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Review on sudden death risk reduction after septal reduction therapies in hypertrophic obstructive cardiomyopathy

Angelos G. Rigopoulos[1] · Muhammad Ali[1] · Elena Abate[1] · Marios Matiakis[1] · Hannes Melnyk[1] · Sophie Mavrogeni[2] · Dionyssios Leftheriotis[3] · Boris Bigalke[4] · Michel Noutsias[1]

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Abstract

Treatment of left ventricular outflow tract (LVOT) obstruction in hypertrophic obstructive cardiomyopathy (HOCM) with septal reduction, either with myectomy or alcohol septal ablation, is aiming to reduce the LVOT gradient and improve symptoms in patients who are refractory to or do not tolerate medical treatment. Apart from contributing to the evolution to heart failure, LVOT obstruction is considered a risk factor for sudden cardiac death (SCD). Both septal reduction treatments have been proven effective in reducing symptoms and seem to improve survival, which has been shown equal to the expected in the normal population. SCD is probably reduced after septal reduction, implying that LVOT obstruction is a major factor predisposing to ventricular tachyarrhythmias. Although available algorithms for SCD stratification have not been tested in patients after septal reduction treatments, effective treatment improves SCD risk profile substantially. Furthermore, high-risk patients with already implanted implantable cardioverter defibrillators (ICDs) before septal reduction show very low appropriate ICD shock rate after effective treatment. It should be noted, however, that the best outcomes for septal myectomy or ablation have been reported in HOCM patients treated in high-volume centres, which substantiates the need to refer patients to centres with high procedural expertise.

Keywords Hypertrophic obstructive cardiomyopathy · Outcome · Surgical myectomy · Treatment · Alcohol septal ablation · Sudden cardiac death · Risk stratification · Prognosis

Abbreviations

ACC American College of Cardiology
AHA American Heart Association
ASA Alcohol septal ablation

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✉ Angelos G. Rigopoulos
angelos.rigopoulos@gmail.com; angelos.rigopoulos@uk-halle.de

Muhammad Ali
Muhammad.Ali@uk-halle.de

Elena Abate
elena.abate@uk-halle.de

Marios Matiakis
marios.matiakis@uk-halle.de

Sophie Mavrogeni
sophie.mavrogeni@gmail.com

Dionyssios Leftheriotis
dleftheriotis@googlemail.com

Boris Bigalke
boris.bigalke@charite.de

Michel Noutsias
michel.noutsias@uk-halle.de

[1] Mid-German Heart Center, Department of Internal Medicine III, Division of Cardiology, Angiology and Intensive Medical Care, University Hospital Halle, Martin-Luther-University Halle-Wittenberg, Ernst-Grube-Strasse 40, 06120 Halle (Saale), Germany

[2] Onassis Cardiac Surgery Center, 50 Esperou Street, Palaeo Faliro, 17561 Athens, Greece

[3] 2nd Department of Cardiology, University of Athens, Attikon University Hospital, Rimini St. 1, Haidari, 12462 Athens, Greece

[4] Department of Cardiology, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany

CMR	Cardiac magnetic resonance
ESC	European Society of Cardiology
HCM	Hypertrophic cardiomyopathy
HOCM	Hypertrophic obstructive cardiomyopathy
ICD	Implantable cardioverter defibrillator
LGE	Late gadolinium enhancement
LV	Left ventricular
LVOT	Left ventricular outflow tract
SAM	Systolic anterior motion
SCD	Sudden cardiac death

Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited cardiac conditions, with a prevalence of 1:500 in the general population [1]. It is characterised by the presence of increased left ventricular (LV) wall thickness of various morphologies and a wide spectrum of clinical and haemodynamic manifestations. The structural as well as the functional abnormalities of the ventricular myocardium in HCM are not explained by inappropriate loading conditions or other cardiac conditions, such as valve or congenital defects. About two thirds of the patients present a dynamic obstruction in the LV cavity (hypertrophic obstructive cardiomyopathy, HOCM), which can be present at rest or appear only after provocation [2]. LV obstruction in HCM is associated with greater propensity to develop heart failure symptoms, exertional syncope, or SCD [3].

