Heart, Lung and Circulation (2019) **28,** 146–154
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.07.019

REVIEW

Sudden Cardiac Death and Ventricular Arrhythmias in Hypertrophic Cardiomyopathy

Benjamin Moore, MBBS, FRACP [a,b], Christopher Semsarian, MBBS, PhD, MPH [a,b,c], Kim H. Chan, MBBS, PhD [a,b], Raymond W. Sy, MBBS, PhD [a,b*]

[a]Sydney Medical School, University of Sydney, Sydney, NSW, Australia
[b]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia
[c]Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Sydney, NSW, Australia

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac condition, with an associated increased risk of ventricular arrhythmias and sudden cardiac death. Young and asymptomatic patients, including professional athletes, are not spared this risk. Implantable cardiac defibrillators (ICDs) are highly effective in terminating malignant ventricular arrhythmias in this group, but they are associated with significant morbidity, such as inappropriate shocks and device complications. Accurate prognostication to guide ICD implantation is therefore essential. The interplay of traditional risk factors, risk modifiers and predictive models creates a complex decision-making environment for the HCM clinician. Risk stratifying tools are expanding with improved understanding of advanced imaging modalities, such as late gadolinium enhancement on cardiac magnetic resonance imaging (cMRI). Once the decision to implant a defibrillator is reached, the choice of device and programming in HCM is unique and should take into account disease substrate and younger age of patients.

Keywords Hypertrophic cardiomyopathy • Sudden cardiac death • Defibrillator • Ventricular arrhythmias

Introduction

The first cases of hypertrophic cardiomyopathy (HCM) were described post-mortem in 1958, with ''tumour-like left ventricular hypertrophy'' identified in eight individuals who died suddenly and unexpectedly [1]. HCM is now recognised as the most common inherited cardiac disease, with an incidence of up to 1 in 200 live births [2,3]. These individuals are indeed at higher risk of malignant ventricular arrhythmias and sudden cardiac death (SCD); annual SCD rates in the modern era approximate 0.5–1% [4–6]. One of the major clinical challenges is the identification of the ''at risk'' patient, amongst a relatively young cohort of patients including professional athletes [4,7]. This review describes our current understanding of the pathophysiology, risk factors, prevention and management of ventricular arrhythmias and prevention of SCD in HCM.

Pathophysiology of Ventricular Arrhythmias

Regions of marked hypertrophy in HCM correspond histologically to disorganised cardiomyocyte architecture, with fibrosis and increased deposition of collagen matrix [8,9]. Electrophysiological findings include local conduction delay or block, abnormally fractionated electrograms and reduced voltages [10]. Late gadolinium enhancement on cardiac MRI (cMRI) represents this fibrotic change non-invasively [11]. Ischaemia may also play a role in arrhythmogenesis. Intramural coronary arteries, coursing through hypertrophied myocardium, can remodel over time with wall hypertrophy and luminal narrowing [12]. This may result in downstream myocardial necrosis [13].

On detailed analysis of intracardiac electrograms in high-risk HCM patients with implantable cardiac defibrillators

*Corresponding author at: Department of Cardiology, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, NSW, 2050, Australia. Tel.: +612 9515 8063, Fax: 612 9550 6262., Email: raymond.sy01@gmail.com

(ICDs), both monomorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) were observed with similar frequency [14]. Whilst VF may initiate in disorganised myocardial substrate, monomorphic VT probably represents scar-related re-entry in most cases. Efficacy of anti-tachycardia pacing further supports a re-entrant mechanism [15]. Finally, the HCM substrate appears vulnerable to sympathetic drive, with sinus tachycardia or rapidly conducted atrial fibrillation being frequently observed prior to VT or VF [14]. This may, in part, explain SCD on exertion in professional athletes with HCM.

Prediction of Sudden Cardiac Death

Since the advent of ICDs, significant attention has been given to the prediction and prevention of SCD in the relatively young HCM population. However, contemporary recommendations are largely based on observational and/or retrospective data, rather than from randomised controlled data [16,17]. This is reflected in the differing approaches of international guidelines in their interpretation of current known risk factors for SCD [18–20]. Figure 1 summarises risk factors for SCD in HCM, with the associated strength of recommendation for an ICD.

Established Risk Factors

There is widespread agreement that a **personal history of resuscitated cardiac arrest, VF or sustained VT** confers a high risk of recurrent events [21,22]. These patients should universally be offered ICDs as a class I indication [18,19].

