REVIEW

Management of Hypertrophic Cardiomyopathy

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is clinically defined as unexplained myocardial hypertrophy, and it is an autosomal dominant disease of the cardiac sarcomere. It is present in 1 in 500 in the general adult population, making it the most common genetic cardiovascular disease. The pathophysiology of HCM is complex, leading to significant variability in clinical presentation. This, combined with the lack of randomized trials, makes the management of these patients difficult.

Findings: The majority of patients with HCM are asymptomatic without a substantial reduction in survival. However, a considerable portion of patients will experience significant symptoms and HCM-related death, and effective therapies are available for these patients. Patients may have symptoms of heart failure from outflow tract obstruction and/or restrictive physiology. Medical therapy targeted at the underlying pathophysiology should be used, and surgical myectomy or alcohol septal ablation is available for those with refractory symptoms. While the overall risk of sudden cardiac death (SCD) is low in HCM patients, some are at elevated risk for and experience SCD, a devastating outcome in young patients. Risk stratification for SCD and treatment with implantable cardioverter-defibrillators is paramount. Many HCM patients will also develop atrial fibrillation, and this is often poorly tolerated. A rhythm control strategy with antiarrhythmic drugs or catheter ablation is often necessary, and anticoagulation should be administered to reduce the risk of thromboembolism. Finally, family members of patients with HCM should be regularly screened with electrocardiography and echocardiography.

Conclusions: HCM is a complex disease with heterogeneous phenotypes and clinical manifestations. The management of HCM focuses on reducing symptoms of heart failure, preventing SCD, treating atrial fibrillation, and screening family members. Treatment should be tailored to the unique characteristics of each individual patient.

Keywords: alcohol septal ablation, genetic screening, hypertrophic cardiomyopathy, implantable cardioverter-defibrillators, sudden cardiac death, surgical myectomy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is defined by the presence of myocardial hypertrophy in the absence of systemic disease (eg, aortic stenosis, amyloidosis) capable of producing the magnitude of hypertrophy.[1] It was first described in the late 1950s by Brock and Teare. In 1990, the first mutation in a gene encoding the β-myosin heavy chain in familial HCM was identified,[2] and it is now recognized that HCM is a genetic disease of the cardiac sarcomere with an autosomal dominant pattern of inheritance. The prevalence in the adult general population is 0.2% (1:500) with approximately 600,000 affected in the United States, making HCM the most common genetic cardiovascular disease.[1]

HCM is diagnosed when echocardiography or cardiac magnetic resonance (CMR) imaging reveals unexplained left ventricular hypertrophy (LVH), usually ≥15 mm.[3] Although asymmetric septal hypertrophy is most common, there is significant heterogeneity in the degree and pattern of LVH.[4] In addition, there is considerable variability in the clinical presentation, natural history, and prognosis in patients with HCM. Although HCM disease expression usually occurs during adolescence or young adulthood, it can occur at any time as late onset disease has been described with certain gene mutations.[5,6] Although the majority of patients are asymptomatic, others are afflicted with incapacitating dyspnea or suffer sudden cardiac death, a devastating outcome in young patients.[7] This heterogeneity combined with the limited exposure of clinicians to HCM has led to controversy in managing patients with HCM.[8,9] This review focuses on the current management of patients with HCM.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The majority of patients with HCM are asymptomatic, and the diagnosis is often made incidentally or during family screening.[10] Asymptomatic patients tend to do

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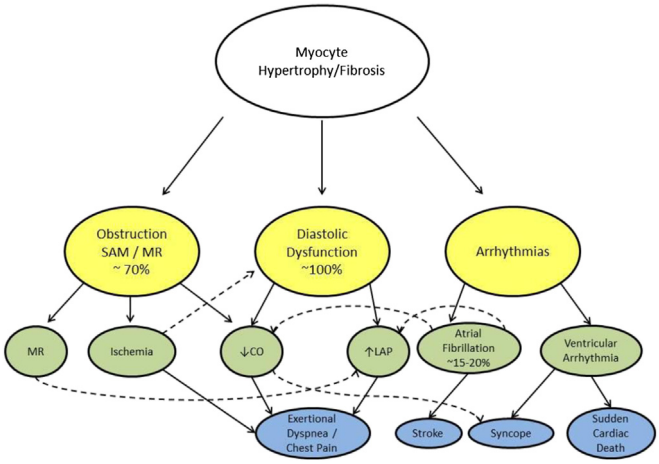