The typical area of obstruction, which is readily addressed by septal reduction treatments, is the left ventricular outflow tract (LVOT). Drag forces lead to systolic anterior motion (SAM) of the mitral valve during ventricular ejection, which leads to LVOT obstruction and concomitant leak of the mitral valve [4, 5]. Due to its dynamic nature, LVOT obstruction can be influenced by numerous physiological conditions, as well as drugs, which either reduce preload or afterload or increase contractility (Table 1). This is something that should always be considered during the assessment of HOCM patients and the decision-making for the most appropriate treatment.

Treatment of patients with severe LVOT obstruction and drug refractory symptoms of heart failure, either with surgery (myectomy) or intervention (alcohol septal ablation; ASA), has shown efficacy in relieving heart failure symptoms, improving quality of life and long-term survival [7–10]. HOCM and the status after septal ablation have been entered in the MOGE(S) classification of cardiomyopathies [11]. The MOGE(S) classification is a phenotype-genotype-based classification system for cardiomyopathies, which follows the TNM classification scheme for tumours. It is based on five attributes, including morphofunctional characteristics (M), organ involvement (O), genetic or familial inheritance pattern (G), etiological annotation (E) and optional information about the functional status (S) using the American College of Cardiology/American Heart Association (ACC/AHA) stages A–D and/or the New York Heart Association (NYHA) functional classes I–IV.

Obstruction and risk of SCD

An LVOT gradient > 30 mmHg either at rest or with provocation signifies the diagnosis of HOCM. Apart from the worsening quality of life, existence of obstruction at rest is associated with a bad prognosis, underscored by progression to heart failure and death from heart failure and stroke [3]. Invasive reduction of LVOT obstruction seems to improve survival in comparison with conservative treatment [12].

The presence of a resting intraventricular gradient has been also associated with increased rates of SCD; however, as SCD is a rather rare event, the observed difference between obstructive and nonobstructive patients was relatively small (0.6%/year) with patients with LVOT obstruction having an annual SCD risk of 1.5% [3]. Interestingly, patients already at NYHA class III or IV were excluded from this analysis. In a study from a different patient population, not only the existence of a resting gradient (as a binary variable) was associated with the

Table 1 Clinical risk factors for SCD in HCM according to ACC/ESC consensus 2003 and 2011 ACC/AHA Guidelines for HCM. Definitions according to [6]

Risk factor	Examination	Criteria of positivity
Nonsustained ventricular tachycardia	48-h Holter monitoring	Run of three or more consecutive ventricular beats at a rate of ≥ 120 beats/min, lasting < 30 s
Abnormal exercise blood pressure response	Exercise test in the upright position	Failure of blood pressure to rise, or a fall in blood pressure during exercise
Family history of premature sudden death	Family history—pedigree	Sudden cardiac death in two or more first-degree relatives < 40 years old
Unexplained syncope	Personal history	One or more episodes of unexplained loss of consciousness within the last 12 months
Severe left ventricular hypertrophy	Cardiac imaging	Maximal wall thickness ≥ 30 mm

risk of sudden death, but there was also an association of the SCD rate with the magnitude of the gradient. The prediction of risk in this study did not relate entirely to the presence of an LVOT obstruction but was additionally dependent on the existence of other clinical risk factors (Table 1). The risk of SCD in asymptomatic HOCM patients with LVOT obstruction but no other risk factors was relatively low (< 0.4%/year) [13].

In the last two decades, it has been acknowledged that ICD implantation in HCM patients with presumed increased risk for sudden cardiac death (SCD) improves survival. It is believed that HCM nowadays can be considered a condition characterised by low mortality, mainly owing to the application of contemporary treatments such as ICD and septal reduction therapy [14]. Nonetheless, a more liberal use of ICDs for HCM or HOCM patients with a presumed SCD risk would be counterbalanced by the high rate of inappropriate shocks equalling the rate of appropriate shocks (about 5% per year) [15], as well as of course the complications related to the ICD implantation, which are not negligible [16].

Risk stratification for SCD in HOCM

The endeavour for a risk stratification model for the primary prevention of SCD in HCM began already before the end of the last century. The initial model according to the American College of Cardiology (ACC)/European Society of Cardiology (ESC) consensus was based on the evaluation of 5 clinical risk factors (Table 1) [17]. The presence of ≥ 2 of these risk factors would warrant ICD implantation. A modified model was presented in the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines, in which family history of SCD, severe LV hypertrophy and recent unexplained syncope were considered more significant so that the presence of only one of them would be enough to indicate ICD implantation. The other two remaining risk factors would need the presence of additional parameters in order to pass the threshold for ICD indication [18].