A **family history of a first degree relative suffering SCD or resuscitated cardiac arrest** is associated with a relative

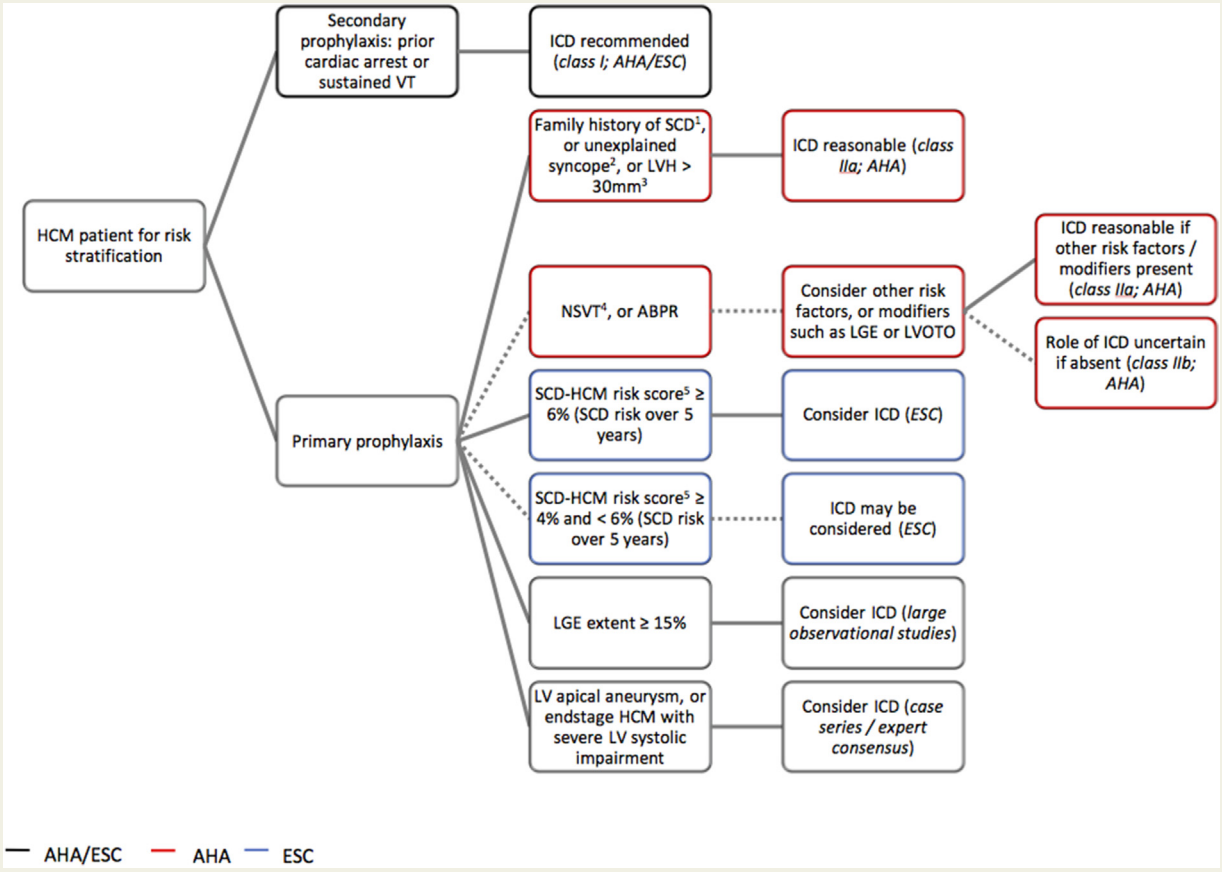

Figure 1 Indications for implantation of defibrillators in HCM.
[1]Risk increased if multiple family members affected, particularly at a younger age.
[2]Risk increased if syncopal episode within last 6 months.
[3]Risk increased in younger patients.
[4]Risk may be increased with more frequent and prolonged episodes.
[5]O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J. 2014;35(30):2010-20.
Abbreviations: HCM, hypertrophic cardiomyopathy; VT, ventricular tachycardia; ICD, implantable cardiac defibrillator; SCD, sudden cardiac death; LVH, left ventricular hypertrophy; NSVT, non-sustained ventricular tachycardia; ABPR, abnormal blood pressure response; LGE, late gadolinium enhancement; LVOTO, left ventricular outflow tract obstruction; LV, left ventricle; EF, ejection fraction.

increased risk of SCD in the order of 20%, compared to HCM patients without significant family history [23]. Although there is some heterogeneity in the definition of ''significant family history" in the literature, (ranging from one affected family member under 50 years of age to at least two first degree relatives [24,25]), current guidelines have accepted any affected first degree relative to be sufficient. Risk almost certainly increases if multiple family members have suffered SCD or resuscitated cardiac arrest, particularly at a younger age [26].

