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REVIEW ARTICLE

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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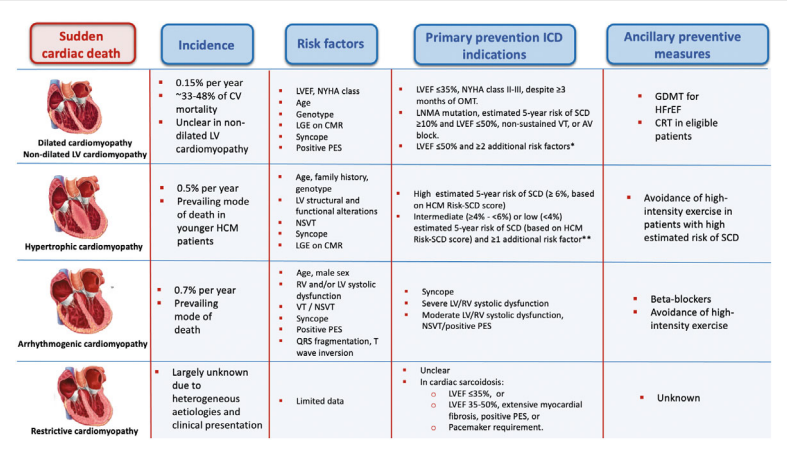
Graphical Abstract



Sudden cardiac death in cardiomyoptahies: 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)	Contribution to myocyte contraction	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
Cytoskeleton Z-disk						
DES (desmin)	Myofibrillar protein	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 NDLVC 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	High
DSG2 (desmoglein-2)	Same as above	5–26% in ARVC		Frequent LV involvement, overlap with DCM	Epsilon waves	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) Ring-like LGE on CMR	Very high
DSC2 (desmocollin-2)	Same as above	1–5% in ARVC		ARVC	Same as for PKP2	High
JUP (plakoglobin)	Same as above	<1% in ARVC Higher in Naxos, Greece		ARVC	Naxos disease (cardiocutaneous disease)	High
Other genes						
RBM20 (RNA-binding motif protein 20)	RNA-binding protein–spliceosome	2–5% in DCM	Adolescence through fourth decade	DCM, overlap with NDLVC	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 NDLVC 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	Posteroinferior '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, atrioventricular; 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.
[a]The list is not exhaustive. Modified from references[21–26]

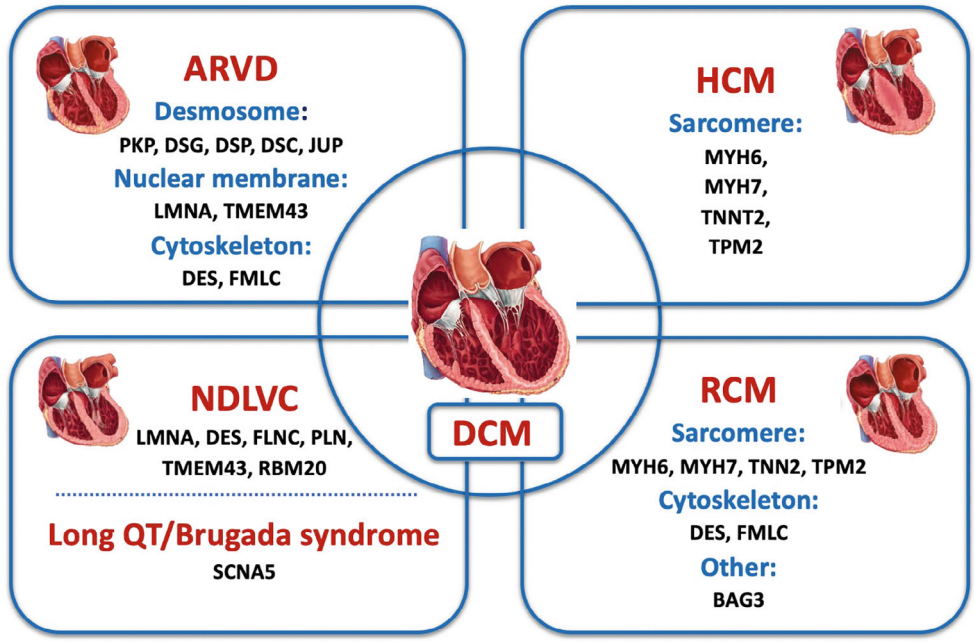


Figure 1 Overlapping genetic background in cardiomyopathies. ARVC, arrhythmogenic right ventricular cardiomyopathy; BAG3, Bcl-2–associated athanogene-3; DCM, dilated cardiomyopathy; DES, desmin; DSC, desmocollin, DSG, desmoglein; DSP, desmoplakin; FLMC, filamin C; HCM, hypertrophic cardiomyopathy; JUP, plakoglobin; LMNA, lamin A/C; MYH6, α-myosin heavy chain; MYH7, β-myosin heavy chain; NDLVC, non-dilated left ventricular cardiomyopathy; PKP, plakophilin; PLN, phospholamban; TMEM43, transmembrane protein 43; TNNT2, cardiac muscle troponin T; TPM2, β-tropomyosin; RBM20, RNA-binding motif protein 20; RCM, restrictive cardiomyopathy; SCN5A, sodium channel protein type 5.

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 ≥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 ∼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.

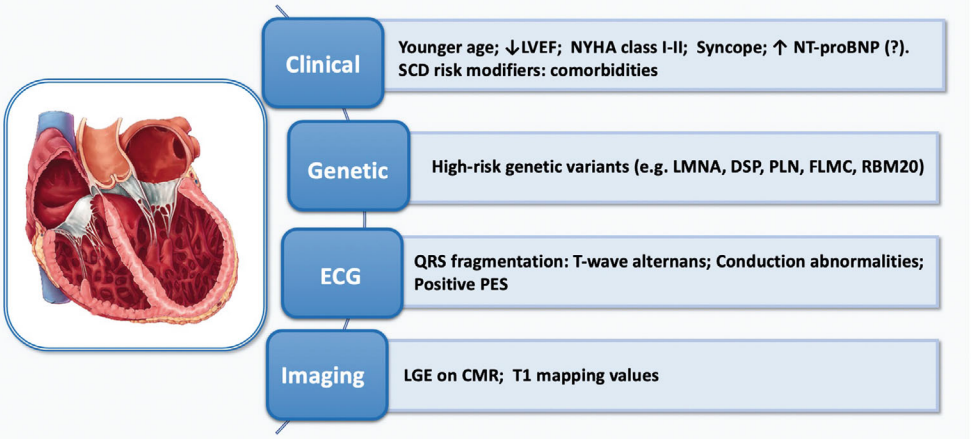


Figure 2 Established and emerging risk factors for sudden cardiac death (SCD) in dilated cardiomyopathy. CMR, cardiac magnetic resonance; DSP, desmoplakin; ECG, electrocardiogram; FLMC, filamin C;LGE, late gadolinium enhancement; LMNA, lamin A/C; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal 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 ≥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 ≥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] underling 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 SCD[66] or all-cause

