

## MYOCARDIAL DISEASE

## Prevention of sudden cardiac death in hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac muscle with a prevalence of 1 in 500 of the general population.<sup>w1</sup> In most adults, HCM is inherited as an autosomal dominant trait caused by mutations in genes encoding cardiac sarcomere proteins.<sup>1</sup> The disease is clinically defined by left ventricular hypertrophy (LVH) unexplained by abnormal loading conditions,<sup>2</sup> and is often associated with left ventricular outflow tract obstruction (LVOTO) caused by the systolic anterior movement of the mitral valve.<sup>w2</sup> Histologically, HCM is characterised by cardiomyocyte hypertrophy and disarray, myocardial fibrosis, and small vessel disease.<sup>1 w3</sup>

Sudden cardiac death (SCD), heart failure, and thromboembolism are the main causes of death.<sup>3</sup> Early studies of small HCM cohorts from tertiary referral centres reported cardiovascular mortality rates of ~6%/year, but later less selected studies demonstrated a more favourable clinical course with an overall cardiovascular mortality of ~2%/year.<sup>3</sup> Nevertheless, SCD still occurs with an incidence of ~0.8%/year, peaking in early adulthood.<sup>4 5</sup> As observational data suggest that implantable cardioverter defibrillators (ICDs) can prevent SCD, there is a clinical need to identify accurately individual patients at high risk.

**CAUSES OF SCD**

Numerous cardiac arrhythmias have been reported in association with SCD in HCM, including asystole,<sup>w4</sup> atrioventricular block,<sup>w5</sup> pulseless electrical activity,<sup>w6 w7</sup> and supraventricular arrhythmias.<sup>w8</sup> Data from chance electrocardiographic recordings and stored intracardiac electrograms from ICDs suggest that SCD in HCM is most commonly caused by ventricular fibrillation (VF).<sup>w9 w10</sup> The characteristic cellular disarray and cardiac hypertrophy facilitate the development of re-entry arrhythmias,<sup>w11</sup> and delayed after depolarisations caused by calcium (Ca<sup>2+</sup>) leak from the sarcoplasmic reticulum render the myocardium vulnerable to triggered activity.<sup>w12</sup> Increased myofilament Ca<sup>2+</sup> sensitivity also causes shorter effective refractory periods and increased dispersion of repolarisation, predisposing to functional re-entry.<sup>w13</sup>

Despite the presence of these proarrhythmic abnormalities, the incidence of SCD is low. This may be because ventricular arrhythmias are precipitated only when the arrhythmogenic substrate is made vulnerable by transient pathophysiologic factors such as myocardial ischaemia and LVOTO (figure 1).<sup>w14</sup> A better understanding of the arrhythmogenic substrate and its modulators is, therefore, crucial in

developing risk stratification strategies to identify those vulnerable to SCD.

