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Canadian Cardiovascular Society Clinical Practice Update on Contemporary Management of the Patient with Hypertrophic Cardiomyopathy

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General Clinical Practice Update

Canadian Cardiovascular Society Clinical Practice Update on Contemporary Management of the Patient With Hypertrophic Cardiomyopathy

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ABSTRACT

Numerous guidelines on the diagnosis and management of hypertrophic cardiomyopathy (HCM) have been published, by learned societies, over

RÉSUMÉ

De nombreuses lignes directrices sur le diagnostic et la prise en charge de la cardiomyopathie hypertrophique (CMH) ont été publiées par des

Hypertrophic cardiomyopathy (HCM) is a common and frequently inherited disease, characterized by thickening of the left ventricular (LV) myocardium with an estimated prevalence of 1/500.[1] HCM is a major cause of morbidity and mortality, including exertional symptoms, heart failure, atrial fibrillation (AF), stroke, and ventricular arrhythmias, potentially resulting in sudden cardiac arrest or death.

Significant advances in the understanding of HCM pathophysiology, epidemiology, and patient management have been recently accomplished. These include: (1) an improved understanding of the genetic basis of HCM[2-4]; (2) better recognition of sporadic (nonfamilial) HCM cases diagnosed in older populations with comorbidities[5,6]; (3) availability of a novel drug class of direct cardiac myosin inhibitors (CMIs)[7,8];

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The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of interdisciplinary experts on this topic. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources.

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the past decade. Although helpful they are often long and less adapted to nonexperts. This writing panel was challenged to produce a document that grew as much from years of practical experience as it did from the peer-reviewed literature. As such, rather than produce yet another set of guidelines, we aim herein to deliver a concentrate of our own experiential learning and distill for the reader the essence of effective and appropriate HCM care. This Clinical Practice Update on HCM is therefore aimed at general cardiologists and other cardiovascular practitioners rather than for HCM specialists. We set the stage with a description of the condition and its clinical presentation, discuss the central importance of "obstruction" and how to look for it, review the role of cardiac magnetic resonance imaging, reflect on the appropriate use of genetic testing, review the treatment options for symptomatic HCM—crucially including cardiac myosin inhibitors, and deal concisely with practical issues surrounding risk assessment for sudden cardiac death, and management of the end-stage HCM patient. Uniquely, we have captured the pediatric experience on our panel to discuss appropriate differences in the management of younger patients with HCM. We ask the reader to remember that this document represents expert consensus opinion rather than dogma and to use their best judgement when dealing with the HCM patient in front of them.

sociétés savantes au cours de la dernière décennie. Bien qu'utiles, elles sont souvent longues et peu adaptées aux non-spécialistes. Notre groupe de rédaction a été mis au défi de produire un document qui émane aussi bien des années d'expérience pratique que de la littérature évaluée par les pairs. Ainsi, plutôt que de produire un énième ensemble de directives, nous visons ici à fournir un concentré de notre propre apprentissage expérientiel et à distiller pour le lecteur l'essence des soins efficaces et appropriés pour a CMH. Cette mise à jour de la pratique clinique centrée sur la CMH s'adresse donc aux cardiologues généralistes et autres praticiens cardiovasculaires plutôt qu'aux spécialistes de la CMH. Nous commençons par une description de la condition et de sa présentation clinique; nous discutons de l'importance centrale de l'"obstruction" et de la manière de la rechercher; nous examinons le rôle de l'imagerie par résonance magnétique cardiaque; nous réfléchissons à l'utilisation appropriée des tests génétiques; nous passons en revue les options thérapeutiques pour la CMH symptomatique — en particulier les inhibiteurs de la myosine cardiaque; et nous traitons de manière concise les questions pratiques concernant l'évaluation du risque de mort subite cardiaque et la prise en charge du patient atteint de CMH en phase terminale. De manière unique, nous avons intégré l'expérience pédiatrique dans notre panel afin de discuter des différences appropriées dans la prise en charge des jeunes patients atteints de CMH. Nous demandons au lecteur de se rappeler que ce document représente une opinion consensuelle d'experts plutôt qu'un dogme, et de faire preuve de jugement dans la prise en charge des patients qui se présentent avec une CMH.

(4) better risk stratification of sudden cardiac death (SCD) in children and adults[9-11]; and (5) improved understanding of the safety of exercise.[12]

The present Clinical Practice Update (CPU) from the Canadian Cardiovascular Society (CCS) is the first such effort from the CCS to address the management of patients with HCM. This CPU provides a broad overview of the clinical management of HCM relevant to cardiovascular health care providers, including practical expert advice in addition to reviewing supporting data. It should be considered as an expert consensus, rather than an in-depth evidence-based guidelines document.

I. Diagnosing Hypertrophic Cardiomyopathy

Practical Tips

- HCM is diagnosed in presence of end diastolic LV wall thickening that is not entirely explained by another etiology (Fig. 1; Supplemental Appendix S1).
  - In adults: ≥ 15 mm, or ≥ 13 mm in presence of either family history of HCM and/or a (likely) pathogenic genetic variant causing HCM.
  - In children: *z*-score ≥ 2.5, or ≥ 2.0 in the presence of either family history of HCM and/or a (likely) pathogenic genetic variant causing HCM.
- A subset of apical HCM cases is characterized by relative hypertrophy (apical wall thickness < 15 mm with an apex:base wall thickness ratio > 1) with associated marked T-wave inversions in the electrocardiogram (ECG) precordial leads (Fig. 2).
- Diagnosing HCM in the presence of hypertension can be challenging. Severe hypertension with mild symmetric hypertrophy favours hypertensive heart disease, whereas mild hypertension with asymmetric and/or severe wall thickening favours HCM.

