		High
DSP (desmoplakin)	Same as above	1–14% in ARVC		Frequent LV dominant disease; overlap with DCM	Same as for PKP2 + Carvajal syndrome (woolly hair, palmoplantar keratoderma)	Very high
DSC2 (desmocollin-2) JUP (plakoglobin)	Same as above Same as above	1–5% in ARVC <1% in ARVC Higher in Naxos, Greece		ARVC ARVC	Ring-like LGE on CMR Same as for PKP2 Naxos disease (cardiocutaneous disease)	High High
Other genes RBM20 (RNA-binding motif protein 20)	RNA-binding protein—spliceosome	2–5% in DCM	Adolescence through fourth decade	DCM, overlap with NDLCV	Rapidly progressive DCM with advanced HF occurring by fourth decade Ventricular arrhythmias	Very high
SCN5A (sodium channel protein type 5, α subunit)	Sodium ion channel	2–4% in DCM	Variable, adolescence through third decade	DCM, long QT syndrome, Brugada syndrome	Early onset DCM usually with atrial fibrillation Conduction abnormalities Not associated with ventricular arrhythmias	Uncertain
PLN (phospholamban)	Sarcoplasmic reticulum; modulates contractility	1% in DCM	Variable	DCM, overlap with NDLCV or ARVC (rare)	Conduction abnormalities Ventricular arrhythmias Inferolateral subepicardial and midwall fibrosis on CMR	Very high

Table 1 (Continued)

Gene/protein location	Protein function	Estimated prevalence	Age of phenotypic expression	Phenotypes	Distinctive features and diagnostic red flags	Risk of SCD
DMD (dystrophin)	Sarcolemma; connects the cytoskeleton to the surrounding extracellular matrix	...	Third through fourth decades	Duchenne and Becker muscular dystrophy	Posterior inferior 'pseudoinfarction' pattern Universal cardiac involvement with early onset of DCM in Duchenne muscular dystrophy Later onset of DCM in some patients with Becker muscular dystrophy	Low (patients more likely to succumb to progressive HF)
BAG3 (Bcl-2-associated athanogene-3)	Multifunctional protein: sarcomere stabilization nuclear envelope integrity; β -adrenergic receptor and L-type Ca^{2+} channel coupling; activation of autophagy and inhibition of apoptosis, inflammasome modulation	0.3%	Variable	DCM, overlap with RCM	Prolonged QRS duration, as well as negative T waves LV hypertabeculation HF less responsive to medical treatment	High

ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atriocentric; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HF, heart failure; LGE, late gadolinium enhancement; LV, left ventricular; NDLVC, non-dilated left ventricular cardiomyopathy; RBBB, right bundle branch block; RCM, restrictive cardiomyopathy; SCD, sudden cardiac death.

^aThe list is not exhaustive. Modified from references^{7,11–26}



QTc dispersion, signal-averaged electrocardiogram, premature ventricular complexes, NSVT) or disturbances in autonomic modulation (e.g. heart rate variability, heart rate turbulence, baroreflex sensitivity) were evaluated for SCD risk assessment in DCM. A meta-analysis suggested the greatest odds for SCD prediction with QRS fragmentation (i.e. additional R wave or notching in the nadir of the S wave), and T-wave alternans (i.e. beat-to-beat variability in the timing, shape, and/or amplitude of T waves), whilst no predictive value was demonstrated for markers of autonomic disbalance.³² The authors acknowledged a high risk of bias for reporting positive findings, which attenuated the predictive performance of the investigated parameters.³² Further limitations include small sample sizes, variable cut-off metrics, low sensitivity and specificity for SCD, and no or few validation reports. In addition, earlier findings may not be applicable to contemporary patients, given that longitudinal studies suggested an improvement in markers of electrical inhomogeneity (e.g. QRS duration and QTc dispersion) over the past decades with the use of disease-modifying therapies.⁷ On that basis, it is unlikely that electrical markers alone could provide added value in SCD risk stratification in unselected patients with DCM. However, their utility could be further evaluated in multiparametric risk models (perhaps aided by emerging digital health techniques), which may allow for an integrated approach to identification of high risk patients.³³

Electrophysiological study and programmed electrical stimulation (PES) have been suggested to refine risk assessment for primary ICD implantation in selected patients with DCM.⁴ A small study of DCM patients with an LVEF $\geq 40\%$ suggested that a positive PES (i.e. inducible sustained ventricular tachycardia [VT]) may assist in identifying individuals with subsequent appropriate ICD activations, whereas a negative PES had a high negative predictive value.³⁴

Myocardial fibrosis

Distribution and extent of replacement fibrosis in DCM can be documented and quantified with late gadolinium enhancement (LGE), which is present in $\sim 30\%$ of patients with DCM, usually with the midwall (in patients with LMNA mutations), ring-like (in patients with DSP and FLNC mutations) or subepicardial distribution (in post-myocarditis cardiomyopathy).^{35,36} Extracellular matrix expansion due to interstitial fibrosis can be detected with native and contrast-enhanced T1 mapping.³⁷

Multiple studies have documented a strong association between the presence of LGE on cardiac magnetic resonance (CMR) and the risk of SCD, whereas the association with death due to progressive HF was less compelling.^{38–41} The detection of even small amounts of LGE was found to predict an increased risk of SCD, whilst the greatest risk was observed with the more extensive LGE (e.g.