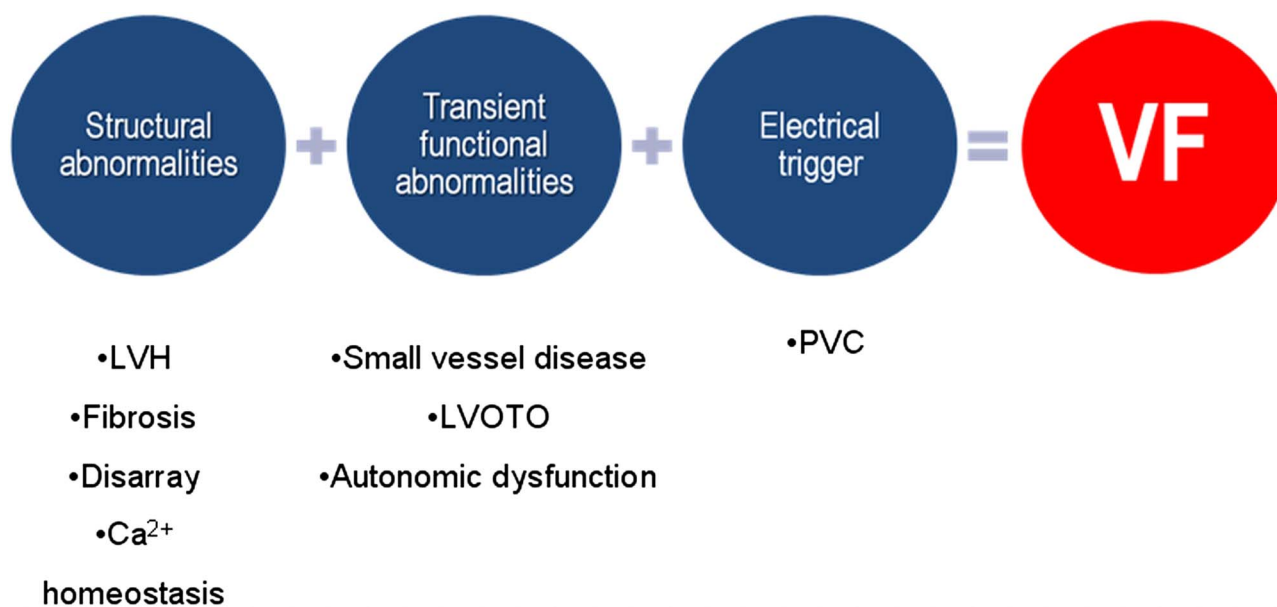
**IDENTIFYING THE HIGH RISK PATIENT**

The first step in the prevention of SCD is the identification of individuals who are at sufficiently high risk to justify prophylactic medical intervention. Data on risk stratification come principally from observational, retrospective, longitudinal cohort studies which used multivariable survival analysis to examine various clinical characteristics and their association with SCD. Five clinical characteristics are considered by international guidelines<sup>6 7</sup> as 'major' and have been the subject of a recent systematic meta-analysis<sup>8</sup> (summarised in box 1). In addition, a number of other phenotypic characteristics have been independently associated with SCD in multivariable survival analyses (also summarised in box 1). For example, the risk of SCD increases with the severity of LVOTO,<sup>9 10 w15</sup> left atrial dilation<sup>11</sup> and chronic atrial fibrillation,<sup>w16</sup> and decreases with advancing age.<sup>11</sup> Fractionation of paced right ventricular electrograms has been associated with SCD,<sup>w11</sup> but the invasive nature of this test makes it an unattractive risk stratification tool. Numerous other clinical features have been associated with SCD in univariable analyses or comparative studies—for example, left ventricular apical aneurysms<sup>w17</sup>—but the limited nature of these data makes it difficult to justify their routine use in risk stratification. Surprisingly this is also true for genotype as substantial intra- and inter-family variability, weak genotype–phenotype correlations, and the limited availability of clinical genetic testing restrict the utility of genetic information in risk prognostication.<sup>12 w18 w19</sup> Late gadolinium enhancement (LGE) on MRI has also been investigated as a risk factor of SCD. LGE represents extracellular myocardial collagen deposition and is associated with the presence of other risk factors for SCD, in particular non-sustained ventricular tachycardia (NSVT).<sup>w20</sup> A recent meta-analysis has failed to show a significant independent association between LGE and SCD.<sup>13</sup>

**Major risk factors****Non-sustained ventricular tachycardia**

Several studies have shown that NSVT, defined as ≥3 consecutive ventricular beats at ≥120 beats/min lasting <30 s, is independently associated with SCD.<sup>10 14 w21</sup> NSVT is detected in approximately 20–30% of patients on Holter monitoring and exhibits an important interaction with age, in that NSVT in patients aged ≤30 years is associated with a

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**Figure 1** Sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM). A model for SCD in HCM, modified from Myerburg *et al* (*Am J Cardiol* 1989;63:1512–16). Sarcomeric protein gene mutations cause structural and functional abnormalities promoting ventricular arrhythmias. Powerful modulators which transiently act on this substrate reduce the threshold for ventricular arrhythmias in HCM are precipitated by premature ventricular complexes.<sup>w14</sup> LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; PVC, premature ventricular contraction; VF, ventricular fibrillation.

fourfold increase in the risk of SCD, but there is no significant association in older patients.<sup>14</sup> Exercise induced ventricular arrhythmia, present in ~2% of

patients, is also independently associated with a threefold increase in SCD risk.<sup>15</sup>

#### Left ventricular hypertrophy

Severe LVH (maximum wall thickness (MWT)  $\geq 30$  mm) as assessed by echocardiography is associated with SCD,<sup>10 14 16 17 w22–w24</sup> but poor echocardiographic windows may limit patient assessment and standardised measurements should be taken to avoid observer variability. Another limitation is that the thickness of a single myocardial segment may not adequately represent the true burden of hypertrophy—for example, a patient with isolated apical hypertrophy of 20 mm is considered to have the same risk as a patient with 20 mm LVH in all myocardial segments.