Diagnostic criteria for HCM

The diagnosis of HCM is contingent on the identification of LV hypertrophy using cardiac imaging in the absence of another etiology that could account for this finding.[13-15] Figure 1 shows specific diagnostic criteria for adults and children. The diagnosis of HCM can sometimes be considered in cases with milder LV wall thickening after expert evaluation, such as in apical HCM (Fig. 2) and in "end stage" ("burned-out") HCM with LV systolic dysfunction.

Diseases and conditions that can mimic isolated HCM

Some patients might present with a phenotype that is similar or even identical to HCM because of acquired conditions or rare genetic diseases that might cause LV wall thickening, sometimes with subtle extracardiac anomalies. It is imperative for clinicians to be aware of these "mimics" because accurate diagnosis might affect treatment (eg, enzyme therapy in Fabry disease). Supplemental Appendix S1 shows a summary of the common "HCM mimics." A detailed discussion of each mimic is beyond the scope of this CPU. More extensive lists of genes linked to HCM genocopies have been published elsewhere.[4]

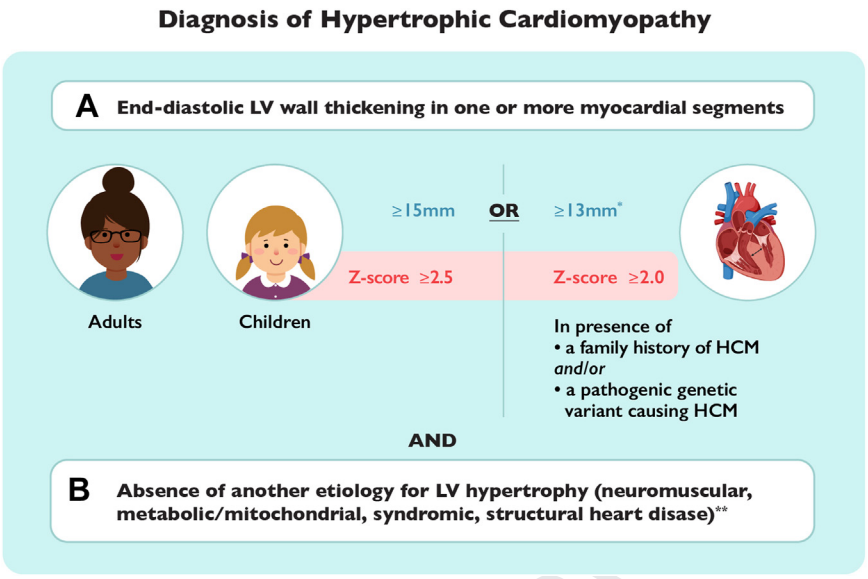


Figure 1. Diagnostic criteria for hypertrophic cardiomyopathy (HCM) in adults and children. (**A**) Left ventricular (LV) wall thickening; and (**B**) absence of another pathology that could explain LV hypertrophy.
* HCM can sometimes be diagnosed with lower magnitudes of wall thickening (eg, 13-14 mm in adults) in other circumstances such as in presence of deep precordial T-wave inversions with relative apical hypertrophy (Fig. 2) or in the presence of systolic dysfunction.
** See Supplemental Appendix S1 for a summary description of the most common HCM "mimics."

HCM in the presence of systemic hypertension

LV hypertrophy in the presence of hypertension might lead to diagnostic ambiguity. Hypertension does not usually cause severe LV hypertrophy (> 18 mm) and tends to cause symmetric hypertrophy. More advanced diastolic dysfunction and LV hypertrophy out of proportion to the clinical hypertension severity should indicate the possibility of HCM. On imaging, isolated basal septal hypertrophy (sigmoid septum) in the elderly individual with hypertension is a common conundrum and the distinction between a benign or pathologic condition might not be clear. Data from large international HCM registries indicate that hypertension is present in one-quarter to one-third of patients recently diagnosed with HCM.[5,6] As such, hypertension and HCM often coexist and the presence of hypertension does not preclude a diagnosis of HCM but may be considered as a risk factor for HCM.[3] Ultimately, the magnitude of hypertrophy in patients with increased afterload must be interpreted within the clinical context to render a probabilistic diagnosis of HCM.

II. Genetic Testing and Family Screening

Practical Tips

- Genetic testing
  - Genetic testing should be offered to all individuals with a clinical diagnosis of HCM, to exclude rare genetic diseases that mimic HCM, and to facilitate family screening.
  - In families where a (likely) pathogenic genetic variant has been identified, counselling and genetic testing should be offered to all relatives regardless of age.
- Clinical screening
  - First-degree relatives of patients with a clinical diagnosis of HCM should generally have baseline clinical screening with echocardiography and a resting ECG.
  - In families where a (likely) pathogenic variant has been identified, relatives who do not carry the variant can be discharged from follow-up if they have normal baseline clinical screening.
  - Periodic clinical screening should be offered to carriers of a (likely) pathogenic genetic variant and to first-degree relatives of genotype-elusive HCM cases (ie, in whom a [likely] pathogenic variant has not been identified).
  - Clinical screening should be individualized. The yield of clinical screening in families with genotype-elusive HCM, especially if HCM is mild and diagnosed at an old age in a single relative, is likely to be relatively low.

