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Chapter 19

Hypertrophic Cardiomyopathy: Treatment, Risk Stratification, and Implantable Defibrillators

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Additional information is available at the end of the chapter

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Abstract

Hypertrophic cardiomyopathy (HCM) affects 1:500 individuals, and in majority of cases, a mutation in sarcomere proteins can explain the disease. Phenotype is heterogeneous and thus the prognosis. Many patients suffer from dyspnoea, especially at exercise. Unfortunately, sudden cardiac death (SCD) does occur at all ages and is a major cause of death in young adults. There is no proven pharmacological treatment to reduce hypertrophy or fibrosis, but beta-blockers are first-line treatment. In patients with obstruction, myectomy is preferred in the young, but in older patients, alcohol septal ablation is tried to reduce symptoms and possibly prognosis. Risk stratification of sudden cardiac death is challenging. The major established risk factors are extreme myocardial thickness, non-sustained ventricular tachycardia, unexplained syncope, abnormal exercise blood pressure response, and family history of sudden cardiac death. In 2014, a novel risk calculator was developed that also takes age, outflow gradient, and left atrial seize into account. Implantable defibrillator treatment is effective in HCM, but complications requiring surgery and inappropriate shocks remain a problem.

Keywords: complications, hypertrophic cardiomyopathy, implantable defibrillator, inappropriate shock, risk stratification, risk markers, sudden cardiac death

1. Diagnosis

Hypertrophic cardiomyopathy (HCM) implies increased ventricular thickness that is not only a response to hypertension, aortic stenosis, or any other loading condition with abnormal loading of the ventricle [1]. In adults, a wall thickness of ≥15 mm is typically required for

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diagnosis. In borderline cases (≥13 mm), a thorough evaluation including family history is needed [1, 2]. In siblings, parents or children of a HCM patient, 13-mm thickness is enough for diagnosis [1, 2]. In children and adolescents, a wall thickness more than two standard deviations in the corresponding age group should raise suspicion of the diagnosis of HCM [3]. An ultrasound of the heart, echocardiography, typically reveals the diagnosis of HCM. Echocardiography is usually readily available, but occasionally other imaging techniques are needed. Cardiac magnetic resonance (CMR), computed tomography (CT) or rarely positron emission tomography (PET) is sometimes used for diagnostic purposes or to gain additional information for optimal disease management [4]. The hypertrophied segment is almost always affecting the left ventricle even though right wall involvement does occur [1, 2]. Typically, the septal part is enlarged, either the basal part or the middle part, but could affect lateral, posterior and apical part, or a combination thereof [1]. A concentric hypertrophic is often associated with secondary causes of hypertrophy but does occur as HCM entity. If an isolated hypertrophy solely involves the basal part of the septal wall in an elderly and no other signs or family history of HCM is found, often an explanation such as hypertension is the major cause [1, 2]. Even though the diagnosis of most cases of HCM is straight forward, careful attention to other causes and robust imaging techniques, including a cardiologist with expertise in the field, is warranted. Because HCM is a life-long disease with consequences not only for the patient but also for relatives, a correct diagnosis is indeed important.

2. Symptoms and signs

Dyspnoea is the predominant symptom of HCM that leads to evaluation with an echocardiogram. Shortness of breath is pronounced at exertion due to relaxation disturbance of the left ventricle during diastole and/or outflow tract obstruction. This latter form is called hypertrophic obstructive cardiomyopathy, and the obstruction is often dynamic with regard to filling pressure, heart rate and body position and affected by medications with effect on the cardiovascular system. Often the patient has an adopted life style to decreased physical stamina, and often the diagnostic presentation is rather vague including tiredness. The HCM diagnosis is often delayed or sometimes misclassified from the initial diagnostic work-up.

A progressive HCM may sometimes lead to deterioration of the systolic function of the left ventricle. The ventricle dilates and hypertrophic segments remodel into dilatation, which sometimes can make it difficult to discern from other cardiomyopathies with dilated morphology. This condition is called end stage and indicates a worse prognosis [5–8].

Chest pain without coronary disease may also lead the physician to evaluate alternative diagnosis, and sometimes HCM is revealed. Microvascular dysfunction and fibrosis are part of the disease progression; biopsies show myocardial disarray, and modern PET imaging techniques confirm structural and functional abnormalities, which explain symptoms. However, biopsies are not indicated as part of routine evaluation as the same information would be gained non-invasively [2, 4]. Syncope evaluation is sometimes the initial work-up that leads to the diagnosis of HCM. The mechanisms could be either hemodynamic or cardiac

arrhythmias [9]. Less specific symptoms such as pre-syncope, near-syncope or vertigo will often include ECG and that in turn will lead to suspicion of morphological disease.