#### Exercise blood pressure responses

During upright exercise testing, approximately one third of adult HCM patients develop an abnormal systolic blood pressure response to exercise (ABPRE), characterised by progressive hypotension or a failure to augment the systolic blood pressure.<sup>w25</sup> Haemodynamic studies indicate that ABPRE is caused by an inappropriate drop in systemic vascular resistance during exercise and a poor cardiac output response to exercise.<sup>w25–w27</sup> ABPRE should be assessed during a maximal symptom limited protocol and in the absence of any medication which can potentially modify the haemodynamic response. ABPRE is associated with SCD in patients  $\leq 40$  years,<sup>18</sup> but is not an independent predictor in multivariable analyses.<sup>10 14–16 w15 w24</sup> The prognostic significance of ABPRE in patients  $>40$  years has not been examined.

### Box 1 Risk factors for SCD in HCM

#### Major risk factors

- ▶ NSVT (HR 2.89, 95% CI 2.21 to 3.58)
- ▶ FHSCD (HR 1.27, 95% CI 1.16 to 1.38)
- ▶ ABPRE (HR 1.30, 95% CI 0.64 to 1.96)
- ▶ Unexplained syncope (HR 2.68, 95% CI 0.97 to 4.38)
- ▶ MWT  $\geq 30$  mm (HR 3.1, 95% CI 1.81 to 4.40)

#### Other clinical features associated with increased SCD risk

- ▶ Young age
- ▶ Left ventricular outflow tract obstruction
- ▶ Atrial fibrillation
- ▶ Left atrial dilation
- ▶ Fractionation of paced ventricular electrograms
- ▶ Myocardial ischaemia
- ▶ Genetic mutations
- ▶ Left ventricular apical aneurysm

The hazard ratio (HR) and 95% confidence intervals (CI) data are reported by Christiaans *et al*.<sup>8</sup> The difficulties in diagnosing syncope are likely to be responsible for the wide CIs. ABPRE also has wide CIs which may relate to the different definitions of ABPRE and the difficulty in measuring blood pressure during exercise. Not all of these risk factors have been shown to be independent predictors of SCD in multivariable survival analyses, which severely limits their usefulness.

ABPRE, abnormal blood pressure response to exercise; FHSCD, family history of sudden cardiac death; HCM, hypertrophic cardiomyopathy; MWT, maximal wall thickness; NSVT, non-sustained ventricular tachycardia; SCD, sudden cardiac death.

### Family history of SCD

SCD in families of patients with HCM was examined as a predictor of SCD using survival analysis in a number of studies, but only three, using different definitions for family history of SCD (FHSCD), have shown a significant association.<sup>10 w15 w21</sup> In general, FHSCD is considered significant if one or more first degree relatives died suddenly at a young age (<40–50 years of age, with or without the diagnosis of HCM) or SCD occurred in a first degree relative (at any age) with an established diagnosis of HCM. Assessing FHSCD is challenging as witnesses, death certificates, and post-mortem examinations are not always available. The significance of SCD in second degree relatives is not known.

### Unexplained syncope

The assessment of syncope in HCM is challenging as there are multiple causes including supraventricular arrhythmias,<sup>w28</sup> bradyarrhythmias,<sup>w5</sup> abnormal vascular responses,<sup>w26</sup> LVOTO,<sup>w2</sup> neurally mediated syncope (vasovagal, situational, and carotid sinus syncope), and orthostatic hypotension. Depending on the cause, treatment of the underlying mechanism may be sufficient—for example, pacing for bradyarrhythmias, or LVOTO therapy. Unexplained syncope (non-vasovagal) has been associated with SCD<sup>10 11 w24 w29</sup> and is regarded as a major risk factor in current guidelines.