The recent European Guidelines for HCM introduced the HCM SCD risk score calculated by a complex mathematical formula based on the old clinical risk factors (with the exclusion of the abnormal blood pressure response) and with the incorporation of three more parameters, evaluated as continuous variables (age, left atrial diameter, LVOT gradient). This score represents the expected SCD risk in the next 5 years. A score under 4% signifies low risk, while a score over 6% signifies high risk and would warrant ICD implantation. For a score between those values (intermediate risk) an ICD could be considered according to the weight of the individual risk factors and clinical judgement [1]. An online calculator is also available (http://www.doc2do.com/hcm/webHCM.html). The development of the ESC HCM SCD risk score is based on a multicentre, retrospective, longitudinal cohort study of 3675 patients [19]. For the time being, it seems that this model is the best tool we have for the prediction of SCD in HCM. Validation studies have shown its superiority in comparison with the older models [20–22].

Based on the ESC HCM SCD risk score, a high LVOT gradient can lead to a completely different recommendation for ICD implantation (Table 2). Nevertheless, the existence of a high gradient does not seem to influence the decision of clinical experts, who would decide based on clinical judgement [23]. In fact, as the ESC HCM SCD risk score has not been developed for patients after septal reduction treatments, we should not use it to estimate SCD risk after a supposedly effective treatment in the patient example of Table 2; however, a primarily non-significant gradient (25 mmHg) without any change in the other patient characteristics and risk factors would yield a substantially reduced expected SCD risk and thus alter the recommendation for ICD implantation. In a way, it seems that LVOT obstruction, being a continuous variable, is being regarded as a modifiable risk factor for SCD, whose reduction, i.e. after septal reduction treatment, could mitigate SCD risk.

Septal reduction therapies and SCD mortality

There are mainly two available invasive treatment modalities for septal reduction in HOCM. The historically older is the surgical myectomy, during which the surgeon removes a part of the hypertrophied septum through an aortotomy, thus widening the LVOT [24]. The more recently introduced and less invasive than surgery is the ASA, in which the interventional cardiologist injects alcohol in the septal perforator branch perfusing the basal part of the septum involved in the obstruction, leading to the induction of a myocardial scar with a gradual reduction of the septal thickness and widening of the LVOT [25].

The indication for both treatment modalities depends not on the mere existence of LVOT obstruction but rather on a relevant symptomatic status remaining refractory to drug therapy [1]. At present, both treatment modalities are exclusively indicated for symptomatic relief and not for the improvement of SCD risk.

Apart from the observational data showing a definitive improvement of symptoms after septal reduction in the majority of patients with symptomatic HOCM, there is growing evidence indicating a probable beneficial influence on SCD risk (Figs. 1–4).

A comparison of 289 operated HOCM patients with a matched population of 228 nonoperated HOCM patients, as well as 820 patients with (nonobstructive) HCM in the Mayo Clinic, has shown that the former had a significantly higher survival without SCD (99% at 10 years), with a corresponding survival of 89% for the nonoperated HOCM patients [7]. Similarly, a contemporary study from Toronto on 338 patients who underwent myectomy showed 4% mortality from SCD at

Table 2 Example of a patient with H(O) CM with different values of ESC HCM SCD risk score according to different values of the LVOT gradient

Patient characteristics for ESC SCD risk score calculation		Max LVOTG	ESC SCD risk score	ESC recommendation
Age	25 years	5	3.97	III (ICD not recommended)
Maximum LV wall thickness	20 mm	25	4.34	IIb (ICD may be considered)
LA diameter	55 mm	100	6.01	IIa (ICD should be considered)
SCD in the family	No			
NSVT	No			
Syncope	No			

The first condition with nonobstructive HCM (first row) does not pose an indication for an ICD, whereas the presence of a high LVOT gradient (third row) would bring the ESC HCM SCD risk score just over the limit for an ICD indication. If we hypothesise that the LVOT gradient could be effectively reduced from 100 mmHg (third row) to 25 mmHg (second row), the predicted risk in this patient would be significantly smaller, thus rendering the indication for an ICD much weaker

ESC European Society of Cardiology, *ICD* implantable cardioverter defibrillator, *FHSD* family history of sudden death, *LA* left atrial, *LV* left ventricular, *Max LVOTG* maximal left ventricular outflow tract gradient, *NSVT* nonsustained ventricular tachycardia, *SCD* sudden cardiac death

10 years [8], which is a rate that seems to be low compared with 13% of the total cardiovascular deaths.

