Title: Sudden Cardiac Death in Inherited Cardiomyopathy

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Abstract

Cardiomyopathy is an important cause of sudden cardiac death particularly in adolescents and young adults. The risk of sudden cardiac death varies between individual cardiomyopathies and is dependent on the severity of disease, age and gender. Although rare in cardiomyopathies, a fundamental aspect of clinical management is a systematic and thorough clinical assessment to identify the small number of individuals who are at risk and who can be protected with prophylactic ICD therapy.

Introduction

Sudden cardiac death (SCD) can be defined as an unexpected death from cardiac causes within one hour of symptom onset with or without known cardiac disease. Sudden cardiac death (SCD) accounts for approximately 25% of all cardiovascular deaths worldwide and in most cases is attributable to coronary artery disease.[1] Most evidence suggests that it is usually caused by ventricular arrhythmia (VA) and less commonly by bradyarrhythmia with conduction abnormalities.[1]

Non-ischaemic causes of SCD are more prevalent in young adults and inherited conditions such as channelopathies or cardiomyopathies are evident in up to 50% of families of young victims of SCD.[2] Cardiomyopathies are a diverse group of disorders characterised by structural and functional abnormalities of the heart muscle that are unexplained by coronary artery disease, hypertension or valvular disease.[3] They are grouped into morphological and functional subtypes, each of which can be caused by genetic and non-genetic mechanisms.

The risk of SCD varies between cardiomyopathies and is dependent on the severity of disease, age and gender. The approach to primary prevention of SCD varies and is supported by variable level of evidence between diseases. We briefly consider current evidence of SCD prevention in the most common cardiomyopathy subtypes.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined by increased left ventricular (LV) wall thickness that is not explained solely by abnormal loading conditions.[4] Screening studies suggest a population prevalence of 1 in 500 although the number of diagnosed cases is much less.[3,4] HCM can lead to early death due to heart failure (HF), stroke or SCD and is usually inherited as an autosomal dominant trait caused by mutations in genes encoding

cardiac sarcomeric proteins. Rarer causes of HCM include metabolic and mitochondrial disorders, congenital malformations and endocrinopathies.[4]

Contemporary reports show an overall cardiovascular mortality in HCM of 2% per year with an SCD incidence of 0.8% per year that peaks in early adulthood.[5] Different arrhythmias are responsible but the most frequent is spontaneous ventricular fibrillation (VF).[1,4]

Several clinical features are associated with SCD including non-sustained ventricular tachycardia (VT), severe LV hypertrophy, unexplained syncope, family history of SCD and abnormal blood pressure response to exercise.[4] Patients with none of these "major" risk factors are generally at low risk for SCD whereas those with multiple risk factors are considered candidates for an ICD.[4] The 2014 ESC guidelines on HCM recommended an individualised approach to risk estimation that takes into account the unique contribution of each clinical risk factor (HCM RISK–SCD) as seen in *figure 1*.[4,6] With the exception of abnormal blood pressure response, the model uses the same risk factors recommended in previous guidelines with the addition of left atrial diameter, LV outflow tract gradient and patient age. These are integrated into an on-line calculator that can be used to estimate a five year risk of SCD [http://www.doc2do.com/hcm/webHCM.html].

Survivors of VF or sustained VT are at very high risk of subsequent lethal cardiac arrhythmias and should all receive an ICD for secondary prevention.[7] For primary prophylaxis, ESC guidelines recommend that patients with a five year risk ≥ 6% should be considered for ICD therapy.[4] ICDs may also be appropriate in people with an intermediate risk of 4-6% in the ESC model.[4]

Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy (DCM) is defined as LV dilatation with systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease significant to cause ventricular dysfunction.[3] It has a prevalence of 1 in 2500 and is familial in at least 25% of

cases.[8] Causative mutations occur in genes encoding proteins in the cytoskeleton, sarcomere, nuclear membrane and intercalated discs with other causes including myocarditis, metabolic and mitochondrial disease.[1] The major causes of cardiovascular death in DCM are progressive HF and SCD secondary to ventricular arrhythmia or, less commonly, bradyarrhythmia. All-cause mortality in DCM has improved substantially with the use of conventional HF medications and device therapy as seen in *figure 2*.[9] Many non-invasive parameters have been suggested as predictors of SCD, but in a recent meta-analysis of 45 studies, functional and electrocardiographic parameters provided only modest discrimination between high and low risk patients.[10]

