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Sudden Cardiac Death

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1. Introduction

Sudden cardiac death (SCD) is a major cause of death in the USA and accounts for almost half of all cardiovascular deaths. The estimated annual incidence of SCD in the USA stands at 300,000 to 350,000. A significant fraction of the patients who die from SCD have underlying cardiovascular pathology, most commonly some form of cardiomyopathy but, often the disease remains unrecognized presenting with SCD as the first event. Ischemic heart disease is overwhelmingly the commonest cause of SCD but other forms of cardiomyopathy become more important cause of SCD in younger population. Although the patients with cardiomyopathy account for a small fraction of population burden of SCD, a subset of these patients are at high risk and this rationalizes aggressive preventive strategy in them (figure 1). Lower prevalence of ischemic heart disease in younger population makes other forms of cardiomyopathy more important in that population. Moreover, the relative contribution of SCD in the population has changed as the epidemiology, natural course and outcomes of lifestyle related cardiovascular diseases, particularly ischemic heart disease, have changed. In this chapter we will review sudden cardiac death in patients with cardiomyopathies focusing on epidemiology and risk stratification of SCD, and approaches for primary and secondary prevention strategies in them.

2. Sudden cardiac death and various forms of cardiomyopathy

Most cardiomyopathies with primary myocardial pathology predispose to sudden cardiac death. These include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), left ventricular noncompaction and arrhythmogenic right ventricular cardiomyopathy (ARVC). Apart from the primary pathologies involving the myocardium, various other conditions can affect the myocardium secondarily due to myocardial stress, ischemia and

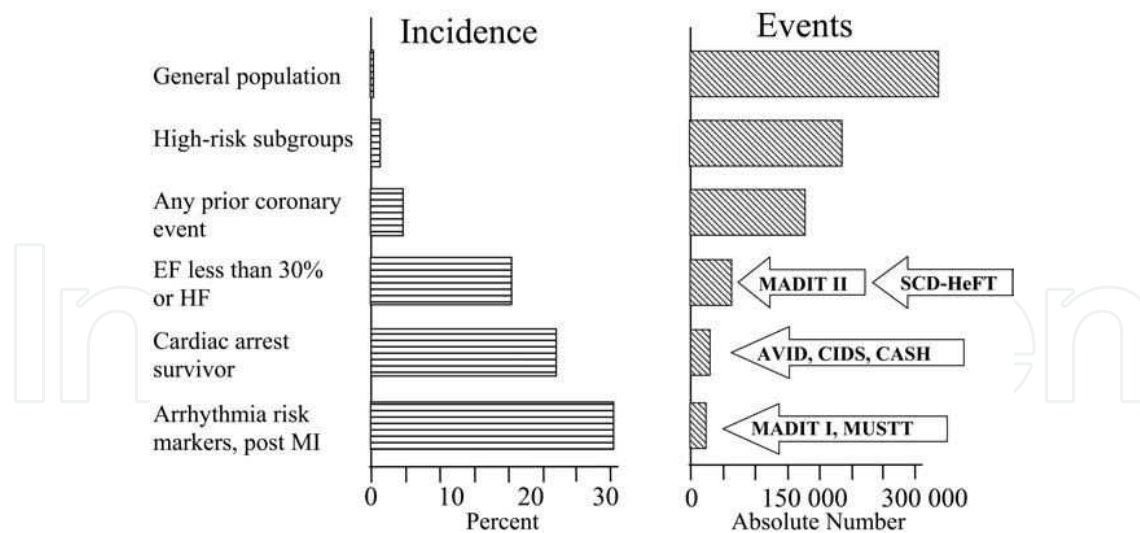


Figure 1. Absolute numbers of events and event rates of SCD in the general population and in specific subpopulations over 1 y. General population refers to unselected population age greater than or equal to 35 y, and high-risk subgroups to those with multiple risk factors for a first coronary event. Clinical trials that include specific subpopulations of patients are shown in the right side of the figure. AVID _ Antiarrhythmics Versus Implantable Defibrillators; CASH _ Cardiac Arrest Study Hamburg; CIDS _ Canadian Implantable Defibrillator Study; EF _ ejection fraction; HF _ heart failure; MADIT _ Multicenter Automatic Defibrillator Implantation Trial; MI _ myocardial infarction; MUSTT _ Multicenter UnSustained Tachycardia Trial; SCD-HeFT _ Sudden Cardiac Death in Heart Failure Trial. (Adapted with permission from reference 165)

infiltration. These conditions though not strictly classifiable as cardiomyopathies, but are important and common causes of SCD in the setting of myocardial dysfunction. They include ischemic heart disease, hypertension, valvular heart disease, and myocardial involvement with conditions like sarcoidosis, amyloidosis.

3. Etiopathogenesis and pathophysiology of sudden cardiac death

The commonest mechanism of SCD is a ventricular arrhythmia, most often ventricular tachycardia leading to ventricular fibrillation. This accounts for 75-80% of all SCDs; the remainder are the result of bradyarrhythmias. [1] Bradyarrhythmias including high grade AV block and sinus node dysfunction may potentially be a mechanism of sudden death in cardiomyopathies. However, assessing the exact electrophysiological mechanism of sudden death may be complex since ventricular fibrillation may arise as an aftermath of a bradyarrhythmia. Furthermore patients having suffered a VF arrest may be found to be in asystole (the end stage of all arrhythmic sudden death) when first coming to medical attention, so both mechanisms may be involved either as an initiator or as perpetuator in the event of sudden death. In the Implanted Cardioverter Defibrillator (ICD) era with aborted sudden deaths due to ICD shocks, bradyarrhythmic mechanisms of sudden death may be masked effectively by back up bradycardia pacing by the ICDs.

Ventricular arrhythmias associated with cardiomyopathies result from primary electrical defects inherent to the cardiomyopathy and activation of the neuro-humoral system in the

body as a compensatory hemodynamic mechanism. The efficacy of neuro-humoral blockers like beta-blocker and renin-angiotensin-aldosterone axis blockers in effectively reducing the risk of sudden cardiac death in cardiomyopathy, and relation of the risk of sudden cardiac death to degree of hemodynamic jeopardy with cardiomyopathy suggest the latter mechanism. In the following sections we will discuss the current knowledge of mechanisms of sudden death in various forms of cardiomyopathies.

3.1. Ischemic cardiomyopathy

Ischemic cardiomyopathy is by far the most common cardiomyopathy leading to SCD. Commonest cause of SCD in these patients is ventricular tachyarrhythmia. Beyond the early post-MI period, when recurrent MI and associated complications (mechanical and arrhythmic) are more likely, almost three-fourth of patient deaths among those with prior MI (more than three months old) and LV dysfunction are sudden and presumably arrhythmic, most likely due to ventricular arrhythmias. [2] Susceptibility to ventricular arrhythmia in these patients has multiple mechanisms. Scar resulting from myocardial infarction provides substrate for reentrant ventricular tachycardia. Re-entry circuits involve areas of residual viable relatively slowly conducting myocardial tissue inside the scars. These tracks of slowly conducting myocardial tissue inside a scar, called isthmus, connecting two healthy or relatively healthy areas form a full circuit for re-entrant arrhythmia. Patients with larger myocardial scar are more likely to have reentrant circuit. [3] Moreover, larger scars also lead to more ventricular remodeling and LV dysfunction, leading to activation of compensatory neuro-humoral factors in the setting of left ventricular dysfunction and heart failure. These factors lead to changes in repolarization and conduction properties of myocardial cells and abnormalities in intracellular calcium homeostasis which are potentially arrhythmogenic by promoting triggered activity and facilitating reentry. [4] Moreover, patients with ischemic cardiomyopathy have areas of ischemic myocardium which predispose to the arrhythmia by changes in the myocyte automaticity, excitability and refractoriness leading to dispersion of repolarization. The border zones of the myocardial scars are important substrates for arrhythmia as they are composed of fibrotic tissue as well as viable myocardium which are often ischemic. Heterogeneity of infarct tissue as assessed by magnetic resonance imaging has been shown to predispose to arrhythmia. Additionally, myocardial infarction leads to disturbances in the autonomic innervation of the myocardium in the area surrounding the post-infarct scar which makes the surrounding myocardium more susceptible to arrhythmia due to prolongation of refractory periods in the denervated myocardium. [5] Apart from these, a patient with ischemic heart disease is predisposed to SCD due to acute coronary syndrome.

3.2. Hypertrophic cardiomyopathy

Studies of HCM patients with ICDs have suggested that ventricular arrhythmias are the major causes of SCD in this group of patients, [6], [7] although availability of back up pacing for bradyarrhythmia precludes the ability of an ICD study to exclude the possibility of a bradyarrhythmic etiology. [6] Bradyarrhythmias are, however, reported rarely in HCM so this seems an unlikely possibility. Multiple pathologic, molecular and physiologic mechanisms could

contribute to the causation of ventricular arrhythmias in patients with HCM. HCM is characterized pathologically by hypertrophied myocardium along with increased fibrosis and myocardial disarray (figure 2). [8-10] Apart from these histopathological features that predispose to ventricular arrhythmias, there are also abnormalities of calcium handling at molecular level. Cardiomyocytes in patients with systolic and diastolic heart failure have impaired ability of calcium cycling due to altered expression and phosphorylation of sarcoplasmic calcium ATPase 2 (SERCA 2) and ryanodine receptor 2, key proteins involved in intracellular calcium handling. [11], [12] Perturbed calcium fluxes have also been seen in HCM. [13], [14] Inefficient energy utilization in some of the HCM associated mutations of troponin lead to insufficient energy for the cardiomyocytes to maintain cellular calcium hemostasis, leading to increased risk of arrhythmia especially during exercise. [15], [16] Microvascular dysfunction with myocardial ischemia along with increased energy needs is another important factor contributing to the arrhythmogenicity in HCM. [17], [18] Left ventricular outflow tract obstruction (LVOTO) and altered systolic blood pressure response to exercise may mechanistically predispose to SCD by electromechanical dissociation and demand ischemia. Hence arrhythmogenic substrates in HCM potentially include altered cellular handling of calcium, with myocardial ischemia, patchy myocardial fibrosis and hypertrophy maintaining the arrhythmias. Moreover, presence of systolic or diastolic heart failure itself may contribute to the risk by neuro-humoral activation. Apart from these intrinsic predispositions to arrhythmogenesis in the natural course of disease, there has been recent concern of iatrogenic arrhythmias in patients undergoing alcohol septal ablation, which leaves a large ventricular septal scar predisposing to scar-related re-entrant ventricular arrhythmias. [19]-[21]

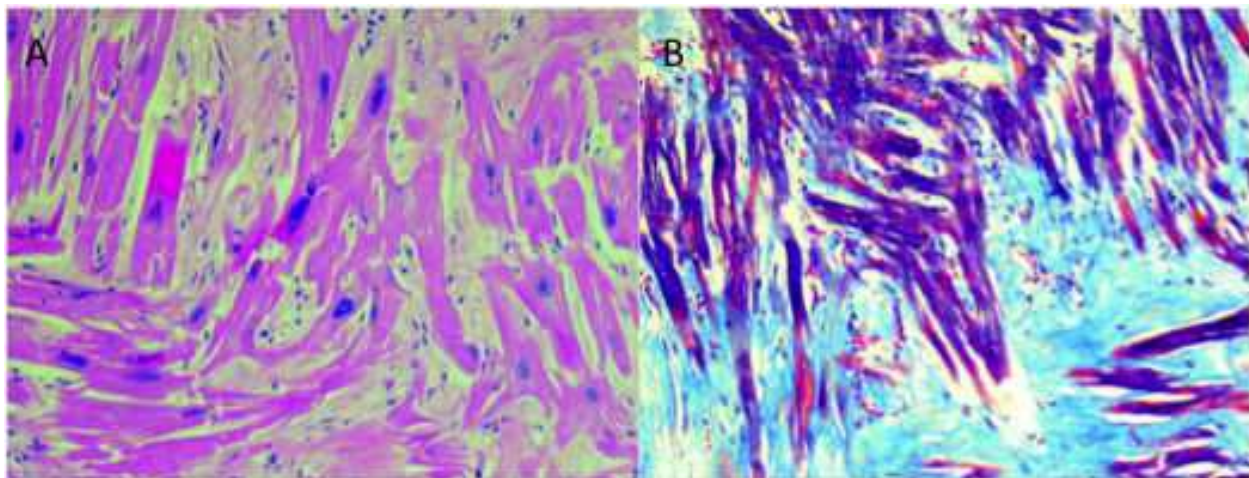


Figure 2. Photomicrographs showing hematoxyline and eosin-stained section with florid myocyte disarray and fibrosis in familial HCM. Disarray is characterized by hypertrophic myocytes with enlarged and pleomorphic nuclei aligned at odd angles to one another (panel A). Photomicrograph showing Masson's trichrome stain with marked increase in interstitial fibrosis, a hallmark of HCM (panel B). **Adapted with permission from chapter 'Cardiomyopathy' by Sian Hughes from the book 'Cardiac Pathology: A Guide to Current Practice' eds' S. Kim Suvarna ISBN: 978-1-4471-2406-1 (Print) 978-1-4471-2407-8 (Online) (Springer).**