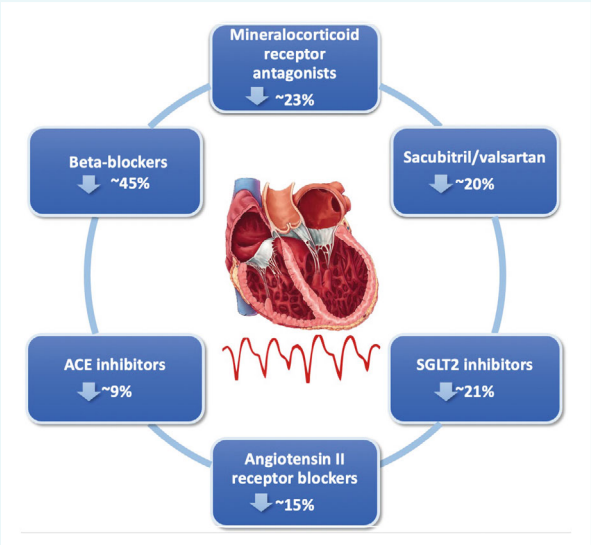


Figure 3 Estimated risk reduction in sudden cardiac death in clinical trials with disease-modifying medical therapies for heart failure with reduced ejection fraction (including patients with dilated cardiomyopathy). According to references.[49–56] ACE, angiotensin-converting enzyme; SGLT2, sodium–glucose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

mortality[67] 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 form 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 an 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 Terminated early due to futility	NR
AMIOVIRT[69,73]	2003	Non-ischaemic HF, LVEF ≤35%, NYHA class I–III, NSVT	103	~14	ICD vs. amiodarone	All-cause death Terminated early due to futility	NR
DEFINITE[74]	2004	Non-ischaemic HF, LVEF <36%, NYHA class I–III, NSVT or PVC	458	29	ICD vs. OMT	All-cause death ICD vs. OMT: HR 0.65; 95% CI 0.40–1.06; $p = 0.08$	HR 0.20; 95% CI 0.06–0.71; $p = 0.006$
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	All-cause death or all-cause hospitalization (all patients)* CRT-P vs. OMT: HR 0.81; 95% CI 0.69–0.96; $p = 0.014$; adjusted $p = 0.015$ CRT-D vs. OMT: HR 0.80; 95% CI 0.68–0.95; $p = 0.010$; adjusted $p = 0.011$ *Interaction p-value for HF aetiology was non-significant	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, $p = 0.06$ *Interaction p-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; $p = 0.28$	HR 0.50; 95% CI 0.31–0.82; $p = 0.005$

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 ≤35%, NYHA class II–III, despite ≥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 ≥10% (https://lmna-riskvta.fr/), and in the presence of non-sustained VT, or AV block.
- LVEF ≤50% and ≥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 ≥16 years and an estimated 5-year risk of SCD ≥6% (based on HCM SCD-Risk score).
- In patients aged ≥16 years with an intermediate 5-year risk (≥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 (≥15% of LV mass); or
- LVEF <50%; or
- LV apical aneurysm; or
- Sarcomeric pathogenic gene mutations.
- Children aged <16 years with a high (≥6%) or intermediate (≥4% to <6%) 5-year risk of SCD (based on HCM Risk-Kids score)

Arrhythmogenic right ventricular cardiomyopathy

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

Sarcoidosis

- LVEF ≤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.

[a]Modified from references[4,27,79]

[b]Same 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 NDLVC, 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 NDLVC 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 ∼40% of sporadic and ∼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 ≥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

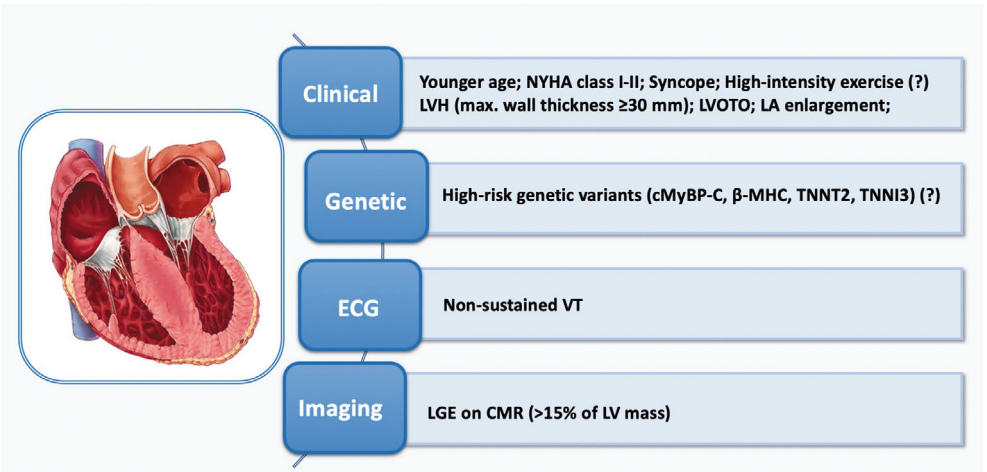


Figure 4 Established and emerging risk factors for sudden cardiac death in hypertrophic cardiomyopathy. β-MHC, β-myosin heavy chain; CMR, cardiac magnetic resonance; cMyBP-C, cardiac myosin-binding protein C; ECG, electrocardiogram; LA, left atrial; LGE, late gadolinium enhancement; LVH, left ventricular 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 score[105] 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 ≥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 ~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 ∼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