Historically, HCM has been regarded as an autosomal dominant condition caused by a single rare variant in genes coding for the cardiac contractile apparatus called the sarcomere (ie, "monogenic HCM," or "sarcomeric HCM"). In recent years, it has become increasingly recognized that in most adult cases (approximately 70%), HCM is not caused by a single rare variant but a combination of genetic variants that each only modestly increases risk of HCM, in addition to comorbidities such as hypertension (ie, polygenic/multifactorial HCM).[2,3] Figure 3 shows a summary of the differences in monogenic and polygenic/multifactorial HCM. A detailed review of the complex genetic architecture of HCM has recently been published.[16]

Genetic testing for patients with HCM

Genetic testing involves sequencing of genes for the purpose of identifying (likely) pathogenic genetic variants (ie, variants that play a major role in HCM) and to inform family screening when

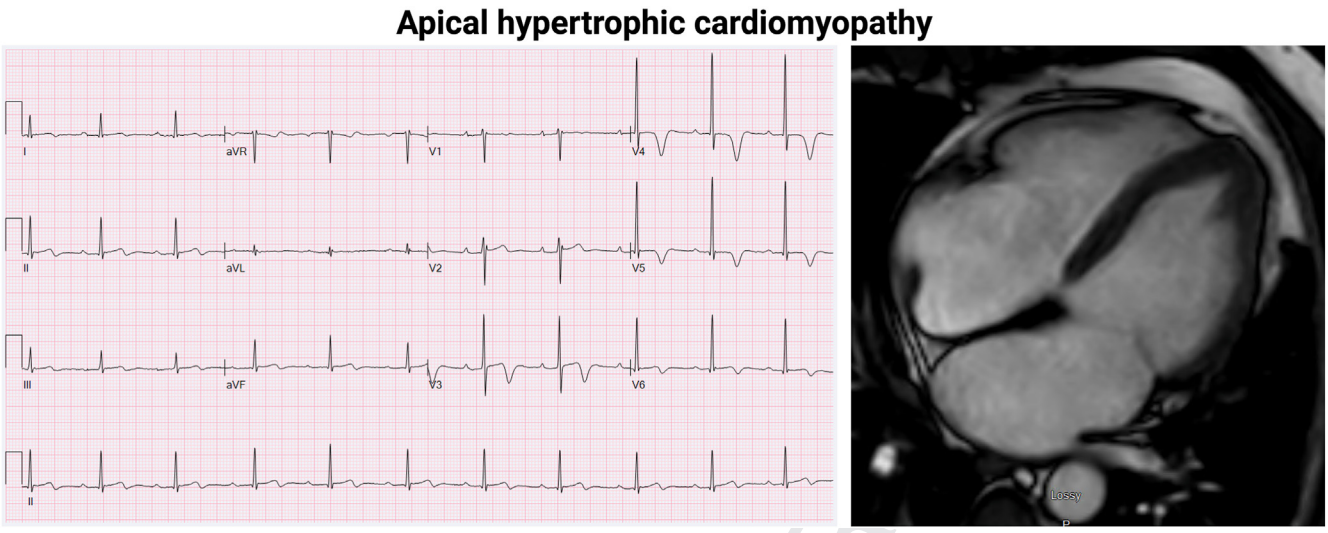


Figure 2. Apical hypertrophic cardiomyopathy (HCM). Typical electrocardiogram changes (**left**) with deep T-wave inversions in precordial leads (V_3-V_6), and relative apical hypertrophy shown with cardiac magnetic resonance imaging (**right**) in a patient with apical HCM. In this adult patient, apical HCM was diagnosed with left ventricular wall thickness of 13-14 mm within apical segments despite the absence of family history or (likely) pathogenic genetic variant.

the genetic cause of disease is found. There is limited evidence linking long-term outcomes to specific genetic variants for HCM apart from earlier onset of disease and worse outcomes for individuals who carry a disease-causing genetic variant (Fig. 3).[11,17,18] Genetic testing should be offered to all individuals with a clinical diagnosis of HCM, although the likelihood of identifying the genetic cause of disease differs on the basis of the family history,[19-21] age of onset,[19,20] location of ventricular hypertrophy,[22] and presence of additional risk factors (ie, hypertension and obesity[19,20]).

The discovery of genes associated with HCM is ongoing. It is generally recommended that genetic testing should include a panel of genes with good evidence (definitive, strong, or moderate evidence[4,23,24]), implicating them in HCM, and also genes that might be associated with "HCM mimics" with subtle extracardiac features that might be overlooked (Supplemental Appendix S2).

Genetic testing might lead to the following results: (1) informative (ie, a disease-causing pathogenic, or likely pathogenic genetic variant is identified); (2) inconclusive (ie, a variant of uncertain significance is identified); and (3) "negative" (ie, no variant or only benign/likely benign variant identified).

Additional points to consider regarding genetic testing for HCM include:

(1) genetic variant interpretation is complex and should integrate most recent guidelines.[25] Because of the complexity of some genetic results, genetic testing results should be interpreted by health care professionals with expertise in genetics with access to pre- and post-test genetic counselling.[26] Variants should be periodically reinterpreted (eg, every 3-5 years) because 10%-15% if variants are reclassified on follow-up.
(2) Genetic testing must start with an affected individual. Genetic testing is not recommended for unaffected family members unless a genetic cause has been identified in the family.
(3) For individuals with HCM in whom no genetic cause is identified, updates to genetic panels or technology should be reviewed every 3-5 years, especially for families with multiple affected individuals. Universal repeat testing is, however, not recommended considering its low yield.

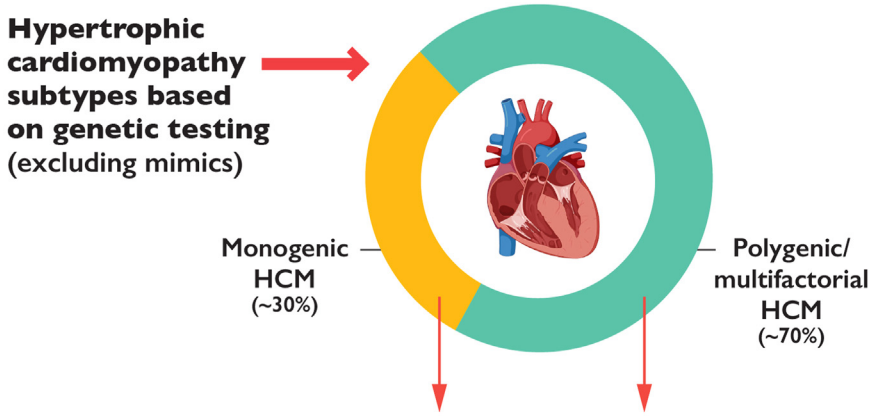
Genetic and clinical screening of family members

The primary goal of family screening is diagnosis of HCM in asymptomatic individuals with the purpose of preventing serious adverse outcomes. The provision of written information to patients for sharing with family members is considered a standard of practice (Supplemental Appendix S3). The general approach to screening of relatives is shown in Figure 4, with important detailed advice provided in Supplemental Appendix S4.