3.3. Arrhythmogenic cardiomyopathy

The hallmark of arrhythmogenic cardiomyopathy (previously called arrhythmogenic right ventricular cardiomyopathy) is a defect in cell-cell adhesion caused by genetic defects most commonly affecting the desmosomal proteins. Such defects lead to myocyte loss with fibrofatty replacement of the myocardial tissue (figure 3), most commonly involving the right ventricle, with left ventricular and biventricular involvement less commonly. This provides a substrate for ventricular tachycardia from re-entry around the fibrous scar. [22] Reports of ventricular arrhythmia in subjects harboring the genes of arrhythmogenic cardiomyopathy even in the absence of detectable histopathological and MRI changes in the myocardium suggest an additional electrical substrate distinct from simple reentry involving perhaps intracellular signaling process or heterogeneity in conduction. Gap junction remodeling with paucity of gap junctions in the myocardial cells of affected patients may also provide a substrate for arrhythmia. [23]

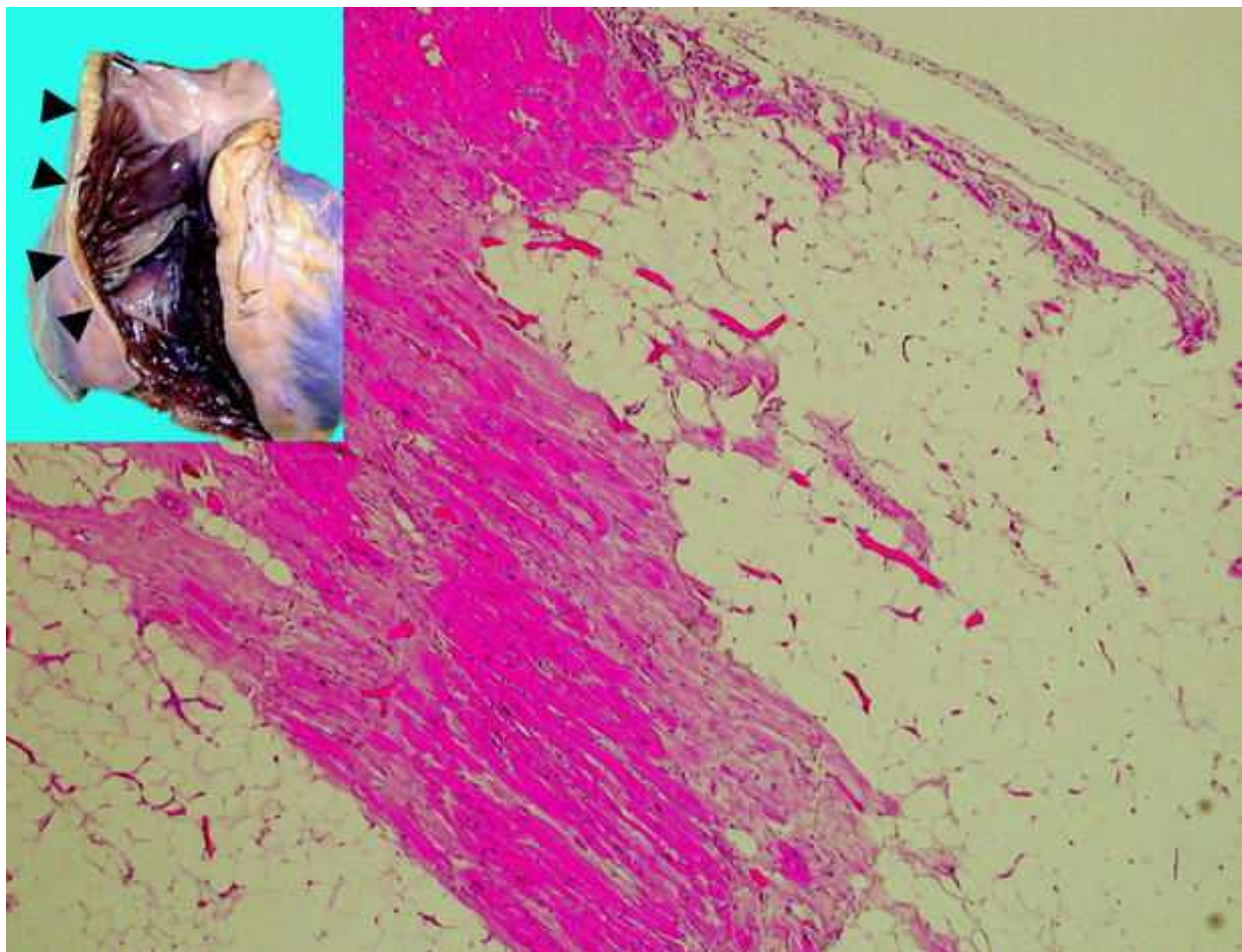


Figure 3. Fibroadipose infiltration of the right ventricle, seen in the inset macroscopically top right, arrowed. Histology shows the adipose and fibrous tissue replacement of the myocyte architecture (hematoxylin & eosin). **Adapted with**

permission from chapter 'Cardiomyopathy' by Sian Hughes from the book 'Cardiac Pathology: A Guide to Current Practice' eds' S. Kim Suvarna ISBN: 978-1-4471-2406-1 (Print) 978-1-4471-2407-8 (Online) (Springer).

3.4. Dilated cardiomyopathy

Dilated cardiomyopathy is characterized by loss of myocardial cells with interstitial, perivascular and replacement fibrosis, which provide an arrhythmogenic substrate (figure 4). [24], [25] Frequently the reentry circuits of these arrhythmias exit on the epicardial aspect of the myocardium, as distinct from ischemic cardiomyopathy where endocardial circuits are the rule. [25] This is related to the differences in the pathogenetic mechanism of scar formation in the two groups of patients, patients with ischemic cardiomyopathy having predisposition to endocardial scar due to subendocardial ischemia and acute coronary events, while patients with dilated cardiomyopathy having epicardial scar more often than ischemic cardiomyopathy. This also has implications on therapeutic approach as patients with nonischemic cardiomyopathy with VT frequently require epicardial approach for catheter ablation. [26] Arrhythmic events occurring in patients with idiopathic dilated cardiomyopathy are nonsustained and sustained VT and ventricular fibrillation in addition to isolated ventricular ectopy. [27], [28] Bundle branch reentry VT is relatively commoner form of VT in patients with dilated cardiomyopathy, constituting 6-11% of patients referred for catheter mapping of monomorphic VT. [26], [29] Spontaneous sustained VT is rare in DCM and this diagnosis should raise the suspicion of other types of cardiomyopathies that do commonly cause scar related ventricular arrhythmias, including sarcoidosis, Chagas disease and left dominant arrhythmogenic cardiomyopathy. Spontaneous sustained VTs are caused by scar-related reentry or bundle branch reentry. [25], [29] Neurohumoral activation, myocardial stretch secondary to mechanical overload and electrolyte disturbance all can contribute to arrhythmogenesis by a non-reentrant mechanism facilitating focal mechanisms of arrhythmogenesis like triggered activity and focal automaticity. [28]

3.5. Left Ventricular noncompaction

Left ventricular noncompaction is a recently recognized form of cardiomyopathy. Also referred to as left ventricular hypertrabeculation, LV myocardium in these patients shows increased trabeculation, unlike normal compact structure of the LV. Imaging with echocardiography or cardiac MRI, showing thick endocardial noncompact layer of myocardium and relatively thin epicardial compact myocardium, usually makes the diagnosis. Apart from heart failure and thromboembolic events, patients with ventricular noncompaction are known to be at an increased risk of sudden cardiac death due to ventricular arrhythmias. Life-threatening ventricular tachycardias are reported in almost one fifth of the patient. The arrhythmogenic substrate is in the form of subendocardial fibrosis due to microcirculatory dysfunction (figure 5). [30], [31]

3.6. Other cardiomyopathies

Sarcoidosis frequently involves the myocardium, causing infiltration and scarring. Although at least 25% of patients with sarcoidosis have cardiac involvement based on autopsy data, only 5% have cardiac symptoms. Patients with sarcoid cardiomyopathy are at an increased risk of