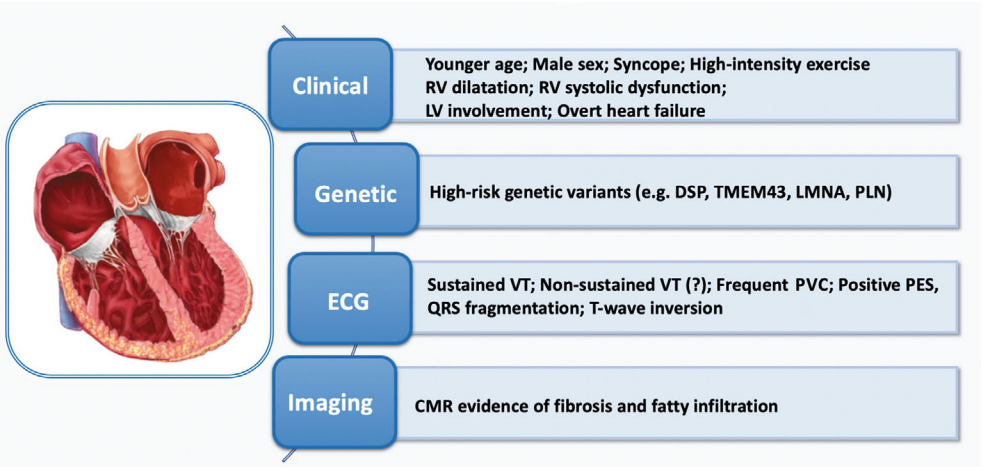


Figure 5 Established and emerging risk factors for sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy. CMR, cardiac magnetic resonance; DSP, desmoplakin; ECG, electrocardiogram; LMNA, lamin A/C; LV, left ventricular; PES, programmed electrical stimulation; PLN, phospholamban; PVC, 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 ^{18}F-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 amioloidosis

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.

References

1. Seferović PM, Polovina M, Bauersachs J, Arad M, Ben Gal T, Lund LH, *et al.* Heart failure in cardiomyopathies: A position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:553–576. https://doi.org/10.1002/ejhf.1461
2. Seferović PM, Polovina M, Rosano G, Bozkurt B, Metra M, Heymans S, *et al.* State-of-the-art document on optimal contemporary management of cardiomyopathies. *Eur J Heart Fail* 2023;**25**:1899–1922. https://doi.org/10.1002/ejhf.2979
3. Packer M. What causes sudden death in patients with chronic heart failure and a reduced ejection fraction? *Eur Heart J* 2020;**41**:1757–1763. https://doi.org/10.1093/eurheartj/ehz553
4. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, *et al.* 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126. https://doi.org/10.1093/eurheartj/ehac262
5. Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. *Circulation* 1993;**88**:2953–2961. https://doi.org/10.1161/01.cir.88.6.2953
6. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, *et al.* Declining risk of sudden death in heart failure. *N Engl J Med* 2017;**377**:41–51. https://doi.org/10.1056/NEJMoa1609758
7. Cubbon RM, Gale CP, Kearney LC, Schechter CB, Brooksby WP, Nolan J, *et al.* Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: A study across therapeutic eras. *Circ Heart Fail* 2011;**4**:396–403. https://doi.org/10.1161/CIRCHEARTFAILURE.110.959882
8. Merlo M, Cannatà A, Pio Loco C, Stolfo D, Barbati G, Artico J, *et al.* Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2020;**22**:1111–1121. https://doi.org/10.1002/ejhf.1914
9. Gorgels AP, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest-the relevance of heart failure. The Maastricht Circulatory Arrest Registry. *Eur Heart J* 2003;**24**:1204–1209. https://doi.org/10.1016/s0195-668x(03)00191-x
10. Grimm W, Christ M, Bach J, Müller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: Results of the Marburg Cardiomyopathy Study. *Circulation* 2003;**108**:2883–2891. https://doi.org/10.1161/01.CIR.0000100721.52503.85
11. Kjekshus J. Arrhythmias and mortality in congestive heart failure. *Am J Cardiol* 1990;**65**:42I–48I. https://doi.org/10.1016/0002-9149(90)90125-k
12. Friedman DJ, Al-Khatib SM, Zeitler EP, Han J, Bardy GH, Poole JE, *et al.* New York Heart Association class and the survival benefit from primary prevention implantable cardioverter defibrillators: A pooled analysis of 4 randomized controlled trials. *Am Heart J* 2017;**191**:21–29. https://doi.org/10.1016/j.ahj.2017.06.002
13. Butt JH, Yafasova A, Elming MB, Dixen U, Nielsen JC, Haarbo J, *et al.* NT-proBNP and ICD in nonischemic systolic heart failure: Extended follow-up of the DANISH trial. *JACC Heart Fail.* 2022;**10**:161–171. https://doi.org/10.1016/j.jchf.2022.01.003
14. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, *et al.*; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230. https://doi.org/10.1056/NEJMoa1608029
15. Elming MB, Nielsen JC, Haarbo J, Videbæk L, Korup E, Signorovitch J, *et al.* Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017;**136**:1772–1780. https://doi.org/10.1161/CIRCULATIONAHA.117.028829
16. Pun PH, Al-Khatib SM, Han JY, Edwards R, Bardy GH, Bigger JT, *et al.* Implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in CKD: A meta-analysis of patient-level data from 3 randomized trials. *Am J Kidney Dis* 2014;**64**:32–39. https://doi.org/10.1053/j.ajkd.2013.12.009
17. Rørth R, Dewan P, Kristensen SL, Jhund PS, Petrie MC, Køber L, *et al.* Efficacy of an implantable cardioverter-defibrillator in patients with diabetes and heart failure and reduced ejection fraction. *Clin Res Cardiol* 2019;**108**:868–877. https://doi.org/10.1007/s00392-019-01415-z
18. Mozaffarian D, Anker SD, Anand I, Linker DT, Sullivan MD, Cleland JGF, *et al.* Prediction of mode of death in heart failure. *Circulation* 2007;**116**:392–398. https://doi.org/10.1161/CIRCULATIONAHA.106.687103
19. Shadman R, Poole JE, Dardas TF, Mozaffarian D, Cleland JG, Swedberg K, *et al.* A novel method to predict the proportional risk of sudden cardiac death in heart failure: Derivation of the Seattle Proportional Risk Model. *Heart Rhythm* 2015;**12**:2069–2077. https://doi.org/10.1016/j.hrthm.2015.06.039
20. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, *et al.* 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm* 2019;**16**:e301–e372. https://doi.org/10.1016/j.hrthm.2019.05.007
21. Tayal U, Ware JS, Lakdawala NK, Heymans S, Prasad SK. Understanding the genetics of adult-onset dilated cardiomyopathy: What a clinician needs to know. *Eur Heart J* 2021;**42**:2384–2396. https://doi.org/10.1093/eurheartj/ehab286
22. Peña-Peña ML, Monserrat L. Risk stratification in patients with Nonisquemic dilated cardiomyopathy. The role of genetic testing. *Rev Esp Cardiol (Engl Ed)* 2019;**72**:333–340. https://doi.org/10.1016/j.rec.2018.10.017