Unexplained syncope was found to increase the risk of sudden death in a retrospective multicentre study of 1,511 patients [27]. The effect was most marked (at five-fold) in those with recent episodes within the previous 6 months. Conversely, patients older than 40 with a syncopal episode ≥5 years ago did not have an elevated risk. Syncope conferred the highest risk of any isolated risk factor for appropriate ICD interventions (five interventions per 100 patient years followed) in a HCM ICD registry study [28]. Guidelines allow consideration of any unexplained syncopal episode, with a recent event of particular concern.

Increasing magnitude of left ventricular hypertrophy (LVH) is associated with risk of SCD in a linear relationship [29]. The risk when septal hypertrophy exceeds 30 mm is particularly marked, even moreso in younger patients [15,29,30]. The negative predictive value of this cut-off is limited however, as most SCD occurs in those with <30 mm of hypertrophy [30].

Non-sustained ventricular tachycardia (NSVT) has been found to increase risk of SCD [31] and of appropriate shocks in HCM ICD populations [32]. It is important to note that NSVT is common in HCM, occurring in up to 30%, and hence positive predictive value for SCD is low [33]. It remains unclear whether NSVT of any duration increases risk equally [31], or whether sustained and more frequent runs convey a greater risk [32]. Until this issue is clarified, it is reasonable to monitor the burden of NSVT, either via Holter or more prolonged monitoring, in borderline cases [18]. It may be that more ''haemodynamically compromising" NSVT conveys a worse prognosis, with one study of 230 patients finding SCD risk was only increased in the setting of NSVT associated with impaired consciousness [34].

An **abnormal blood pressure response (ABPR) to exercise** is commonly seen in up to 33% of HCM patients, but has been associated with an increased risk of SCD [35]. ABPR is defined either as a failure to augment systolic blood pressure by at least 20 mmHg, or by a fall of at least 20 mmHg during exercise. Positive predictive value is unsurprisingly low at 15% [35], and as a result this factor is rarely the sole indication for an ICD [16].

Late Gadolinium Enhancement (LGE) on Cardiac MRI

There is now a growing body of evidence correlating LGE with risk of SCD in HCM (Figure 2). A recent meta-analysis of five studies and 2,993 patients found that the presence of LGE was associated with an odds ratio of 3.41 for SCD [36]. In 1293 patients prospectively followed after cMRI, Chan et al. correlated the *extent* of LGE (as percentage of LV mass) to magnitude of risk in a linear fashion [37]. Notably, a LGE extent ≥15% conveyed a two-fold increased risk in otherwise ''low risk" patients by traditional assessment. Absence of LGE was associated with a lower risk irrespective of other risk factors, but was *not* absolutely protective against SCD. In a sub-analysis of the same patients, focal LGE at the right ventricular attachment to the inter-ventricular septum appeared to be a benign variant [38]. Presence of LGE has been correlated to ventricular ectopic and NSVT burden on Holter monitoring [39].

In interpreting Chan et al.'s study [37], it is important, firstly, to recognise that HCM patients with a pre-existing ICD were excluded, thus selecting out a ''lower risk" population and potentially overestimating the statistical effect of LGE compared to traditional risk factors. Secondly, a 24-hour electrocardiogram (ECG) trace was not performed in 24% of the ''low risk" cohort, and thus, NSVT may have been under-detected. Finally, the predictive power of the study was generated predominantly via patients who had ICD implantation, and received appropriate therapy classified as a ''sudden death event". When ICD therapy was set aside from the analysis, 16/20 SCD events occurred in the presence of minimal LGE. It is also notable that inter-observer variability in quantifying LGE remains an issue [40]. At present, it seems reasonable to use LGE as a modifying factor or arbitrator in borderline cases, and with further research, it may become a potential stand-alone indication in otherwise low-risk patients with a very high LGE burden.