Atrial fibrillation is common among HCM, and thus, the risk of embolization stroke warrants effective anticoagulants even without other risk factors [10, 11]. The CHADSVASC score is not validated for HCM patients, and current guidelines recommend warfarin/dual oral anticoagulants if no contraindication is present [2].

Unfortunately, the first manifestation of HCM could be sudden cardiac death (SCD). In such cases, the autopsy confirms or at least suspects HCM even though the microscopy and post-mortem genetic evaluation will aid. A conclusive diagnosis of HCM is of uttermost importance because of the inheritance pattern and relatives need to be evaluated.

3. Inheritance

In more than half of the HCM cases, modern genetic panels can explain the cause of HCM and partly predict the outcome [12–14]. Of all mutations associated with HCM, the vast majority affects myosin proteins: beta-myosin heavy chain (MYH7) and myosin-binding protein (MYBPC3). Other components of the actin-myosin filaments, such as troponins or tropomyosin, rarely explain disease [2]. However, there is a steady increase in disease causing mutations due to increased research activities and widened genetic panels in everyday practise.

The mutations of HCM are autosomal dominant with the exception of the X-linked Danon disease due to lysosome-associated membrane protein 2 [15]. The most common metabolic disease causing hypertrophy of the heart is Anderson-Fabry, which is a storage dysfunction of the lysosomes. In children, hypertrophy of the heart is part of a syndrome, and constellations of malformations may lead suspicion towards Noonans disease, LEOPARD or even more rare diseases. In adults, amyloidosis should be part of the differential diagnosis. A correct molecular diagnosis can sometimes provide clinicians with specific treatment options and thus improve prognosis for the individual.

Family-history taking is a compulsory part of the initial evaluation of a patient with a suspected or conformed hypertrophy. The clinician should systematically document the patients' report on family members who died suddenly or suffered from unexplained syncope or other symptoms suggesting an inheritance. This history taking may include not only first or secondary degree relatives and but also often tedious and administrative efforts to search for older documents, medical records, military service tests like ECG and autopsy protocols. In families who have members who moved to other regions or emigrated from the country, this can be especially challenging. A portion of detective abilities and a critical approach to information from historical medical records or a patients' explanation to a sudden death may be unmasked by a pedigree of suspected HCM. In these efforts, a specialized health care provider trained in history taking, administrative paths and updated knowledge of genetic counselling including bioinformatics will be valuable in conjunction with the cardiologist.

4. Epidemiology

Since the first descriptions of hypertrophy of the heart, numerous labels have been used [2, 16]. Still hypertrophic *obstructive* cardiomyopathy is frequently used, sometimes to stress that an individual patient is symptomatic due to obstructive. While this can be illustrative in a case eligible for septal reductive procedures such as myectomy or alcohol ablation, it can often confuse health care providers, patients and relatives. Furthermore, since the dynamic state of the disease, it can be difficult to assess even though guidelines provide support for establishing degree of obstruction using pharmacological and physiological provocations of obstructiveness. Nowadays, guidelines recommend the usage of HCM and avoid former nomenclature [2].

In echocardiographic studies of populations in the USA, the prevalence of HCM is 1:500, which has been confirmed in other geographical parts of the world with highly available resources of diagnostic tools [17, 18]. Interestingly, also if patients without hypertrophy (phenotype) but who have mutations associated with HCM (genotype), the prevalence is 1:350 [19]. This makes HCM the most prevalent inherited myocardial disease. Because of the high prevalence, a basic knowledge about the disease is needed among a broad spectrum of heath care providers and managers.

The public awareness of HCM has been increased. This is probably due the journalistic attention to sudden death among young people especially during sport activities. In fact, in some countries and certain sport associations, screening of members of athletes is established. However, the approach to screening has been a matter of controversies and the benefits questioned and criticism of the resources it takes and the number of borderline cases that has to be evaluated and managed [20–23].

Nevertheless, HCM or at least unexplained post-mortem left ventricular hypertrophy is considered the most common cause of sudden cardiac death among sport persons younger than 35 years of age; HCM accounts for a half of the cases [24]. A historical perspective on this topic found HCM as a major cause of sudden death in the young [25]. A recent study in Denmark of all cases of SCD in the country reported a lower number [26]. From this Danish cohort, the cases of HCM were further analysed with regard to medical attention before death and about half of the cases had been evaluated for symptoms associated with HCM [26]. This stresses the importance of a qualified disease management including risk stratification of sudden cardiac death.

5. Pharmacological treatment

Recommendations of pharmacological treatment are based on smaller trials or empirical findings on HCM patients or evidence from other patient groups. No drug has been proven to reverse disease progression, but reduction in symptoms can often be achieved. Treatment strategies are based on whether the patient suffers from left ventricular outflow tract obstruc-

tion or not. A peak gradient of ≥30 mmHg is considered as obstruction, but one should bear in mind that this varies over time due to the hemodynamic situation [2].