Figure 1. Pathophysiology (yellow, green) and clinical manifestations (blue) of hypertrophic cardiomyopathy. **Abbreviations**: CO, cardiac output; LAP, left atrial pressure; MR, mitral regurgitation; SAM, systolic anterior motion of the mitral valve.

very well with survival comparable to the general population.[7,11] However, up to 25% of patients will develop significant symptoms or HCM-related death.[7] Patients can present with multiple symptoms due to a complex interplay of multiple factors (Fig. 1), but there are primarily three pathways of clinical progression:

1. Heart failure with exertional dyspnea, chest pain, or a combination of the two. This is due to left ventricular outflow (LVOT) obstruction, diastolic dysfunction with restrictive physiology, or both.
2. Sudden cardiac death (SCD). Myocardial fibrosis combined with ischemia due to microvascular disease may predispose patients with HCM to ventricular tachyarrhythmias.[12,13] The incidence of SCD is ≤1% per year in the HCM population, but it is devastating as it generally occurs in asymptomatic or mildly symptomatic young patients without warning.
3. Atrial fibrillation (AF). AF develops in ~20% of patients with HCM and is associated with an increased risk for stroke, heart failure, and death.[14,15] More than 20% of these patients will suffer from thromboembolism.

MANAGEMENT OF HYPERTROPHIC CARDIOMYOPATHY

The management of patients with HCM is directed at control of heart failure symptoms, prevention of SCD, treatment of AF, and screening of family members. Figure 2 depicts treatment strategies for each clinical scenario in patients with HCM.

Heart Failure with LVOT Obstruction

Seventy percent of patients have dynamic LVOT obstruction at rest or provoked with exercise.[16,17] Of these patients, ~10% will progress to New York Heart Association (NYHA) class III/IV symptoms and require therapeutic intervention.[16,18]

Pharmacologic Therapy

β-Adrenergic antagonists, verapamil, and disopyramide are the mainstays of medical therapy in HCM with outflow tract obstruction.[3] These agents improve LVOT obstruction and symptoms by slowing the heart rate thereby improving left ventricular (LV) filling, decreasing myocardial oxygen demand, or through negative inotropic effects.

β-Adrenergic antagonists. It was first recognized that β-blockers are efficacious in patients with obstructive HCM in the 1960s.[19] Subsequent studies with propranolol demonstrated a reduction in outflow gradients (particularly with exercise), the alleviation of dyspnea, chest pain, palpitations, dizziness, and syncope.[20,21] β-Blockers are considered first-line therapy for the treatment of symptomatic patients with obstructive HCM.[3]

Calcium-channel blockers. Non-dihydropyridine calcium-channel blockers (CCBs) also improve symptoms in obstructive HCM. Verapamil is the most well-studied and most widely used CCB, and it decreases resting outflow gradients and improves diastolic function.[22,23] However, verapamil has vasodilatory effects, and adverse reactions such as hypotension, exacerbation of outflow gradients, and pulmonary edema have been reported.[24] Because of this, verapamil is only recommended as second-line therapy, and should be used with caution in patients with high LVOT gradients, pulmonary hypertension, or advanced heart failure.[3] Diltiazem is also used but has not been well studied.

Disopyramide. Disopyramide is a class 1a antiarrhythmic agent, and it exerts negative inotropic effects by altering Na^+-Ca^+ exchange.[25] It has been shown to alleviate resting outflow gradients and improve heart failure symptoms, perhaps to a greater degree than β-blockers.[26,27] Because disopyramide can increase atrioventricular (AV) nodal conduction leading to faster ventricular rates during