III. Imaging HCM

Practical Tips

- Perform transthoracic echocardiography (TTE) at diagnosis and periodically thereafter (eg, every 1-2 years) to assess:
  - Maximal wall thickness
  - Left atrial diameter and volume
  - Obstruction—location and severity
  - Mitral regurgitation (MR)—mechanism (systolic anterior motion [SAM], intrinsic, etc) and severity
  - Presence of LV apical hypertrophy and aneurysm
  - Systolic and diastolic function
  - Global longitudinal strain depending on image quality, particularly when infiltrative disease is suspected
- LV outflow tract (LVOT) obstruction is present in 30% at rest and 30% only with provocation. Provocation should include Valsalva manoeuvre, positional change, and/or exercise.
- Cardiac magnetic resonance (CMR) imaging should be considered in all patients with suspected HCM and is complementary to TTE.



Genetic testing	Positive	Negative
Dominant cause	Pathogenic genetic variant*	Polygenic risk Comorbidities
Age at diagnosis	Younger	Older
Prevalence of LVOT obstruction	Lower	Higher
Lifetime risk of AF VT/VF/SCD Heart failure	Higher	Lower
Risk of HCM in relatives	Higher (up to 50%)	Lower**

Figure 3. Differences in monogenic hypertrophic cardiomyopathy (HCM) mainly caused by pathogenic variants in genes coding for the cardiac sarcomere and polygenic/multifactorial HCM. AF, atrial fibrillation; LVOT, left ventricular outflow tract; VT/VF/SCD, sustained ventricular tachycardia/fibrillation (including appropriate defibrillator therapies) or sudden cardiac death.
* In monogenic HCM, polygenic risk also underlies variability of disease expression in carriers of pathogenic variants.
** In some cases of HCM with genetic testing that did not show pathogenic variants in genes coding for the cardiac sarcomere (eg, familial or early onset), the risk in relatives might be higher, justifying a need for periodic screening.

Echocardiography

LV structure: Echocardiography reports the pattern and distribution of LV hypertrophy along with the magnitude of maximal wall thickness at end diastole and should be assessed in all LV segments. Measurements should be conducted perpendicular to the LV cavity (to avoid foreshortening) while avoiding trabeculations, sigmoid septum, and papillary muscles. Papillary muscle abnormalities are common in patients with HCM and might have implications for surgical planning. Although papillary muscle morphology can be evaluated using TTE, it is more accurately evaluated using CMR imaging. The presence of an apical aneurysm should be reported because of potential implications on arrhythmic and thromboembolic risks, including consideration for oral anticoagulation.

Systolic function: Hyperdynamic ventricular contraction is a hallmark of HCM, especially early in its natural history. Therefore, even an LV ejection fraction (LVEF) of 50%-55% might represent early impairment of ventricular function. Systolic dysfunction is defined as a LVEF $< 50\%$ and represents a risk factor for SCD and heart failure in patients with HCM.[27] Longitudinal strain imaging might help differentiate HCM from other types of cardiomyopathies (eg, specific regional strain patterns in amyloid and Fabry disease) and might provide incremental risk stratification.[28] Strain correlates with degree of hypertrophy and extent of delayed gadolinium enhancement in CMR imaging.[29]

Obstruction: LVOT obstruction is present or develops over time in more than 60% of patients with HCM.[30,31] It can be the result (or combination) of septal hypertrophy with narrowing of the outflow tract, anterior malposition of papillary muscles, SAM of the mitral valve, and intrinsic abnormalities of the mitral valve leaflets.

Obstructive HCM is defined by a peak instantaneous LVOT gradient of ≥ 30 mm Hg either spontaneously at rest or provoked (ie, LVOT gradient < 30 mm Hg at rest but ≥ 30 mm Hg with provocative manoeuvres). Because LVOT obstruction