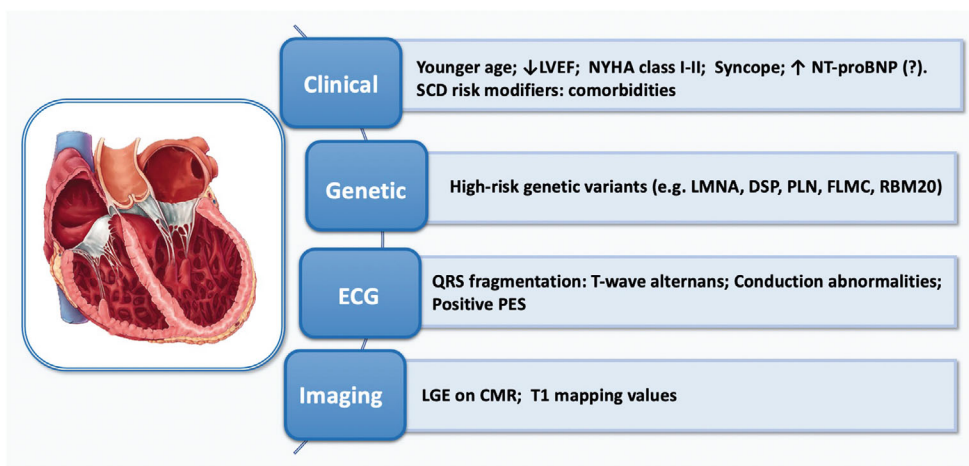


Figure 2 Established and emerging risk factors for sudden cardiac death (SCD) in dilated cardiomyopathy. CMR, cardiac magnetic resonance; DSP, desmoplakin; ECG, electrocardiogram; FLMC, filamin C; LGE, late gadolinium enhancement; LMNA, lamin A/C; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PES, programmed electrical stimulation; PLN, phospholamban; RBM20, RNA-binding motif protein 20.

concomitant septal and free-wall LGE).⁴² Even in patients with less severe DCM (LVEF $\geq 40\%$), the presence of midwall LGE may be able to identify those with an increased SCD risk.⁴³ Recently, large multicentre registry data of patients with DCM and an LVEF $< 50\%$ were used to develop a novel risk score that combines clinical variables and CMR evidence of fibrosis to improve risk stratification for major arrhythmic events in DCM beyond standard assessment.⁴⁴

Emerging data point to the possible role of quantitative myocardial tissue assessment with T1 mapping (used alone or in combination with LGE) in predicting ventricular arrhythmias.^{45,46} An ongoing prospective study assesses the utility of CMR parameters, including LGE and T1 mapping in predicting all-cause and cardiovascular mortality, and SCD, in patients with DCM (T1-CMR, NCT02407197).

Although promising, potential role of CMR in assisting the decisions for ICD implantation awaits prospective confirmation. A multicentre randomized trial (CMR GUIDE, NCT01918215) is currently underway, in which patients with an LVEF 36–50% (either ischaemic or non-ischaemic aetiology) on optimal medical therapy, and CMR evidence of fibrosis, will be randomized to receive a primary prevention ICD or an implantable loop recorder. The primary endpoint is the time to SCD or malignant ventricular arrhythmias during an average 4-year follow-up.⁴⁷ A summary of risk factors for SCD in DCM is presented in *Figure 2*.

Prevention of sudden cardiac death

Role of medical treatment

Treatment of HFrEF with disease-modifying drugs has proven beneficial for SCD risk reduction in randomized trials of HFrEF patients, regardless of aetiology (ischaemic vs. non-ischaemic)

(*Figure 3*).^{6,48–56} Recent data suggest that treatment with sacubitril/valsartan can provide an additional 20% risk reduction in SCD compared to enalapril in patients with HFrEF,⁴⁹ and promising results were also observed with sodium–glucose cotransporter 2 inhibitors.^{50,57} Given the strength of evidence, optimized medical treatment for HFrEF should be the key first step in SCD risk reduction in DCM.

Disease-modifying medical therapy for HFrEF also facilitates LV reverse remodelling (LVRR). Contemporary cohort studies suggest that ~ 30 – 40% of patients with DCM experience LVRR with medical therapy.^{58–60} It seems that patients with truncating TTN mutations are more amenable to pharmacologic therapy,⁶¹ and have a higher potential for LVRR compared to other genetic causes of DCM.⁶² Of note, observational data point to a significant attenuation in the long-term risk of SCD (up to 10 years) in patients with LVRR, independently of other factors.⁶⁰ However, maintenance of medical therapies is of paramount importance. A randomized trial suggested that among patients with DCM and improved LVEF (from $< 40\%$ to $\geq 50\%$), 44% experienced a significant decline in LV function within 6 months after withdrawal of HFrEF medications.⁶³ Furthermore, observational data suggest that some patients with an initial LV improvement harbour a risk of later deterioration in LV function despite sustained medical treatment,⁶⁴ underlining the significance of regular follow-up. The occurrence of LVRR bears on the timing of ICD implantation. Accordingly, the IMACS2 registry (Intervention in Myocarditis and Acute Cardiomyopathy) data suggest no survival advantage with an early ICD implantation (within 1 month after diagnosis) in patients with recent onset DCM, indicating that a decision in most cases can be safely postponed while assessing LVRR following institution of medical therapy.⁶⁵

There is no compelling evidence that antiarrhythmic drugs offer an advantage over an ICD for risk reduction in SCD⁶⁶ or all-cause