However, by using the European Risk Stratification Model in such patients undergoing myectomy, a study comprising 1809 patients from the Cleveland Clinic revealed a discrepancy between expected and observed SCD events [26]. The observed primary events rate at 5 years (almost 5%) was similar across the three expected SCD risk categories (low, intermediate and high) and equal to the intermediate expected risk. The difference between observed and expected SCD rate in the categories with low (2.5%) and high expected risk (9%) was significant. Nevertheless, myectomy performed during follow-up seems to be associated with mitigated SCD risk in patients with expected intermediate or high expected risk, since the observed SCD mortality in those patients was < 4% at 5 years.

For the time being, we can only speculate why sudden cardiac death is reduced after myectomy: reduced obstruction leads to reduced ischaemia; the long-standing pressure overload may lead to additional hypertrophy and fibrosis on an already genetically abnormal myocardium; myectomy removes a substantial amount of hypertrophied muscle which is probably also involved in arrhythmogenicity [26].

A similar trend has been observed also after ASA, with lower SCD rates (0.5%/year in the entire cohort, 0.6%/year in the group with expected high-risk) in the long term than the expected risk of 4% for the high-risk patients [27]. The overall survival matches that of the normal population. Moreover, overall survival combined with appropriate ICD discharge after ASA (96%, 90% and 78% at 1, 5 and 10 years respectively) is also comparable with the survival of the general population in the long term [28].

The latest meta-analysis between ASA and myectomy has shown significant differences between the compared groups in some aspects: ASA patients are older, the final remaining LVOT gradient is higher but still < 30 mmHg after ASA, while ASA patients show higher pacemaker dependency because of conduction complications. As expected, ASA patients need more repeat procedures. Nevertheless, there is no difference in long-term mortality and mortality from SCD [29].

Risk factors for SCD after septal reduction

In contrast to myectomy, where the hypertrophic muscle is removed without leaving any significant amount of scar tissue behind, ASA is associated with an induced myocardial scar, which can be detected with cardiac magnetic resonance (CMR) [30]. In line with the prevailing electrophysiological viewpoint on coronary artery disease, a substantial anxiety has been disseminated during the last two decades that this scar could be responsible for future arrhythmic events [31]; however, the scarce arrhythmic events have not confirmed this concept [9, 10, 27, 32]. It should be pointed out that chemical myocardial ablation with alcohol was originally introduced by electrophysiologists for difficult to treat ventricular arrhythmias and led to the "cure" of those arrhythmias [33]. Besides, this treatment is considered to be still actively performed for difficult arrhythmias [34, 35]. Moreover, pathology studies have shown that the myocardial scar after ASA has different characteristics from the one created after an acute myocardial infarction [36, 37]. The scar itself is not associated with any changes in coronary flow after ASA [38]. Furthermore, contrary to the lately prevailing concept on the impact of myocardial fibrosis in the pathophysiology of SCD in HCM [39], an earlier pathology study has highlighted a different aspect: increased incidence of cardiac death in families with HCM has been related to extensive myocardial disarray and not to the existence of fibrosis; the latter was, however, associated with heart failure and nonsustained ventricular tachycardia [40].