23. Xintarakou A, Kariki O, Doundoulakis I, Arsenos P, Soulaidopoulos S, Laina A, *et al.* The role of genetics in risk stratification strategy of dilated cardiomyopathy. *Rev Cardiovasc Med* 2022;**23**:305. https://doi.org/10.31083/j.rcm2309305
24. Bosman LP, Te Riele A. Arrhythmogenic right ventricular cardiomyopathy: A focused update on diagnosis and risk stratification. *Heart* 2022;**108**:90–97. https://doi.org/10.1136/heartjnl-2021-319113
25. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, *et al.* International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the Clinical Genome Resource framework. *Circ Genom Precis Med.* 2021;**14**:e003273. https://doi.org/10.1161/CIRCGEN.120.003273
26. Qu HQ, Feldman AM, Hakonarson H. Genetics of BAG3: A paradigm for developing precision therapies for dilated cardiomyopathies. *J Am Heart Assoc* 2022;**11**:e027373. https://doi.org/10.1161/JAHA.122.027373
27. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, *et al.* 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;**44**:3503–3626. https://doi.org/10.1093/eurheartj/ehad194
28. Wahbi K, Ben Yaou R, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, *et al.* Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation* 2019;**140**:293–302. https://doi.org/10.1161/CIRCULATIONAHA.118.039410
29. Verstraelen TE, van Lint FHM, Bosman LP, de Brouwer R, Proost VM, Abeln BGS, *et al.* Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers – Reaching the frontiers of individual risk prediction. *Eur Heart J* 2021;**42**:2842–2850. https://doi.org/10.1093/eurheartj/ehab294
30. Akhtar MM, Lorenzini M, Cicerchia M, Ochoa JP, Hey TM, Molina MS, *et al.* Clinical phenotypes and prognosis of dilated cardiomyopathy caused by truncating variants in the TTN gene. *Circ Heart Fail* 2020;**13**:e006832. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006832
31. Finocchiaro G, Merlo M, Sheikh N, De Angelis G, Papadakis M, Olivotto I, *et al.* The electrocardiogram in the diagnosis and management of patients with dilated cardiomyopathy. *Eur J Heart Fail* 2020;**22**:1097–1107. https://doi.org/10.1002/ejhf.1815
32. Goldberger JJ, Subačius H, Patel T, Cunnane R, Kadish AH. Sudden cardiac death risk stratification in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol* 2014;**63**:1879–1889. https://doi.org/10.1016/j.jacc.2013.12.021
33. Hammersley DJ, Halliday BP. Sudden cardiac death prediction in non-ischemic dilated cardiomyopathy: A multiparametric and dynamic approach. *Curr Cardiol Rep* 2020;**22**:85. https://doi.org/10.1007/s11886-020-01343-9
34. Gatzoulis KA, Tsiachris D, Arsenos P, Archontakis S, Dilaveris P, Vouliotis A, *et al.* Prognostic value of programmed ventricular stimulation for sudden death in selected high risk patients with structural heart disease and preserved systolic function. *Int J Cardiol* 2014;**176**:1449–1451. https://doi.org/10.1016/j.ijcard.2014.08.068
35. Hammersley DJ, Jones RE, Mach L, Halliday BP, Prasad SK. Cardiovascular magnetic resonance in heritable cardiomyopathies. *Heart Fail Clin* 2021;**17**:25–39. https://doi.org/10.1016/j.hfc.2020.08.004
36. Donal E, Delgado V, Bucciarelli-Ducci C, Galli E, Haugaa KH, Charron P, *et al.* Multimodality imaging in the diagnosis, risk stratification, and management of patients with dilated cardiomyopathies: An expert consensus. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1075–1093. https://doi.org/10.1093/ehjci/jez178
37. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: A comprehensive review. *J Cardiovasc Magn Reson* 2016;**18**:89. https://doi.org/10.1186/s12968-016-0308-4
38. Neilan TG, Coelho-Filho OR, Danik SB, Shah RV, Dodson JA, Verdini DJ, *et al.* CMR quantification of myocardial scar provides additive prognostic information in nonischemic cardiomyopathy. *JACC Cardiovasc Imaging* 2013;**6**:944–954. https://doi.org/10.1016/j.jcmg.2013.05.013
39. Masci PG, Doulaptsis C, Bertella E, Del Torto A, Symons R, Pontone G, *et al.* Incremental prognostic value of myocardial fibrosis in patients with non-ischemic cardiomyopathy without congestive heart failure. *Circ Heart Fail* 2014;**7**:448–456. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000996
40. Marco AD, Brown PF, Bradley J, Nucifora G, Claver E, Frutos F, *et al.* Improved risk stratification for ventricular arrhythmias and sudden death in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol* 2021;**77**:2890–2905. https://doi.org/10.1016/j.jacc.2021.04.030