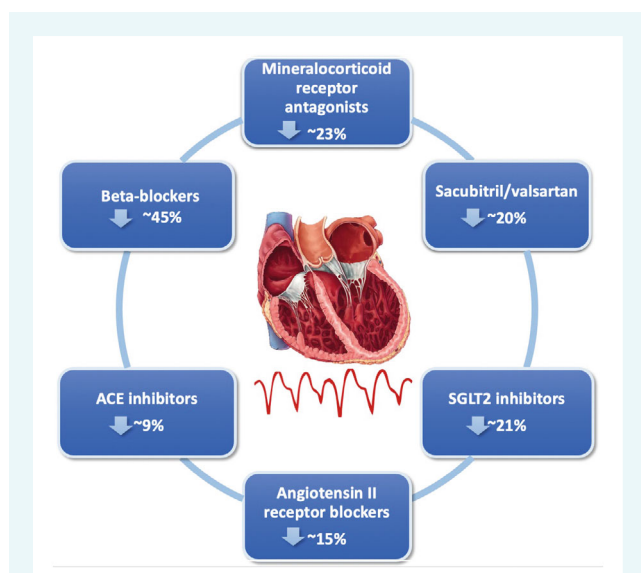


Figure 3 Estimated risk reduction in sudden cardiac death in clinical trials with disease-modifying medical therapies for heart failure with reduced ejection fraction (including patients with dilated cardiomyopathy). According to references.^{49–56} ACE, angiotensin-converting enzyme; SGLT2, sodium–glucose cotransporter 2. Size effect relative to placebo or active comparator and dependent on the clinical trial population and background treatment.

mortality⁶⁷ in patients with DCM. A sub-analysis of the SCD-HeFT trial suggested a potential signal of harm with amiodarone compared with placebo among patients with the more advanced HF (NYHA class III).⁶⁷ A Cochrane database systematic review of the efficacy of amiodarone in primary and secondary prevention of SCD indicated possible advantage in primary prevention over placebo (or no intervention) or other antiarrhythmic drugs, with a caveat of low-quality evidence, and increased risk of thyroid and pulmonary adverse events.⁶⁸ Amiodarone may be considered in suppressing symptomatic ventricular arrhythmias in patients unresponsive to beta-blockers (i.e. following a trial of different evidence-based beta-blockers shown to reduce the risk of SCD in HFREF, such as bisoprolol, carvedilol, or metoprolol succinate).⁶⁹

Role of cardiac resynchronization therapy

In patients with an indication for cardiac resynchronization therapy (CRT), this therapy provides further attenuation in the risk of SCD on top of medical treatment. According to the CARE-HF trial (Cardiac Resynchronization-Heart Failure), randomization to CRT was associated with a 50% risk reduction in SCD, independent of other covariates.⁷⁰ Of note, LVRR following CRT implantation appears to be a strong predictor of subsequent risk reduction in SCD. In the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) there was an independent 20% reduction in major arrhythmic events with each 10% reduction in LV end-systolic volumes with CRT-defibrillator.⁷¹

Role of implantable cardioverter-defibrillators

Six primary prevention trials assessed the effectiveness of ICD (or CRT-defibrillator) for reduction in all-cause mortality in patients with non-ischaemic HFREF, as summarized in *Table 2*. Although the first two smaller trials (CAT and AMIOVIRT) were terminated prematurely for futility, later trials (DEFINITE, COMPANION, and SCD-HeFT) demonstrated overall reduction in mortality with ICD (or CRT-defibrillator) compared with medical treatment (*Table 2*).^{14,66,72–75} However, the most recent DANISH trial, focusing exclusively on patients with non-ischaemic HFREF (76% with DCM), failed to show lower risk of either all-cause or cardiovascular mortality in patients randomized to an ICD, despite a significant 50% reduction in SCD.¹⁴ The DANISH trial patients were treated according to contemporary standards, including a high proportion being implanted with CRT if indicated (58%). However, there was no evidence of a heterogeneity in ICD effectiveness depending on the presence of a CRT.¹⁴ The lack of benefit with primary prevention ICD was subsequently confirmed in a long-term follow-up of the DANISH trial patients (median 9.5 years),⁷⁶ as well as in a subgroup of patients with non-ischaemic HFREF from the SCD-HeFT trial, followed for a median of 11 years.⁷⁷ However, the original DANISH trial did show a significant risk reduction in all-cause and cardiovascular mortality in patients <70 years of age,¹⁵ which was maintained over an extended follow-up.⁷⁶ This solidifies the notion that among DCM patients with low competing risk of non-sudden death, primary prevention ICD improves overall survival. A recent updated meta-analysis of ICD in non-ischaemic cardiomyopathies showed no benefit of ICD when CRT was indicated, while in patients with ICD indication only, the absolute risk reduction was 3.7% over 3 years resulting in a number needed to treat of 27.⁷⁸

Current European Society of Cardiology (ESC) guidelines recommend primary ICD implantation in patients with DCM according to the indications outlined in *Table 3*.^{4,27,79} The recent 2023 Guidelines for the management of cardiomyopathies stress the importance of SCD risk assessment beyond LVEF by suggesting that patients with high-risk genetic background (e.g. LMNA, TMEM43, DSP, RBM20, PLN, FLNC-truncating variants) should be considered for primary prevention ICD implantation with LVEF thresholds >35%, particularly in the presence of additional risk factors (e.g. significant LGE on CMR, unexplained syncope, NSVT, frequent ventricular premature complexes, positive PES) (*Table 3*).²⁷ A shared decision-making is advised considering patients' preferences, beliefs and values, with a thorough discussion of gaps in evidence, competing risks and device-related complications.²⁷ Furthermore, intense exercise should be avoided in individuals with DCM and a history of cardiac arrest/unexplained syncope, LVEF <45%, frequent ventricular arrhythmias on ambulatory electrocardiogram, extensive LGE on CMR and high-risk genotype.⁸⁰ Strategies for the SCD risk assessment and prevention in some of the specific aetiologies of DCM are discussed in online supplementary material.