A number of trials have compared ICD therapy alone or in combination with cardiac resynchronization therapy against placebo or amiodarone in patients with DCM.[11,12] For secondary prophylaxis, all guidelines recommend ICD implantation, although only three small trials (Antiarrhythmics vs Implantable Defibrillators (AVID), the Cardiac Arrest Study Hamburg (CASH), and the Canadian Implantable Defibrillator Study (CIDS) have examined ICD therapy in patients with a history of resuscitated cardiac arrest or symptomatic VT.[11] For primary prophylaxis, ESC guidelines recommend an ICD in patients with DCM, symptomatic HF (NYHA class II–III) and an EF ≤35% despite ≥3 months of treatment with optimal pharmacological therapy.[1] This is based on a meta-analysis of 5 studies[12] but some doubt has been cast on this advice with the recent Danish trial, reporting that prophylactic ICD implantation was not associated with lower long-term mortality rates.[13] No study has prospectively investigated the benefit of ICDs in specific aetiological subgroups of DCM which is important as some genetic forms of DCM for example disease caused by mutations in the Lamin AC gene (LMNA) have a high risk of SCD, sometimes with only mild LV dilatation and systolic impairment.[14]

Restrictive Cardiomyopathy

The term restrictive cardiomyopathy (RCM) refers to hearts in which there is restrictive physiology, normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes and normal ventricular wall thickness.[15] Restrictive cardiomyopathy is the least common of all the cardiomyopathies and is caused by a number of genetic and acquired disorders such as amyloidosis. Poor outcomes are associated with RCM due to progressive HF but cases of VA can occur. Data is limited in RCM and primary prophylactic ICD therapy should be based as per other cardiomyopathies accounting for the underlying aetiology.[1]

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive heart muscle disorder characterised by ventricular arrhythmia, HF and SCD. Its hallmark is replacement of cardiomyocytes by adipose and fibrous tissue. Clinically, it is defined by structural and functional abnormalities of the right ventricle, but LV involvement occurs in 50% of patients.[16,17]

Arrhythmogenic right ventricular cardiomyopathy occurs in up to 1/1000 of the population and is an important cause of SCD in athletes and young adults. It mostly follows an autosomal dominant pattern of inheritance with rare recessive forms associated with cutaneous disease.[17] Clinical manifestations usually develop between the second and fourth decade of life.[17]

The annual mortality rate in ARVC varies depending on the characteristics of reported cohorts. Data from one meta-analysis reports an annualised rate for cardiac mortality, non-cardiac mortality and heart transplantation of 0.9, 0.8 and 0.9%, respectively.[18]

Most studies on risk stratification in ARVC are retrospective and of relatively small high-risk cohorts recruited from single centres. In a recent systematic review and meta-analysis (18 of 610, the annualised appropriate ICD intervention rate was 9.5%.[18]

Patients with a history of aborted SCD, poorly tolerated ventricular arrhythmia and syncope have the greatest risk of SCD (up to 10% per annum) and ICD therapy is recommended in this group.[1] Other reported risk factors for SCD include sustained VT, unexplained syncope, a family history of SCD, extensive right ventricular disease, marked QRS prolongation, late gadolinium enhancement on CMR, LV dysfunction and VT induction during electrophysiology studies.[1,18] Current consensus guidelines recommend consideration of an ICD in patients with unexplained syncope and in the presence of clinical risk factors although these are not weighted or integrated into a quantitative risk score.[1]

Conclusions

Sudden cardiac death poses a significant burden of cardiovascular deaths worldwide. While it is an important complication of most cardiomyopathies, the risk is generally low in asymptomatic patients with mild disease. A fundamental aspect of clinical management is a systematic and thorough clinical assessment to identify the small number of individuals who are at risk and who can be protected with prophylactic ICD therapy.