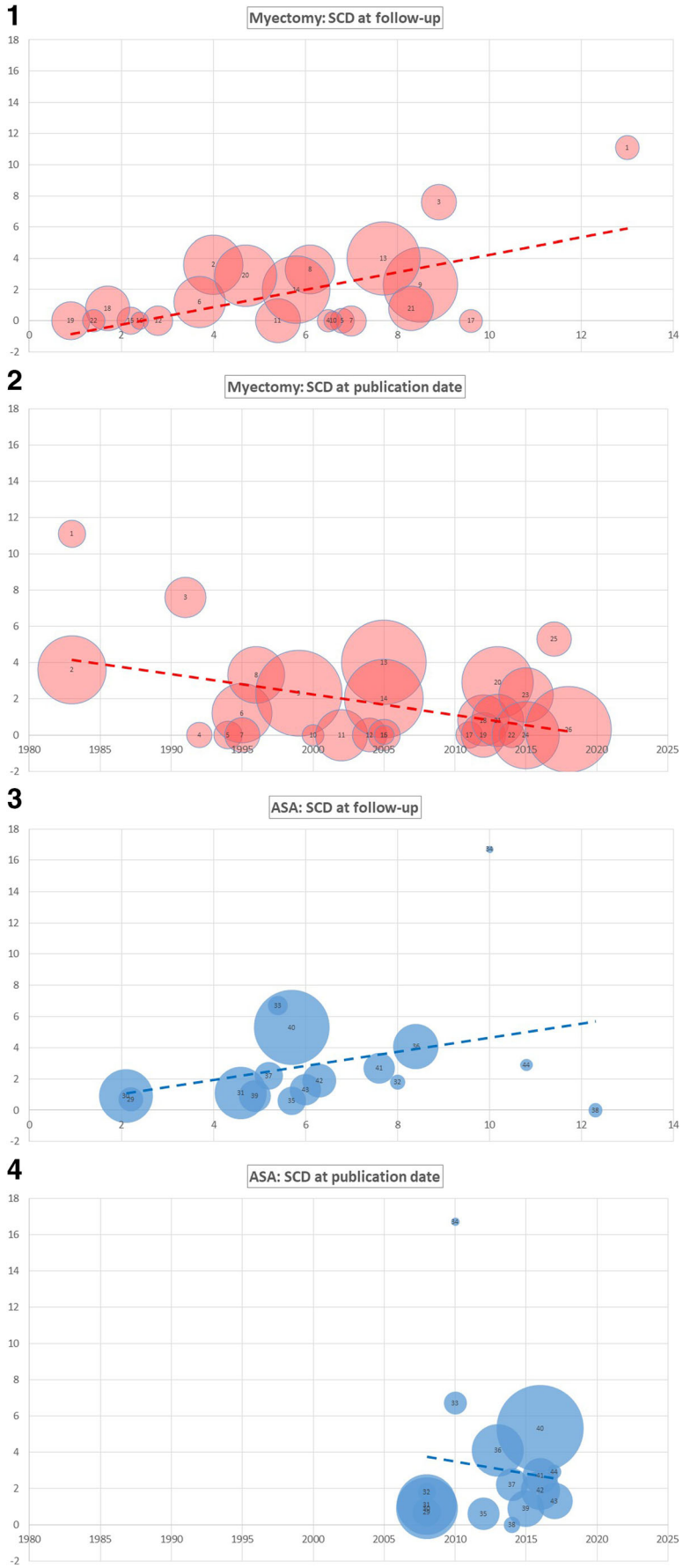

Fig. 1–4 The published SCD event rates of HOCM patients after septal reduction treatments, myectomy (**1**, **2**) and ASA (**3**, **4**). **1** and **3** illustrate the % SCD event rate for myectomy (**1**) and ASA (**2**) according to follow-up time in the studies (in years). **2** and **4** indicate the % SCD event rate for myectomy (**2**) and ASA (**4**) according to the year of study publication. The size of the bubbles represents the number of patients included in each study. The trend lines indicate that, although the SCD event rate is expected to rise with increasing follow-up time, there is a trend for lower SCD events in the newer studies compared to the older ones, owing probably to the increasing experience of the operators in centres with high expertise. This is more obvious with myectomy and less clear with ASA as the timespan of the conducted studies with myectomy is significantly longer

In general, clinical risk estimation with a SCD risk score has not been expanded to all patient categories. Patients after septal reduction therapies, as well as children, were excluded from the original publication of the ESC SCD risk score [19]. Expected risk, especially in low- or intermediate-risk patients, could be perhaps better defined with the aid of other parameters such as late gadolinium enhancement (LGE) in CMR [41, 42].

In a North American study of 1809 patients with 64% of them receiving septal myectomy and 20% presenting atrial fibrillation at follow-up, adding those additional factors (myectomy and atrial fibrillation) to the ESC clinical prediction model led to a significant increase in the prognostic utility [26].