41. Alba AC, Gaztañaga J, Foroutan F, Thavendiranathan P, Merlo M, Alonso-Rodriguez D, *et al.* Prognostic value of late gadolinium enhancement for the prediction of cardiovascular outcomes in dilated cardiomyopathy: An international, multi-institutional study of the MINICOR Group. *Circ Cardiovasc Imaging* 2020;**13**:e010105. https://doi.org/10.1161/CIRCIMAGING.119.010105
42. Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, *et al.* Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. *JACC Cardiovasc Imaging* 2019;**12**:1645–1655. https://doi.org/10.1016/j.jcmg.2018.07.015
43. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, *et al.* Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. *Circulation* 2017;**135**:2106–2115. https://doi.org/10.1161/CIRCULATIONAHA.116.026910
44. Guaricci AI, Masci PG, Muscogiuri G, Guglielmo M, Baggiano A, Fusini L, *et al.* CarDiac magnEtic Resonance for prophylactic Implantable-cardioVerter defibrillAtor ThErapy in Non-Ischaemic dilated CardioMyopathy: An international registry. *Europace* 2021;**23**:1072–1083. https://doi.org/10.1093/europace/euaa401
45. Chen Z, Sohal M, Voigt T, Sammut E, Tobon-Gomez C, Child N, *et al.* Myocardial tissue characterization by cardiac magnetic resonance imaging using T1 mapping predicts ventricular arrhythmia in ischemic and non-ischemic cardiomyopathy patients with implantable cardioverter-defibrillators. *Heart Rhythm* 2015;**12**:792–801. https://doi.org/10.1016/j.hrthm.2014.12.020
46. Li Y, Xu Y, Li W, Guo J, Wan K, Wang J, *et al.* Cardiac MRI to predict sudden cardiac death risk in dilated cardiomyopathy. *Radiology* 2023;**307**:e222552. https://doi.org/10.1148/radiol.222552
47. Selvanayagam JB, Hartshorne T, Billot L, Grover S, Hillis GS, Jung W, *et al.* Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE): Study protocol for a randomized controlled trial. *Ann Noninvasive Electrocardiol* 2017;**22**:e12420. https://doi.org/10.1111/anec.12420
48. Packer M. Major reduction in the risk of sudden cardiac death in patients with chronic heart failure with the use of drug and device combinations that favourably affect left ventricular structure. *Eur J Heart Fail* 2019;**21**:823–826. https://doi.org/10.1002/ejhf.1501
49. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, *et al.* Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J* 2015;**36**:1990–1997. https://doi.org/10.1093/eurheartj/ehv186
50. Curtain JP, Docherty KF, Jhund PS, Petrie MC, Inzucchi SE, Køber L, *et al.* Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. *Eur Heart J* 2021;**42**:3727–3738. https://doi.org/10.1093/eurheartj/ehab560
51. Garg R, Yusuf S; Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;**273**:1450–1456. https://doi.org/10.1001/jama.1995.03520420066040
52. Krum H, van Veldhuisen DJ, Funck-Brentano C, Vanoli E, Silke B, Erdmann E, *et al.*; CIBIS III Investigators. Effect on mode of death of heart failure treatment started with bisoprolol followed by enalapril, compared to the opposite order: Results of the randomized CIBIS III trial. *Cardiovasc Ther* 2011;**29**:89–98. https://doi.org/10.1111/j.1755-5922.2010.00185.x
53. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, *et al.*; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. *Circulation* 2002;**106**:2194–2199. https://doi.org/10.1161/01.cir.0000035653.72855.bf
54. Effect of metoprolol CR/XL in chronic heart failure. Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007. https://doi.org/10.1016/S0140-6736(99)04440-2
55. Solomon SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJ, *et al.* Effect of candesartan on cause-specific mortality in heart failure patients: The Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation* 2004;**110**:2180–2183. https://doi.org/10.1161/01.CIR.0000144474.65922.AA
56. Rossello X, Ariti C, Pocock SJ, Ferreira JP, Girerd N, McMurray JJV, *et al.* Impact of mineralocorticoid receptor antagonists on the risk of sudden cardiac death in patients with heart failure and left-ventricular systolic dysfunction: An individual patient-level meta-analysis of three randomized-controlled trials. *Clin Res Cardiol* 2019;**108**:477–486. https://doi.org/10.1007/s00392-018-1378-0
57. Oates CP, Santos-Gallego CG, Smith A, Basyal B, Moss N, Kawamura I, *et al.* SGLT2 inhibitors reduce sudden cardiac death risk in heart failure: Meta-analysis of randomized clinical trials. *J Cardiovasc Electrophysiol* 2023;**34**:1277–1285. https://doi.org/10.1111/jce.15894
58. Amorim S, Campelo M, Martins E, Moura B, Sousa A, Pinho T, *et al.* Prevalence, predictors and prognosis of ventricular reverse remodeling in idiopathic dilated cardiomyopathy. *Rev Port Cardiol* 2016;**35**:253–260. https://doi.org/10.1016/j.repc.2015.11.014