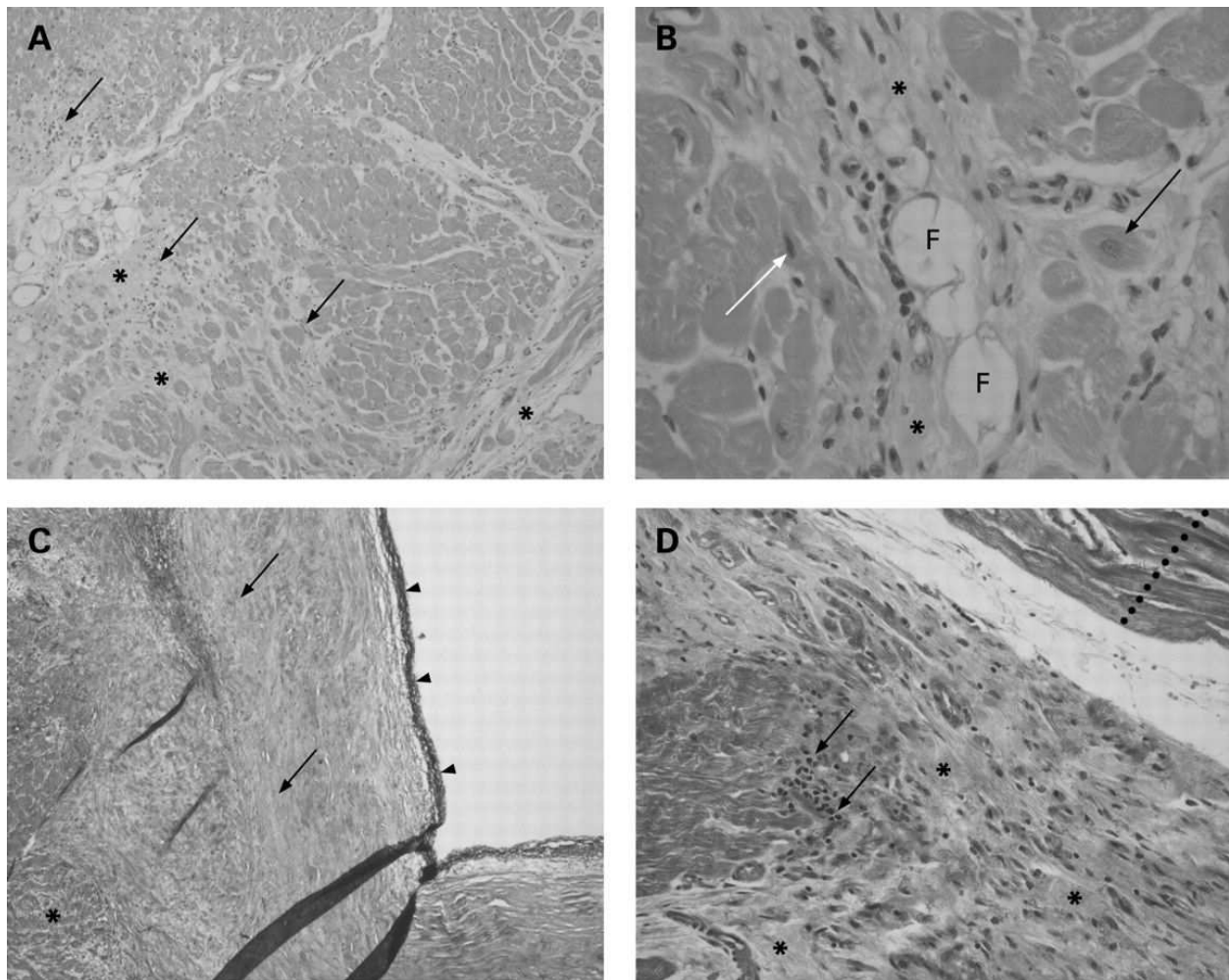


Figure 4. Photomicrographs of the myocardium from a 35-year-old female. (A) Shows evidence of myofibre hypertrophy, interstitial fibrosis (*) and areas of lymphocytic infiltration (arrows) consistent with resolving myocarditis (H&E). (B) While some myocytes are hypertrophied with enlarged nuclei (black arrow), others are thinned and elongated with nuclei that occupy almost the entire width of the myocyte (white arrow). Some myocytes appear “empty”; likely due to diminished numbers of myofibrils. Areas of interstitial fibrosis (*) and fat infiltration (F) can also be seen (H&E). (C) Photomicrograph showing evidence of interstitial fibrosis (*), subendocardial fibrosis (arrows) and endocardial fibroelastic changes (arrowheads) (H&E). (D) Microphotograph of myocardium showing degenerative changes in the left bundle (dotted line). These changes may appear as a bundle branch block on ECG. Areas of interstitial fibrosis (*) and lymphocytic infiltration (arrows) are also seen (elastic trichrome stain). **Adapted with permission from Luk et al, Dilated cardiomyopathy : a review. J Clin Pathol 2009;62:219-225.**

developing a conduction system abnormality due to involvement of basal part of the inter-ventricular septum and this may result in complete heart block [32], [33] and potentially sudden cardiac death. Ventricular arrhythmia is another mechanism of sudden cardiac death in patients with cardiac sarcoidosis. Resolving inflammation and resulting scarring of the myocardium provides substrate for reentrant ventricular arrhythmias. [34], [35]

Cardiac amyloid infiltration is another disorder associated with increased risk of sudden cardiac death. Amyloid infiltration with perivascular fibrosis and small vessel ischemia [36] is instrumental in pathology of cardiac conduction system and myocardium. These pathological changes lead to the electrophysiological abnormalities responsible for sudden cardiac

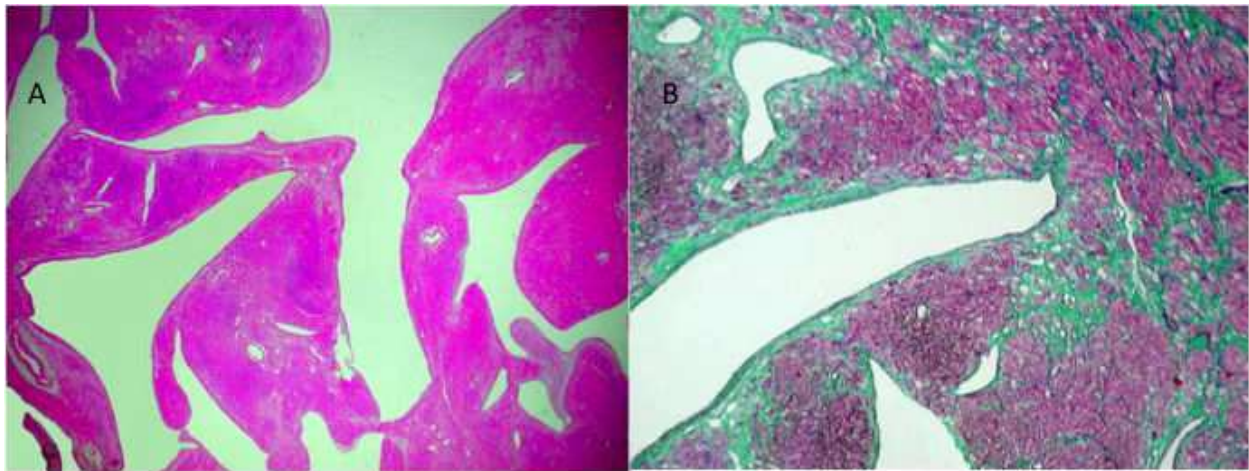


Figure 5. Photomicrographs of myocardium from a patient with LV noncompaction. Panel A shows low-power hematoxylin- and eosin-stained photograph from noncompacted layer showing 'fingerlike' projections. Panel B has a photomicrograph with Masson's trichrome stain showing prominent endocardial and subendocardial fibrosis, which is a feature of this disease due to abnormal myocardial microperfusion. **Adapted from chapter 'Cardiomyopathy' by Sian Hughes from the book 'Cardiac Pathology: A Guide to Current Practice' eds' S. Kim Suvarna ISBN: 978-1-4471-2406-1 (Print) 978-1-4471-2407-8 (Online) (Springer).**

death due to bradyarrhythmia or ventricular tachyarrhythmia. [37] Frequently the cause of sudden death in these patients is pulseless electrical activity, presumably resulting from the severe diastolic dysfunction associated with amyloidosis. [38]

Inherited muscular dystrophies like Duchenne and Becker muscular dystrophies have skeletal and cardiac muscle involvement and cardiac pathology essentially manifests as dilated cardiomyopathy with associated heart failure and risk of sudden cardiac death. However, muscular dystrophies like Emery-Dreifuss (X-linked and autosomal variants), limb girdle muscular dystrophy type 1B, entity of DCM with conduction system disease (associated with lamin A/C mutations) and myotonic dystrophy are associated with high risk of sudden cardiac death. In these conditions sudden cardiac death was traditionally thought to be primarily due to conduction system disease and bradyarrhythmia. However, after routine implantation of pacemakers, it has been recognized that ventricular arrhythmias also contribute to sudden cardiac death in these patients. These conditions are associated with cardiomyopathy, with LV dysfunction as a late feature in the natural course of disease; sudden cardiac death is an early feature of cardiac involvement. The molecular pathogenesis of cardiac arrhythmias and conduction system disease in these patients is an area of active research. [39]

4. Risk of sudden cardiac death in cardiomyopathy: Epidemiology and risk stratification

The epidemiologic risk of sudden cardiac death in cardiomyopathy is often difficult to assess because it is frequently impossible to determine the size of the population at risk. Determination of risk is skewed by referral bias. The risk of sudden death has been studied with these

limitations in several groups of patients, most notably in those with ICM but also in hypertrophic cardiomyopathy and arrhythmogenic cardiomyopathy. Attempts to identify features predicting higher risk of sudden cardiac death have helped in management decisions. In this section we will discuss available knowledge about risk of sudden death and risk stratification in patients with cardiomyopathy.

Hypertrophic cardiomyopathy	Dilated cardiomyopathy
<p>Major risk factors</p> <ul style="list-style-type: none"> · Prior cardiac arrest · Spontaneous sustained VT · Family history of 1 or more instances of SCD · Nonsustained VT (≥ 3 consecutive beats at ≥ 120 bpm) · Failure of systolic BP to rise by ≥ 20 mm Hg during maximal upright exercise testing · Unexplained syncope · Maximum LV wall thickness ≥ 30 mm <p>Other risk factors</p> <ul style="list-style-type: none"> · Resting LV outflow tract obstruction · Microvascular ischemia · Diffuse late gadolinium enhancement on cardiovascular magnetic resonance · Paced electrogram fractionation analysis · Prior alcohol septal ablation · Burnt out disease · High-risk mutation 	<ul style="list-style-type: none"> · Prior cardiac arrest · Left Ventricular systolic function · History of syncope · Genetic factors · NYHA functional class · Prolongation of QRS · QT dynamicity · QRS fragmentation · Heart rate variability, heart rate turbulence and heart rate recovery, · Baroreflex sensitivity · T-wave alternans · Myocardial fibrosis: serum markers, cardiac MRI
<p>Arrhythmogenic right ventricular cardiomyopathy</p> <ul style="list-style-type: none"> · Prior cardiac arrest · History of syncope · RV dilatation/dysfunction · LV involvement · QRS dispersion · Right precordial QRS prolongation and late potentials on SAECD 	<p>Ischemic cardiomyopathy</p> <ul style="list-style-type: none"> · Prior cardiac arrest outside the setting of acute coronary syndrome · LV systolic function · NYHA functional class · QRS duration · QT interval prolongation · QT dispersion, · T-wave alternans · Abnormal SAECD · Heart rate variability, heart rate turbulence and heart rate recovery, · Baroreflex sensitivity

Table 1. Risk predictors for SCD in cardiomyopathies

4.1. Ischemic cardiomyopathy

Attempts at risk stratification for SCD initially included patient with history of myocardial infarction and LV systolic dysfunction emerged as the strongest predictor of overall mortality and SCD in them. [40]-[45] Many other potential risk factors have been studied, but LVEF remains the strongest and most widely used predictor of SCD risk. ICD trials for prevention of SCD have established the role of LV systolic function as the most important risk predictor. Other important predictors of SCD in these patients include electrocardiographic parameters, functional class, inducibility of ventricular arrhythmia with programmed ventricular stimulation, autonomic and neuro-humoral predictors and disturbances in autonomic innervation of the myocardium.

1. *LV systolic function* emerged from studies in post-MI patients as a predictor of SCD. An analysis of 20 studies found the relative risk of a major arrhythmic event in patients with $LVEF \leq 30\%$ to 40% to be 4.3. [46] The Second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) and the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) clearly demonstrated the benefit of ICD implantation in patients with LVEF less than 30% or 35% respectively in preventing sudden death and reducing absolute mortality in patients with history of myocardial infarction. [47], [48]
2. *Functional class* is a surrogate of severity of heart failure and heart failure severity predisposes to arrhythmogenesis by neuro-humoral mechanisms and homeostatic and hemodynamic changes. NYHA class has been used as criterion to enroll patients in the ICD trials and some of these studies have found its predictive value. Subgroup analysis of SCD-HeFT enrolling patients with congestive heart failure with either ischemic or nonischemic cardiomyopathy showed that patients with NYHA class III did not appear to benefit as opposed to patients with NYHA class II. [48] On the other hand in MADIT-II patients, there were no significant differences in the outcomes based on NYHA class. [47] NYHA functional class III was found to be the strongest independent predictor of ICD therapy in the Trigger Of Ventricular Arrhythmia (TOVA) trial. [49]
3. *Programmed ventricular stimulation* with inducible VT/VF has been recognized as a predictor of sudden cardiac death in patients with history of myocardial infarction. MADIT-I study which included patients with inducible VT/VF and $LVEF \leq 35\%$ showed a 26% absolute reduction in mortality at 27 months follow-up. [50] The reduction in mortality was much lower at 6-7% absolute reduction in mortality in patients with MADIT-II trial which enrolled patients with $LVEF \leq 30\%$ and in a mixed population of ischemic and nonischemic cardiomyopathy patients in SCD-HeFT enrolling patients with $LVEF \leq 35\%$ without electrophysiological assessment of inducibility. [47], [48] The Multicenter UnSustained Tachycardia Trial (MUSTT), enrolling patients with $LVEF \leq 40\%$ and inducible VT on invasive assessment showed similarly high absolute reduction in mortality of 31% at five years of follow up. [51]
4. *Ventricular ectopy and NSVT* has been shown to increase the risk of sudden cardiac death in patients with history of MI in multiple studies. In the early observational studies from