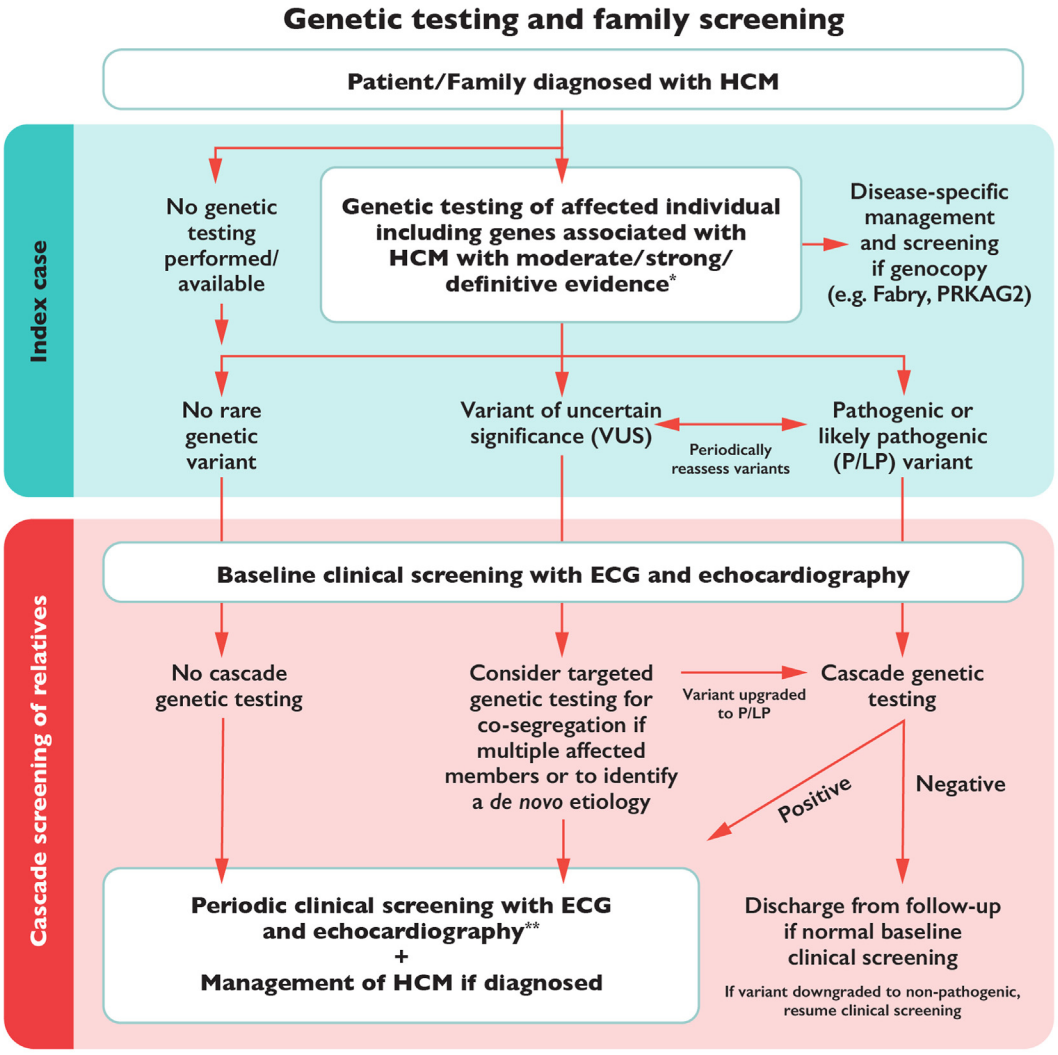


Figure 4. General approach to genetic testing and family screening. ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; P/LP, pathogenic or likely pathogenic.

* See Supplemental Appendix S2 for the genes commonly included in current testing panels.

** Cardiac magnetic resonance may be considered in cases with nondiagnostic or equivocal echocardiography (eg, in presence of symptoms and/or abnormal ECG). Frequency and duration of ongoing screening depend on family history and genetic findings, as well as patient age, clinical history, participation in sports, occupation, and preference. See Supplemental Appendix S4 for details.

is dynamic, various provocative manoeuvres (Valsalva, squat to stand, exercise stress echocardiography via upright treadmill or supine bike[32]) might be required to unmask obstruction. Stress imaging is particularly important in symptomatic patients with resting or provocable gradients < 50 mm Hg, because higher inducible gradients might alter therapeutic decision-making when symptoms are severe. It is also important to differentiate SAM-mediated LVOT obstruction from midventricular obstruction and MR velocity. The Doppler profile of MR usually has a higher velocity and longer systolic duration, whereas LVOT has a "dagger" shape.

Mitral regurgitation: Contact of the anterior mitral valve leaflet with the septum (SAM) creates a failure of coaptation with the posterior leaflet that results in posteriorly directed MR predominantly during mid to late systole. Enlarged and elongated mitral valve leaflets contribute to SAM. In some cases, nonposteriorly directed MR can still be related to SAM because of differences in leaflet geometry that alter the direction of the jet either centrally or anteriorly. However, suspicion of intrinsic mitral valve disease (mitral annular calcification, mitral prolapse, ruptured chordae with leaflet flail, abnormal mitral valve leaflet, abnormal insertion of papillary muscle, leaflet destruction due to infective endocarditis, etc) should be raised when MR is not posteriorly directed.

Diastolic function: Abnormal relaxation and elevated LV filling pressures are a major component of the pathophysiology of HCM resulting from myocardial hypertrophy with reduction in chamber compliance, delayed relaxation, ischemia, and myocardial fibrosis. This will often result in symptomatic heart failure and/or reduced exercise tolerance in patients with or without obstruction. However, estimation of diastolic function with usual echocardiographic parameters (transmitral flow velocities and tissue Doppler imaging) often results in modest correlation with LV end diastolic pressure.[33] Comprehensive

diastolic evaluation in HCM is often necessary, including, E/e' ratio, left atrial volume index, pulmonary vein atrial reversal velocity, and tricuspid regurgitation peak velocity.

Exercise stress echocardiography: Exercise stress echocardiography may be conducted with an upright treadmill preferably or supine bicycle as an alternative (Fig. 5). The search for gradients should be exhaustive, particularly when the patient's description of symptoms is strongly suggestive of obstruction. If the goal is to achieve the highest success of showing someone has obstructive physiology then the patient should abstain from medications (disopyramide, β-blockers, and calcium channel blockers), for 48 hours before the study. Otherwise, there can be a role for patients to continue taking medications to assess the efficacy of gradient reduction therapy with therapy. On rare occasions, it might be worth considering postprandial exercise testing, because the associated splanchnic dilatation and increased cardiac output might unmask an occult gradient.[34]

For a comprehensive review of the utility of TTE in HCM, please see the reports by Turvey et al[35] and Abbasi et al.[36]

Cardiac magnetic resonance

The role of CMR has continued to evolve in patients with HCM for diagnosis and risk stratification (Supplemental Appendix S5, Figs. 6-8). CMR is important in the assessment of: (1) resting LVOT obstruction; (2) mitral valve abnormalities (including quantification of mitral insufficiency, leaflet elongation/prolapse, apical papillary muscle displacement, etc); (3) late gadolinium enhancement (LGE) presence and quantification; (4) microvascular disease (stress perfusion protocols); and (5) for planning of septal intervention procedures.[37,38]