The principle behind treatment options in patients with obstruction is to avoid severe dehydration with risk of low filling pressures, which could be deleterious for certain patients. Therefore, dehydration, drugs with vessel dilatation actions, or increase in heart rate is disadvantageous. Atrial arrhythmias are frequently encountered in HCM, and often a trigger of unbearable symptoms leads the patient to hospitalization. If the patient is admitted within 48 hours or properly anticoagulated, direct electrical conversion is preferred. However, this is often not the case. In such circumstances, beta-blockers are the drug of choice and digoxin should be avoided due to inotropic increase in myocardium [2].

The first-line treatment option is beta-blocking agents [2]. Notably, the beta-blocker carvedilol exerts vaso-dilating effects and should be avoided. Historically, propranolol was used, but nowadays metoprolol is often the drug of choice. Unfortunately, beta-blockers commonly imply side effects like cognitive impairment and exercise intolerance. This limit dosage titration and compliance to the drug may be questioned. It is important to recognize side effects and discuss alternatives rather than prompt withdrawal, which could possibly provoke worsening of symptoms and cause arrhythmias due to rebound effects on beta-receptors.

The calcium channel antagonist verapamil is often the drug of choice when beta-blockers are not reducing symptoms enough or not tolerated due to side effects. Diltiazem is an alternative choice but not dihydropyridine calcium antagonists because of their vascular effects. Contraindications of verapamil are systolic heart failure and conduction disturbances, i.e., bundle branch block.

The class 1A drug disopyramide has been studied in HCM cohorts and may relieve obstructive symptoms and are considered safe with regard to risk of ventricular arrhythmias. It can be prescribed in addition to beta-blockers. In practise, intolerance is frequent due to anticholinergic side effects (dry mucous membrane, urinary retention, and obstipation), and in some countries, it is not available.

In patients without obstructive component of HCM, the same principle to diminish relaxation disturbance of the left ventricle holds true. Loop diuretics and thiazides can be used without the same precautions as in HCM with obstruction. If disease progression reaches the crossroad with decreased systolic function with ejection fraction below 50%, treatment options include the same drugs as in heart failure due to other causes: beta-blockers, ACE/ARB-inhibitors, aldosterone receptor blockers, and diuretics.

6. Septal reduction therapy

In patients with symptoms due to pronounced obstruction (≥50 mmHg) despite pharmacological treatment, invasive options remain. Myectomy requires open-heart surgery and can be performed concomitant mitral plasty or replacement [27]. The incision is typically up to 70 mm and provides long-term success even though complications, i.e., atrioventricular block, aortic

valve insufficiency, septal shunts occur. Perioperative death is 1–4% and increase with age, left atrial size, and female sex [28].

Alcohol septal ablation implies injection in an arterial branch with resulting necrosis and decreased obstruction. It is less invasive but requires careful judgement of the targeted vessel and still AV-block complications in up to 20% of patients in some series and overall mortality comparable to myectomy. Typically, alcohol ablation is the preferred method for older patients and can be performed multiple times in the same patient. It is important to stress that the decision to performed either alcohol septal ablation or myectomy should be done in centres with expertise in the field and adequate volumes.

There has been a preference of myectomy over alcohol ablation in the USA compared to Europe. The low number of myectomies in Europe has been criticized by experts [29].

Moreover, both myectomy and alcohol septal ablation result in scarring tissue, which have been reported to be a substrate for ventricular arrhythmias have been a matter of debate. However, in larger series, both methods seem to be safe at middle or long-term follow-ups even if individual risk stratification is important even after successful septum reduction procedure [30].

7. Pacemaker therapy

A pacemaker protects from bradycardia and is indicated in high degree AV-block, tachy-brady, and occasionally to reduce outflow gradients in patient where options are not suitable [2, 31]. Ventricular pacing from the right apical part may relieve obstruction by an electrical dyssynchrony between septal and lateral segments of the left ventricle. Earlier studies showed promising results, but current guidelines have constrained indications to include selected patients described above [2, 31, 32]. In the case of indication of an implantable cardioverter defibrillator (ICD) in patients with obstruction, patients should be considered for a dual chamber system for this reason.

Cardiac resynchronization therapy (CRT) has evaluated in smaller observational trial of HCM patients [33]. The experience is that it provides improved exercise capacity, functional class and ejection fraction, and biomarker levels. The vast experience and solid scientific ground of CRT treatment in patients with functional class II–IV, EF ≤ 35% despite optimal pharmacological treatment in left bundle branch block gives a rationale for usage in HCM patients with end-stage heart failure [31, 34, 35].

8. End-stage heart failure

Lowering EF is a predictor of worse outcome and is sometimes called 'burned-out HCM.' It is important to recognize the beginning of this stage and take prompt action including optimal pharmacologic treatments and device therapy. Notably, many patients have supernormal EF

for several years, and when EF is below 50%, this is a turning point. An EF < 50% also predicts risk of life threatening ventricular arrhythmias. This marks a risk for appropriate ICD therapy and should thus imply consideration for preventing sudden cardiac death [34, 35].