1970s and 1980s, VPBs (≥ 10 per hour) and NSVT in post-MI patients showed increased risk of overall mortality. [40], [42], [52], [53] Similar effect of ventricular ectopy and NSVT in post-MI patients has also been seen in the era of thrombolytic therapy for acute MI. [45], [54]-[57] GISSI-2 trial showed a mortality of 5.5% at six months after MI in patients with more than 10 VPBs per hour compared to 2% in those with less frequent VPBs. [57] Positive predictive value of VPBs in predicting cardiac arrhythmic events is in the range of 5% to 15% with negative predictive value of in the range of 90%. [58] However, when combined with LV ejection fraction, ventricular ectopy becomes a stronger risk predictor of SCD in post-MI patients. In European Myocardial Infarction Amiodarone Trial (EMIAT), post-MI patients with LVEF $\leq 40\%$ had higher mortality in the presence of frequent or complex arrhythmias on ambulatory ECG than in their absence (20% vs. 10%). [59] Moreover, MADIT-I and MUSTT enrolled patients based on the presence of NSVT and showed benefit in terms of reduction in all-cause mortality and SCD with ICD, all these patients had to have inducible ventricular arrhythmia for being enrolled into the study. [50], [51]

5. *Electrocardiographic parameters* have been studied in multiple studies and can be divided into parameters assessing ventricular conduction abnormality and parameters of ventricular repolarization abnormality. Parameters of conduction abnormality including QRS duration, abnormalities on signal averaged ECG, and fractionation of QRS have been studied in many studies. Parameters of repolarization abnormality including QT interval prolongation, QT dispersion, T wave variance, QT dynamics, QT/RR slope and T-wave alternans have all been studied in many studies. Each of these parameters confer a small risk of sudden cardiac death individually. [60]-[62]
6. *Parameters of autonomic function* include heart rate variability, heart rate turbulence, baroreceptor sensitivity and deceleration capacity. These again have been found to increase the risk of sudden death in patients history of myocardial infarction with in many small studies. [60]-[62]
7. *Myocardial scar* is instrumental in the pathogenesis of ventricular tachycardia by providing the substrate for reentry circuit. Myocardial scar area assessed by cardiac MRI has been demonstrated to be a predictor of inducible VT on electrophysiological study. [3] Moreover, heterogeneity of scar in the border zone of infarct can be assessed by MRI and has been shown to be a predictor of inducible and spontaneous ventricular arrhythmias. [63], [64]
8. *Cardiac autonomic denervation* has been suggested a potential risk for arrhythmogenesis in post-MI patients. Although denervation of peri-infarct tissue was found to be a risk factor for inducible ventricular arrhythmia in animal model, [65] it failed to show any value in a small clinical study. [66] However, a study in a population of heart failure patients including both ischemic and nonischemic cardiomyopathy, showed increased risk of ventricular arrhythmia with disturbances in myocardial innervation assessed by mIBG scintigraphy. [67]

9. *Combinations of risk factors:* As individual risk factor are not strong enough to predict SCD and probably in isolation do not justify the use of ICD therapy to prevent SCD with the current level of evidence, there has been an attempt to combine multiple risk factors to create a model to enhance the predictability of SCD. Although there are multiple small studies combining various risk factors to achieve the goal of refining the risk stratification strategy, there is a need to assess these risk models in a prospective manner. [61], [68]

Study	Patient population	LVEF of enrolled patients (%)		All-cause mortality (%)		Risk reduction (%)	
		Relative	Absolute				
Control	ICD						
<i>Primary prevention ICD trials</i>							
AVID	VFib, VT with syncope, VT with EF $\leq 40\%$	32	25	18	27	7	
CIDS	VFib, out-of-hospital cardiac arrest due to VFib or VT, VT with syncope, VT with symptoms and EF $\leq 35\%$, unmonitored syncope with subsequent spontaneous or induced VT	34	21	15	30	6	
CASH	VFib, VT	46	44	36	23	8	
<i>Primary prevention ICD trials</i>							
MADIT	Prior MI, EF $\leq 35\%$, N-S VT, inducible VT non-suppressible with IV procainamide	26	32	13	59	19	
CABG Patch	Coronary bypass surgery, EF $< 36\%$, SAECG (+)	27	18	18	-	-	
MUSTT	CAD (prior MI $\sim 95\%$), EF $\leq 40\%$, N-S VT, inducible VT	30	55	24	58	31	
MADIT II	Prior MI (> 1 month), EF $\leq 30\%$	23	22	16	28	6	
DEFINITE	Nonischemic CM, Hx HF, EF $\leq 35\%$, ≥ 10 PVCs/hr or N-S VT	21	14	8	44	6	
DINAMIT	Recent MI (6-40 days), EF $\leq 35\%$, abnormal HRV or mean 24-hr heart rate > 80 /min	28	17	19	-	-	
SCD-HeFT	Class II-III CHF, EF $\leq 35\%$	25	36	29	23	7	

Table 2. ICD trials

4.2. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is frequently complicated by sudden cardiac death, and SCD in, for example, athletes is frequently caused by HCM. This being said, early estimates of the gravity of the prognosis of HCM were probably driven by referral bias of difficult cases to specialist centers, and studies of more inclusive cohorts of patients indicate a much more favorable prognosis. [69] A study by Maron et al analyzing a cohort of 774 non-referral-based HCM patients showed an incidence of SCD of 0.7% per year. [70] They showed that although SCDs occur across the age groups in patients with HCM, there are two peaks of SCD risk during life, one in the early childhood and the other later in older age group in seventh and eighth decades of life.

Several risk factors associated with SCD in HCM have been identified and it is important to recognize this high-risk subset of patients for management strategies and prognostication.

1. *History of syncope*: In patients with HCM syncope is an important predictor of SCD. This has been confirmed by multiple survival studies and a systematic review of 11 survival studies. [71] Five of these survival studies showed a significant association between history of syncope and SCD in these patients. [72]-[76] and in the systematic review the hazard ratio was 2.68 (95% CI 0.97-4.38) for SCD. This association is clinically important and a history of syncope in a HCM patient is worrisome and should prompt further intensive investigation.
2. *Non-sustained ventricular tachycardia (NSVT)* with ≥ 3 consecutive ventricular beats at a rate of 120 beats per minute lasting for < 30 seconds has been shown to be significantly associated with SCD in patients with HCM. [73], [77]-[79] The systematic study evaluating the risk of SCD with NSVT showed a hazard ratio of SCD of 2.89 (95%CI 2.2-3.6). [71] The risk of SCD associated with NSVT is lower in patients with older age (31-75 years), whereas younger patient (14-30 years of age) have more than a four-fold increased risk of SCD (HR 4.35, 95% CI 1.54-12.28). [77]
3. *Severe left ventricular hypertrophy (LVH)* has been found to be a predictor of sudden cardiac death in multiple studies. [8], [72], [77], [80]-[82] In a recent systematic review the risk of SCD was found to be three-fold (hazard ratio 3.1, 95%CI 1.81-4.4) despite variable definitions. [71] Although most of the studies used a cut off for maximum wall thickness of ≥ 30 mm, there has been concern about variability in measurement across the studies and lack of data about pattern of LVH. One study used Wigle scores, a semi-quantitative scoring system described earlier, [83] for LVH severity and showed increased risk of SCD with increasing Wigle score. [81]
4. *Family history of SCD and Genetic markers*: Familial association of SCD has been described in patients with HCM in early studies. [84]-[86] A systematic review of survival studies showed an increased risk of SCD in patients with family history of SCD with hazard ratio of 1.27(95%CI 1.16-1.38) [71] Family members tend to share genetic abnormality, and certain specific genetic mutations have been associated with higher risk of SCD. For example, troponin T mutations have been reported to have association with high risk of SCD, often disproportionate to the other phenotypic expression. [87]

5. *Left ventricular outflow tract obstruction (LVOTO)*: The severity of the dynamic LVOTO is associated with an increased risk of SCD. The mechanism of this could be reduction of cardiac output and electromechanical dissociation, but myocardial ischemia induced by increased ventricular stress is also of possible etiologic significance. An instantaneous pressure gradient of 50 mmHg across the LVOT is considered to be clinically significant. Five studies have shown significant association between LVOTO and SCD in patients with HCM. [73], [76], [79], [88]
6. *Systolic blood pressure response to exercise* is altered in many patients with HCM probably due to decreased systemic vascular resistance. [89] Sadoul et al demonstrated in 161 HCM patients ≤ 40 years old that failure of systolic blood pressure to rise ≥ 20 mmHg during exercise or a fall of >20 from the peak systolic blood pressure was associated with an increased risk of SCD (15% vs 3%, $p < 0.009$). [90] However, analysis of multiple survival studies with data from a wider age range did not confirm this association (hazard ratio 1.23, 95%CI 0.64-1.96) [71] but four of these studies did show abnormal systolic blood pressure response to be a risk factor for SCD in subjects ≤ 40 years old. [73], [76], [77], [80]
7. *Other factors: Atrial fibrillation and left atrial size* may reflect the risk of SCD as they reflect the severity of left ventricular pathology. [74], [91] *NYHA functional class* is also a function of diastolic dysfunction, myocardial ischemia, LVOTO, atrial arrhythmias and adverse remodeling, and potentially can be associated with SCD, but studies reporting survival analysis for SCD did not report any significant association. *Late gadolinium enhancement* on MRI, which is suggestive of presence of extracellular myocardial collagen deposition and a potential substrate for ventricular arrhythmias, was not associated with SCD in a recent study, although it was associated with cardiovascular morbidity and mortality. [10] *Increased fractionation* of the paced right ventricular electrogram at invasive electrophysiological study has been found to be associated with SCD in patients with HCM and this is presumably a reflection of myofibrillar disarray. HCM patients with *LV systolic dysfunction* should be considered at a higher risk of SCD similar to other causes of LV systolic dysfunction. Age of the patient modifies the risk of SCD in patients with HCM as suggested by multiple studies with higher risk in adolescence and early adulthood. The survival study by Spirito et al showed a significant reduction in SCD risk with increasing age, however, this study did not include other established risk factors in multivariate analysis.[74]

4.3. Arrhythmogenic cardiomyopathy

Ventricular arrhythmia, principally VF is the mode of SCD in patients with arrhythmogenic cardiomyopathy. The absolute risk of SCD in a patient with ARVC has been reported, although inconsistencies between different studies make it hard to establish the degree of risk. The annual risk of SCD in studies from the pre-ICD era in high-risk cohorts was in the range of 1-1.5%. [92]-[94] Sports activity increases the risk of SCD by five fold. [95] Although more recent follow-up studies of patients with ICDs have shown a higher annual rate of ICD intervention, of 5-8%, [96], [97] an ICD intervention may not be a good surrogate for SCD. A follow-up study of patients diagnosed on the basis of aggressive screening of the family members of the

probands showed much lower annual incidence of SCD at 0.08% per year. [98] This suggests a strong selection bias of high-risk patients in the previous follow-up studies and with current approach of aggressive screening of the family members of probands; the previous estimates of the degree of risk of SCD may not be applicable. Many studies have tried to establish parameters to predict the risk of sudden death.