59. Kubanek M, Sramko M, Maluskova J, Kautznerova D, Weichet J, Lupinek P, *et al.* Novel predictors of left ventricular reverse remodeling in individuals with recent-onset dilated cardiomyopathy. *J Am Coll Cardiol* 2013;**61**:54–63. https://doi.org/10.1016/j.jacc.2012.07.072
60. Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. *J Am Coll Cardiol* 2011;**57**:1468–1476. https://doi.org/10.1016/j.jacc.2010.11.030
61. Jansweijer JA, Nieuwhof K, Russo F, Hoorntje ET, Jongbloed JD, Lekanne Deprez RH, *et al.* Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy. *Eur J Heart Fail* 2017;**19**:512–521. https://doi.org/10.1002/ejhf.673
62. Verdonschot JAJ, Hazebroek MR, Wang P, Sanders-van Wijk S, Merken JJ, Adriaansen YA, *et al.* Clinical phenotype and genotype associations with improvement in left ventricular function in dilated cardiomyopathy. *Circ Heart Fail* 2018;**11**:e005220. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005220
63. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, *et al.* Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): An open-label, pilot, randomised trial. *Lancet* 2019;**393**:61–73. https://doi.org/10.1016/S0140-6736(18)32484-X
64. Merlo M, Stolfo D, Anzini M, Negri F, Pinamonti B, Barbati G, *et al.* Persistent recovery of normal left ventricular function and dimension in idiopathic dilated cardiomyopathy during long-term follow-up: Does real healing exist? *J Am Heart Assoc* 2015;**4**:e001504. https://doi.org/10.1161/JAHA.114.000570
65. Sheppard R, Mather PJ, Alexis JD, Starling RC, Boehmer JP, Thohan V, *et al.*; IMAC Investigators. Implantable cardiac defibrillators and sudden death in recent onset nonischemic cardiomyopathy: Results from IMAC2. *J Card Fail* 2012;**18**:675–681. https://doi.org/10.1016/j.cardfail.2012.07.004
66. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, *et al.*; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237. https://doi.org/10.1056/NEJMoa043399
67. Poole JE, Olshansky B, Mark DB, *et al.* on behalf of the SCD-HeFT Investigators. Long-term outcomes of implantable cardioverter-defibrillator therapy in the SCD-HeFT. *J Am Coll Cardiol* 2020;**76**:405–415.
68. Claro JC, Candia R, Rada G, Baraona F, Larrondo F, Letelier LM. Amiodarone versus other pharmacological interventions for prevention of sudden cardiac death. *Cochrane Database Syst Rev* 2015;**2015**:CD008093. https://doi.org/10.1002/14651858.CD008093.pub2
69. Strickberger SA. Multicenter randomized trial comparing amiodarone to implantable defibrillator in patients with nonischemic cardiomyopathy and asymptomatic nonsustained ventricular tachycardia: AMIOVIRT trial. *Circulation* 2000;**102**:2794. https://doi.org/10.1161/01.CIR.102.22.2794
70. Uretsky BF, Thygesen K, Daubert JC, Erdmann E, Freemantle N, Gras D, *et al.* Predictors of mortality from pump failure and sudden cardiac death in patients with systolic heart failure and left ventricular dyssynchrony: Results of the CARE-HF trial. *J Card Fail* 2008;**14**:670–675. https://doi.org/10.1016/j.cardfail.2008.06.001
71. Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, *et al.* Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2011;**57**:2416–2423. https://doi.org/10.1016/j.jacc.2010.12.041
72. Bänsch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, *et al.* Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: The Cardiomyopathy Trial (CAT). *Circulation* 2002;**105**:1453–1458. https://doi.org/10.1161/01.cir.0000012350.99718.ad
73. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, *et al.*; AMIOVIRT Investigators. Amiodarone versus implantable cardioverter-defibrillator: Randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia – AMIOVIRT. *J Am Coll Cardiol* 2003;**41**:1707–1712. https://doi.org/10.1016/s0735-1097(03)00297-3
74. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, *et al.*; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;**350**:2151–2158.
75. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, *et al.*; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;**350**:2140–2150. https://doi.org/10.1056/NEJMoa032423
76. Yafasova A, Butt JH, Elming MB, Nielsen JC, Haarbo J, Videbæk L, *et al.* Long-term follow-up of DANISH (the Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure on Mortality). *Circulation* 2022;**145**:427–436. https://doi.org/10.1161/CIRCULATIONAHA.121.056072
77. Poole JE, Olshansky B, Mark DB, Anderson J, Johnson G, Hellkamp AS, *et al.*; SCD-HeFT Investigators. Long-term outcomes of implantable cardioverter-defibrillator therapy in the SCD-HeFT. *J Am Coll Cardiol* 2020;**76**:405–415. https://doi.org/10.1016/j.jacc.2020.05.061
78. Theuns DA, Verstraelen TE, van der Lingen ACJ, Delnoy PP, Allaart CP, van Erven L, *et al.* Implantable defibrillator therapy and mortality in patients with non-ischaemic dilated cardiomyopathy: An updated meta-analysis and effect on Dutch clinical practice by the Task Force of the Dutch Society of Cardiology. *Neth Heart J* 2023;**31**:89–99. https://doi.org/10.1007/s12471-022-01718-3
79. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
80. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, *et al.* 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;**42**:17–96. https://doi.org/10.1093/eurheartj/ehaa605
81. O'Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, *et al.* International external validation study of the 2014 European Society of Cardiology guidelines on sudden cardiac death prevention in hypertrophic cardiomyopathy (EVIDENCE-HCM). *Circulation* 2018;**137**:1015–1023. https://doi.org/10.1161/CIRCULATIONAHA.117.030437
82. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, *et al.* Epidemiology of hypertrophic cardiomyopathy-related death. *Circulation* 2000;**102**:858–864. https://doi.org/10.1161/01.cir.102.8.858
83. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;**357**:420–424. https://doi.org/10.1016/S0140-6736(00)04005-8
84. Minami Y, Haruki S, Yashiro B, Suzuki T, Ashihara K, Hagiwara N. Enlarged left atrium and sudden death risk in hypertrophic cardiomyopathy patients with or without atrial fibrillation. *J Cardiol* 2016;**68**:478–484. https://doi.org/10.1016/j.jjcc.2016.01.006
85. Efthimiadis GK, Parcharidou DG, Giannakoulas G, Pagourelias ED, Charalampidis P, Savvopoulos G, *et al.* Left ventricular outflow tract obstruction as a risk factor for sudden cardiac death in hypertrophic cardiomyopathy. *Am J Cardiol* 2009;**104**:695–699. https://doi.org/10.1016/j.amjcard.2009.04.039
86. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1999;**33**:2044–2051. https://doi.org/10.1016/s0735-1097(99)00094-7
87. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation* 1997;**96**:2987–2991. https://doi.org/10.1161/01.cir.96.9.2987
88. Rowin EJ, Maron BJ, Carrick RT, Patel PP, Koethe B, Wells S, *et al.* Outcomes in patients with hypertrophic cardiomyopathy and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2020;**75**:3033–3043. https://doi.org/10.1016/j.jacc.2020.04.045
89. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, *et al.* Hypertrophic cardiomyopathy with left ventricular apical aneurysm: Implications for risk stratification and management. *J Am Coll Cardiol* 2017;**69**:761–773. https://doi.org/10.1016/j.jacc.2016.11.063
90. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, *et al.*; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). *Eur Heart J* 2014;**35**:2010–2020. https://doi.org/10.1093/eurheartj/eht439
91. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: An independent marker of sudden death risk in young patients. *J Am Coll Cardiol* 2003;**42**:873–879. https://doi.org/10.1016/s0735-1097(03)00827-1
92. Maron BJ, Casey SA, Hurrell DG, Aeppli DM. Relation of left ventricular thickness to age and gender in hypertrophic cardiomyopathy. *Am J Cardiol* 2003;**91**:1195–1198. https://doi.org/10.1016/s0002-9149(03)00266-2
93. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS, *et al.* Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation* 2009;**119**:1703–1710. https://doi.org/10.1161/CIRCULATIONAHA.108.798314