If not CRT is enough in end-stage heart failure due to HCM, the same approach as in life threatening heart failure should apply. Rarely, very small left ventricular chamber cavity or intractable ventricular arrhythmia situation without systolic dysfunction may be an indication. Totally, 1–7% of all transplants have HCM as the indication [36]. Left ventricular assist devices may be an option, and continuous axial flow assist therapy has shown promising results in a small series [37].

9. Risk assessment

HCM is heterogeneous disease in many aspects including the risk of sudden cardiac death. The combined risk of cardiovascular mortality is estimated to 6% per year [2]. The cardiovascular mortality constitutes heart failure, sudden cardiac death, and stroke. Many HCM cohorts from highly specialized centres do not necessarily reflect the mortality of the whole HCM population. In fact, a report with less selection bias reported a mortality of 2% [2]. In elderly patients, above 65 years old, the mortality is similar to age- and sex-matched population according to US data [2]. However, sudden cardiac death does occur at all ages and is notably high in early adulthood when sudden cardiac death otherwise is rare.

Survivors of cardiac arrest due to spontaneous ventricular fibrillation or sustained ventricular tachycardia with hemodynamic compromise have 33% mortality at seven years or 41% appropriate ICD therapy at five years [2, 38]. The survival after a cardiac arrest is approximately 10% in the general population. Because of the low chance of survival of cardiac arrest, these patients need an ICD. Thus, these patients are eligible for ICDs as secondary prevention of SCD, and the decision to implant is usually straight forward.

In patients who had not experienced a life threatening ventricular arrhythmia (primary prevention), the decision to implant an ICD requires careful judgement of clinical risk markers and consideration of comorbidities and risk of complications.

There have been three guidelines covering the complex task of ICD as primary prevention of SCD; a joint guideline between the American College of Cardiology/American Heart Association and European Society of Cardiology from 2003, an updated guideline 2011 from ACC/AHA and an ESC guideline launched in August 2014 [2, 39, 40]. The 2003 and 2011 guidelines provide readily evaluated risk factors from history taking, echocardiography and exercise test. Often, one risk factor is considered enough for offering an ICD, but there are differences between countries and centres. It has also not been conclusive if more than risk factor actually correlates with increased risk of appropriate ICD therapy even though more recent studies point in that direction. In addition, possible risk markers have been suggested based on observational studies on ICD cohorts or case reports or expert opinions.

According to guidelines from 2003 and 2011, five major risk factors are established: nonsustained ventricular tachycardia (NSVT), family history of sudden cardiac death (FHSCD), abnormal blood pressure response (ABPRE), unexplained syncope, and MWT 30 mm. A meta-analysis from 2010 based on 30 articles confirmed these risk factors [41]. From this meta-analysis, the presence of left ventricular outflow tract obstruction showed convincing evidence to support in association with SCD. There also seemed to be higher risk for younger patients even though there is no age above which could be safe, but SCD occurs at all ages in HCM [2]. Atrial dilatation and subsequent atrial fibrillation also correlated with SCD in some studies [2]. In patients with concomitant coronary ischemic disease, there was possibly an additional risk as well as in the small subset of patients with left ventricular apical aneurysms [2]. Genetic factors are indirectly included because of the risk factor FHSCD but guideline stress phenotype on an individual level; however, the presence of certain mutations, especially in the cases of double or multiple mutations, there seemed to be an increased risk. ECG is abnormal in 90% of HCM patients, and efforts have been made to correlate abnormalities to risk of SCD suggesting QRS amplitudes and/or fragmentation as risk markers [2]. However, ECG pattern has not been part of guidelines. SCD in athletes due to HCM is well known, and 2003 guideline considered intense (competitive) physical exertion a possible risk factor [39]. Fibrosis assessed on CMR has been studied is advocated as risk factor but is not yet part of guidelines [42, 43].

The evolving criticism on guidelines resulted in a completely new algorithm to assess 5-year risk of SCD in HCM [44]. The article preceding the guidelines change in August 2014 argued that previous guideline considered the clinical parameters left ventricular hypertrophy as binary (30 mm), and in the new guideline, it is treated as continuous [2]. They also included age as the validation work was based on cohorts where risk was higher in the young. Atrial enlargement was again considered a risk factor and included in the algorithm are treated as a continuous variable. The new European algorithm is based on 3,675 patients from six centres and follow-up time of more than 24,000 patient years. One of the centres constituted an external validation. Since the introduction of the 2014 ESC guidelines, external validation work has been published [45]. These two reports support for using the new guidelines. The sophisticated statistics behind the new guideline resulting in a formula with a prognostic index as an exponential function have been overcome by an open access link where a clinician within a few minutes can calculate 5-year risk in an individual patient [2, 46]. However, one should consider the aim of the new guidelines carefully and recognize its limitations. The authors of the new algorithm considered the rationale for the new approach because previous guideline would lead to overuse of ICD; many patients would experience harm of the ICD and never have benefit of the device. One should bear in mind that the underlying patient cohorts were adults and risk stratification in children and adolescent should be used with caution. Hypertrophic as part of metabolic disease or syndromes were not part of study base. Paradoxically, extreme left myocardial thickness 35 mm had low SCD risk, but this subset of patient was few and the model does not seem to cover all ranges. Furthermore, the model does not take into account the obstruction only at exercise but at rest.