1. *History of syncope* has been documented as a precursor of SCD in multiple studies. [93] In a study by Nava et al syncope was the only clinical variable predictive of SCD in probands, while none of the family members of the proband had history of syncope. [98] The Darwin II study and data from the Johns Hopkins arrhythmogenic cardiomyopathy clinic have evaluated the importance of history of syncope in patients receiving ICD. The multi-center Darwin II study showed that syncope is a strong predictor of life-saving device intervention in patients with ICD. In the Johns Hopkins cohort, although 75% of the patients with AC receiving appropriate ICD therapy did not have history of syncope, one half of patients with history of syncope prior to the implantation of ICD received appropriate ICD therapy (9%/year). A recent history of syncope was even stronger predictor of appropriate ICD therapy compared to remote history of syncope. [99]
2. *Prior history of hemodynamically unstable ventricular arrhythmia or cardiac arrest* is a strong predictor of SCD. A history of arrhythmic cardiac arrest or hemodynamically unstable VT, but not a history of hemodynamically stable VT, was found to be independent predictor of life-saving ICD therapy in a study by Corrado et al. [96] In another study by Canu et al with retrospective analysis of 22 patients, previous history of resuscitated VF was present in two out of three patients who died suddenly. [100]
3. *Electrocardiographic parameters* including QRS dispersion, right precordial QRS prolongation and late potentials on signal-averaged ECG (SAECG) have been found to be associated with risk of SCD. Turrini et al demonstrated longer QRS duration in right precordial leads in patients with SCD as compared to those without. [101] QRS dispersion of >40 msec was strong independent predictor of SCD in this study. Late potential on SAECG have not been found to predict arrhythmic risk in these patients. [102]-[104] Although in the study by Turrini et al late potentials were univariate predictors of sustained VT, decreased RV ejection fraction remained the only independent predictor in multivariate analysis. [104]
4. *RV dilatation/dysfunction and LV involvement* are important predictors of poor outcome [105] and SCD [106] in arrhythmogenic cardiomyopathy. RV dysfunction has been associated with increased risk of ICD discharges and sustained VT. [97], [104], [107] It is not clear as yet if LV involvement detected by tissue characterization without LV dilatation or dysfunction increases the risk of SCD.
5. *Other factors:* Most of the *genetic variants* of arrhythmogenic cardiomyopathy have similar risks of SCD. However a very malignant genetic variant with TMEM43 gene mutation significantly increases the risk of SCD. [108] Studies evaluating the significance of *programmed ventricular stimulation* as a predictor of SCD in the patients with arrhythmogenic cardiomyopathy has shown mixed results. The DARVIN studies and the study by

Wichter et al did not show any significant predictive value of programmed ventricular stimulation in predicting ICD discharges. [96], [97], [109] Although the Johns Hopkins study did show some relationship between programmed stimulation of ventricular arrhythmia and later ICD shocks, the association did not confer good positive and negative predictive values (65% and 75% respectively). [99] Hence, withholding ICD therapy on the basis of negative EP study should not be recommended and other parameters for risk stratification should be taken into consideration to make a decision for ICD implantation.

4.4. Dilated cardiomyopathy

SCD in patients with dilated cardiomyopathy is one of the major causes of mortality, constituting nearly one-third of all deaths. Left ventricular systolic function as determined by LVEF and NYHA functional class have become the most extensively used variable to stratify risk of SCD in this group of patients. Other parameters including a history of syncope, genetic factors and programmed ventricular stimulation have been evaluated to stratify the risk of SCD in these patients, and these are summarized below.

1. *Left Ventricular systolic function* is associated with increased overall mortality and SCD in patients with nonischemic dilated cardiomyopathy. [110]-[112] This has been reaffirmed by the reduction in SCD seen with ICD implantation in patients with NIDCM with LV systolic dysfunction in DEFINITE and SCD-HeFT ICD trials. [48], [113]
2. *NYHA functional class* is important determinant of overall survival and SCD in patients with systolic heart failure. [114] However, with worsening NYHA functional class, non-sudden death becomes relatively more important in patients with heart failure compared to SCD. Patients with NYHA class III were significantly more likely to receive ICD therapy for ventricular arrhythmia even after adjusting for LVEF in TOVA study, however, there were very few patients with NYHA class IV in this study. [49] NYHA class IV patients, although at risk of arrhythmic death, are less likely to benefit from ICD due to competing risk of non-sudden heart failure death. Majority of patients in the major ICD trials (SCD-HeFT and DEFINITE) were class II and class III patients, and the reduction in SCD in these groups of patients is well established. [48], [113] However, NYHA class I patients were largely under-represented in majority of the ICD trials with the exception of DEFINITE study which had 21.6% patients in NYHA class I.
3. *History of syncope* increases the risk of SCD in patients with heart failure with dilated cardiomyopathy. In a SCD-HeFT sub-study patients with history of syncope had higher frequency of receiving appropriate ICD therapy compared to those without a history of syncope. Moreover, patients with history of syncope had similarly increased risk of mortality in ICD (HR: 1.54, 95% CI 1.04-2.27), amiodarone (HR: 1.33, 95% CI 0.91-1.93) and placebo (HR: 1.39, 95% CI 0.96-2.02) arms ($p=0.86$ for test of difference between the three arms).
4. *Genetic factors*: There has been a recent recognition of certain genetic mutations associated with increased risk of SCD in patients with dilated cardiomyopathy. For example, dilated

cardiomyopathy associated lamin A/C gene (LMNA), which is also associated with cardiac conduction defects, has been found to have particularly high risk of SCD. A significant proportion of these patients received appropriate ICD therapy even before the development of heart failure. [116], [117] These patients are at a higher risk of sudden death with lower degree of LV systolic dysfunction and a recent study has suggested high risk of malignant ventricular arrhythmia in patients who are male, have dilated LV, have NSVT or LVEF < 45%. [118] SCN5A overlap syndrome with dilated cardiomyopathy are at increased risk of SCD.

5. *NSVTs and PVBs* have not been found to have predictive value in of arrhythmic event in patients with DCM. In medically stabilized patients Zecchin et al failed to show any difference in arrhythmic event between patients with and without NSVTs. [119] NSVT was not evaluated for prediction of SCD in the large primary prevention trial like DEFINITE and SCD-HeFT, [48], [113]
6. *Others factors: Electrocardiographic parameters* have been evaluated to identify the groups of dilated cardiomyopathy patients with risk of SCD. [120], [121] Prolongation of QRS and presence of left bundle branch block are independent predictors of SCD. Parameters of QT dynamicity and QRS fragmentation may be useful in risk stratification of SCD. [122], [123] SAECG, heart rate variability, heart rate turbulence, heart rate recovery, baroreflex sensitivity and T-wave alternans have been evaluated and each individual risk factor has a small effect size. [61], [62] As discussed earlier in the section on ischemic cardiomyopathy, these ECG parameters and parameter of autonomic function have small effect when used individually and may have a stronger risk predictive value in combination. [61], [68] Assessment of myocardial fibrosis by various methods including serum markers of fibrosis and cardiac MRI with late gadolinium enhancement may potentially become a tool in risk stratification for sudden cardiac death in patients with dilated cardiomyopathy. [124]

4.5. Other cardiomyopathies

Left ventricular noncompaction is associated with left ventricular dysfunction and risk of ventricular arrhythmia. Studies to assess the degree of risk and parameters to stratify the risk have not been done in this group of patients, but it is noteworthy that the diagnosis has only recently been recognized. LV systolic dysfunction may be a predictor of SCD in these patients, although concerns have been raised about its value. [125] Any other parameter to stratify the risk is still speculative.

Patients with *cardiac sarcoidosis* have poorer prognosis compared to idiopathic dilated cardiomyopathy with similar degree of LV systolic dysfunction. [126], [127] Patients ventricular tachycardia or atrioventricular block are at a high risk of adverse cardiac events. Presence of AV block in patients with cardiac sarcoidosis younger than 55 years increase the risk of adverse cardiac outcomes over 2 years by ten-fold as compared to patients without cardiac sarcoidosis. [32] Asymptomatic cardiac involvement in sarcoidosis has been largely reported to have benign prognosis, [128]-[130] although one recent report recorded 19% mortality (5 out of 21 patients with MRI diagnosed cardiac sarcoidosis) over a follow-up period of 21 months. [131]

Assessment of SCD risk in *cardiac amyloidosis* is not well defined. Little data is available on risk stratification, and the usual approach in these patients is secondary prophylaxis or extrapolation of risk factors from other types of cardiomyopathies, e.g., LV systolic dysfunction. The degree of myocardial involvement in sarcoidosis may be important in clinical decision-making. Patients with *hereditary dystrophies* behave largely like dilated cardiomyopathy and risk stratification in these patients again conforms to the risk stratification of dilated cardiomyopathy.

5. Management

5.1. Pharmacotherapy and sudden cardiac death prevention

The role of pharmacotherapy in the prevention of SCD is two-fold. First, many neuro-humoral modifiers for the treatment of heart failure result in reverse remodeling of the left ventricle and may therefore reduce the overall mortality, and the risk of SCD. Examples include ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists and beta-blockers. Second, antiarrhythmic medications have been used in patients with cardiomyopathy to reduce the risk of SCD. Examples would be beta-blockers including sotalol, amiodarone and other antiarrhythmic medications.

Amiodarone has been evaluated in large randomized trials in post-MI patients. The Canadian amiodarone myocardial infarction arrhythmia trial (CAMIAT) conducted in 1202 post-MI patients with a mean LVEF of 30% and greater than 10 PVC's per hour demonstrated a small but significant reduction in arrhythmic death (4.5% versus 6.9%, $P = 0.016$) but no reduction in all-cause mortality in patients on amiodarone. [56] The European Myocardial Infarct Amiodarone Trial (EMIAT) of 1486 similar patients did not show any difference in arrhythmic or all-cause mortality between the two groups of patients. [59] A meta-analysis of 15 randomized controlled trials in a total of 8522 patients that evaluated amiodarone for prevention of SCD showed a small but significant reduction in SCD (7.1% vs 9.7%; OR 0.71, $p < 0.001$) but no important change in overall mortality. [132] In the general population of heart failure patients the SCD-HeFT trial did not show any reduction in all-cause mortality with amiodarone treatment in comparison with placebo. [48]

Sotalol a beta-blocker that is also a class III antiarrhythmic drug (i.e., prolongs QT interval) has been studied for prevention of SCD in patients with post-MI LV systolic dysfunction with mixed results. A study by Julian et al evaluated the role of racemic d,l-sotalol in 1456 patients 5-14 days after MI. Racemic sotalol exhibits both beta blocking properties (the l-isomer) and class III antiarrhythmic effects (the d-isomer), and this combination showed a nonsignificant reduction in mortality over one-year follow up. [133] By contrast, oral d-sotalol, in the SWORD, trial showed increased mortality in 3121 patients with recent (6-42 days) MI or with remote (>42 days) MI with symptomatic CHF with LVEF $\leq 40\%$. [134] This lack of benefit or actual harm seen in SWORD trial may be due to lack of beta-blocking property of d-sotalol, which probably led to some benefit seen in the study by Julian et al using racemic sotalol. [135] As a result of the SWORD trial, d-sotalol was abandoned. On the other hand a multicenter placebo

controlled trial in patients with ICD showed a reduction in mortality and ICD shocks in patients receiving d,l-sotalol. Moreover, the mortality benefit in this study did not differ between patients with LVEF <30% and >30%. [136]

Beta-blockers has a proven role in reducing cardiovascular mortality and SCD in patients with heart failure either from non-ischemic cardiomyopathy or ischemic heart disease. [114], [137]-[139] Similarly, ACE inhibitors, ARBs and aldosterone antagonist are used in heart failure patients to reduce all-cause mortality, however, neither ACE inhibitors nor ARB actually reduce SCD in patients with LV systolic dysfunction. [140]-[142] ELITE did show an unexpected reduction of SCD with losartan but this was a non-prespecified endpoint and was never confirmed prospectively. [143]

Class I antiarrhythmic drugs have not been found to reduce SCD in patients with history of MI and LV systolic dysfunction, and in fact most often result in an increase in mortality. The Cardiac Arrhythmia Suppression Trial (CAST) and CAST-II trials, for example, showed increased mortality with the use of class Ic antiarrhythmic drugs in post MI patients. [144] Similarly, propafenone showed increased mortality compared to ICD in Cardiac Arrest Study Hamburg (CASH). [145]

As the data of ICD trials showed reduction in all-cause mortality and SCD in patients with cardiomyopathy as compared to amiodarone, the role of antiarrhythmic drugs in prevention of SCD has become adjunctive, with the goal of reducing ICD shocks. Beta-blockers and other humoral modifiers are generally used in the management of heart failure and improve survival in heart failure patients.