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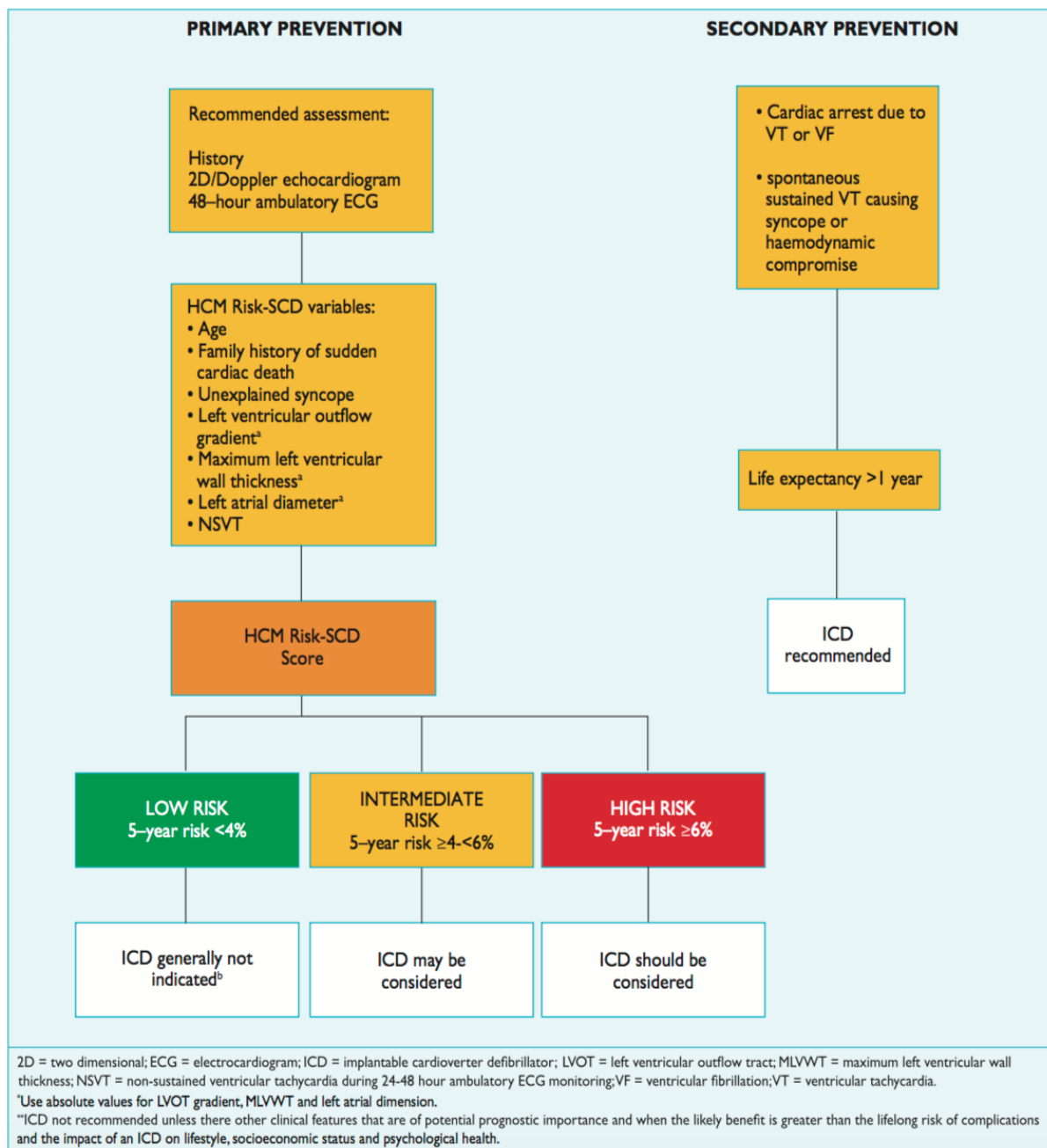
Figures

Figure 1

Flowchart for ICD consideration in hypertrophic cardiomyopathy. The flowchart illustrates a systematic approach to management using the HCM Risk-SCD model and organizing individuals based on their SCD risk estimate at 5 years.[4]
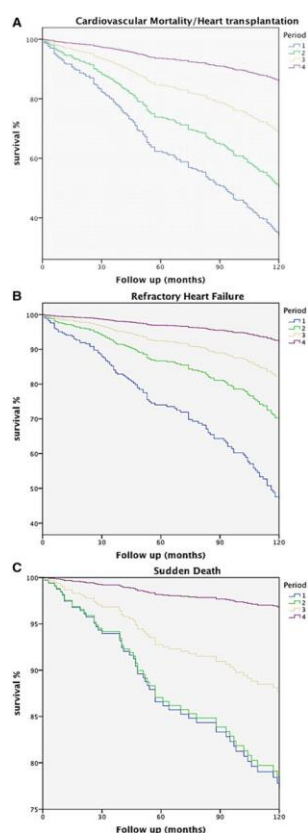
Figure 2

Cox multivariate regression survival plot (adjusted for age, New York Heart Association [NYHA] class, sex, left ventricular ejection fraction and indexed left atrium diameter) indicating differences in outcome over 4 enrollment periods in an Italian centre [(1) 1977–1984 (n=66); (2) 1985–1990 (n=102); (3) 1991–2000 (n=197); (4) 2001–2011 (n=238)] for the 3 study end points; A, All-cause mortality/heart transplantation; (B) death for refractory heart failure; and (C) sudden death. This figure illustrates the contemporary improvement in survival rates for all-cause mortality, death due to refractory heart failure and sudden cardiac death with the introduction of conventional heart failure medical therapy and ICD therapy.[9]