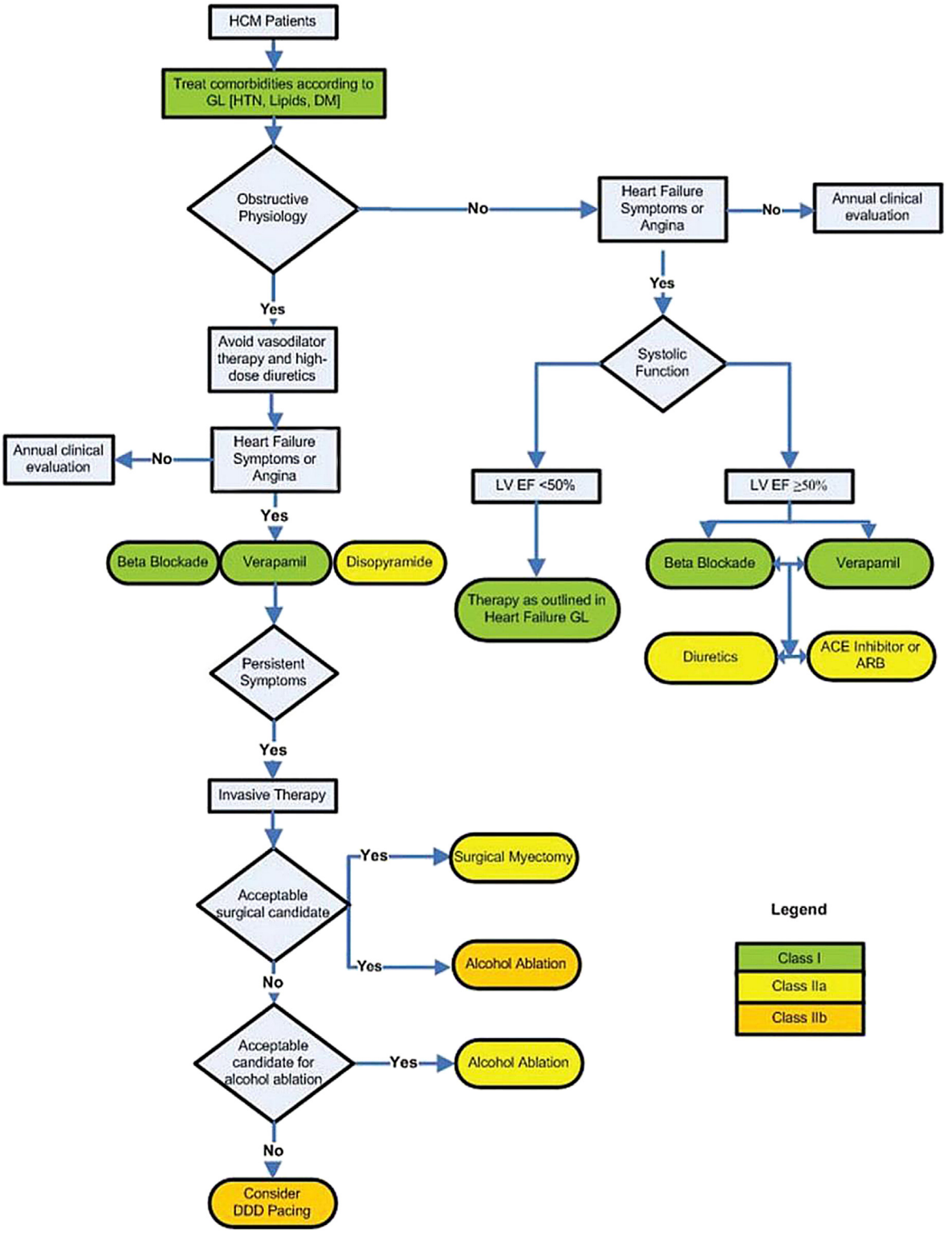


Figure 2. Treatment algorithm (reproduced with permission from Gersh et al.[3]). **Abbreviations**: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DM, diabetes mellitus; EF, ejection fraction; GL, guidelines; HCM, hypertrophic cardiomyopathy; HTN, hypertension; LV, left ventricular.

atrial fibrillation/flutter, it should be given in conjunction with a β-blocker or CCB.[14] Disopyramide is considered third-line therapy and should be used when β-blockers or verapamil fail to control symptoms.

Medications to be avoided or used with caution. Vasodilators such as nifedipine, nitrates, and angiotensin-converting enzyme inhibitors can cause venodilation, a fall in systemic vascular resistance, or a

combination of both. This can exacerbate LVOT obstruction and lead to hypotension and worsening of heart failure symptoms. Similarly, digoxin should be avoided because of the positive inotropic effect. Diuretics, on the other hand, may be useful in patients with persistent symptoms despite treatment with β-blockers or verapamil.[3] However, they should be administered with caution in patients with LVOT obstruction.