The role of amiodarone for prevention of SCD in HCM is controversial. In a study by McKenna et al, [146] amiodarone found to be effective but it is noteworthy that this study was used historical controls receiving either mexiletine, disopyramide or quinidine. In other studies antiarrhythmic drugs for the prevention of SCD in HCM have not been found to be effective. [147] Similarly, beta-blockers, sotalol and amiodarone have been used to suppress ventricular arrhythmias in ARVC. Efficacy has been variable [148], [149] and, with the increasing practice of use of ICD in the prevention of SCD in these patients, antiarrhythmic drugs are again used to reduce the need for ICD intervention.

5.2. Device therapy: Implantable cardioverter-defibrillator

Implantable cardioverter-defibrillator therapy has emerged as the most important management strategy for prevention of SCD in patients with cardiomyopathy at high risk of sudden cardiac death. The high incidence and high individual risk of SCD in cardiomyopathy patients with impaired left ventricular function, especially in those who had survived a ventricular arrhythmia, and the relative ineffectiveness of antiarrhythmic drugs in these patients led to a series of trials aimed at assessing the role of ICD therapy. This strategy was first tested in trials of patients with highest degree of risk. These were sudden death and ventricular arrhythmia survivors, and the studies are collectively referred to as secondary prevention trials. These trials were followed by trials of increasingly lower risk patients, principally those with heart failure, in primary prevention trials. The major message of these trials is that cost effectiveness

is highest in highest risk patients, but that in this group, numerically the number of lives saved by defibrillators is relatively small. Use of defibrillators in lower risk cohorts decreases cost effectiveness, but increases the chance of making a numerical impact of the incidence of SCD in the contemporary US population.

5.3. Secondary prevention ICD trials

Antiarrhythmics versus implantable defibrillators (AVID), Canadian implantable defibrillator study (CIDS) and Cardiac arrest study Hamburg (CASH) trials gave an insight into the benefits of use of ICDs in secondary prevention of SCD after an arrhythmic event. In these studies patients with history of aborted SCD or patients with ventricular arrhythmia in the setting of reduced LV systolic function were enrolled.

The *AVID trial*, which enrolled 1016 patients with history of VF, VT with syncope or VT with LVEF $\leq 40\%$ and symptoms of hemodynamic compromise (near syncope, congestive heart failure and angina). This study showed reduction in all-cause mortality from 25% to 18% (absolute risk reduction of 7% and relative risk reduction of 27%). The patients had a mean LVEF of 32% in this study. In each arm, 45% of the patients had history of VF and the rest of the patients had history of VT as the inclusion criteria for the study. *CIDS* enrolled 659 patients with VF, out of hospital cardiac arrest due to VF or VT, VT with syncope, VT with symptoms of presyncope or angina and LVEF $\leq 35\%$, and unmonitored syncope with subsequent spontaneous or induced VT. The mean LVEF in these patients was 34%. After follow-up of 3 years there was a nonsignificant reduction in all-cause mortality (10.2% per year to 8.3% per year, $p=0.142$), and of arrhythmic death (4.5% per year to 3.0% per year, $p=0.094$) in ICD patients. At 2 years there was a reduction in all-cause mortality from 21% to 15% (absolute and relative risk reduction of 30% and 6% respectively).

The *CASH study* was a much smaller study with enrollment of 191 patients with a history of VF or VT without an identified transient reversible cause. In contrast to AVID and CIDS the mean LVEF was 46% making them healthier group of patients. Over a mean follow-up of 57 months the reduction in mortality was from 44% in control to 36% in those receiving ICD (absolute and relative risk reduction of 23% and 8% respectively). Overall survival was higher in the ICD arm, though not statistically significant (hazard ratio 0.766, 97.5% CI upper bound 1.112; $p=0.081$). There was higher survival free of sudden death in the ICD arm (hazard ratio 0.423, 97.5% upper bound 0.721; $p=0.005$).

Thus the trials were consistent in their message although CASH and CIDS trials were relatively underpowered to assess the reduction in all-cause mortality. A meta-analysis showed a 28% relative reduction in all cause mortality and a 50% reduction in SCD in patients receiving ICDs. [150] Patients with LVEF $< 35\%$ derived the most benefit with hazard ratio for this group of 0.66 (95% CI 0.53-0.83). [150] and overall the number needed to treat to save a life per year of follow-up was 29. [151] When the individual trials are compared it is noteworthy that LVEF was much higher in CASH, and that CIDS included a group of patients with unexplained syncope and VT inducible at EP study. These factors are markers of a lower risk population and reduced that trials' ability to detect the benefit of ICDs in reducing all cause mortality.

Later subgroup analysis of these studies showed that the benefit of ICD therapy was largely restricted to patients with lower LVEF. A subgroup analysis of 396 patients in the AVID trial with LVEF >35% failed to show any survival benefit. In addition a smaller group of 140 patients in this study with LVEF <20% did not show statistically significantly survival benefit. This was in contrast to the 473 patients with LVEF between 20% and 34% who had significantly improved survival. [152] Similarly, in CIDS trial the benefit of ICD therapy was restricted to the patients with higher risk features (age >70 years, LVEF <35% and NYHA class III or IV). [153]

5.4. Primary prevention ICD trials

Primary prevention ICD trials in patients with heart failure due to ischemic and nonischemic cardiomyopathies have provided insights into prevention of SCD in a larger group of patients who are at a high risk of SCD based on epidemiological studies, but are at lower risk than patients who have suffered a ventricular arrhythmia. These studies have played instrumental role in formulation of guidelines for primary prevention of SCDs in patients with cardiomyopathies. The trials include MADIT (I and II), CABG Patch, MUSTT, DINAMIT, DEFINITE and SCD-HeFT.

Multicenter Automatic Defibrillator Implantation Trial (MADIT-I) was the first trial evaluating the efficacy of ICD on survival in patients with history ischemic heart disease. Patients with an LVEF ≤35%, non-sustained VT who also sustained VT induced at a ventricular stimulation study and not suppressed by procainamide were randomized to receive best medical therapy or an ICD. 196 of these very high-risk patients were enrolled and mean LVEF was 26%. All cause mortality was reduced from 32% to 13% in the ICD group after 2 years, for a relative risk reduction of 59% [50]

The *Multicenter Unsustained Tachycardia Trial (MUSTT)* trial recruited a lower risk IHD cohort, with NSVT and a LVEF ≤40%. All patients underwent a ventricular stimulation study, and those with inducible sustained ventricular tachycardia were randomized to receive either no specific antiarrhythmic therapy or antiarrhythmic therapy (either an antiarrhythmic drug or an ICD) guided by further ventricular stimulation studies. Patients not inducible into sustained VT were followed in a registry. Among 704 enrolled patients, the median LVEF was 30%. In comparison to controls, patient treated with antiarrhythmic drugs had an increase in overall mortality (from 48% to 55%) whereas patients receiving ICDs all cause mortality improved from 48% in controls to 24% in patients receiving ICD with absolute and relative risk reduction of 24% and 50% in a 5 year analysis (figure 6). [51] Interestingly the cohort of patients not inducible into VT who received no specific antiarrhythmic therapy had a significantly lower mortality than patients who were inducible into sustained VT, but the absolute improvement in mortality predicted by a negative EP study was small (absolute risk reduction and relative risk reduction of 7%, and 25% at 2 years and 4% and 8.3% at 5 years). [154] This study was the first to point out the limited value of ventricular stimulation studies in assessing SCD risk. These studies have now largely been abandoned, and future ICD trials have concentrated on wider, lower risk, patient cohorts.

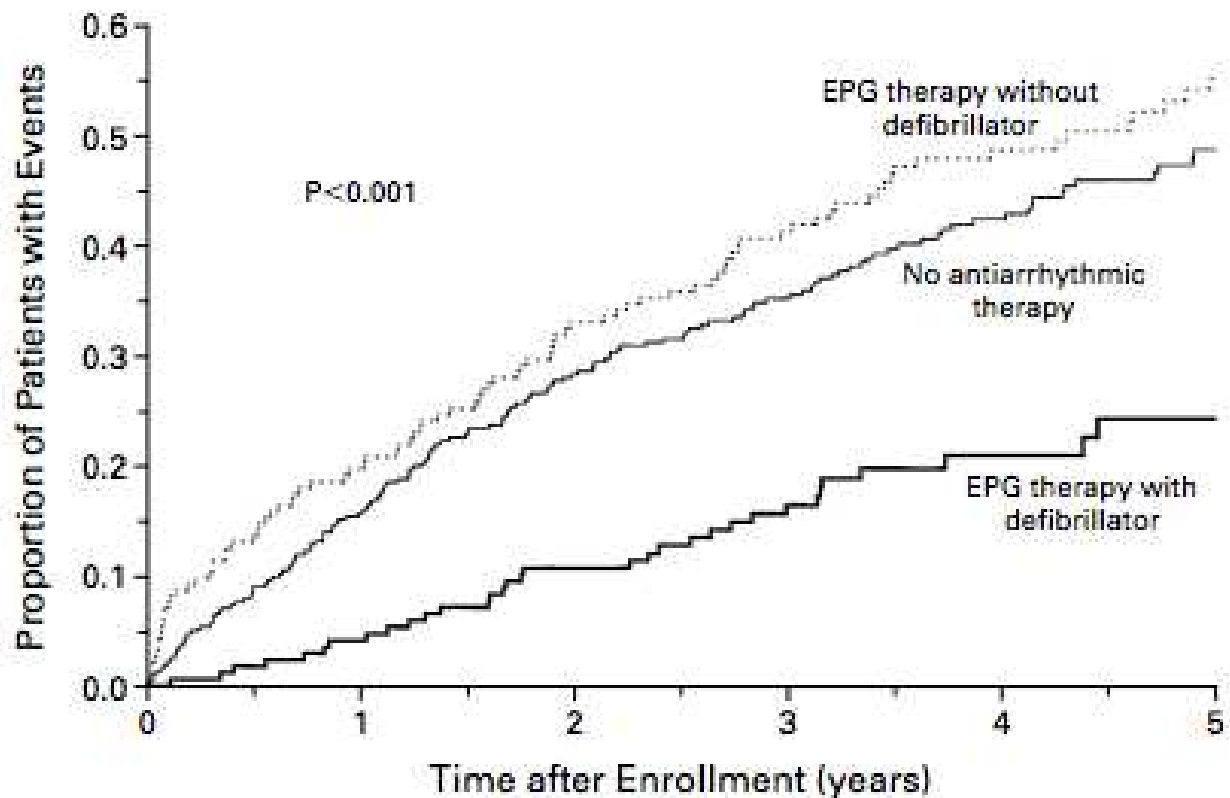
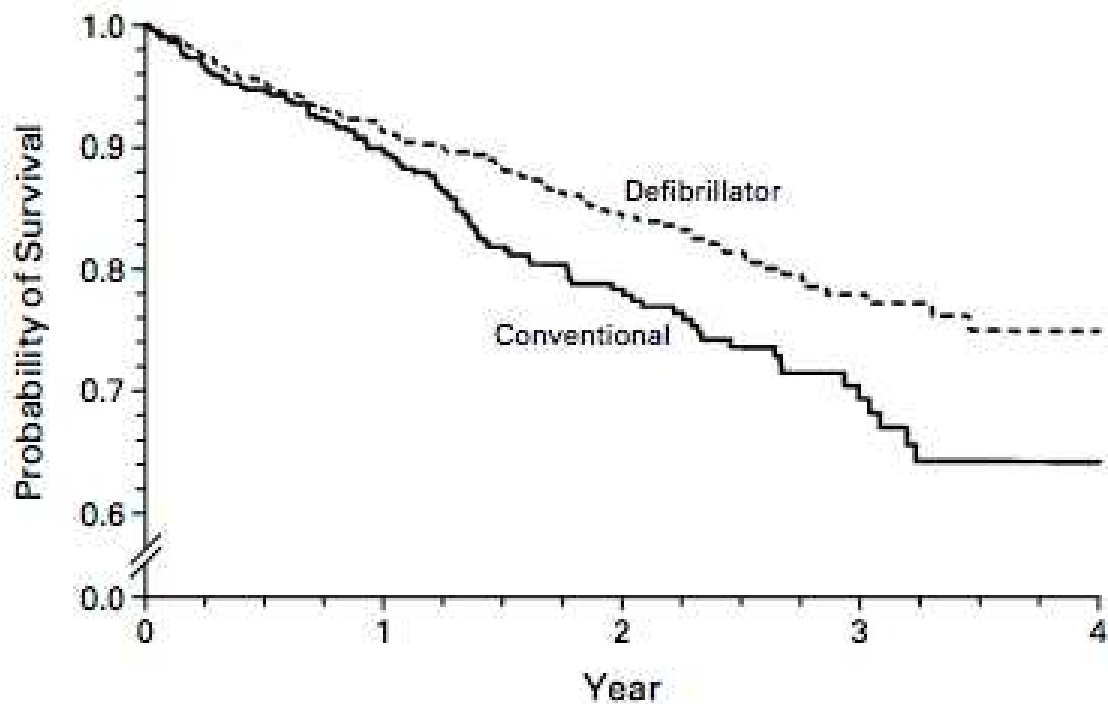