94. Maron BJ, Haas TS, Ahluwalia A, Murphy CJ, Garberich RF. Demographics and epidemiology of sudden deaths in young competitive athletes: From the United States National Registry. *Am J Med* 2016;**129**:1170–1177. https://doi.org/10.1016/j.amjmed.2016.02.031
95. Lampert R, Olshansky B, Heidbuchel H, Lawless C, Saarel E, Ackerman M, *et al.* Safety of sports for athletes with implantable cardioverter-defibrillators. *Circulation* 2017;**135**:2310–2312. https://doi.org/10.1161/CIRCULATIONAHA.117.027828
96. Saberi S, Wheeler M, Bragg-Gresham J, Hornsby W, Agarwal PP, Attili A, *et al.* Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: A randomized clinical trial. *JAMA* 2017;**317**:1349–1357. https://doi.org/10.1001/jama.2017.2503
97. Sedaghat-Hamedani F, Kayvanpour E, Tugrul OF, Lai A, Amr A, Haas J, *et al.* Clinical outcomes associated with sarcomere mutations in hypertrophic cardiomyopathy: A meta-analysis on 7675 individuals. *Clin Res Cardiol* 2018;**107**:30–41. https://doi.org/10.1007/s00392-017-1155-5
98. Maron MS. Family history of sudden death should be a primary indication for implantable cardioverter defibrillator in hypertrophic cardiomyopathy. *Can J Cardiol* 2015;**31**:1402–1406. https://doi.org/10.1016/j.cjca.2015.05.004
99. Gimeno JR, Tomé-Esteban M, Lofiego C, Hurtado J, Pantazis A, Mist B, *et al.* Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2009;**30**:2599–2605. https://doi.org/10.1093/eurheartj/ehp327
100. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, *et al.* Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation* 2014;**130**:484–495. https://doi.org/10.1161/CIRCULATIONAHA.113.007094
101. Weng Z, Yao J, Chan RH, He J, Yang X, Zhou Y, *et al.* Prognostic value of LGE-CMR in HCM: A meta-analysis. *JACC Cardiovasc Imaging* 2016;**9**:1392–1402. https://doi.org/10.1016/j.jcmg.2016.02.031
102. O'Mahony C, Tome-Esteban M, Lambiase PD, Pantazis A, Dickie S, McKenna WJ, *et al.* A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. *Heart* 2013;**99**:534–541. https://doi.org/10.1136/heartjnl-2012-303271
103. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, *et al.* 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2020;**76**:e159–e240. https://doi.org/10.1016/j.jacc.2020.08.045
104. Nauffal V, Marstrand P, Han L, Parikh VN, Helms AS, Ingles J, *et al.* Worldwide differences in primary prevention implantable cardioverter defibrillator utilization and outcomes in hypertrophic cardiomyopathy. *Eur Heart J* 2021;**42**:3932–3944. https://doi.org/10.1093/eurheartj/ehab598
105. Norrish G, Ding T, Field E, Ziółkowska L, Olivotto I, Limongelli G, *et al.* Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM Risk-Kids). *JAMA Cardiol* 2019;**4**:918–927. https://doi.org/10.1001/jamacardio.2019.2861
106. Melacini P, Maron BJ, Bobbo F, Basso C, Tokajuk B, Zucchetto M, *et al.* Evidence that pharmacological strategies lack efficacy for the prevention of sudden death in hypertrophic cardiomyopathy. *Heart* 2007;**93**:708–710. https://doi.org/10.1136/hrt.2006.099416
107. Vriesendorp PA, Liebregts M, Steggerda RC, Schinkel AF, Willems R, Ten Cate FJ, *et al.* Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. *JACC Heart Fail* 2014;**2**:630–636. https://doi.org/10.1016/j.jchf.2014.06.012
108. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, *et al.*; EXPLORER-HCM Study Investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;**396**:759–769. https://doi.org/10.1016/S0140-6736(20)31792-X
109. Hegde SM, Lester SJ, Solomon SD, Michels M, Elliott PM, Nagueh SF, *et al.* Effect of mavacamten on echocardiographic features in symptomatic patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2021;**78**:2518–2532. https://doi.org/10.1016/j.jacc.2021.09.1381
110. de Boer RA, Heymans S, Backs J, Carrier L, Coats AJS, Dimmeler S, *et al.* Targeted therapies in genetic dilated and hypertrophic cardiomyopathies: From molecular mechanisms to therapeutic targets. A position paper from the Heart Failure Association (HFA) and the Working Group on Myocardial Function of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2022;**24**:406–420. https://doi.org/10.1002/ejhf.2414
111. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, *et al.* Arrhythmogenic right ventricular cardiomyopathy: Clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol* 2016;**68**:2540–2550. https://doi.org/10.1016/j.jacc.2016.09.951
112. Bosman LP, Sammani A, James CA, Cadrin-Tourigny J, Calkins H, van Tintelen JP, *et al.* Predicting arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy: A systematic review and meta-analysis. *Heart Rhythm* 2018;**15**:1097–1107. https://doi.org/10.1016/j.hrthm.2018.01.031
113. Agbaedeng TA, Roberts KA, Colley L, Noubiap JJ, Oxborough D. Incidence and predictors of sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy: A pooled analysis. *Europace* 2022;**24**:1665–1674. https://doi.org/10.1093/europace/euac014
114. Saguner AM, Vecchiati A, Baldinger SH, Rüeger S, Medeiros-Domingo A, Mueller-Burri AS, *et al.* Different prognostic value of functional right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circ Cardiovasc Imaging* 2014;**7**:230–239. https://doi.org/10.1161/CIRCIMAGING.113.000210
115. Schuler PK, Haegeli LM, Saguner AM, Wolber T, Tanner FC, Jenni R, *et al.* Predictors of appropriate ICD therapy in patients with arrhythmogenic right ventricular cardiomyopathy: Long term experience of a tertiary care center. *PLoS One* 2012;**7**:e39584. https://doi.org/10.1371/journal.pone.0039584
116. Chivulescu M, Lie ØH, Popescu BA, Skulstad H, Edvardsen T, Jurcut RO, *et al.* High penetrance and similar disease progression in probands and in family members with arrhythmogenic cardiomyopathy. *Eur Heart J* 2020;**41**:1401–1410. https://doi.org/10.1093/eurheartj/ehz570
117. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation* 2004;**110**:1879–1884. https://doi.org/10.1161/01.CIR.0000143375.93288.82
118. Sadjadieh G, Jabbari R, Risgaard B, Olesen MS, Haunsø S, Tfelt-Hansen J, *et al.* Nationwide (Denmark) study of symptoms preceding sudden death due to arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2014;**113**:1250–1254. https://doi.org/10.1016/j.amjcard.2013.12.038
119. Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M, *et al.* Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. *Circulation* 2010;**122**:1144–1152. https://doi.org/10.1161/CIRCULATIONAHA.109.913871
120. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, *et al.* A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2019;**40**:1850–1858. https://doi.org/10.1093/eurheartj/ehz103
121. Choudhary N, Tompkins C, Polonsky B, McNitt S, Calkins H, Mark Estes NA, *et al.* Clinical presentation and outcomes by sex in arrhythmogenic right ventricular cardiomyopathy: Findings from the North American ARVC Registry. *J Cardiovasc Electrophysiol* 2016;**27**:555–562. https://doi.org/10.1111/jce.12947
122. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2017;**136**:2068–2082. https://doi.org/10.1161/CIRCULATIONAHA.117.030792
123. Ruwald AC, Marcus F, Estes NA 3rd, Link M, McNitt S, Polonsky B, *et al.* Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: Results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2015;**36**:1735–1743. https://doi.org/10.1093/eurheartj/ehv110
124. Milting H, Klauke B, Christensen AH, Müsebeck J, Walhorn V, Grannemann S, *et al.* The TMEM43 Newfoundland mutation p.S358L causing ARVC-5 was imported from Europe and increases the stiffness of the cell nucleus. *Eur Heart J* 2015;**36**:872–881. https://doi.org/10.1093/eurheartj/ehu077
125. Groeneweg JA, Bhonsale A, James CA, te Riele AS, Dooijes D, Tichnell C, *et al.* Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circ Cardiovasc Genet* 2015;**8**:437–446. https://doi.org/10.1161/CIRCGENETICS.114.001003
126. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JD, *et al.* Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J* 2015;**36**:847–855. https://doi.org/10.1093/eurheartj/ehu509
127. Bhonsale A, James CA, Tichnell C, Murray B, Gagarin D, Philips B, *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. *J Am Coll Cardiol* 2011;**58**:1485–1496. https://doi.org/10.1016/j.jacc.2011.06.043