## PREVENTION OF SCD

### Exercise restriction

As HCM is a cause of death in competitive athletes,<sup>w30 w31</sup> international guidelines recommend that patients with the disease should be excluded from competitive sports and discouraged from intense physical activity.<sup>6 7 w32</sup> Data on the effect of pre-participation screening on mortality are conflicting.<sup>w33 w34</sup> The exact mechanisms by which physical exertion precipitates SCD is not known, but probably include exercise induced hypotension, LVOTO, and myocardial ischaemia. However, documented exercise induced sustained ventricular arrhythmias are rare and most ICD therapies for ventricular arrhythmias occur in the absence of tachycardia or physical exertion.<sup>15 w14 w35</sup> Even though the exact risk associated with strenuous physical activity is not known, exercise restriction seems a reasonable intervention, especially in patients with risk factors for SCD and/or significant LVOTO.

### Antiarrhythmics

The class III antiarrhythmic drug amiodarone increases the threshold for VF and in one small observational study reduced SCD in HCM patients with NSVT on Holter monitoring.<sup>w36</sup> However, observational data suggest that amiodarone often fails to prevent SCD.<sup>w37</sup> The class I antiarrhythmic drug disopyramide, frequently used for the treatment of symptomatic LVOTO, does not appear to have a significant impact on SCD.<sup>w38</sup> In summary,

there are no data to support the use of antiarrhythmic agents for the prevention of SCD in HCM.

### Implantable cardioverter defibrillators

A major advance in the prevention of SCD from ventricular arrhythmias came with the development of the ICD in 1980. Randomised controlled trials have shown a survival benefit in some cardiac conditions, but there are no such data in patients with HCM. The justification for ICD therapy in HCM is that patients treated with an ICD receive appropriate shocks to terminate potentially life threatening ventricular arrhythmias<sup>19</sup> and at the same time do not die suddenly (with the exception of rare cases due to device malfunction, non-VF causes of SCD or ineffective defibrillation<sup>w7 w39 w40</sup>). These data have been interpreted as evidence of survival benefit and contemporary guidelines recommend ICD therapy for the primary and secondary prevention of SCD.<sup>6 7</sup>

Survivors of VF or sustained ventricular tachycardia are at very high risk of subsequent lethal cardiac arrhythmias<sup>20 w41</sup> and should all receive an ICD for secondary prevention. In clinical practice this population is small because most patients do not survive out-of-hospital cardiac arrest and ICD therapy in this context rarely poses dilemmas. However, as the vast majority of HCM patients do not have a prior history of cardiac arrest, identification of individuals at high risk of SCD who would benefit from a primary prevention ICD remains a challenge and is a cause of anxiety for patients and physicians alike.

In 2003, the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) jointly proposed an SCD risk stratification and treatment algorithm based on the assessment of NSVT, severe LVH (MWT  $\geq 30$  mm), FHSCD, ABPRE, and unexplained syncope.<sup>6</sup> This guidance is based on observational data that the numeric sum of risk factors in a particular patient reflects the severity of the arrhythmic substrate and is thus a manifestation of SCD risk.<sup>5 16</sup> Patients without risk factors are considered at low risk of SCD and no specific treatment is recommended. On the other hand, patients with multiple risk factors are thought to have a high enough risk of SCD to justify the implantation of an ICD. Although patients with a single risk factor have a similar incidence of SCD as those without any risk factors,<sup>5</sup> the ACC/ESC guidelines recommend that an ICD should be considered at the discretion of the treating physician.

In 2011, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published an updated treatment algorithm<sup>7</sup> with similar recommendations for patients with multiple risk factors, but with new advice that ICD implantation is reasonable treatment in patients with severe LVH, unexplained syncope or FHSCD in isolation. The 2003 ACC/ESC and the 2011 ACCF/AHA guidelines are summarised in table 1. Importantly, the ACCF/AHA guidelines consider NSVT and ABPRE as clinically