Unique High-Risk Groups

Two subsets of HCM patients with abnormal left ventricles warrant special consideration for ICDs. Left ventricular apical aneurysm, albeit uncommon, appears to significantly increase the risk of SCD with reported annual rates of 4.7% [41]. Apical HCM variants are more susceptible to aneurysmal formation. End-stage HCM manifests as LV systolic impairment, with widespread scarring and chamber dilatation. These patients have an increased risk of appropriate shocks in ICD registries, and defibrillator implantation should be considered when LV systolic function is severely impaired as per standard guidelines [15,42].

Areas of Uncertainty or Limited Utility in Risk Stratification

A weak association between left ventricular outflow tract (LVOT) gradient >30 mmHg and SCD has been reported in two studies [43,44], but the observation has not been reproducible [45]. One of the limitations is that LVOT gradient fluctuates as loading conditions change. As a result, this factor should not be used in isolation to guide defibrillator implantation, but can be considered as a modifying factor in borderline cases. Left atrial dilatation [46], fragmentation of the QRS complex and longer QTc interval [47] may add

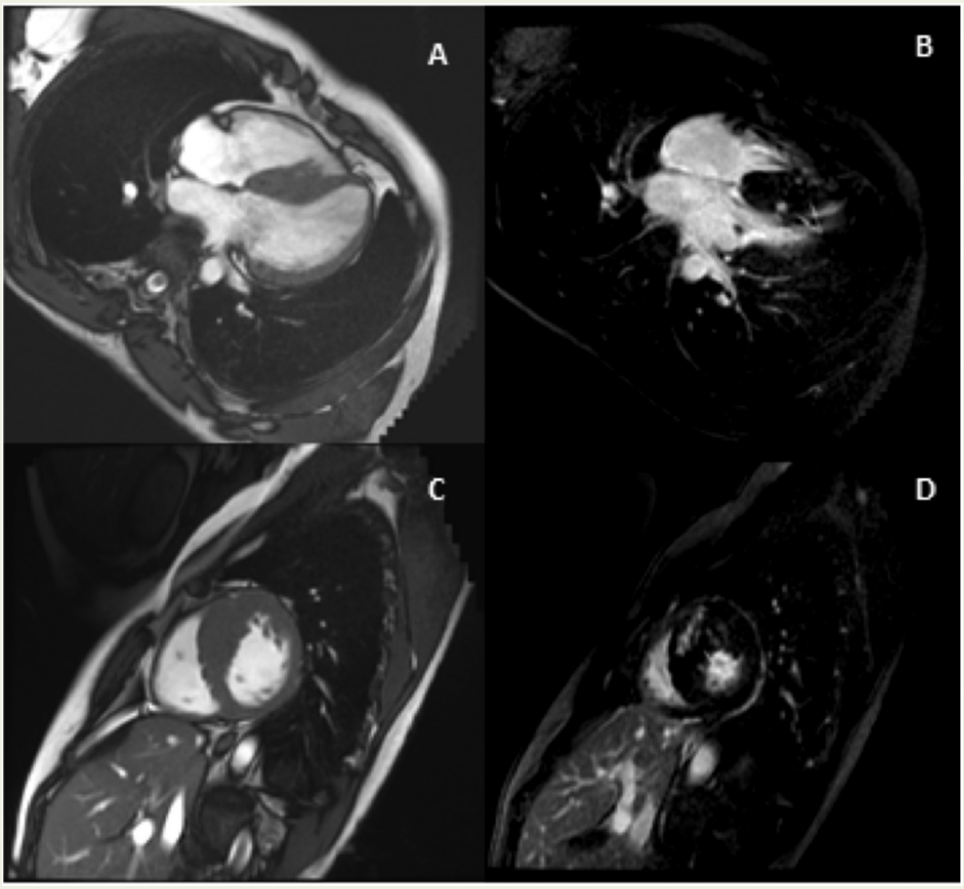

Figure 2 Late gadolinium enhancement on cardiac MRI in HCM.
A: Four chamber view (steady-state free precession).
B: Four chamber view, late-gadolinium enhancement in septum indicated by green arrows.
C: Short axis view (steady-state free precession).
D: Short axis view, late gadolinium enhancement again indicated by green arrow.
Abbreviations: MRI, magnetic resonance imaging; HCM, hypertrophic cardiomyopathy

incremental value, but require further validation before mainstream application.