128. Link MS, Laidlaw D, Polonsky B, Zareba W, McNitt S, Gear K, *et al.* Ventricular arrhythmias in the North American multidisciplinary study of ARVC: Predictors, characteristics, and treatment. *J Am Coll Cardiol* 2014;**64**:119–125. https://doi.org/10.1016/j.jacc.2014.04.035
129. Orgeron GM, James CA, Te Riele A, Tichnell C, Murray B, Bhonsale A, *et al.* Implantable cardioverter-defibrillator therapy in arrhythmogenic right ventricular dysplasia/cardiomyopathy: Predictors of appropriate therapy, outcomes, and complications. *J Am Heart Assoc* 2017;**6**:e006242. https://doi.org/10.1161/JAHA.117.006242
130. Lie ØH, Rootwelt-Norberg C, Dejgaard LA, Leren IS, Stokke MK, Edvardsen T, *et al.* Prediction of life-threatening ventricular arrhythmia in patients with arrhythmogenic cardiomyopathy: A primary prevention cohort study. *JACC Cardiovasc Imaging* 2018;**11**:1377–1386. https://doi.org/10.1016/j.jcmg.2018.05.017
131. Aquaro GD, De Luca A, Cappelletto C, Raimondi F, Bianco F, Botto N, *et al.* Prognostic value of magnetic resonance phenotype in patients with arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol* 2020;**75**:2753–2765. https://doi.org/10.1016/j.jacc.2020.04.023
132. Corrado D, Wichter T, Link MS, Hauer RN, Marchlinski FE, Anastasakis A, *et al.* Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: An international task force consensus statement. *Circulation* 2015;**132**:441–453. https://doi.org/10.1161/CIRCULATIONAHA.115.017944
133. Cadrin-Tourigny J, Bosman LP, Wang W, Tadros R, Bhonsale A, Bourfiss M, *et al.* Sudden cardiac death prediction in arrhythmogenic right ventricular cardiomyopathy: A multinational collaboration. *Circ Arrhythm Electrophysiol* 2021;**14**:e008509. https://doi.org/10.1161/CIRCEP.120.008509
134. Casella M, Gasperetti A, Gaetano F, Busana M, Sommariva E, Catto V, *et al.* Long-term follow-up analysis of a highly characterized arrhythmogenic cardiomyopathy cohort with classical and non-classical phenotypes – A real-world assessment of a novel prediction model: Does the subtype really matter. *Europace* 2020;**22**:797–805. https://doi.org/10.1093/europace/euz352
135. Ermakov S, Gerstenfeld EP, Svetlichnaya Y, Scheinman MM. Use of flecainide in combination antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm* 2017;**14**:564–569. https://doi.org/10.1016/j.hrthm.2016.12.010
136. Cappelletto C, Gregorio C, Barbati G, Romani S, De Luca A, Merlo M, *et al.* Antiarrhythmic therapy and risk of cumulative ventricular arrhythmias in arrhythmogenic right ventricle cardiomyopathy. *Int J Cardiol* 2021;**334**:58–64. https://doi.org/10.1016/j.ijcard.2021.04.069
137. Assis FR, Tandri H. Epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy. *Card Electrophysiol Clin* 2020;**12**:329–343. https://doi.org/10.1016/j.ccep.2020.05.005