**Table 1** The 2003 ACC/ESC and 2011 ACCF/AHA guidelines

2003 ACC/ESC guidelines	2011 ACCF/AHA guidelines
Assessment	<ul style="list-style-type: none"> <li>▶ Non-sustained ventricular tachycardia</li> <li>▶ Blood pressure response to exercise</li> <li>▶ Unexplained syncope</li> <li>▶ Family history of sudden cardiac death</li> <li>▶ Maximal wall thickness</li> <li>▶ Other modifiers/risk factors</li> </ul>
Recommendation	<p>No risk factors: <i>ICD not recommended</i></p> <p>Single risk factor: Recent syncope, or maximal wall thickness &gt;30 mm or family history of sudden cardiac death: <i>ICD reasonable Consider ICD</i></p> <p>Multiple risk factors: Non-sustained ventricular tachycardia or abnormal blood pressure response to exercise with other risk factors or modifiers: <i>ICD can be useful</i></p> <p><i>ICD implantation</i> Non-sustained ventricular tachycardia or abnormal blood pressure response to exercise in isolation: <i>ICD uncertain</i></p>

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ESC, European Society of Cardiology; ICD, implantable cardioverter defibrillator.

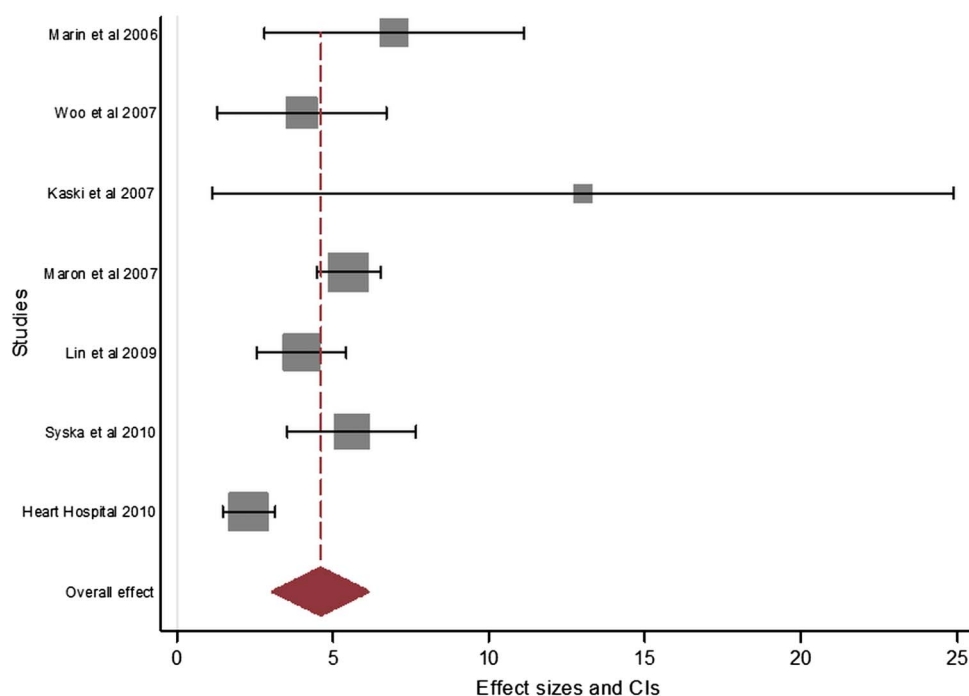
important only when they occur in the presence of other risk factors. This departure from the ACC/ESC 2003 guidelines is based on data from studies of ICD recipients where the rate of appropriate ICD shocks was not associated with the risk factor profile.<sup>19 w39 w42</sup> However, extrapolating the findings of ICD studies which consist of highly selected HCM patients to the general HCM patient population addressed by current guidelines is inappropriate.

It is important to stress that all guidelines recommend the individualisation of treatment and