Nonpharmacologic Treatment of Outflow Obstruction in HCM

In the vast majority of patients, symptoms can be managed with medical therapy, as only 5% of patients will require invasive therapy for symptom control.[28] Nevertheless, a group of HCM patients will have refractory symptoms on maximal medical therapy and will be candidates for surgical myectomy, alcohol septal ablation, or a dual-chamber pacemaker. Septal reduction therapy with myectomy or alcohol septal ablation is indicated in patients with dyspnea (NYHA class III or IV), chest pain, or syncope refractory to medical therapy and the presence of LVOT gradient ≥50 mm Hg at rest or provoked with exercise.[3]

Surgical Myectomy

Historically, surgical myectomy has been the gold standard for the relief of LVOT obstruction in patients with HCM. Partial-thickness septal myectomy was first performed in the early 1960s, and transaortic septal myectomy, often extended toward the apex, is now the standard surgical treatment for obstructive HCM.[29] If valvular or subvalvular anomalies are present, these also can be corrected during the surgery.

Perioperative mortality. Early studies described high operative mortality rates of 4% to 6%, reflecting the initial surgical inexperience.[30] More recent studies from experienced centers have shown that myectomy can be performed safely and with perioperative mortality rates of ≤1%.[31-33]

Complications. Ventricular septal defects (VSDs) are a serious complication of myectomy that may be more common in patients with only a mildly hypertrophied septum.[34] However, these occur in ≤1% with the use of intraoperative echocardiography.[21,29,35] Complete heart block requiring a permanent pacemaker (PPM) occurs in only 1% to 2% if the patient does not have a pre-existing right bundle-branch block.[29,36]

Long-term outcomes. The LVOT gradient is nearly abolished in almost all patients with HCM (90%-95%) after myectomy.[30-33] Also, mitral regurgitation is usually virtually absent after myectomy without the need for additional mitral valve surgery.[37] There is also significant improvement in heart failure symptoms after myectomy with most patients experiencing NYHA class I-II symptoms after surgery.[31-33]

Myectomy is associated with excellent long-term survival when performed at experienced centers. In two series, 1- and 10-year survival rates were 98% and 83%, respectively, and similar to matched controls.[28,31] There also may be a lower incidence of SCD after myectomy, possibly due to relief of LVOT obstruction and regression of LVH and LV mass after the procedure.[31,38-40]

Alcohol Septal Ablation

Transcatheter ablation of the septum with ethanol was first performed in 1994, and its use has grown dramatically since then.[41] It involves coronary angiography and injection of ethanol directly into the proximal septal perforators supplying the hypertrophied anteroseptum, causing a directed myocardial infarction.[18,42] This results in a reduction in LVOT gradient and symptoms through LV remodeling, regression of LVH, and induction of asynchrony.[43-45]

Complications. Procedure-related mortality for alcohol septal ablation has been reported at up to 4% but is around 1% to 2% at experienced centers.[18,46] Septal ablation induces a myocardial infarction encompassing up to 10% of the overall LV mass, and there has been concern that this scar could act as a substrate for ventricular arrhythmia.[28] Although ventricular arrhythmias occur in ~5% of patients during hospitalization, a recent study did not show a higher risk for SCD.[47,48] The most common complication of alcohol septal ablation is AV block, with 10% to 20% of patients experiencing persistent complete heart block requiring a PPM.[46,49]

Clinical outcomes. As with myectomy, the complication rate and clinical outcomes are dependent on the experience of the operator. At experienced centers, it is successful in 75% to 80% of patients, and approximately 8% will require repeat intervention.[46,48] Observational studies of alcohol septal ablation show that the reduction in outflow gradient and improvement in symptoms are comparable to surgical myectomy. However, it may take up to 3 months for the benefits to become clinically apparent.[50] Survival after alcohol septal ablation is also excellent. Two studies with 5- and 10-year follow-up, respectively, found that survival after ablation is comparable to myectomy and to an age- and sex-matched population.[48,51]

Surgical Myectomy versus Alcohol Septal Ablation

Septal myectomy and alcohol septal ablation are both performed in clinical practice, and the clinical eligibility criteria are the same for both according to the 2011 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (see earlier mention).[3] In order to minimize the risk for VSD, patients undergoing ablation or myectomy should have a septal thickness ≥16 mm and ≥18 mm, respectively.[21,49] Despite

identical indications, alcohol septal ablation is currently used significantly more often than septal myectomy.[28]

There are no randomized trials comparing the 2 approaches. Meta-analyses suggest no difference in mortality or symptomatic improvement, but myectomy results in lower LVOT gradients and a much lower rate of complete heart block requiring pacemaker implantation.[52,53] Table 1 summarizes the advantages and disadvantages and differences between myectomy and alcohol septal ablation.