CMR is complementary to echocardiography and provides operator-independent imaging for accurate and serially reproducible ventricular measures, particularly in patients with more subtle phenotypes, and regional or apical forms of the disease.[39-43] LV morphology, wall thickness, and mitral valve characteristics might also be helpful in determining the type of septal reduction therapy (myectomy vs alcohol septal ablation) and for planning the procedure itself (eg, anterior mitral leaflet plication and papillary muscle release in myectomy).[37,38,44]

In children, z-scores should be provided in addition to absolute measurements of ventricular parameters for diagnostic purposes.[13,14,45] Use of CMR imaging can be challenging in younger children. Right ventricular (RV) hypertrophy, when present, should also be reported inclusive of maximal RV wall thickness and RV mass.[46] RV involvement in patients with HCM has been shown to be an independent predictor of adverse outcomes.[47] Ventricular volumes and LVEF are also useful to identify patients with adverse LV remodelling at risk for end stage heart failure.

CMR imaging evaluation has become an important component of SCD risk prediction in patients with HCM (see section VII) and a number of morphological factors have been integrated into practice guidelines.[13,14] Specifically, extensive LGE comprising ≥ 15% of LV mass is considered an SCD risk marker to consider prophylactic implantable cardiac defibrillator (ICD) implantation. Comparisons of additional CMR parameters with traditional SCD risk markers have shown greater sensitivity for appropriate ICD therapies.[48,49]

IV. Screening for Arrhythmia

Practical Tips

- Patients with HCM should undergo screening for AF and for nonsustained ventricular tachycardia (NSVT).
- Ambulatory ECG monitoring (24-48 hours) should be conducted at diagnosis and annually thereafter.
- Consider longer-duration monitoring in patients at high risk of AF, including:
  - severe left atrial dilatation,
  - high burden of atrial ectopy,
  - palpitations suggestive of AF, and
  - unexplained embolic events.
- Patients with a pacemaker or ICD who have an atrial lead do not require ambulatory ECG monitoring because the devices can detect AF.
- Implanted loop recorders can be considered, particularly for unexplained syncope when an ICD is not being considered.

Screening for AF and NSVT is an important component of HCM follow-up.[50] AF is the most common arrhythmia in patients with HCM with a prevalence of 22%-33% in adults.[50] Risk factors for developing AF include increased left atrial volume, age, female sex, New York Heart Association (NYHA) class, hypertension, and vascular disease.[51,52] Thromboembolism risk is high in patients with HCM and AF.[53] Patients who report symptoms suggestive of AF, such as palpitations, should undergo rhythm monitoring for symptom/rhythm correlation. In the absence of symptoms, periodic screening is recommended because up to 50% of patients with HCM have subclinical AF.[14] NSVT detected on ambulatory ECG monitoring is a risk marker for SCD and should be considered for risk stratification of SCD[54] as discussed in section VII.

V. Management of AF

Practical Tips

- In the absence of contraindications, all patients with HCM and AF should receive oral anticoagulation medication.
- Decisions regarding rate vs rhythm control of AF in patients with HCM is similar to that in non-HCM patients (see the CCS AF guidelines[55]), with the following HCM-specific considerations:
  - Rate control can be attempted with β-blockers and/or non-dihydropyridine calcium channel blockers. Digoxin is generally avoided, especially in patients with obstructive HCM, because of its positive inotropic effects.
  - Rhythm control can be attempted with sotalol, disopyramide, or amiodarone. All 3 antiarrhythmic drugs require monitoring for QT prolongation.
  - AF ablation with pulmonary vein isolation may be considered for rhythm control of AF in HCM patients, however, AF ablation is less effective than in patients without HCM.
  - Atrioventricular node ablation and pacemaker implantation ("ablate and pace") can be considered in refractory patients.

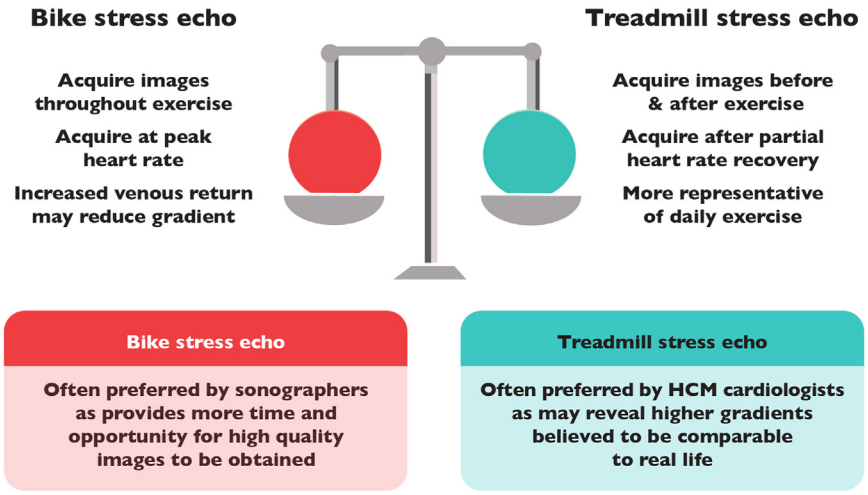


Figure 5. Choosing between supine bicycle and treadmill stress echocardiography (echo). HCM, hypertrophic cardiomyopathy.

Oral anticoagulation

Patients with HCM and AF have up to an eightfold increase in stroke risk compared with those without AF.[56] In the absence of a contraindication, patients diagnosed with AF should receive anticoagulation with a vitamin K antagonist or a direct oral anticoagulant.[57,58] Anticoagulation with a direct oral anticoagulant is generally preferred in patients with HCM, as it is for the broader AF population.[55]

Rate and rhythm management

There are limited data to support a general strategy of rhythm vs rate control in patients with HCM. β-Blockers, verapamil, or diltiazem can be used for a rate control strategy, but digoxin is usually avoided in patients with HCM because of its positive inotropic effects. When AF is poorly tolerated, a rhythm control strategy can include either drug therapy or ablation.