The rapid expansion of genetic testing will almost certainly lead to a more pivotal role in HCM risk stratification in the future [48]. High risk families, such as those with *MYH7* mutations or multiple mutations, have been identified [26,49,50]. Nevertheless, the extreme genetic heterogeneity in HCM precludes routine genome-guided risk stratification for the present time.

There is now a consensus that routine electrophysiological testing does not have a role in risk stratification of HCM, and it can be associated with significant adverse events [18,19]. Although studies from the 1990s suggested a link between induced VT and future cardiac arrest [34], these patients were typically ''high-risk'' already by today's standards, stimulation protocols were aggressive and endpoints were non-specific with polymorphic VT being the most common induced arrhythmia. In modern cohorts, there does not appear to be any link between induced arrhythmias and appropriate ICD discharges [14].

Synthesising the Evidence: Current Guidelines and Risk Models

The 2011 ACCF/AHA guidelines advocate for appraisal of individual risk factors in ICD decision making [19]. The presence of either a family history of SCD, unexplained syncope or severe LVH generates a class IIa indication for an ICD. NSVT and an ABPR are class IIb indications in isolation, with a strengthened IIa recommendation if a ''modifier'' is present (such as significant LGE on cMRI). Total risk can be additive when $\geq$2 risk factors are present [31], but a significant proportion of appropriate ICD shocks occur in patients with a single risk factor [51]; this warns against necessitating that multiple risk factors be present for an ICD indication. Importantly, age over 60 years, even in the presence of risk factors, appears to be protective [52]. Interestingly, in a recent registry study of childhood-diagnosed HCM (with median 16-year follow-up), the overall risk of

SCD was low (<2% per decade), albeit remaining the single most common cause of late death [53]. Implantable cardiac defibrillators were implanted in 21% of the population. Limitations in the evidence base for prediction of SCD render the ACCF/AHA guidelines imperfect, with a single risk factor often having a low positive predictive value and SCDs still occurring in low-risk individuals.

In an attempt to address limitations in the ''risk factor'' approach, the European Society of Cardiology (ESC) moved to a risk prediction model in 2014 [18]. This was designed from a retrospective multicentre cohort of 3,675 HCM patients, with all predictors of SCD (of ≥15% significance) extracted and given a relative weight in the model [46]. High risk of SCD was defined as ≥6% over 5 years and low risk as ≤4% over 5 years. Statistical validation in retrospective 706 and 502 patient cohorts concluded that it had a better discriminative C-statistic than the existing ''risk factor'' approach [54,55]. However, application to a real-world cohort of 1,629 American Heart Association (AHA) risk stratified patients, found that only 20% who had suffered SCD or appropriate shocks were deemed ''high risk'' by the ESC risk model [56]. The authors suggested caution before accepting the ESC model as current standard of care.

At present, whether individual risk factors, modifiers or a risk model are applied, the decision on whether to implant a defibrillator must be made on a case-by-case basis, taking into account patient preferences and limitations of current evidence.

Implantable Cardioverter Defibrillators

Efficacy

The efficacy and utility of ICDs in HCM has now been well established in the literature. In the largest study of 506 adults with ICDs followed for a mean of 3.7 years, the rate of appropriate intervention for secondary prevention patients was 10.6% per year and for primary prevention was 3.6% per year [28]. Other smaller studies [15,57,58], including paediatric and adolescent cohorts [59], have reported similar results with high rates of effective defibrillation. Not infrequently, a lag time of up to 10 or more years between implantation and first appropriate shock has been observed [60], highlighting the unpredictability of the arrhythmogenic substrate. It is worth noting, however, that ''appropriate ICD therapy'' includes many VT events that may have been self-terminating, particularly in the era of programmed long-detection zones [61], therefore does not represent an exact surrogate for prevented SCD.

Transvenous ICDs and Defibrillation Threshold Testing

Table 1 displays common decisions that need to be considered in device selection, implantation and programming specific to HCM. Given the potential need for multiple lead implants in this younger population, a single chamber ICD should be implanted in the vast majority of cases [18]. Furthermore, the addition of an atrial lead does not reduce inappropriate shocks [62]. Certain exceptions that warrant a dual chamber device exist, namely: a co-existing indication for pacing, impaired left ventricular systolic function with potential need for cardiac resynchronisation or elderly patients with drug-refractory symptomatic severe LVOT obstruction [18,19]. Symptomatic relief has been reported in the latter group with sequential pacing using a short AV delay [63].