Myectomy is considered first-line therapy for medically refractory HCM with LVOT obstruction.[3] This is because of its very low perioperative mortality, higher success rates, lower risk for PPM implantation, and availability of long-term efficacy data. Myectomy should be performed in younger patients (especially in those ≤40 years old), patients with massive hypertrophy, and those with concomitant valvular or other cardiac disease. Alcohol septal ablation is ideally for patients who are not surgical candidates (eg, elderly individuals).

As with any choice, patient preference is of utmost importance in the decision-making process, and a thorough discussion of the risks and benefits of each treatment modality should be undertaken. It is important to reiterate that experienced operators should perform these interventions, and local availability of each service may govern clinical decision making.

Dual-Chamber Pacing

Observational studies in the 1990s reported that dual chamber (DDD) pacing with short AV delays could relieve subaortic gradients and treat severe heart failure symptoms by inducing asynchrony.[54] However, subsequent randomized trials showed that only a small number of patients actually benefit and that prior reported improvements were due to a significant placebo effect with pacemaker implantation.[55,56] In light of this evidence, the 2011 ACC/AHA guidelines recommend that DDD pacing should only be considered if a patient has an existing device or has refractory symptoms with LVOT obstruction and is not a candidate for septal reduction therapy.[3]

HEART FAILURE WITHOUT LVOT OBSTRUCTION AND END-STAGE HCM

Patients without LVOT obstruction and normal LV function may develop symptoms of heart failure due to restrictive physiology and diastolic dysfunction. In this setting, β-blockers and verapamil also may be used to control the heart rate and to improve ventricular filling, with β-blockers again considered first-line therapy.[3] Disopyramide does not have a role in nonobstructive HCM, and diuretics may be used more aggressively in this setting. A small (~5%) but important subset of patients will progress to end-stage or "burned-out" HCM characterized by thinned myocardium, left ventricular dilation, and systolic dysfunction.[57,58] These patients should receive guideline-directed medical therapy for heart failure.[3] This is the only subgroup of patients with HCM for which cardiac transplantation may be considered.

SUDDEN CARDIAC DEATH

Implantable cardioverter defibrillators (ICDs) are the treatment of choice for the prevention of SCD in patients with HCM.[59] The data supporting the efficacy of ICDs in these patients come from observational studies illustrating the rate of SCD and appropriate ICD therapy in high-risk patients with an ICD.[60-62] The largest of these studies included 506 patients and showed that appropriate ICD therapy is frequent with an annual rate of 5.5% and that ICDs are effective in terminating ventricular tachycardia and ventricular fibrillation despite the complex HCM phenotype.[60]

Table 1. Comparison of Septal Myectomy and Alcohol Septal Ablation

Parameter	Myectomy	Ablation
Procedural mortality (at experienced centers)	<1%	1%-2%
Procedural success	90%-95%	75%-80%
Gradient reduction (at rest)	to <10 mm Hg	to <25 mm Hg
Effectiveness despite anatomic variability	Usually	Uncertain (variable septal coronary anatomy)
Symptoms (subjective and objective)	Decreased	Decreased
Survival	Similar to age- and sex-matched controls	Similar to age- and sex-matched controls
Recovery	Weeks	Days
Treatment of concomitant valvular or subvalvular disease	Yes	No
Need for pacemaker (high grade AV block)	1%-2%	10%-20%
Sudden death risk (long-term)	Very low and may reduce risk	No definitive evidence of increased risk despite concern because of scar
Available follow-up	>50 y	~15 y

Risk Stratification

Because of the unpredictable nature of SCD in patients with HCM, identifying patients at high risk for SCD is of utmost importance. Many risk markers for SCD have been studied with varying positive predictive values. There is universal agreement that patients with HCM who survive sudden cardiac arrest or have episodes of sustained ventricular tachycardia should receive secondary prevention ICDs.[3,63,64]

Established Risk Markers

Family history of sudden death. A family history of HCM-related SCD is associated with an increased risk for death in affected family members. The risk is particularly high if there are multiple SCD events in one family and if the events occur at a young age.[65,66]

Syncope. Syncope, if not attributable to another cause, is a risk factor for SCD in patients with HCM.[67] The risk is highest if syncope occurs with exertion, is repetitive, or occurs in children.