Choices for pharmacologic rhythm control therapy of AF in patients with HCM are limited. Although amiodarone is generally considered the most effective and preferred therapy, its long-term use, particularly in young or comorbid patients is limited by well described toxicities. Alternative anti-arrhythmic drugs that have been used include disopyramide and sotalol. Disopyramide might be preferred in individuals that have LVOT obstruction in whom there is a secondary benefit of obstruction relief.[59,60] Sotalol is commonly used because of its low rate of discontinuation and has a favourable safety profile in patients with HCM. Sotalol, disopyramide, and amiodarone require QTc monitoring. Q4

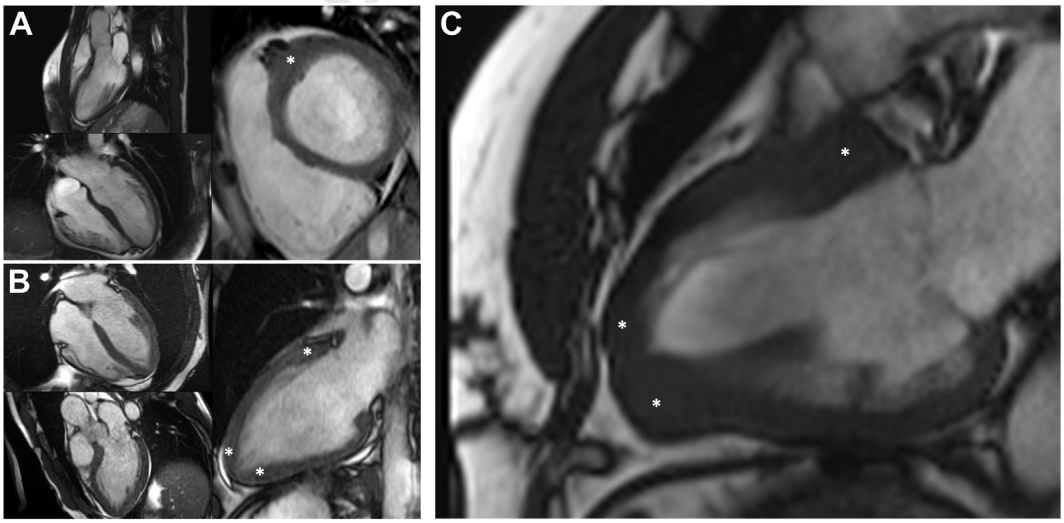


Figure 6. Recognition of subtle hypertrophic cardiomyopathy using cardiac magnetic resonance in 3 different patients. (**A**) Mild hypertrophic cardiomyopathy phenotype with focal basal anterior wall hypertrophy (**asterisk**) that was nondiagnostic using echocardiography. (**B**) Young patient with marked T-wave inversions across the precordial leads. Echocardiogram was reported as unremarkable, cardiac magnetic resonance revealed subtle left ventricular thickening (**asterisks**) at the apex relative to the mid ventricle. Note that there is also slightly disproportionate thickening of the basal segment (**asterisk**). (**C**) The same phenomenon of apical/basal hypertrophy (**asterisks**) is more readily appreciated in this third example.

There have been numerous studies of catheter ablation for AF in patients with HCM that have shown that ablation is effective in treating patients who have failed to respond to antiarrhythmic drugs. However, although the safety profiles are comparable, catheter ablation of AF is less effective in patients with HCM compared with those without structural heart disease, with a twofold greater risk of relapse.[61] In a recent meta-analysis, there was evidence to support catheter ablation for AF in patients with HCM, particularly those with paroxysmal AF who experienced a 12-month single-procedure success rate of 64% (95% confidence interval [CI], 47%-80%).[62] However, for long-term freedom from AF, there was a general trend that patients with HCM were more likely to require multiple interventions and concomitant long-term antiarrhythmic therapy. In patients who undergo surgical intervention for HCM, surgical AF ablation should be considered.[63] Device implantation with atrioventricular (AV) node ablation might also be considered for refractory patients.[64]

VI. Management of Obstruction and Heart Failure

Practical Tips

- The identification of intracardiac obstruction is fundamental to HCM management.
- Management of symptomatic obstruction is step-wise and includes lifestyle changes, pharmacologic therapy, and invasive procedures (Fig. 9).
  - Educate patients regarding avoidance of hypovolemia and the Valsalva manoeuvre.
  - Avoid vasodilators and diuretics unless required.
  - First-line treatment: nonvasodilating β-blockers and/or nondihydropyridine calcium channel blockers.
  - Second-line treatment:
    - Drugs (disopyramide or a myosin inhibitor, such as mavacamten).
    - Invasive therapies (alcohol septal ablation or surgical myectomy).
  - Myosin inhibitors are an effective and well tolerated treatment in patients with symptomatic obstructive HCM. Close monitoring of systolic function is required.
  - Myosin inhibitors should not be used in patients with LVEF < 55% and therapy should be interrupted if LVEF decreases to < 50% during follow-up.
  - Invasive septal reduction therapy should be conducted in high-volume expert centres.
- Symptomatic nonobstructive HCM might be challenging to effectively treat.
  - Use of β-blockers and/or nondihydropyridine calcium channel blockers can be attempted.
  - Diuretics can be used if filling pressure is elevated.
  - Clinical trials of myosin inhibitors are ongoing.
- HCM patients with reduced LVEF have a poor prognosis.
  - Use of guideline-directed medical therapies (see the CCS heart failure guidelines[65]), and adapting treatment to patient physiology (eg, low contractile reserve, restrictive physiology) is suggested.
  - Early referral should be used for advanced heart failure therapies.