Defibrillation threshold testing is no longer an absolute requirement in HCM, but rather left to the physician's discretion. Defibrillation thresholds in 89 HCM patients were similar to 600 controls [64], prompting the authors of that study to argue against routine testing. Massive LVH and concurrent amiodarone use, however, have been associated with unsuccessful defibrillation threshold testing (DFT) testing by others [62,65,66]. Dual coil defibrillators have historically been favoured due to concerns regarding DFT, even though single coil leads are easier to extract. In a small study of 20 patients, equally effective defibrillation at 25J was achieved with the SVC coil turned ''on'' or ''off'' (i.e. effectively acting as a single coil device in the ''off'' mode) [67].

Complications of ICDs and Programming Considerations

Five-year lead failure rates range from 5 to 15% in HCM [68,69]. Patients with HCM are typically younger than those with acquired cardiac disease, and as such they have a higher cumulative incidence of lead fractures, which may be further compounded by the association between increased activity levels and lead stress [60,70]. Rates of infection and haemorrhage/thrombosis in HCM ICD patients approximately parallel the general ICD population (3.8% and 1.6% respectively in a cohort followed for a median of 3.7 years) [28].

Inappropriate shocks remain the most common complication of ICDs in HCM, with a psychological impact that should not be underestimated [28,57,62]; annual incidence is 5–6% [62,71]. Younger age and co-existing atrial fibrillation increase risk, with the latter documented in over 50% of inappropriate shocks [62]. T-wave oversensing is implicated in a smaller subset. Anti-tachycardia pacing is reasonably efficacious in terminating monomorphic VT in HCM [14,15], but unfortunately does not seem to reduce appropriate shocks [72]. Higher rate treatment zones for fast VT or VF, coupled with delayed therapy, may help to reduce this burden [14,71,73]. Disappointingly, the rate of inappropriate shocks remained high in a cohort of HCM ICD patients with modern programming algorithms (62). European Society of Cardiology guidelines recommend a VF zone of >220 bpm [18]. Algorithms for discriminating ventricular and supraventricular tachycardia may also be considered, although

Table 1 **Decision making in device selection and programming for HCM patients.**

Decision	Considerations
Single or dual chamber?	*Single*
	• Guideline recommended first line.
	• Potential for multiple leads in young patient.
	• Atrial lead does not reduce inappropriate shocks.
	Dual
	• Concurrent pacing indication.
	• Concurrent CRT indication.
	• Elderly with symptomatic LVOT obstruction for sequential short AV delay pacing.
DFT?	• Not routinely required – physician discretion.
	• Massive LVH or amiodarone use may increase threshold – consider testing.
Single or dual coil?	*Single*
	• Easier to extract single coil lead.
	Dual
	• No evidence that dual coil leads significantly reduce DFT in HCM.
ATP?	• Effective in terminating monomorphic VT in HCM.
	• Not proven to reduce appropriate shocks.
Treatment zones?	• Consider dual zone programming and long detection window.
	• VF zone >220 bpm recommended to reduce inappropriate shocks from rapidly conducted AF/SVT.
SVT discriminators?	• May reduce inappropriate shocks, but evidence lacking for benefit in HCM.
Subcutaneous ICD?	• Reduce transvenous lead complications in younger HCM patients.
	• Careful screening – HCM associated with screening failure.
	• T-wave oversensing most common cause of inappropriate shocks in HCM.
	• Increased BMI may increase threshold for defibrillation.

Abbreviations: CRT, cardiac resynchronisation; LVOT, left ventricular outflow tract; AV, atrio-ventricular; LVH, left ventricular hypertrophy; DFT, defibrillation threshold testing; ATP, anti-tachycardia pacing; VT, ventricular tachycardia; HCM, hypertrophic cardiomyopathy; VF, ventricular fibrillation; AF, atrial fibrillation; SVT, supraventricular tachycardia; BMI, body mass index.

evidence for their efficacy in this population is lacking at present [72].