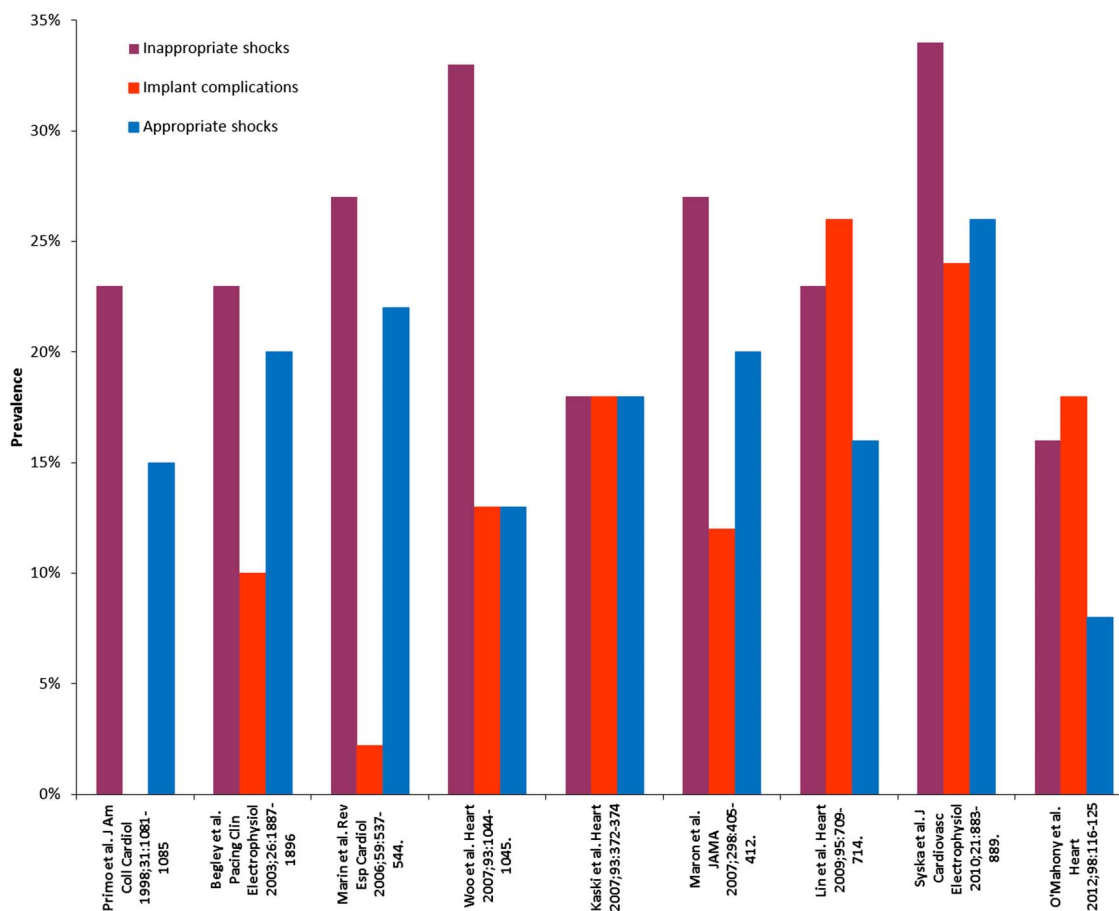
suggest the assessment of other variables such as LVOTO when evaluating risk. However, there is a lack of clear, practical advice on how to use additional information to individualise treatment. In effect, current guidelines classify patients into predefined risk groups depending on their risk factor profile, and each group is given a treatment recommendation. The failure to provide each patient with an individualised SCD risk is the biggest limitation of all contemporary guidelines.

### Outcomes of ICD recipients and the accuracy of the current risk stratification guidelines

Only a small subgroup of HCM patients treated with an ICD receives potentially lifesaving shocks to terminate ventricular arrhythmias. The overall annual incidence of appropriate shocks is 4.6% (figure 2). At the same time, a large number of ICD recipients experience inappropriate shocks and implant complications (figure 3). The accuracy of the current algorithms to discriminate high from low risk primary prevention patients has only recently been examined in a validation study using time-dependent receiver operator characteristic curves.<sup>5</sup> Existing guidelines have limited discriminatory power as indicated by an area under the curve of 0.64 and 0.63 for the ACC/ESC and ACCF/AHA algorithms, respectively (figure 4A). The 2003 ACC/ESC guidelines recommend an ICD for patients with  $\geq 2$  risk factors and the positive predictive value for SCD of this treatment threshold is 23.3% at 5 years. In comparison, the 2011 ACCF/AHA guidelines recommend