Nonsustained ventricular tachycardia. Nonsustained ventricular tachycardia (NSVT) is considered a risk marker for SCD, although not all studies have shown that it is an independent risk factor for SCD.[3] Intuitively, more weight should be placed on more frequent, faster, and longer episodes of NSVT. Its positive predictive value may be greatest in those aged $\leq$30 years.[68,69]

Massive LV hypertrophy. Approximately 10% of patients with HCM will have LV wall thickness $\geq$30 mm.[70,71] In a study of 480 patients, the risk for SCD was 0% for a wall thickness $\leq$15 mm and 1.8% per year for a wall thickness $\geq$30 mm.[70] Moreover, the incidence of SD nearly doubled for each 5 mm increase in wall thickness.

Abnormal blood pressure response to exercise. Between 20% and 40% of patients with HCM fail to augment their blood pressure (BP) during exercise, likely due to outflow obstruction and autonomic dysfunction.[72] In one study, 15% of patients with an abnormal BP response with exercise (<20 mm Hg increase in systolic BP at peak exercise or a decrease of more than 20 mm Hg from peak value during exercise) suffered SCD compared with 3% of those with a normal response.[72]

Potential Risk Markers

There are a number of features in HCM that have a possible but unclear association with SCD. These may be useful as arbitrators in resolving debates as to whether a patient should be offered preventative therapy for SCD on a case-by-case basis.

LV apical aneurysm. Whereas LV apical aneurysms are rare in patients with HCM (2%, especially in patients with apical or mid-wall hypertrophy), one study reported an incidence of SCD/ICD therapy of 3.6% per year in this population.[73]

LVOT obstruction. LVOT obstruction is recognized as an independent predictor of progression to severe heart failure symptoms or death.[40] However, not all studies have shown an increased risk for SCD with significant LVOT obstruction.[40,74]

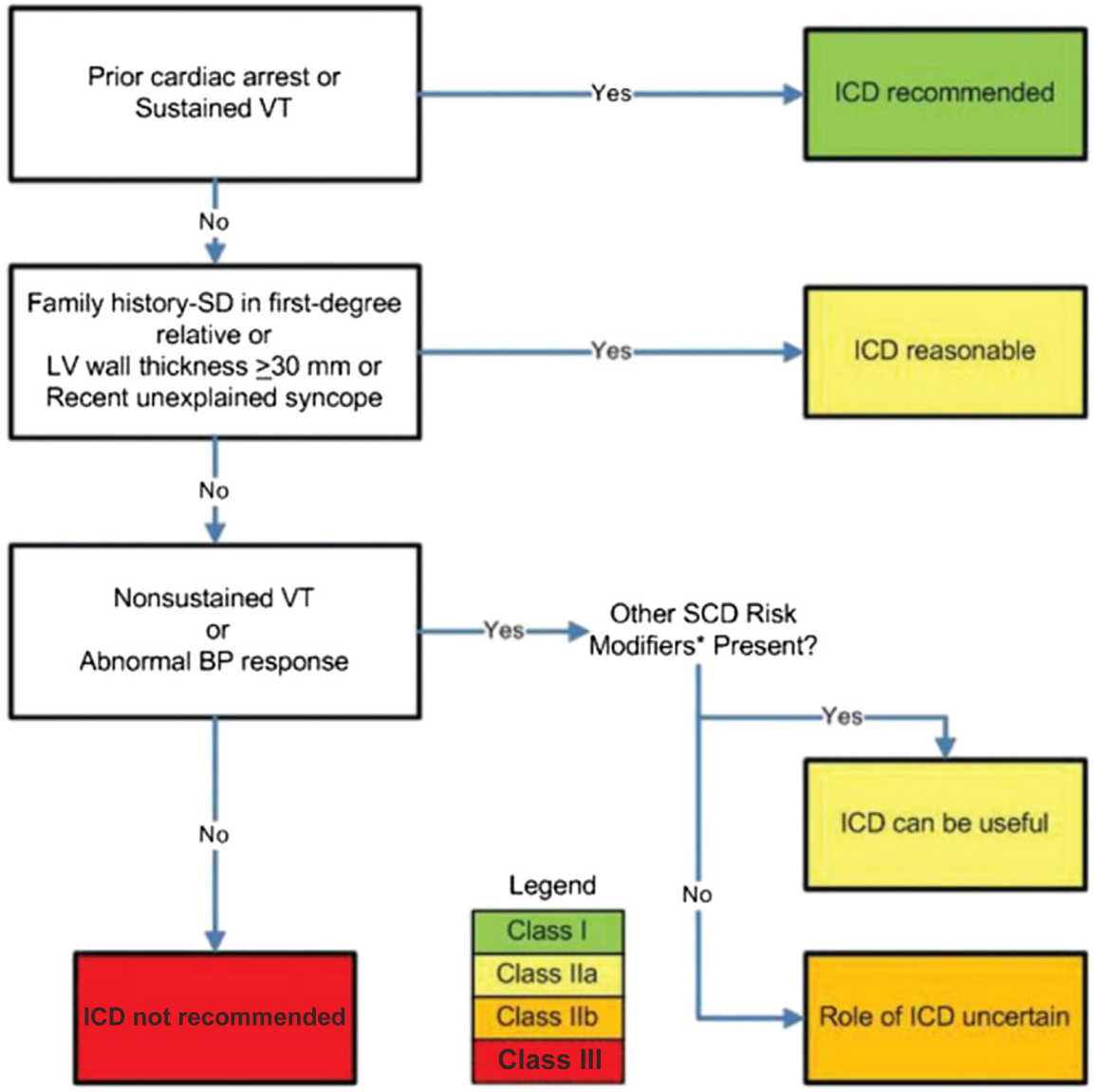
Late gadolinium enhancement on CMR. Late gadolinium enhancement (LGE) on CMR corresponds to myocardial fibrosis, and some studies have shown that LGE is associated with an increased risk for SCD.[75,76] However, the positive predictive value of LGE for SCD is low, likely because up to 60% of all patients with HCM will have LGE on CMR. Emerging evidence suggests that the extent of LGE rather than simply the presence of LGE is predictive of SCD, and current studies will better define the utility of LGE in the near future.[1,77]