Table 2 Randomized clinical trials of primary prevention with implantable cardioverter-defibrillators including patients with dilated cardiomyopathy

Trial	Year of publication	Inclusion criteria	N	Mean/median follow-up (months)	Intervention	Primary endpoint	Sudden cardiac death risk reduction
CAT ⁷²	2002	Non-ischaemic HF, LVEF <30%, NYHA class II–III	104	~26	ICD vs. OMT	All-cause death	NR
AMIOVIRT ^{69,73}	2003	Non-ischaemic HF, LVEF ≤35%, NYHA class I–III, NSVT	103	~14	ICD vs. amiodarone	Terminated early due to fatality	NR
DEFINITE ⁷⁴	2004	Non-ischaemic HF, LVEF <36%, NYHA class I–III, NSVT or PVC	458	29	ICD vs. OMT	Terminated early due to fatality All-cause death	HR 0.20; 95% CI 0.06–0.71; <i>p</i> = 0.006
COMPANION ⁷⁵	2004	Ischaemic and non-ischaemic HF (~45%), LVEF ≤35%, NYHA class III–IV, QRS >120 ms	1520	~14.8–16.0	CRT-P vs. CRT-D vs. OMT	ICD vs. OMT: HR 0.65; 95% CI 0.40–1.06; <i>p</i> = 0.08 All-cause death or all-cause hospitalization (all patients)* CRT-P vs. OMT: HR 0.81; 95% CI 0.69–0.96; <i>p</i> = 0.014; adjusted <i>p</i> = 0.015 CRT-D vs. OMT: HR 0.80; 95% CI 0.68–0.95; <i>p</i> = 0.010; adjusted <i>p</i> = 0.011	NR
SCD-HeFT ⁶⁶	2005	Ischaemic and non-ischaemic HF (~47%), LVEF <35%, NYHA class II–III	2521	45.5	ICD vs. amiodarone vs. placebo	All-cause death* ICD vs. placebo, non-ischaemic group: HR 0.73; 95% CI 0.50–1.07, <i>p</i> = 0.06 *Interaction <i>p</i> -value for HF aetiology 0.68	NR
DANISH ¹⁴	2016	Non-ischaemic HF, LVEF <35% NYHA class II–III (IV if CRT) NT-proBNP >200 pg/ml	1116	67.6	ICD vs. OMT	All-cause death HR 0.87; 95% CI 0.68–1.12; <i>p</i> = 0.28	HR 0.50; 95% CI 0.31–0.82; <i>p</i> = 0.005

CI, confidence interval; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complexes; NT-proBNP, N terminal pro-B-type natriuretic peptide; NR, not reported; NYHA, New York Heart Association; OMT, optimal medical therapy.

Table 3 Recommendations for prophylactic implantable cardioverter-defibrillator in cardiomyopathies based on the relevant European Society of Cardiology guidelines^a

Primary prevention ICD is a viable option in patients with at least one of the following characteristics

Dilated cardiomyopathy

2021 ESC Guidelines for the management of acute and chronic heart failure, 2022 ESC Guidelines of the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, and 2023 ESC Guideline for the management of cardiomyopathies:

- LVEF \leq 35%, NYHA class II–III, despite \geq 3 months of optimal medical treatment.

2022 ESC Guidelines of the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death:

- Confirmed pathogenic LMNA mutations if the estimated 5-year risk of SCD is \geq 10% (<https://lmna-riskvta.fr/>), and in the presence of non-sustained VT, or AV block.
- LVEF \leq 50% and \geq 2 additional risk factors (syncope, LGE on CMR, inducible sustained VT at PES, pathogenic mutations in LMNA, PLN, FLNC, and RBM20).

2023 ESC Guideline for the management of cardiomyopathies^b:

- In patients with a high-risk genotype for SCD and LVEF $>$ 35% in the presence of additional risk factors.
- In patients with DCM with a high-risk genotype for SCD and LVEF $>$ 35% without additional risk factors.
- In patients without a high-risk genotype for risk and LVEF $>$ 35% in the presence of additional risk factors.

Hypertrophic cardiomyopathy:

- In patients aged \geq 16 years and an estimated 5-year risk of SCD \geq 6% (based on HCM SCD-Risk score).
- In patients aged \geq 16 years with an intermediate 5-year risk (\geq 4% to $<$ 6%) or a low 5-year risk ($<$ 4%) of SCD, a shared decision-making process may be considered, taking into account lifelong risk of complications and the presence of additional risk factors:
- Significant LGE at CMR (\geq 15% of LV mass); or
- LVEF $<$ 50%; or
- LV apical aneurysm; or
- Sarcomeric pathogenic gene mutations.
- Children aged $<$ 16 years with a high (\geq 6%) or intermediate (\geq 4% to $<$ 6%) 5-year risk of SCD (based on HCM Risk-Kids score)

Arrhythmogenic right ventricular cardiomyopathy

- Arrhythmic syncope.
- Severe LV or RV systolic dysfunction.
- Moderate RV or LV systolic dysfunction and either non-sustained VT or inducible VT at PES.

Sarcoidosis

- LVEF \leq 35%.
- With an indication for permanent pacemaker (ICD should be considered regardless of LVEF).
- LVEF $>$ 35% and extensive LGE on CMR.
- LVEF 35–50% (with or without minor LGE on CMR) and inducible sustained VT at PES.

AV, atrioventricular; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ESC, European Society of Cardiology; FLNC, filamin C; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LMNA, lamin A/C; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PES, programmed electrical stimulation; PLN, phospholamban; RBM20, RNA-binding motif protein 20; RV, right ventricular; SCD, sudden cardiac death; VT, ventricular tachycardia.

^aModified from references^{4,27,79}

^bSame recommendations apply to patients with non-dilated left ventricular cardiomyopathy.