Even though the new model has been widely recognized, it is still unclear to what degree it is actually used globally. Recently, an independent assessment of the ESC risk model concluded

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that the model was unreliable because many patients with SCD or appropriate ICD therapy had a low risk score. The implementation of new guidelines may take time or require further refinement. Probably it will not replace previous strategies completely but serve as important tool. Risk stratification is and will always be a complex task.

10. Age and gender

Most studies found no significant association with age and sudden death in HCM cohorts, but these studies are typically ICD populations selected from tertiary centres [47]. Furthermore, usually these studies do not take age- and sex-matched comparison with general population into account. Many studies on ICD cohorts lack statistical power to detect differences at different age strata. In two studies, there was an inverse relationship between age and sudden cardiac death, but in the majority of studies, no association was demonstrated [2]. In a recently published nationwide Swedish study without selection, bias age was not significantly associated with appropriate ICD therapy [34, 35]. In American guidelines, age is not part of risk stratification, whereas in the European guidelines, age is part of the equation based on validation of cohorts, which showed an increased risk in younger patients [2]. The association between age and other risk factors is quite complicated, but there seems to be data supporting the rationale for offering ICDs with NSVT, severe left ventricular hypertrophy (LVH) and unexplained syncope in younger patients [2]. Age is further complicated by the individual comorbidities and the discrepancy between biological and calendric age. From other guidelines on general ICD candidates, guidelines state at least 2 years of life expectancy to be eligible for an ICD. An experienced clinician may reflect about age in the individual case but cannot neglect local resources and risk of complications in addition to effective patient communication on prognosis.

Most HCM cohorts have a majority of males. In the six cohorts in the ESC risk algorithm, the proportion of males ranged from 59 to 72% (mean 64%) [2]. This pattern is also seen in several ICD cohorts [34, 35, 47]. However, there does not seem to be a significant difference with regard to risk of appropriate ICD therapy in these cohorts. It is important to recognize the individual risk factor profile rather than gender itself. Neither previous nor current guidelines use gender as part of risk stratification. Notably, females may have a higher risk for complications related to the ICD system [47].

11. Nonsustained ventricular tachycardia (NSVT)

The presence of NSVT has been part on guidelines since it first appeared in 2003 after several reports on the association to sudden cardiac death in HCM. This is in contrast to general ICD population with ischemic or dilated CM with low EF in which NSVT is not part of guidelines The definition of NSVT is at least three beats in a row of ventricular origin but varies with regard to cycle length; the formal cut-off of 100 bpm is seldom used, and 120 or 150 bpm is

typically used [2]. The association of life threatening arrhythmias does not seem to vary with length or cycle length. The maximal duration of NSVT is 30 seconds while longer duration is called sustained ventricular tachycardia. The diagnosis of NSVT could be from an ambulatory monitor such as Holter for 24–48 hours as prescribed in the evaluation of HCM patients. However, sometimes NSVT is detected from telemetry in the ward or from a cardiac device, i.e., a pacemaker EGM or implantable loop recorder. Interestingly, NSVT seems to be quite common in ICD recipients. Thus, the more often a HCM patient is monitored for NSVT, the higher the likelihood for detecting the risk factor NSVT. Prolonged monitoring with implantable devices or non-invasive ECG patches is currently not indicated without a history of syncope but remains to be evaluated in the future.

12. Syncope

Syncope deserves special attention when it comes to interviewing the patient about the actual episode. This includes observations from witness about duration (which often may be overestimated) and signs before or after the loss of consciousness. Certain situations may be typical for vaso-vagal syncope (i.e., defection, micturition), situational or orthostatic hypotension. Carotid sinus mechanism for syncope can sometimes be reproduced. The body position and activity may aid important clues. If exercise-induced syncope is experienced, this should imply prompt evaluation because a malignant cause is likely. Notably, tiredness and seizure may indicate epilepsy but do not rule out cardiac causes as severe cerebral hypoxia mimics the clinical scenario. In some studies, unexplained syncope within six months seems to predict worse outcome to higher extent [2]. Nevertheless, a syncopal episode suggestive or arrhythmic cause independent of when it happened should warrant careful evaluation.