In patients who underwent ASA, the ESC HCM SCD risk score seems to predict sudden cardiac death risk after ASA accurately, with slight overestimation of risk especially in the higher risk category [43]. In this multicentre cohort of patients undergoing ASA, ESC SCD risk score performed better than the 2003 ACC/ESC recommendation [17] and the 2011 ACC/AHA recommendation [18]. As predictors of sudden cardiac death during long-term follow-up (mean follow-up 6.5 ± 4.2 years) were identified the maximum left-ventricular wall thickness > 30 mm, syncope after ASA and the 2014 ESC recommendation for primary prophylactic ICD implantation according to the ESC HCM SCD risk model. Similar to what is already known so far about clinical risk factors for sudden death in HCM, those two clinical risk factors (maximum left-ventricular wall thickness > 30 mm, syncope after ASA) retained a high specificity but lower sensitivity for predicting SCD when compared with the existing different SCD risk prediction models.

Arrhythmic events in patients with ICDs after septal reduction

In HOCM patients with already implanted ICDs, myectomy is associated with reduced annual ICD discharge rates compared with the nonoperated patients after a mean follow-up of 4.4 ± 4.1 years (0.24% versus 4.3%, $p = 0.004$) [44]. The great majority of those patients received ICD for primary prevention and there were no differences between patients receiving myectomy and those treated conservatively in terms of NYHA functional class, anti-arrhythmic drug usage, LV wall thickness and reasons for ICD implantation.

The same has been shown in a study of 32 patients with already implanted ICDs before ASA [45]. After 5 years follow-up, the ESC SCD risk score appeared significantly reduced as a result of the reduced risk factors after successful ASA, something that has been shown also in a larger cohort of patients after ASA [27]. The events observed were 1 noncardiac death, 2 appropriate ICD discharges (1 appropriate in a young patient soon after stopping the beta-blocker medication, 1 inappropriate due to lead failure) and 3 antitachycardia pacing events (2 appropriate and 1 probably due to sinus tachycardia). The appropriate ICD interventions in this cohort were associated with a very high ESC SCD risk score at baseline. Interestingly, the cutoff ESC risk score between patients with events and those without was 14.3%.

It seems that relief of the obstruction in HOCM has a beneficial effect on prognosis, also irrespective of the creation of a myocardial scar after ASA. The remaining gradient after septal reduction rather signifies the remaining risk. A remaining LVOT obstruction > 30 mmHg after ASA is associated with risk for ICD discharge and resuscitation at long-term follow-up [46]. An earlier study with the same result concluded that for every 10 mmHg of remaining LVOT gradient, the risk rises with a hazard ratio of 2.66 (95% CI 1.55–4.56) [47].

Impact of institutional experience and volume

The optimal results showing an improved prognosis after septal reduction in HOCM come from observations in high-volume centres with high expertise in performing myectomy or ASA. Centres with high expertise in ASA have been shown to have better haemodynamic results which offer better symptomatic relief [48]. Institutional experience has also been inversely related to cardiac death after ASA [49], although SCD events were too scarce to draw a safe conclusion. Unfortunately, most centres in the USA perform a very low number of operations or interventions: less than 10/year [50], which raises the risk of complications and cardiac mortality more than 10 times in comparison with centres with high expertise.

Conclusions

LVOT obstruction guides the strategy to be followed for treatment of symptoms and is also a modifiable risk factor for SCD in HOCM. Risk stratification for SCD should be regularly performed irrespective of any symptomatic treatment. The ESC HCM SCD risk score is, at the moment, the most reliable risk prediction model; however, its predictive accuracy after septal reduction treatments can be probably enhanced by the use of additional risk markers. Clinical reasoning is nonetheless always warranted.

Existing evidence points out that effective septal reduction with ASA or myectomy in symptomatic patients may reduce the risk of SCD as well as the potential for ventricular arrhythmias in high-risk patients. Closing, it should be emphasised that institutional expertise is essential in order to achieve best results.

Compliance with ethical standards

Conflict of interest AR and MA have received honoraria for presentations from AstraZeneca. MN has received grants by the Deutsche Forschungsgemeinschaft (DFG) through the Sonderforschungsbereich Transregio 19 "Inflammatory Cardiomyopathy" (SFB TR19) (TP B2), and by the University Hospital Giessen and Marburg Foundation Grant "T cell functionality" (UKGM 10/2009). MP has received a grant by the DFG (SFB TR19 TP A2). MN has been consultant to the IKDT (Institute for Cardiac Diagnosis and Therapy GmbH, Berlin) 2004–2008 and has received honoraria for presentations and/or participated in advisory boards from AstraZeneca, Bayer, Boehringer Ingelheim, Fresenius, Miltenyi Biotech, Novartis, Pfizer and Zoll.

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