Non-dilated left ventricular cardiomyopathy

Non-dilated LV cardiomyopathy is defined as the presence of non-ischaemic LV scarring or fatty replacement on CMR in

the absence of LV dilatation with or without global/regional LV wall motion abnormalities, or as isolated global LV hypokinesia (i.e. LVEF $<$ 50%), unexplained by abnormal loading conditions.²⁷ NDLVC shares similar genetic background with DCM and ARVC (Figure 1), and most data on the natural history and SCD risk in NDLVC are derived from studies including patients with DCM

and ARVC. High-risk genetic background (e.g. LMNA, TMEM43, DSP, RBM20, PLN, FLNC-truncating variants) represents the major determinant of SCD risk in NDLCV, whilst there are no reliable data on risk assessment in patients without known gene mutations. Pending further evidence, current guidelines suggest that primary ICD implantation in patients with NDLCV should follow the same recommendations as for patients with DCM (Table 3).^{4,27}

Hypertrophic cardiomyopathy

Incidence and risk factors for sudden cardiac death

Contemporary data suggest that the incidence of SCD in HCM is 0.5% per year,⁸¹ and it is the prevailing mode of death in younger patients with HCM.⁸²

Clinical characteristics

Several key features of cardiac remodelling in HCM portend a higher risk of SCD. Increasing LV hypertrophy (in particular, maximum wall thickness ≥ 30 mm) was associated with an incremental increase in SCD risk in HCM.⁸³ Enlarged left atrial diameter also portends a higher risk.⁸⁴ LV outflow tract obstruction appears to have a low positive (8%) and a high negative (92%) predictive value.⁸⁵ Evidence is less compelling for an independent predictive value of abnormal blood pressure response during exercise (in particular in patients aged >40 years),^{86,87} LV systolic dysfunction (LVEF $<50\%$)⁸⁸ and the presence of LV apical aneurysms (regardless of size).⁸⁹ Prospective assessment has identified age as an independent predictor inversely associated with the risk of SCD.⁹⁰ Risk factors such as severe LV hypertrophy, NSVT and unexplained syncope seem to have stronger implications for SCD risk in younger patients.^{91–93} A history of a recent syncope (i.e. within 6 months before evaluation) has been associated with a five-fold higher risk of SCD.⁹³ SCD is also more prevalent among HCM patients with no or mild symptoms (NYHA class I–II, 71%) compared with the more symptomatic individuals (NYHA class III, 29%).⁹⁰

The association between physical activity and SCD in HCM appears to be more ambiguous and most SCD events occur at rest, but SCD may occur during or immediately after some level of physical activity.⁹⁰ Likewise, among young athletes who experienced SCD, HCM was the single most common disorder discovered on autopsy, accounting for 36% of SCD victims.⁹⁴ On the other hand, recent data did not show evidence of a higher risk of SCD in patients with HCM who continued participating in sport activities after ICD implantation.⁹⁵ A small interventional study suggested that HCM patients who participated in moderate-intensity exercise training experienced improvement in exercise capacity, without suffering major adverse events.⁹⁶ These data underline the need to further define the appropriate intensity and long-term safety of exercise in HCM.

Genetic background

Pathogenic variants in sarcomere genes can be detected in $\sim 40\%$ of sporadic and $\sim 60\%$ of familial cases of HCM, most commonly affecting cardiac myosin-binding protein C (cMyBP-C), β -myosin heavy chain (β -MHC) and cardiac troponin T and I (TNNT2 and TNNI3). A meta-analysis of 51 studies (total of 7675 HCM patients) investigating genotype–phenotype associations, linked the presence of pathogenic gene variants with a clinical phenotype, characterized by earlier disease onset, greater propensity for conduction abnormalities, and higher risk of SCD and progressive HF.⁹⁷ However, prognostic significance of sarcomere gene variants beyond established risk factors for SCD remains to be confirmed. A history of SCD attributable to HCM in a first-degree relative <40 years old, has been associated with an increased individual risk of SCD, particularly in combination with other risk factors.⁹⁸

Markers of electrical instability

Detection of NSVT (defined as ≥ 3 consecutive ventricular beats at ≥ 120 bpm, lasting <30 s) on ambulatory electrocardiogram monitoring at rest, during physical exertion, or immediately afterwards, indicates an increased risk of SCD in patients with HCM.^{91,99} The prognostic relevance was higher in younger patients, whilst the frequency, duration, and rate of NSVT episodes had no prognostic association.⁹¹

Myocardial fibrosis

A prospective cohort study identified extensive myocardial fibrosis on CMR (LGE $\geq 15\%$ of LV mass) as a predictor of a two-fold increased risk of SCD in HCM, regardless of other risk factors.¹⁰⁰ Inclusion of LGE improved prediction of SCD compared with conventional risk factors.¹⁰⁰ This was corroborated by a meta-analysis of seven studies (a total of 2993 patients) demonstrating that for each 10% increase in LGE there was an independent 36% increase in the risk of SCD in patients with HCM.¹⁰¹ A summary of risk factors for SCD in HCM is presented in Figure 4.