Figure 6. MUSTT: Kaplan–Meier Estimates of the Rates of Overall Mortality According to Whether the Patients Received Treatment with a Defibrillator. The P value refers to two comparisons: between the patients in the group assigned to electrophysiologically guided (EPG) therapy who received treatment with a defibrillator and those who did not receive such treatment, and between the patients assigned to electrophysiologically guided therapy who received treatment with a defibrillator and those assigned to no antiarrhythmic therapy. (From reference 51)

The *MADIT II* trial assessed the effect of an ICD in 1232 patients with prior myocardial infarction (>one month) and LVEF $\leq 30\%$. In this study, mainly of long term infarct survivors, mean LVEF was 23% and in the ICD group all-cause mortality was reduced at 16% compared to 22% in the controls after 2-year follow up (absolute and relative risk reduction of 6% and 28% respectively, figure 7). [47] In this cohort of IHD patients without inducible VT the benefit of an ICD was smaller, but the potential population of identified patients who could benefit from ICD therapy is much wider.

Defibrillator use early after acute myocardial infarction trial: The *DINAMIT* trial evaluated the role of ICD in potentially improving the survival of patients during acute phase of MI (6 to 40 days after MI) with reduced LVEF $\leq 35\%$ and impaired cardiac autonomic function, assessed as impaired baroreflex sensitivity. During a mean follow-up of 2½ years, there was no reduction in overall mortality in these patients. Although there was a reduction in death due to arrhythmia, the benefit was offset by death from non-arrhythmic causes. [155] These data are challenging because the implication is that ICD implantation enhanced the risk for non-arrhythmic death, principally death from heart failure. If the amount of right ventricular pacing in the ICD group accounted for more than 5-10% of heart beats this is a plausi-



No. AT RISK					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Figure 7. MADIT II: Kaplan–Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy. The difference in survival between the two groups was significant (nominal $P=0.007$, by the log-rank test). (From reference 47)

ble mechanism because RV pacing in heart failure patients is known to exacerbate heart failure mortality. [156]-[158]

Defibrillators in non-ischemic cardiomyopathy: The *DEFINITE* trial investigated the benefit of prophylactic ICD therapy in 458 enrolled patients with non-ischemic cardiomyopathy with LVEF <36% and premature ventricular complexes or NSVT. The patients were mainly symptomatic for heart failure with NYHA functional class of I-III and mean LVEF of the study population was 21%. At two years, the mortality in ICD group was 8% compared to 14% in the standard therapy group (absolute and relative risk reduction of 6% and 44% respectively). However this reduction in overall mortality was not statistically significant with hazard ratio of 0.65 among patients receiving ICD (95% CI 0.40-1.06). This difference reached statistical significance in patients with NYHA class III in subgroup analysis and showed a relative risk of death of 0.37 (95% confidence interval 0.15-0.90). Moreover, the difference in survival was significantly more in males receiving ICD (HR 0.49, 95%CI 0.27-0.90; $p=0.018$). [113].

Sudden cardiac death in heart failure (SCD-HeFT) trial was conducted in patients with heart failure due to ischemic or nonischemic cardiomyopathy with LVEF≤35% and with NYHA functional class II-III. More than 2500 optimally medically managed patients were equally divided into

three groups: ICD, amiodarone and placebo. Mean LVEF was 25%; 52% of the patients had ischemic cardiomyopathy and the remainder were non ischemic. All cause mortality at 5 years in patients receiving ICD was 29% compared to 36% for the control with absolute and relative risk reduction of 7% and 23%. Amiodarone arm did not show any significant reduction in risk of death (HR: 1.06; 97.5% CI 0.86-1.30; $p=0.53$)(see figure 8). In subgroup analysis by type of cardiomyopathy, reduction in the mortality risk were similar in both ischemic (HR: 0.79, 97.5% CI 0.60-1.04) and nonischemic cardiomyopathy (HR: 0.73, 97.5% CI 0.50-1.07) patients with ICD therapy compared to placebo, although the risk reduction did not reach a statistical significance. NYHA class did affect the effect of amiodarone as well as ICD therapy compared to placebo. Amiodarone was shown to increase the risk of mortality in NYHA class III by 44% (HR: 1.44, 97.5 CI 1.05-1.97), which was not seen in patients with NYHA class II (HR: 0.85, 97.5% CI 0.65-1.11). Similarly, with ICD therapy, patients with NYHA class III did not get mortality benefit (HR: 1.16, 97.5% CI 0.84-1.61) as opposed to patients with NYHA class II (HR: 0.54; 97.5% CI 0.40-0.74) [48]

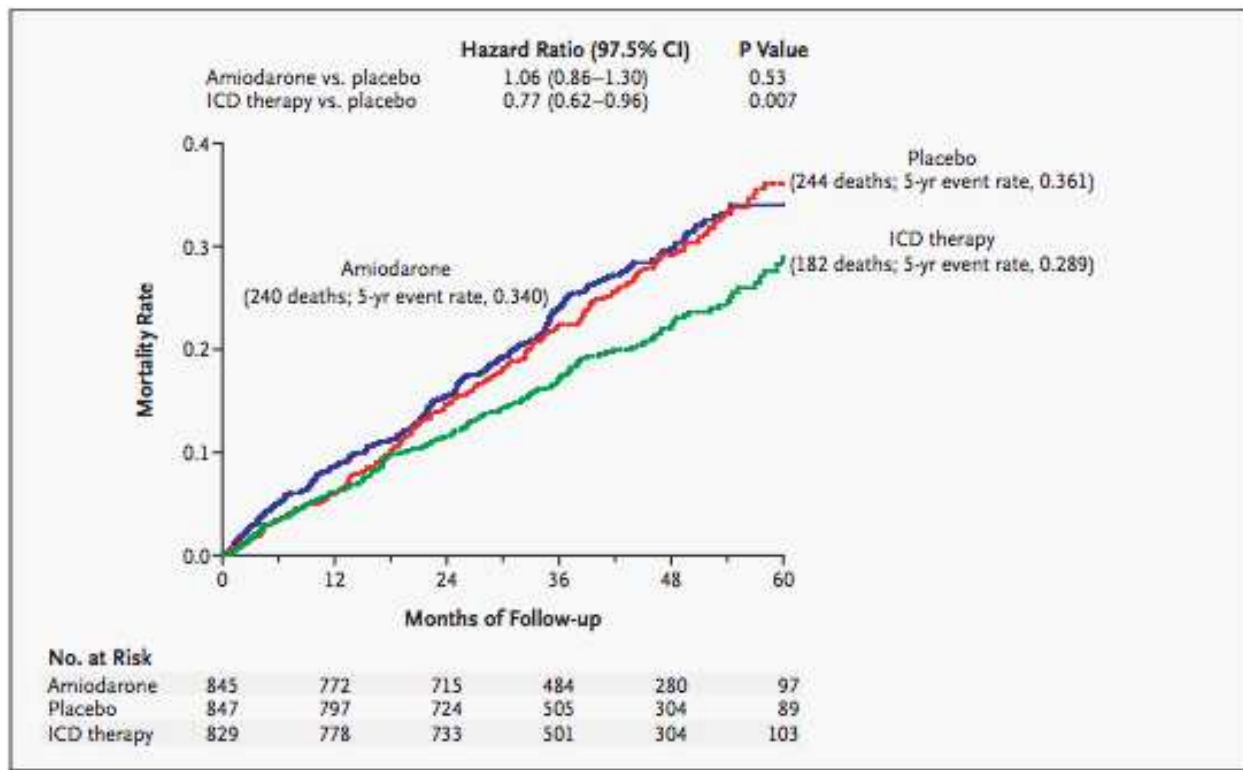


Figure 8. SCD-HeFT: Kaplan–Meier Estimates of Death from Any Cause. (From reference 48)

A meta-analysis of the primary prevention trials in patients with low ejection fraction due to coronary artery disease or dilated cardiomyopathy including eight trials and total of 5343 patients showed reduction of arrhythmic mortality (relative risk: 0.40; 95% CI: 0.27-0.67) and all-cause mortality (relative risk: 0.73; 95% CI: 0.64-0.82). The benefit of ICD therapy was similar in ischemic (relative risk: 0.67; 95% CI: 0.51-0.88) and non-ischemic (RR: 0.74; 95% CI: 0.59-0.93) cardiomyopathies. [159] Another important issue is that the age of the people enrolled in the

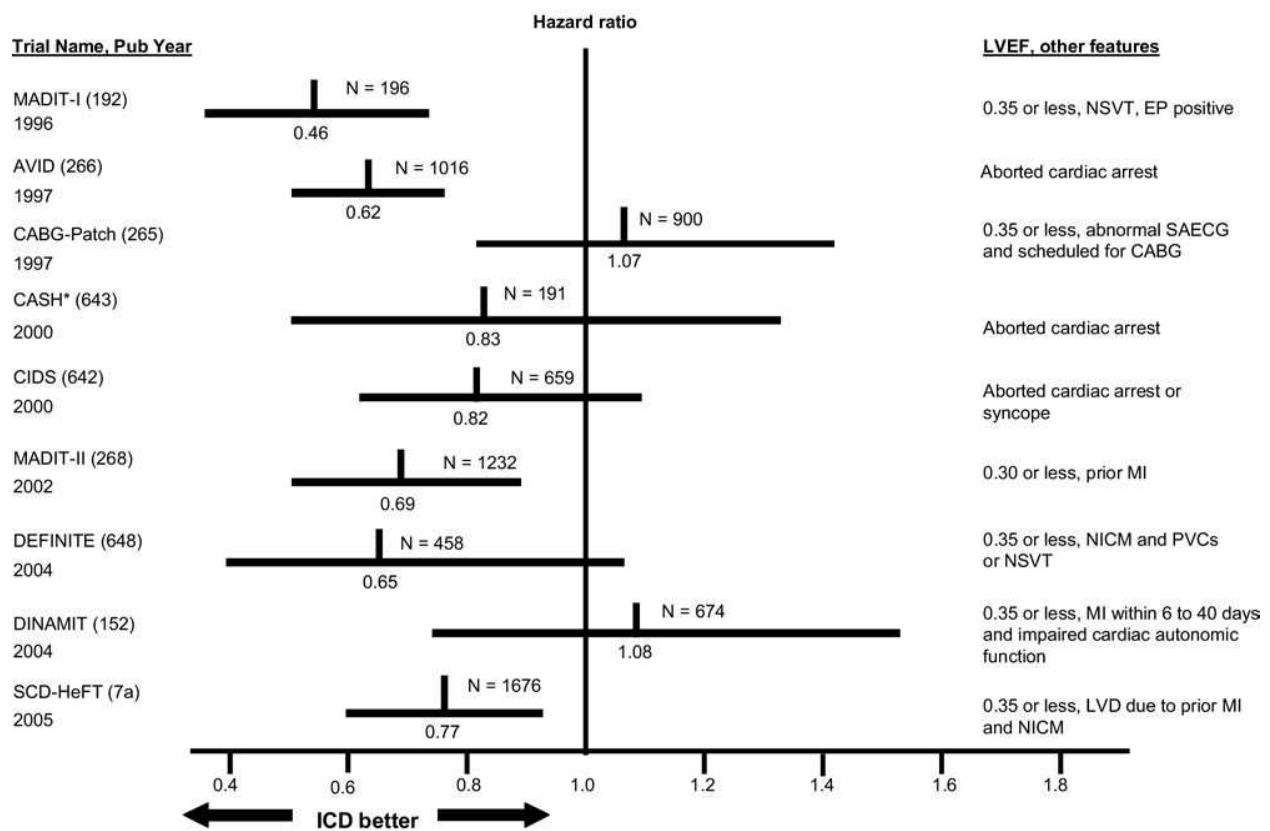


Figure 9. Major implantable cardioverter-defibrillator (ICD) trials. Hazard ratios (vertical line) and 95% confidence intervals (horizontal lines) for death from any cause in the ICD group compared with the non-ICD group. *Includes only ICD and amiodarone patients from CASH. For expansion of trial names, see Appendix 3. CABG: coronary artery bypass graft surgery; EP: electrophysiological study; LVD: left ventricular dysfunction; LVEF: left ventricular ejection fraction; MI: myocardial infarction; N: number of patients; NICM: nonischemic cardiomyopathy; NSVT: nonsustained ventricular tachycardia; PVCs: premature ventricular complexes; SAECG: signal-averaged electrocardiogram. (Adapted with permission from reference 165)