**Figure 2** Appropriate implantable cardioverter defibrillator shocks in hypertrophic cardiomyopathy. Random effect meta-analysis with adjusted weight ratios Forest plot of previously reported appropriate shock rates. The size of the box depends on the weight estimated for each study by the random effect model (Der Simonian and Laird). The confidence intervals (CIs) of each study are also shown. The overall appropriate shock rate is 4.6%/year (95% CI 3.1% to 6.1%). Reproduced from O'Mahony *et al.*<sup>19</sup>



**Figure 3** Implant complications, inappropriate and appropriate shocks in hypertrophic cardiomyopathy (HCM). The prevalence of implant complications, inappropriate shocks, and appropriate shocks in the short to medium term in patients with HCM treated with an implantable cardioverter defibrillator. The studies shown have not used uniform reporting criteria and the follow-up periods are variable (mean follow-up period range 1.7–4.9 years). Begley *et al.* (2003) and Kaski *et al.* (2007) include psychological complications. Primo *et al.* (1998) did not report implant complications. Data from O'Mahony *et al.*<sup>19</sup>

that an ICD is reasonable in patients with FHSCD, or severe LVH, or unexplained syncope, and in individuals with NSVT or ABPRE in the presence of other risk factors; the positive predictive value for SCD at this risk factor profile threshold is 10.5% at 5 years. Thus, the majority of HCM patients currently advised to have an ICD for the primary prevention of SCD are not destined to have an event in the short to medium term.

Another problem is that a large number of SCDs occur in patients who are apparently at low risk. This occurs because, even though those without any risk factors and those with a single risk factor have the lowest SCD rates, these patients form >80% of HCM cohorts, and the large size of these groups means that they contribute the largest number of SCDs (figure 4B).

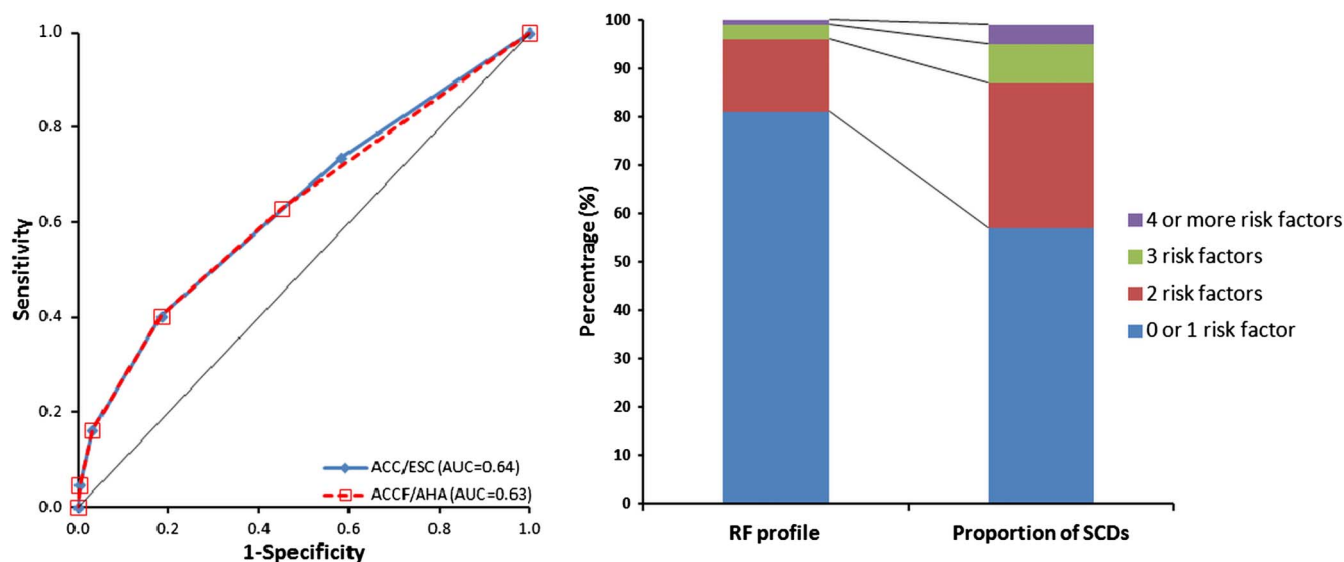
#### Risk stratification in clinical practice and practical aspects of ICD therapy