Prevention of sudden cardiac death

Although SCD may rarely occur in HCM in the absence of known risk markers, event rates are higher in patients with risk factors and their aggregation incrementally increases an individual risk.¹⁰² However, an overall low incidence of SCD in HCM and the hazards of lifelong device therapy, warrant a judicious selection of candidates for primary ICD implantation and a consideration of patients' preferences, beliefs and values, competing risks and device-related complications.^{27,102} There are two established approaches to the SCD risk assessment in HCM. One approach, suggested in the earlier, and updated in the current 2020 American Heart Association/American College of Cardiology guideline stipulates a systematic non-invasive assessment to identify individual risk factors with a strong association with SCD.¹⁰³ ICD is an appropriate option in adults with HCM and ≥ 1 major risk factors.¹⁰³ This approach has led to the greater rates of prophylactic ICD implantation in patients with HCM in the United States compared with other

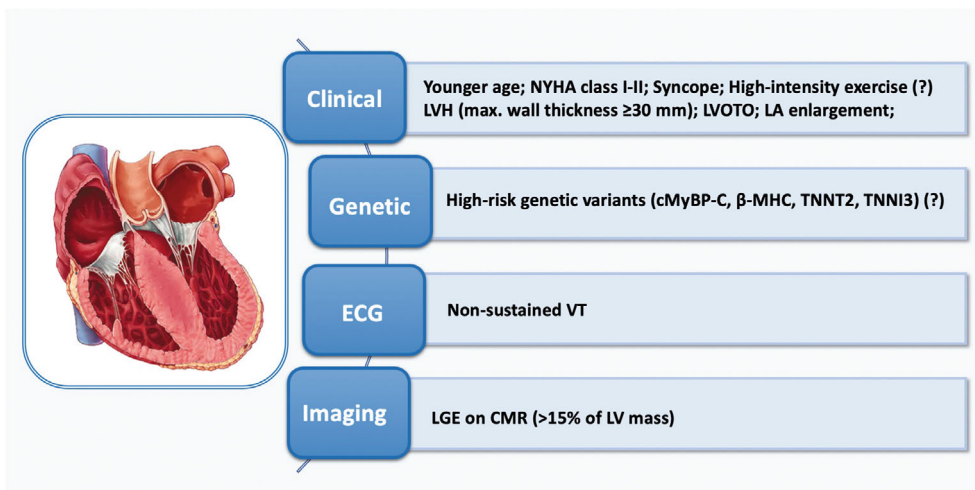


Figure 4 Established and emerging risk factors for sudden cardiac death in hypertrophic cardiomyopathy. β -MHC, β -myosin heavy chain; CMR, cardiac magnetic resonance; cMyBP-C, cardiac myosin-binding protein C; ECG, electrocardiogram; LA, left atrial; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; NYHA, New York Heart Association; TNNT2, cardiac troponin T; TNNI3, cardiac troponin I; VT, ventricular tachycardia.

countries, which was offset by lower rates of appropriate ICD therapy,¹⁰⁴ likely due to an overestimated individual risk.¹⁰² Another approach stipulated by the ESC guidelines^{4,27} suggests calculation of an individualized 5-year risk of SCD, based on a risk prediction tool (HCM Risk-SCD) built by modelling established, independent risk factors for SCD (Table 4).^{90,105} This model was subsequently validated in a large international population of patients with HCM, which confirmed its accuracy to guide selection of candidates for primary prevention ICD implantation.⁸¹ Additional risk factors (not captured by the HCM Risk-SCD model) may be considered in shared decision-making in selected patients (including LV systolic dysfunction, LV apical aneurysm, extensive LGE on CMR, and the presence of single or multiple sarcomere mutations), recognizing a lack of robust supportive data for their independent predictive role.^{4,27} In children aged 1 to 16 years, the HCM Risk-Kids score¹⁰⁵ has been validated in guiding prophylactic ICD implantation (Table 4).^{4,27} A reassessment of SCD risk should be performed at 1-to-2-year intervals, or if a change in clinical status is observed.²⁷

There is little evidence that medical therapies (i.e. beta-blockers, disopyramide, or amiodarone) attenuate the SCD risk in HCM.¹⁰⁶ Likewise, there remains a residual risk of SCD following surgical or alcohol septal reduction, albeit lower compared with medically managed patients.¹⁰⁷ The SCD risk of patients after myectomy appears to be lower than after alcohol septal reduction.¹⁰⁷ There is a current gap in the knowledge on the effect of a selective myosin inhibitor, mavacamten, on the risk of SCD. Despite promising results in improving exercise tolerance and LV outflow obstruction, mavacamten use was associated with a numerically higher rate of a reversible LVEF deterioration,^{108,109} and the potential impact on SCD risk remains unknown. Several novel

drugs are on the horizon, which hold the promise to attenuate arrhythmogenic risk.¹¹⁰ Currently, the only available option for SCD prevention in patients with HCM remains prophylactic ICD implantation.⁴ Furthermore, HCM patients with high-risk features (a history of cardiac arrest/unexplained syncope, intermediate SCD risk estimated $\geq 4\%$ at 5 years, LV outflow tract gradient at rest >30 mmHg, abnormal exercise blood pressure response or exercise-induced arrhythmias) should refrain from high-intensity exercise.⁸⁰

Arrhythmogenic right ventricular cardiomyopathy

Incidence and risk factors for sudden cardiac death

Arrhythmogenic right ventricular cardiomyopathy, including the right ventricular (RV) dominant, LV dominant and biventricular form, portends a high risk of ventricular arrhythmias (incidence 3.7–10% per year).^{111,112} A meta-analysis of 52 cohort studies (total of 5485 ARVC patients) reported the incidence of SCD of $\sim 0.7\%$ per year in ARVC patients without ICD, and a significantly lower SCD incidence (0.65 per 1000 patients per year) in ICD recipients.¹¹³

Clinical characteristics

Available data suggest that the more extensive myocardial disease in ARVC confers a higher risk of malignant ventricular arrhythmias/SCD. Specifically, RV dilatation/systolic dysfunction (in particular reduced fractional area change),¹¹⁴ LV involvement, overt HF,¹¹⁵ and evidence of structural disease progression have been

Table 4 Predictor variables in the HCM Risk-SCD model**Variables in HCM Risk-SCD score**