High-risk genotype. There may be high-risk genotypes for SCD, but the available data have been contradictory, likely because of variable penetrance.[78] This, combined with the vast number of identified mutations (in addition to unidentified mutations), make genotyping for risk stratification clinically impractical.[79]

Selection of High-Risk Patients for ICD Implantation

Identifying which patients with HCM will benefit from ICD implantation remains difficult. Conventional risk factors were generally studied in patients between the ages of 18 and 50, and it is important to recognize that the risk for SCD is very low in HCM patients $\geq$60 years of age.[80] Also, although each of the risk factors is associated with a very high negative predictive value ($\geq$90%), they are limited by positive predictive values in the range of only 15% to 30%.[13] The number of patients with only 1 risk factor ($\sim$15%-35%) exceeds the number of patients with 1 risk factor who will have SCD. Thus, the adoption of a policy of ICD placement for all HCM patients with 1 risk factor would result in the implantation of unnecessary devices, often in young people who are much more likely to experience device complications.[60] Thus, the use of risk factors in decision making for ICD implantation should occur in the context of the characteristics of that individual patient.

A suggested algorithm for ICD implantation is shown in Figure 3. There is general agreement that secondary prevention ICDs are indicated in patients with HCM.[3] It is reasonable to implant a primary prevention ICD in patients with a family history of SCD, LV wall thickness $\geq$30 mm, or unexplained syncope. In patients with only NSVT or an abnormal BP response with exercise, an ICD can be useful if a possible risk marker for SCD (eg, LGE on CMR) is also present.



Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgment, thorough discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision making.

Figure 3. Indications for ICD implantation in HCM. *Possible SCD risk factors: LV apical aneurysm, LVOT obstruction, LGE on CMR, and high-risk genotype (reproduced with permission from Gersh et al.[3]). **Abbreviations**: CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; ICD, implantable cardiac defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVOT, left ventricular outflow; SCD, sudden cardiac death.

Atrial Fibrillation

AF in patients with HCM occurs frequently, is poorly tolerated, and is associated with an increased risk for thromboembolism, heart failure, and death. Thus, patients with HCM often require an aggressive approach to maintaining sinus rhythm. Rate control should be attempted initially, but this often requires high doses of β-blockers or non-dihydropyridine CCBs and is often inadequate.[3] Although there is insufficient evidence to recommend one antiarrhythmic over another, amiodarone or disopyramide may be the most effective in maintaining sinus rhythm in patients with HCM.[14] Sotalol, dofetilide, and dronedarone may be considered alternative agents.[3] If antiarrhythmic therapy is unsuccessful,

pulmonary vein isolation or AV node ablation with pacemaker implantation should be considered. Surgical maze also may be considered.