13. Family history

A family history of SCD is a dramatic event. Relatives of the victim have to deal with their own attitude and subsequent risk assessment beside emotional impact of the lost relative. Unfortunately, not every physician is aware of the inheritance component in family of SCD or the family does not seek medical advice due to this. Documentation from possibly related HCM is often lacking, misinterpreted or unavailable. Current European guidelines state SCD in the first-degree relative before the age of 40, but no age cut-off when SCD can be attributed to HCM [2]. The underlying studies are quite heterogeneous using different age limit. This risk factor is further complicated as it does not take into account second- or third-degree relatives nor the number of siblings in a family. It is understandable that the motivation for patient and clinicians is usually high when there is case of SCD in the family. However, the scientific basis is less strong than for NSVT, unexplained syncope, or MWT, based on three studies, whereas several other studies could not prove an association [2, 48]. If this inability is due to power problems of studies because of the limited number of patients included and/or few outcome of events, is difficult to judge. The heterogeneity of definitions and relative short follow-up time may

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also influence the results. Statistical methods often account for uni- and multi-variable influence of risk factors but have difficulties to prove interaction between risk factors in smaller samples with few events.

14. Wall thickness

In patients with a ≥30 mm maximal wall thickness, there was a three-fold increased risk, which makes it a comparatively strong risk factor. Later analyses suggest a U-shaped correlation to sudden cardiac death [49]. As mentioned above, this risk factor has been treated as binary risk factor previously, at least theoretically, but in practise, it is likely that number patients have been offered an ICD even if they did not fulfil this criterion formally. For example, in a 25-year-old patient with otherwise long-life expectancy, a 29 mm thickness would probably be enough for most clinicians. Another limit is the fact that hypertrophy can be more or less unevenly distributed, and it is not known if this influences risk. Moreover, echocardiography does not always provide accurate estimations and certain parts, i.e., apical parts may be difficult to trace. Other imaging techniques may resolve this problem in individuals. The progression of disease is difficult to predict, but in a young patient, it is more likely and effect of hypertensive disease is more easy to rule out. Future validation work on this risk factor will hopefully elucidate this factor better. Here, CMR and PET may add important knowledge of not only structural findings but also functional and metabolic disturbances associated with risk of arrhythmia.

15. Exercise blood pressure response

The assessment of this risk factor requires referral for ergometer bicycle test or any other exercise test. In series of HCM patients, one third of patients show abnormal blood pressure response [2, 50]. The definition of abnormal blood pressure response varies, but with regard to risk stratification, a failure to increase systolic pressure at least 20 mmHg or a fall of 20 mmHg from peak pressure is considered relevant [2]. This risk factor seems to be more pronounced in patients younger than 40 years old. In some studies, this risk factor has not been analysed because not all patients were systematically assessed. This is understandable as if a clinician already has data enough to support the decision to implant an ICD, there is a rationale for omitting this test as is does not add clinical insight for further management of the individual patient. In the new guidelines, the authors took the decision to abandon exercise test as part of risk stratification, and it remains to be seen if upcoming guidelines will stick to this policy.

16. Atrial fibrillation and left atrial diameter

The increased filling pressures of the left ventricle will result in wall stress of left atrium and risk of dilatation. There is a well-known risk of atrial fibrillation and a dilated left atrium, and

this in turn increases risk of embolic events. In a recent study, AF was a stronger risk factor than the established five major risk factors in both univariable and multivariable analyses in HCM-ICD cohort [34, 35]. AF should be considered as a sole factor for risk stratification and lead to an ICD, but in patients implanted based on the five major risk factors, AF predicted high probability of appropriate ICD therapy [2, 34, 35].

Left atrial diameter is assessed by echocardiography using a parasternal projection and is now part of the risk model algorithm [46]. It is handled as a continuous variable, but it does not take into account the different shapes of the atrium as some patients have elongated atrium mostly visualized in an apical four-chamber view. Neither is the volume calculated, but a simple diameter in one projection sometimes allows inter-user variability and anatomical variation difficult to standardize.

17. LVOT obstruction

The outflow gradient of the left chamber may vary and change with exercise or can be provoked by drugs. In the meta-analysis, they concluded that LVOT gradient should be reassessed as a risk factor based on evidence from numerous observational studies [41, 51, 52]. This also holds true when developing the new algorithm and was then included and treated as a continuous variable.