Subcutaneous ICD (S-ICD)

The S-ICD offers significant potential benefits for the young HCM population, who are particularly exposed to the lifetime risk of lead complications associated with transvenous devices. In the largest study to date, pooling registry data that included 99 patients with HCM [74], DFT testing was successful at implant in 98.9%. Over 637 days of follow-up, three appropriate shocks were delivered to HCM patients without incident. Inappropriate shocks occurred in 6.9% per year, the majority due to T-wave oversensing. Dual zone programming reduced inappropriate shocks from SVT/AF by 47%. A cautionary note should be taken from a smaller study of 15 HCM S-ICD patients, which found increased body mass index was associated with DFT failure [75]. Furthermore HCM itself is associated with *screening* failure [76], and testing in multiple postures, as well as with exercise, seems prudent. It is possible that S-ICD may find increased utility in patients with HCM conditional upon careful patient selection.

Other Non-Device Interventions for Ventricular Arrhythmias

Medical Therapy

It is now well established that both SCD and appropriate shocks in HCM commonly occur on anti-arrhythmics, such as amiodarone [4,28,77]. Pharmacological strategies may have a role in reducing the burden of shocks, or attempting to address inappropriate shocks due to rapidly conducted SVTs, but should not be regarded as a primary preventative measure for SCD.

Catheter Ablation

Catheter ablation of monomorphic VT in HCM appears to have a role for symptomatic relief in carefully selected cases. There is no evidence for ablation as a tool to reduce SCD risk. Case reports and small case series initially described positive outcomes in patients with recurrent VT and shocks, in the setting of a LV apical aneurysm [41,78–80]. Multiple procedures or epicardial ablation were frequently required, with the critical isthmus generally found at the interface of viable

myocardium and scarred aneurysmal myocardium. Outside of the apical aneurysm subgroup, the largest series of ablations for refractory VT was performed in 22 HCM patients with a mean ejection fraction of 34% [81]. Seventy-three per cent were rendered free of VT at 20 months post ablation and 59% required epicardial access. The most common location for ablation was the LV–RV junction at the terminal insertion of the interventricular septum. One case of bundle-branch reentry VT was ablated. In a smaller series of 10 patients, epicardial scar was again prevalent in 80% of patients, with 60% having endocardial scar [82]. Septal thickness may impede the delivery of effective endocardial ablation lesions.

Cardiac Sympathetic Denervation (CSD)

In a small number of HCM patients with symptomatic ventricular arrhythmias refractory to anti-arrhythmics and/or catheter ablation, CSD has successfully achieved a significant reduction in arrhythmia burden over short to medium term follow-up [83,84]. This procedure was traditionally described in patients with long QT syndrome or catecholaminergic polymorphic VT [85]. Via a surgical thoracoscopic approach, the lower half of the stellate ganglion (T1) and the T2-4 ganglia are removed, thus reducing sympathetic input to the left ventricle [86]. This is more commonly done on the left side alone, although relative efficacy of unilateral versus bilateral CSD is still contentious. Complication rates are reasonably low, with transient Horner's syndrome or change in sweating pattern occurring uncommonly. Although evidence is limited to a small number of published cases in HCM, the future use of CSD in refractory cases may expand, particularly given the evidence for increased sympathetic drive precipitating arrhythmias in HCM [14].

Septal Reduction

Surgical myectomy has been found to reduce appropriate ICD discharges compared to untreated HCM in 125 patients (56 post-myectomy, 69 non-operated), although this observational study by itself should not justify myectomy as prophylactic against SCD [87]. The relative arrhythmogenesis of alcohol septal ablation (ASA) versus surgical myectomy is more controversial. In small studies, the rate of ICD discharges was fourfold higher in ASA [28], attributed theoretically to the transmural infarct generated. However a meta-analysis of 19 ASA and eight myectomy studies found similar low rates of SCD after each intervention [88], albeit with a much shorter follow-up in the ASA group. This renders long-term interpretation difficult without assuming a linear rate of SCD after ASA.

Conclusions

Our ability to predict and prevent SCD in HCM has significantly improved over the last few decades. The need to further refine risk stratification however, is understated by the low positive predictive value of existing risk factors and by cases of SCD still occurring, albeit less frequently, in "low-risk" groups. Genetic risk stratification and advanced imaging techniques will likely play an increasing role. Improved device programming and the S-ICD will hopefully reduce both inappropriate shocks and lead complications in this susceptible young population.

Acknowledgements

CS is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (#1059156).

We thank Dr Raj Puranik for his assistance with the cardiac MRI images in this review.

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