- 1 Age at time of evaluation (years)
- 2 Family history of SCD in ≥ 1 first-degree relatives < 40 years of age or SCD in a first-degree relative with confirmed HCM at any age
- 3 LV maximum wall thickness in the parasternal short- and long-axis plane using two-dimensional echocardiography (mm)
- 4 LA diameter by M-mode or two-dimensional echocardiography in the parasternal long-axis plane (mm)
- 5 Maximal instantaneous LV outflow tract gradient at rest and with Valsalva provocation using continuous-wave Doppler echocardiography (mmHg)
- 6 Non-sustained VT defined as ≥ 3 consecutive ventricular beats at a rate of ≥ 120 bpm and < 30 s in duration on Holter monitoring (minimum duration 24 h) at or before first evaluation.
- 7 Unexplained syncope at or before first evaluation

Variables in HCM Risk-Kids score

- 1 Age at time of evaluation (years) – valid for children aged 1–16 years
- 2 Sex
- 3 Weight (kg)
- 4 LV maximum wall thickness (mm)
- 5 LV maximum wall thickness Z-score
- 6 LA diameter in the parasternal long-axis plane at time of evaluation (mm)
- 7 LA diameter Z-score
- 8 Maximal instantaneous LV outflow tract gradient at rest and with Valsalva provocation using continuous-wave Doppler echocardiography (mmHg)
- 9 Non-sustained VT defined as ≥ 3 consecutive ventricular beats at a rate of ≥ 120 bpm and < 30 s in duration on Holter monitoring (minimum duration 24 h) at or before first evaluation
- 10 Unexplained syncope at or before first evaluation

HCM, hypertrophic cardiomyopathy; LA, left atrial; LV, left ventricular; SCD, sudden cardiac death; VT, ventricular tachycardia.
Modified from references^{90,105}

associated with a higher risk of SCD.^{116,117} A history of recent syncope (within 6–12 months) has also been associated with a higher risk of SCD.^{118–120} Multiple studies in ARVC have demonstrated a trend towards higher risk of ventricular arrhythmias/SCD in men compared with women.^{112,121} Although reasons remain unclear, a higher average level of physical exertion in males and specific cellular mechanisms have been hypothesized.¹²² High-intensity physical exertion has been linked to an earlier clinical presentation, higher risk of ventricular arrhythmias/SCD, and greater propensity for development of progressive HF requiring heart transplantation.¹²³ High-intensity exercise is, therefore, not recommended in patients with ARVC (and those who are gene positive but phenotype negative).⁸⁰

Genetic background

In most instances, ARVC is an inherited disorder associated with pathogenic gene variants in desmosome genes or, less frequently, in non-desmosome genes (Table 1). Most variants follow an autosomal dominant pattern of inheritance with incomplete penetrance, except the fully penetrant TMEM43 p.S358L variant, associated with progressive cardiomyopathy and high arrhythmic risk.¹²⁴

Patients with mutations have an earlier disease onset,¹²⁵ and those with more than one mutations have a higher risk of ventricular arrhythmias at an earlier age, and an overall poorer prognosis.¹²⁶ Disease penetrance in family members is $\sim 30\%$ and positive genetic testing identifies individuals at higher risk of developing ventricular arrhythmias.¹²⁵ However, there are conflicting data on an independent predictive value of genetic basis for SCD in ARVC.¹¹³ It is noteworthy that certain non-desmosomal mutations (e.g. TMEM43, LMNA, PLN) are associated with a particularly high risk of SCD.

Markers of electrical instability

Patients with ARVC frequently demonstrate electrocardiographic abnormalities, including T-wave inversion in right precordial leads (usually V1 to V3), low QRS voltages in the peripheral leads and terminal activation delay ('epsilon wave') in the right precordial leads. A history of sustained VT (most often with left bundle branch morphology) has been established as a strong predictor of increased risk of SCD in ARVC.¹¹¹ Some studies have also found an association between other markers of electrical instability and SCD risk, including NSVT, frequent ventricular premature complexes

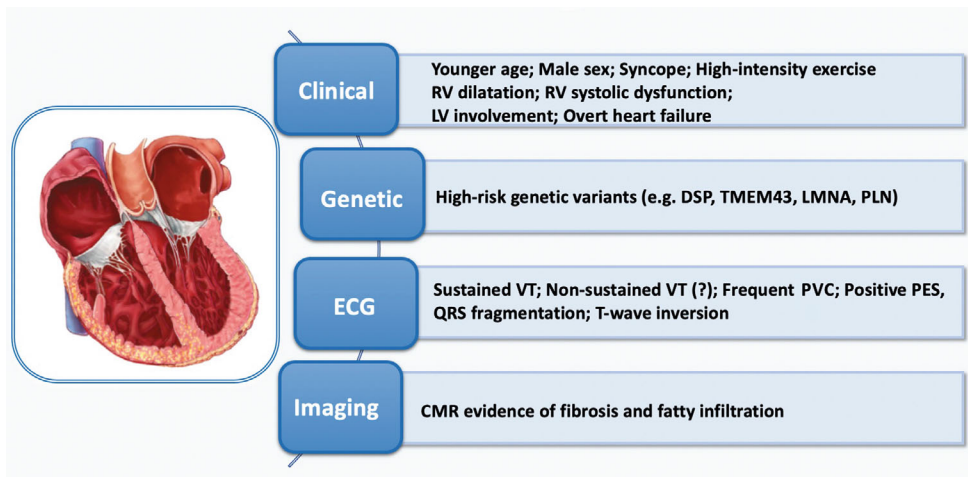


Figure 5 Established and emerging risk factors for sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy. CMR, cardiac magnetic resonance; DSP, desmoplakin; ECG, electrocardiogram; LMNA, lamin A/C; LV, left ventricular; PES, programmed electrical stimulation; PLN, phospholamban; PVC, premature ventricular complexes; RV, right ventricular; TMEM43, transmembrane protein 43; VT, ventricular tachycardia.