18. CMR, CT and PET

Cardiac magnetic resonance using a contrast-enhanced technique has demonstrated association with arrhythmias, and substantial amount of fibrosis may be suggestive increased risk for SCD [53]. The accurate delineation and spatial resolution of CMR may aid in cases where echocardiography is inadequate. However, to assess association between CMR-derived baseline data and outcome such as SCD or appropriate ICD therapy will follow-up time and large cohorts with enough events to prove association. Therefore, CMR has been included in the first prospective registry on HCM patients, and this will hopefully provide gain of insight in this matter. CMR uses magnetic fields instead of ionizing radiation, but contraindication needs to be considered. Notably, ICD patients should be assessed before a device is implanted even though newer ICD model may allow CMR at least 1.5 Tesla investigations but gives rise to artefacts. PET can be used in conjunction within either CT or CMR and is a promising field for research with functional, structural and metabolic assessment, which is available.

19. Driving

While most HCM patients have no driving restrictions, patients with ICD devices need special considerations. This advice needs to be in harmony with national laws besides checking

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international guidelines that provide update recommendation on this topic. A survivor of cardiac arrest should not drive for the first six months after the event, and careful assessment of cognitive function is then advised. The same considerations should be made after stroke, epilepsy, diabetes and other medical conditions. The risk after an arrhythmic event is highest in the first few months, which makes six-month restriction reasonably. In primary prevention of ICD patients, there is no restriction except for unexplained syncope with a typical restriction in the first 6 months. Professional driving (buss, truck, taxi) is not accepted for ICD carriers, independent of indication (primary or secondary) in most countries. Other vehicles, including trains and aeroplanes, need to be considered and legal actions taken.

20. Pregnancy

Pregnancy implies increased loading pressures, and in last semester, a cardiovascular demand may increase risk. HCM is a heterogeneous disease, and risk of SCD during pregnancy needs to be addressed based on individual factors. Few women need to give up a wish to become a biological mother; however, there are fatal cases reported, but these have been in patients with a known high risk. Because of the non-negligible risk, females are advised to plan pregnancy and counselling should be offered during the pregnancy and delivery by a multidisciplinary team. In the rare case of need for ICD implant during pregnancy, efforts need to be taken to provide protection from radiation or using echocardiography to assess position of leads.

21. Combinations of risk markers and modifiers

The new algorithm takes several risk factors into account and weights them using a formula [46]. But even this method has the same lack of accurate estimation of mediating or possibly protective interaction between markers. All markers are somewhat surrogates and life-time risk can never be exactly assessed in the individual. Long-term follow-up in all studies is actually typically less than 10 years for the majority of the patient, and risk is not linear. Besides, risk markers are assessed at the time for decision to implant and may change during the course and should therefore be re-assessed every 1–3 years. Again, a multicentre, international, prospective registry will provide more insights in the challenge to stratify risk in HCM.

22. Children

Risk stratification in children equals adult strategy in many ways, but primary prevention is typically based on two or more risk factors rather than one. Historically, epicardial lead has been used in a growing child, but nowadays subcutaneous ICD may be a more attractive option. A single device (ICD-VVI) is usually sufficient as pacing indication is rare in the young, and this approach seems to limit complications.

23. ICD therapy

ICD is an effective way to prevent sudden cardiac death in HCM. The landmark trial by Maron et al. demonstrated 11% annual rate in secondary and 5% annual rate in primary prevention [54]. Several studies have confirmed the usefulness on ICD in HCM [47]. Schinkel et al. performed a meta-analysis of 2,190 patients from 16 cohorts (mean age 42 years, 62% males) with 83% primary prevention indication [47]. The summary estimate for appropriate ICD therapy was 3.3% per year (95% confidence interval 2.2–4.4%). A later nationwide ICD cohort of unselected patients reported 4.5% appropriate ICD therapy in primary prevention and 7.0% in secondary prevention [34, 35].

It should be noted that *not* every appropriate ICD therapy is indeed lifesaving. A ventricular arrhythmia can self-terminate, which can lead to an overestimation of benefit of ICD. Therefore, it is important to programme a number of intervals to at least 30 before therapy. The detection zones should be carefully considered, and antitachycardia pacing (ATP) should be used to avoid unnecessary shocks. However, the risk of a sustained ventricular below detection zone could lead to fatal hemodynamic collapse including pulseless electrical tachycardia or recurrent ventricular fibrillation when ventricles are finally exhausted. Patients on amiodarone are known to have a slower rate than otherwise [2]. Earlier there have been worries about the efficacy in hypertrophic heart due to increased myocardial mass to discharge, but large series of a patient show efficacy of ICD discharges with very few exceptions. The discussion on DFT testing preoperatively could be extended to HCM populations, but the trend to induce patients more rarely, if at all, will continue for HCM patients. One may argue that induction is not without risk; devices have high voltage and sufficient margin, and the clinical situation is not exactly the same as during implant. Moreover, it may be advisable to choose a type and brand of ICD device capable of wave form optimization and to deliver high voltage discharges. Different devices offer different solutions to avoid T-wave oversense, which should be reflected upon. A T-wave oversense leads to double counting and will deliver inappropriate shocks. Technical failure of lead, fracture and insulation defects, or external noise could lead inappropriate shocks. The overall annual risk of inappropriate shocks is 4.8% in a meta-analysis [47] and confirmed in later analyses of unselected populations [55]. Hopefully, with programming optimization, this could likely be reduced. The most common cause of inappropriate shocks is atrial arrhythmias, predominantly. In addition to programming longer duration, longer cycle length, discrimination algorithm should be considered such as interval stability, but one should neglect the risk of misdiagnosis simultaneous ventricular arrhythmias that need appropriate therapy. Furthermore, other actions to avoid atrial tachycardia and to reduce rapid atrioventricular conduction are needed: beta-blockers, antiarrhythmics, and occasionally His-ablation.