large ICD trials is considerably younger than the people frequently needing ICD implantation in the current clinical practice. This issue has been addressed by two meta-analysis suggesting benefit of ICD therapy in older patients. [160], [161] Another meta-analysis of primary prevention ICD trials showed smaller benefit of ICD in women with dilated cardiomyopathy compared to men. Although overall mortality in both the genders were similar (HR 0.96, 95% CI 0.67-1.39), women received appropriate therapy less frequently compared to men (HR 0.63, 95%CI 0.49-0.82) and hence received less benefit from defibrillator therapy. [162] This as well as another meta-analysis of primary prevention ICD trials failed to show significant mortality benefit of ICD in women. [162]

These ICD trials have established the role of ICDs in the primary and secondary prevention of SCD in patients with non-ischemic and ischemic cardiomyopathy (figure 9). Left ventricular ejection fraction has been recognized as the strongest risk stratifier and has been extensively used in all the trials. Based on these studies guidelines have been formulated for the appropriate indications of ICD therapy in these patients. The table 3 summarizes the guidelines for implantation of ICD for prevention of SCD in these patients.

	Indication for ICD	Level of evidence
Class I		
1	Patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes.	A
2	Patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable.	B
3	Patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or ventricular fibrillation induced at electrophysiological study.	B
4	Patients with LVEF less than or equal to 35% due to prior myocardial infarction who are at least 40 days post-myocardial infarction and are in NYHA functional Class II or III.	A
5	Patients with nonischemic dilated cardiomyopathy who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III.	B
6	Patients with LV dysfunction due to prior myocardial infarction who are at least 40 days post-myocardial infarction, have an LVEF less than or equal to 30%, and are in NYHA functional Class I.	A
7	Patients with nonsustained VT due to prior myocardial infarction, LVEF less than or equal to 40%, and inducible ventricular fibrillation or sustained VT at electrophysiological study.	B
Class IIa		
1	Patients with unexplained syncope, significant LV dysfunction, and nonischemic dilated cardiomyopathy.	C
2	Patients with sustained VT and normal or near-normal ventricular function.	C
3	Patients with hypertrophic cardiomyopathy who have 1 or more major† risk factor for SCD.	C
4	Patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy who have 1 or more risk factor for SCD.	C
5	Patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers.	B
6	Nonhospitalized patients awaiting transplantation.	C
7	Patients with Brugada syndrome who have had syncope.	C
8	Patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest.	C
9	Patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blockers.	C
10	Patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease.	C
Class IIb		
1	Patients with nonischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional Class I.	C
2	Patients with long-QT syndrome and risk factors for SCD.	B
3	Patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause.	C
4	Patients with a familial cardiomyopathy associated with sudden death.	C
5	Patients with LV noncompaction.	C
Class III		
1	Patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the Class I, IIa, and IIb recommendations above.	C
2	Patients with incessant VT or ventricular fibrillation.	C

	Indication for ICD	Level of evidence
3	Patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up.	C
4	NYHA Class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or implantation of a CRT device that incorporates both pacing and defibrillation capabilities.	C
5	Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease.	C
6	Ventricular fibrillation or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with Wolff-Parkinson-White syndrome, right ventricular or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease).	C
7	Patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma).	B

Table 3. ACC/AHA/HRS guidelines for implantation of ICDs (2008): indications in bold fonts refer to the indications for various cardiomyopathies.

5.5. Risk stratification of heart failure patients for sudden death prevention

As data has accumulated suggesting that a strategy of wide ranging ICD implantation in patients with impaired left ventricular systolic function will result in improvements in sudden cardiac death mortality, concerns have been raised about the relatively low incidence of life saving therapies in implanted patients. For example in MADIT II 14% of patients received a potentially life saving defibrillator shock, whilst in SCD-HeFT only 21% of patients received appropriate ICD therapy. In addition it has frequently been noted that an appropriate shock does not necessarily represent an aborted sudden death. These considerations have lead to attempts to derive scoring strategies from the data sets in the large prospective trials to try to identify patients at low risk of requiring device therapy – and those in whom device therapy might be futile.

Data from the MADIT II study in chronic IHD suggested that in very high risk (VHR) patients defined as those with a BUN \geq 50 mg/dl, mortality was high at 50% in two years and was not improved by ICD therapy. ICD implantation in this patient group appears to be unjustified. Among non-VHR patients, SCD risk was to be increased with NYHA functional class $>$ II, a history of atrial fibrillation, QRS duration $>$ 120 ms, age $>$ 70 years and BUN $>$ 26 mg/dl and $<$ 50 mg/dl. Patients with none of these risk factors were at low risk of SCD, and had no benefit from ICD therapy. Patients with one to two risk factors derived benefit from an ICD whereas patients with three or more risk factors did not derive as much benefit and behaved like VHR patients. [163] Similarly, analysis of data from the MUSTT study suggested LVEF alone was of limited value to predict the risk of SCD in this patient group. [164] The concern about using a binary cut off of LVEF in deciding on the advisability or otherwise of ICD therapy to reduce the risk of SCD is that SCD risk is a continuous variable and predicted by more than LVEF alone. Multiple factors predict SCD to some extent and hence a risk score based on multiple risk factors may be a better predictor of SCD. However, it should be noted that the mutiple

risk models have not been evaluated in a prospective study and are entirely data derived. [68] This being said, it seems inevitable that the guidelines for the implantation of ICDs will be refined in the future and that risk scores will be incorporated.

5.6. ICD in other forms of cardiomyopathies

Implantation of ICD in cardiomyopathy other than ischemic and non-ischemic dilated cardiomyopathy is not supported by evidence from large ICD trials. The majority of patients enrolled in the large ICD trials were post-MI patients with LV dysfunction and patients with dilated non-ischemic cardiomyopathy. In other forms of cardiomyopathies, like hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, sarcoidosis and other infiltrative cardiomyopathies, secondary prevention of sudden cardiac death with ICD implantation in survivors of SCD and in patients with history of sustained ventricular tachycardia is generally accepted clinical practice. However, implantation of ICD for primary prevention of SCD has remained an unsolved issue in these patients. This has become more of an issue with development of more effective screening of family members, and pre-participation screening of athletes. Risk stratification in them has been attempted for each of these groups.

Primary prevention in patients with *hypertrophic cardiomyopathy* is guided by multiple risk factors for sudden cardiac death as discussed above. These risk factors have been defined as discussed earlier and include (1) a family history of premature HCM-related sudden death; (2) a history of unexplained syncope; (3) multiple and/or prolonged runs of nonsustained VT on serial 24-hour ambulatory ECG monitoring at heart rates ≥ 120 beats/min; (4) a hypotensive or attenuated blood pressure response to exercise; and (5) massive left ventricular (LV) hypertrophy (maximum wall thickness ≥ 30 mm). The ACC/AHA/ESC guidelines on sudden cardiac death and ventricular arrhythmia recommend implantation of ICD in patients with one or more of these risk factors, for the primary prevention of SCD. [165]

Primary prevention of SCD in *arrhythmogenic right ventricular cardiomyopathy* is also guided by a set of high risk factors. A multicenter study evaluated the use of ICD for primary prophylaxis of SCD in patients with ARVC with at least one risk factor for SCD. These included syncope, NSVT, a malignant family history, and inducibility of ventricular arrhythmias with programmed ventricular stimulation. Over a mean follow-up of 58 months 25 of 106 patients received appropriate ICD intervention. ACC/AHA/ESC guidelines considers secondary prevention of SCD with AICD to be reasonable (class IIa) in patients with ARVC considered high risk due to LV involvement, one or more affected family member with SCD, or undiagnosed syncope when VT or VF has not been excluded as the cause of syncope, while receiving chronic optimal medical therapy. [165] ACC/AHA/HRS guidelines for device therapy for arrhythmia lists ARVC as reasonable indication for primary implantation of ICD in the presence of one or more risk of SCD. [166]

In patients with left ventricular non-compaction, ICD implantation is generally performed for secondary prevention and for primary prevention in the presence of LV systolic dysfunction. Although patients with normal LV systolic function or mild LV systolic dysfunction may be prone to SCD, [125] lack of data makes the decision ICD implantation in these patients difficult.

In patients with sarcoidosis, cardiac involvement with history of spontaneous VT and/or severe LV systolic dysfunction may warrant ICD therapy despite lack of prospective trials. [165] Implantation of ICD in patients with sarcoidosis in the absence of LV systolic dysfunction or history of ventricular arrhythmias remains controversial. The ACC/AHA/HRS guidelines for device therapy lists cardiac sarcoidosis as reasonable indication for ICD implantation. [166] The use of ICD to prevent SCD in patients with cardiac amyloidosis is not well accepted and may not affect the outcome, although it can be used to bridge the patients to cardiac transplantation. [38], [165] Some of the muscular dystrophies with associated cardiomyopathy are treated in a similar way as dilated non-ischemic cardiomyopathy from other causes.

5.7. Device therapy: Permanent pacemaker

Some cardiomyopathies are prone to cause conduction abnormalities. For example patients with muscular dystrophy due to lamin A/C gene mutation are particularly prone to conduction defect and atrioventricular block. The threshold for pacemaker implantation in these patients is very low to prevent SCD. Similarly, infiltrative myocardial diseases such as sarcoidosis can lead to heart block and SCD as a result of this. Other examples include myotonic muscular dystrophy, where SCD can result both from ventricular arrhythmias and from complete heart block.

6. Future directions

The prevention of sudden cardiac death in patients with cardiomyopathy has evolved dramatically in recent years. With the increasing use of ICDs in conjunction with pharmacotherapy for heart failure, large number patients have benefited from prevention of SCD. However, risk assessment for SCD is still far from accurate and many patients receiving ICDs ultimately will not use them. Although, attempts have been made to refine the risk stratification, the current risk stratification is insufficient at least for many kinds of cardiomyopathies. Data from subgroup analysis do provide some parameters for refining risk stratification, but testing them in a prospective study will be an expensive and time-consuming undertaking. Risk stratification for less common forms of cardiomyopathy has not largely been possible. Some newer parameters like genetic evaluation may help in refining the risk assessment in the future as more data on genetic analysis in various forms of cardiomyopathy comes forth. Finally, newer pharmacotherapy may help in reducing the risk of SCD in these patients.

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