(>1000/24 h), inducibility of VT at PES, QRS fragmentation and the extent of T-wave inversion.^{113,119,120,127–129}

Myocardial fibrosis and fatty infiltration

Emerging data indicate that CMR studies may provide valuable prognostic information in ARVC.¹³⁰ Recently, CMR evidence of fibrosis and fatty infiltration was associated with increased risk of adverse events (SCD/aborted SCD, appropriate ICD intervention), with LV dominant and biventricular forms having worse prognosis than lone RV cardiomyopathy.¹³¹ In addition, CMR can be valuable in differential diagnosis of suspected cardiac sarcoidosis (also ¹⁸F-fluorodeoxyglucose positron emission tomography imaging), myocarditis, Chagas disease or other conditions mimicking ARVC. A summary of risk factors for SCD in ARVC is presented in Figure 5.

Prevention of sudden cardiac death

Several approaches have been proposed for risk stratification for primary ICD implantation in ARVC. An international expert consensus document suggested a classification of patients into three groups (high-, intermediate- and low-risk group) based on the presence of well-established risk factors for SCD.¹³² For patients in the high-risk group (i.e. aborted SCD, sustained VT, severe LV/RV dysfunction) or in the intermediate-risk group (presence of ≥ 1 established arrhythmic risk factors), ICD implantation is a viable option, whereas the low-risk patients (e.g. healthy gene carriers) do not meet the sufficiently high risk to warrant ICD implantation.¹³² A calculator to predict the arrhythmic outcome of the classic RV dominant phenotype has been proposed based on multivariable models for quantitative estimates of individual arrhythmic risk. It incorporates several disease-related features into a logistic regression equation aimed to provide estimates of the 5- and 10-year

risk of an incident sustained VT, SCD/aborted SCD, or appropriate ICD therapy in patients without prior sustained VT/SCD.¹²⁰ Since this outcome may overestimate the true risk of SCD, another model was designed to predict life-threatening arrhythmias (SCD, aborted SCD, ICD therapy for fast VT >250 bpm) as a closer surrogate for SCD.¹³³ Both prediction models are available at www.arvcrisk.com. Although this risk model was externally validated to predict the risk in the RV dominant form of the disease, it was reported to underestimate the risk in patients with biventricular and LV dominant cardiomyopathy,¹³⁴ which may impose the limitation for its use. Furthermore, traditionally recognized and clinically validated major risk factors (e.g. a history of NSVT, syncope and the severity of ventricular systolic dysfunction) did not predict the occurrence of life-threatening ventricular arrhythmias in the model. The ESC guidelines recommend ICD implantation in patients with definitive diagnosis of ARVC, according to the traditional risk stratification criteria reported in Table 3.^{4,27} The use of the calculator can be considered in shared decision-making on an individual basis.²⁷

The ICD is the only effective option to prevent SCD in ARVC. Since ventricular arrhythmias more frequently occur during physical exertion, restriction of high-intensity exercise seems reasonable to reduce the arrhythmic risk and disease progression. Beta-blockers may be used as the first-line pharmacological agents to reduce arrhythmic burden, and if unsuccessful, antiarrhythmic drugs (e.g. flecainide, sotalol, amiodarone) may be considered with variable success.^{135,136} In patients with drug-resistant arrhythmias/repeated ICD shocks, catheter ablation performed in experienced centres may be considered, because the arrhythmic substrate tends to be predominantly subepicardially localized, requiring an epicardial ablation approach.¹³⁷

Restrictive cardiomyopathy, metabolic cardiomyopathies and cardiac amyloidosis

Restrictive cardiomyopathy is the rarest of the cardiomyopathies, and there is a major gap in evidence on arrhythmic risk stratification and recommendations for prophylactic ICD implantation. RCM is typically considered to be the consequence of intrinsic myocardial dysfunction/interstitial fibrosis and endomyocardial disorders, but certain metabolic cardiomyopathies (e.g. Anderson–Fabry disease, haemochromatosis), and infiltrative disorders (e.g. cardiac amyloidosis, sarcoidosis), can also take the restrictive phenotype.²⁷ Given the paucity of evidence on SCD risk factors in most aetiologies of RCM and restrictive heart disease, a summary of available data in Anderson–Fabry disease, amyloidosis and sarcoidosis is provided in Data S2.

Conclusions

Despite favourable survival trends over the past decades, patients with cardiomyopathies still experience an excessive risk of SCD ranging between 0.15–0.7% per year. Although arrhythmogenic risk can be attributed to many factors, several have a particularly strong impact regardless of the type of a cardiomyopathy, including age, markers of disease severity, presence of myocardial fibrosis (e.g. LGE on CMR), unexplained syncope, evidence of electrical instability and high-risk genotype. However, there remain gaps in knowledge about genotype–phenotype associations, potential differences in SCD risk assessment and optimal approach to prevention in specific aetiologies of DCM, as well as SCD prevention in NDLVC and different aetiologies or RCM. There is also room for further evidence-based improvement of the existing, and development of new SCD risk prediction models, which may be useful in clinical practice to better inform shared decision-making. In many patients with cardiomyopathies, arrhythmogenic risk assessment and optimal selection of candidates for primary ICD prevention awaits further refinement, which should account for the specific aetiologies, genotype, age, clinical risk factors, lifestyle, response to therapies and optimal timing of ICD implantation.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

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