Compared to other ICD populations where ATP is effective in a vast majority of cases, the proportion of ATP success was less in HCM-ICD cohorts. This has been seen in other HCM trials, and HCM possibly carries an increased risk of rapid ventricular tachycardia or ventricular fibrillation to a larger extent than other ICD groups.

ICD systems offer an alert function for the patient if technical failure or essential clinical episode takes place. Remote monitoring of ICD devices is standard, and this increases safety

as it detects technical problems between follow-ups in clinic or detects atrial fibrillation, which implies decision to anticoagulated.

24. Death despite ICD

The efficacy of ICDs to prevent sudden cardiac death leads to a swift in cases of death. The vast majority of death in the ICD population dies because of progressive heart failure. The standardized mortality was 3.4 (95% confidence interval 2.4–4.5) compared to general population [56]. This implies that heart failure care needs to be addressed if improved survival should be achieved. Importantly, a holistic approach to device patient is warranted, and one should not just focus on the prevention of arrhythmia death.

25. Implant procedure

The procedure to implant an ICD in a HCM patient is essentially the same as in other indication. The vascular access is typically from the left side either through cephalic cut-down or punctures of the axillary or subclavian vein. The ventricular lead is implanted in the apical region of the right ventricle if R-waves and thresholds are acceptable in this position. It is important to check for T-wave oversensing before deciding the final position of the lead. In obstructive HCM, it is of special importance to implant the lead in apex as this could facilitate reduction in outflow gradient if AV-pacing is tried. For the same reason, an atrial lead (ICD-DR) is often preferred. Furthermore, many HCM patients have high beta-blocking dosage, conduction defects or paroxysmal atrial fibrillation with the help of AV synchronous pacing. The ventricle lead could be either single or dual coil. There is a tendency to increased use of single-coil system as possible defibrillation threshold difference is negligible, easier to implant and extract. The device could be implanted subcutaneously or intramuscular. As described above, less number of patients is induced nowadays. The typical procedure time is less than 1 hour, and the patient can often be discharged the same day. The battery of an ICD in a modern system lasts for 8–10 years, depending on amount pacing and, in few cases, the demand of therapies. CRT system in end-stage HCM has been tried with preliminary promising results.

26. Health-related quality of life

In a British study from 1995 on HCM patients, health-related quality of life was decreased [57]. Since then, improvement of health care has been made, and there may be different outcomes in a HCM population that is not selected from a specialized centre. Recently, a study on HCM patients with ICDs confirmed poor quality of life, regardless of sex, age, or primary/secondary indication [58]. Instead, atrial fibrillation and systolic heart failure are determinants of poor quality of life, especially physical aspects. Notably, inappropriate, but appropriate therapies

are associated with poorer mental health. To further address quality of life issues, qualitative studies may provide valuable insights.

27. S-ICD

An subcutaneous-ICD (S-ICD) system contains a subcutaneously implanted lead (in an L-configuration) connected to a device inserted subcutaneously, or preferably intramuscular. It effectively terminates ventricular arrhythmias and can offer supportive post-chock pacing. Current devices cannot be used in patients who need permanent pacing, but technical solutions are developed to combine a leadless pacemaker system communicating with an S-ICD system. This is beneficial in patients with abnormal vascular anatomy, i.e., malformations or vessel occlusions. But, in young patient, there is an increasing interest in S-ICD to save vessels for future interventions and avoid short-term and long-term vessel-related complications. S-ICD has been used in HCM, but careful pre-operative assessment of possibly risk of T-wave oversense is of importance in this group. The cost of S-ICD device is currently much larger than for transvenous device, but this probably diminishes. Studies so far have shown a promising short-term use of S-ICD among HCM patients [59].

28. Future perspectives

There remain many challenges in the field of HCM. A detailed understanding of pathophysiologic mechanism of disease progression, arrhythmia substrate and triggers and molecular-genetic base of the heterogeneous disease is crucial. This could lead to improvement in the therapeutic arsenal, but this development relies on scientific progress in the field of cardiology and basic sciences. Multicentre, prospective registries and other international collaborations to evaluate outcome and refine risk stratification are promising [60, 61].

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