SCD risk assessment is an integral part of patient management and patients should be assessed every 1–2 years or if there is a change in clinical status—

for example, the development of unexplained syncope. In the absence of alternative risk stratification tools, patients with multiple risk factors should continue to be advised that they are likely to benefit from prophylactic ICD implantation. However, these patients should be made aware of the limited discriminatory power of the current algorithms, which means that a large number of treated patients do not experience SCD. Although the vast majority of patients without multiple risk factors have a good prognosis, the intrinsic limitations of the current risk algorithms mean that treatment of these patients will continue to be determined largely by the discretion of treating clinicians in consultation with well informed patients.

Before ICD implantation, patients should be made aware of the risk of inappropriate shocks, implant complications, and social/occupational/driving restrictions. On implantation, defibrillation testing should always be carried out as high defibrillation thresholds have been reported in patients with severe LVH and amiodarone treatment, but only a minority require epicardial lead

## Education in Heart



**Figure 4** The discriminatory power of the current sudden cardiac death (SCD) risk stratification algorithms and the relation of SCD deaths and risk factor profile. Panel A shows the area under the curve for predicting SCD at 5 years, on the basis of the five major risk factors used by current guidelines. Both the American College of Cardiology/European Society of Cardiology (ACC/ESC) and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines have limited discrimination (a perfectly discriminating risk stratification strategy yields an area under the curve of 1.0, whereas purely random predictions result in an area under the curve of 0.5). Panel B shows the relationship between the risk factor (RF) profile and the contribution of each risk group to SCD. The majority of hypertrophic cardiomyopathy patients have a favourable risk factor profile with  $\leq 1$  risk factor, and as a group have the lowest incidence of SCD. However, because this group of patients is the largest, it contributes to most SCDs. Data from O'Mahony *et al.*<sup>5</sup>

placement.<sup>w40 w43–w45</sup> As atrial leads do not reduce the incidence of inappropriate shocks and may predispose to implant complications,<sup>w39 w46</sup> the majority of HCM patients should receive a single lead ICD. However, in patients with LVOTO where pacing with a short atrioventricular (AV) delay may help reduce the severity of obstruction,<sup>w47–w49</sup> implantation of an atrial lead should be considered. Observational data from HCM patients show that

antitachycardia pacing is largely effective in terminating ventricular arrhythmias,<sup>w14 w50</sup> but may not reduce the incidence of appropriate shocks.<sup>w14</sup>

### CARE BEYOND SCD PREVENTION

HCM patients treated with an ICD are effectively protected from SCD, but are not immune to other HCM related complications such as heart failure and systemic embolisation. ICD recipients should be followed up regularly to monitor symptoms, as well as device complications. In patients who develop atrial fibrillation, anticoagulation should always be considered.

### FUTURE DIRECTIONS

No risk stratification strategy will ever be able to predict SCD with absolute certainty, but there is a clear need for improvement. Better patient selection can be achieved by identifying new predictors of SCD, but even with additional risk factors there is still a need for risk prediction models that provide accurate individualised risk estimates.

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### Prevention of sudden cardiac death in hypertrophic cardiomyopathy: key points

- ▶ Ventricular fibrillation is the most common cause of sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM).
- ▶ SCD can be prevented by implantable cardioverter defibrillator (ICD) therapy.
- ▶ Every HCM patient should undergo a comprehensive assessment of SCD risk factors (non-sustained ventricular tachycardia, family history of SCD, unexplained syncope, abnormal blood pressure response to exercise, and maximal wall thickness assessment).
- ▶ ICD therapy should be offered to those with multiple risk factors of SCD.
- ▶ Patients with no risk factors should be reassured and regularly reassessed.
- ▶ Patients with a single risk factor have a good overall prognosis, but ICD therapy can be useful in a minority.
- ▶ Current risk stratification algorithms are limited and only a minority of ICD recipients receive appropriate shock therapy.
- ▶ ICD recipients have a high risk of developing implant complications and receiving inappropriate shocks.
- ▶ There is a clear need for an SCD risk prediction model which provides individualised SCD risk estimates.

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## Prevention of sudden cardiac death in hypertrophic cardiomyopathy

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