Because of the increased risk for thromboembolism, anticoagulation is indicated in all patients with HCM with paroxysmal, persistent, or chronic AF regardless of CHADS2 status.[3] Because even brief episodes of AF have been associated with stroke, there should be a low threshold for initiating anticoagulation in these patients.[81] Historically, warfarin has been used in this population, and there are currently no published data on the use of the novel anticoagulants in patients with HCM.

Asymptomatic Patients and Screening of Family Members

Asymptomatic patients. The majority of patients with HCM will be asymptomatic even in the presence of LVOT obstruction. The effectiveness of β-blockers and CCBs is not established in this setting, and routine use in not recommended. Although some therapies such as angiotensin receptor blockers have been shown to reverse or prevent the development of hypertrophy in animal studies, these have not been demonstrated in humans.[82] Cardiac comorbidities should be treated, and low-level aerobic exercise is permissible.

Screening family members. The offspring of individuals with HCM have a 50% chance of inheriting the mutation. Because of this, screening of first-degree relatives is of paramount importance. Clinical screening should include a history and physical examination, 12-lead electrocardiogram, and echocardiography or CMR. Substantial LV remodeling with the appearance of LVH is usually associated with accelerated body growth during puberty with transformation complete by young adulthood.[63] However, some gene mutations are associated with late onset HCM in mid-life and beyond.[6] Because of this, clinical screening no longer ceases in young adulthood. Table 2 summarizes the clinical screening intervals by group.

Genetic testing. Eleven or more genes with >1000 mutations have been discovered in association with HCM.[1,83] Mutations in β-myosin heavy chain and cardiac myosin binding protein C account for more than 50% of HCM mutations.[84] Genetic testing is most useful in family screening. Current guidelines recommend genetic counseling as part of the assessment of patients with HCM and state that genetic testing in the index patient is reasonable to facilitate family screening.[3] If a patient has a gene mutation, then family members can be screened for that mutation. If the mutation is not present, they do not require further testing.

Screening may identify people with a HCM gene mutation but without evidence of LVH. These "genotype-positive, phenotype-negative" patients should undergo clinical screening as outlined in Table 2. There is currently little evidence regarding screening intervals, use of ICDs, and recommendations for participation in competitive sports. Further studies are required to delineate the best management strategies for this emerging group of patients.

Table 2. Proposed Clinical Screening Strategies with Echocardiography (and 12-Lead ECG) for Detection of HCM in Families*

Group	Screening Recommendation
Age < 12 y	Optional unless: • Malignant family history of premature death or other adverse complications from HCM • Competitive athlete in intense training program • Onset of symptoms • Other clinical suspicion of early LVH
Age 12 to 18-21 y†	Every 12-18 mo
Age >18-21 y†	Every 5 y or with onset of symptoms. More frequent screening may be appropriate with family history of malignant clinical course or late onset HCM.
Genotype-positive, phenotype-negative in family with known mutation	Clinical screening intervals as above. Exercise stress testing and Holter monitoring may be appropriate if there is a family history of SCD.
Genotype-negative in family with known mutation	No screening is needed.

ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; SCD, sudden cardiac death.
*When a genetic mutation is not identified or genetic testing is not performed. In families with an identified mutation, refer to the final two rows.
†Age range reflects individual variability in achieving physical maturity.
Adapted with permission from Maron et al.[85]

CONCLUSION

Hypertrophic cardiomyopathy is a complex, genetic disease with heterogeneous phenotypes and clinical manifestations. The management of any patient with HCM involves: 1) the control of heart failure symptoms, 2) assessment of risk for sudden death, 3) the treatment of AF and reduction of risk for thromboembolism, and 4) screening of family members. Because of the considerable heterogeneity of this disease and lack of randomized data, guidelines for patients with HCM simply provide a framework in which to evaluate and treat an individual patient. Indeed, the unique characteristics and preferences of each individual patient with HCM should play a vital role in decision-making and management strategies.

Further studies are needed to improve the care in this patient population. Long-term data on alcohol septal ablation will define its precise role in relation to myectomy in the management of medically refractory patients with HCM. Improvements in risk stratification for SCD will more accurately identify patients with HCM at risk for SCD, and the development of subcutaneous and leadless ICD systems will likely reduce complications and lower the threshold for device implantation in young patients. The role of genetic testing will also become clearer when genotyping becomes cheaper and more accessible. Finally, ongoing research may identify agents that delay the onset of disease in genotype-positive, phenotype-negative patients or prevent disease progression in asymptomatic patients.

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