Why do we need to identify obstruction?

The identification of intracardiac obstruction is fundamental to the management of HCM,[66] because management of symptoms varies according to its presence/absence. Intracardiac obstruction most frequently results in symptoms of breathlessness, dizziness, and chest pain of varying severity (Supplemental Appendix S6). Most patients with severe obstruction will have symptoms or objective evidence of decreased exercise capacity when measured, but a small percentage might be asymptomatic. Asymptomatic patients might develop symptoms later in life, even in the absence of progressive hypertrophy or worsening gradient; this might be due, in part, to progressive diastolic dysfunction.

Location and mechanism of obstruction

Obstruction might occur at any level within the left ventricle and identification of the location(s) determines therapeutic options. Patients might have obstruction at more than one level and elderly patients might have concomitant aortic valve obstruction. Determination of the location(s) and severity of obstruction are critical for management decisions (Table 1).

A stepwise approach to management of obstruction

It is the presence of symptoms that should drive escalation of therapy in patients with obstructive HCM, because there is no direct evidence of benefit from targeting gradient reduction as a primary aim in the absence of symptoms.

Nonpharmacologic measures. Outflow tract obstruction is a dynamic phenomenon that varies according to the physiologic state of each patient. It is dependent on changes in preload and afterload, such as position, state of hydration, Valsalva, and external temperature. Patients should be provided education regarding manoeuvres to minimize sudden changes in gradients, including adequate hydration and caution in overly hot environments (eg, hot tubs, saunas). The potential risks of vasodilator medications (eg, sildenafil, nitrates), diuretics, and alcohol consumption should also be discussed. Patients should be cautioned against sudden changes in position and the physiology of the Valsalva manoeuvre should be explained in simple terms with emphasis on minimizing such situations in everyday life.

β-Blockers and calcium channel antagonists. β-Blockers and calcium channel blockers are the initial therapies used in patients with obstructive HCM; however, a substantial proportion of patients might not respond or discontinue these therapies because of side effects. In both drug classes, the effect is to reduce hypercontractility, outflow turbulence, and, ultimately, symptoms. Other effects include increasing diastolic filling time to augment cardiac output, as well as reduction of diastolic stiffness through sympatholytic effects.[67]

Any nonvasodilating β-blocker may be used. Metoprolol has been shown to be superior to placebo in the short term with better gradient reduction (rest and provoked) and improved symptom scores.[68] β-Blockers with vasodilatory effects (eg, carvedilol and labetalol) are generally avoided because arterial vasodilation might accentuate dynamic obstruction.

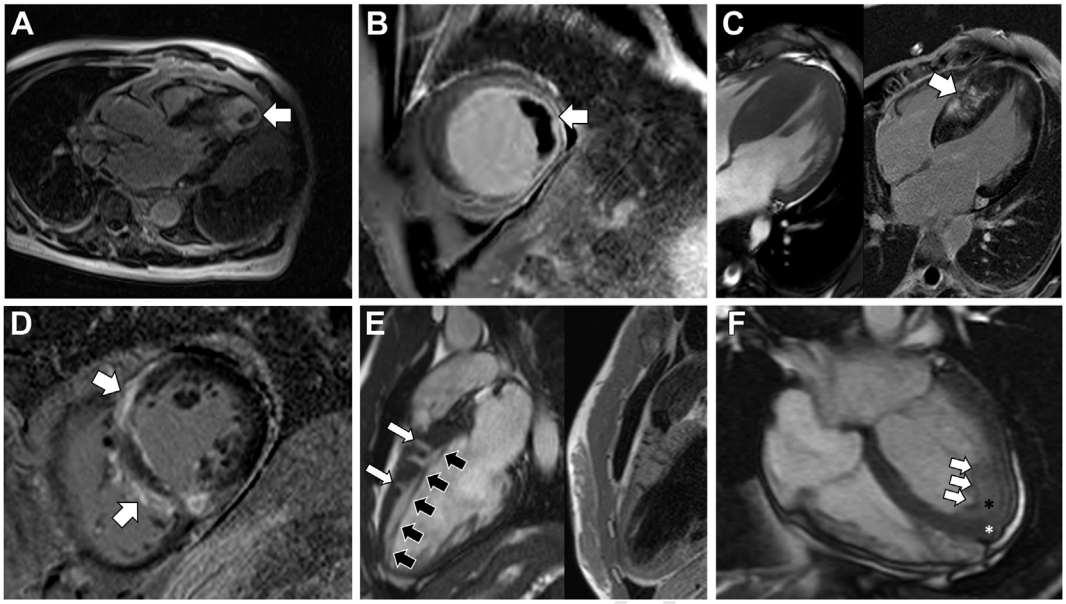


Figure 7. Additional hypertrophic cardiomyopathy (HCM) findings that might be identified using cardiac magnetic resonance. (**A**, **B**) Examples of apical aneurysm containing thrombus (**arrow**). Neither of these thrombi were identified initially using echocardiogram. (**C**, **D**) Examples in 2 different patients of severe fibrosis with late gadolinium enhancement imaging (**arrows**); a risk factor for major adverse cardiac events, including heart failure and sudden cardiac death. (**E**) Subtle findings in mild HCM might include myocardial crypts (**white arrows**), as well as a prominent apicobasal muscle bundle (**black arrows**). (**F**) Example of an apical HCM phenocopy—this is endomyocardial fibrosis; note the 3-layer appearance with myocardium (**white asterisk**), inflammatory infiltrate (**black asterisk**), and a thin rim of thrombus (**arrows**). Cardiac magnetic resonance imaging has sensitivity for differentiating endomyocardial fibrosis from apical HCM.

Nondihydropyridine calcium antagonists (verapamil and diltiazem) might be alternatives in patients intolerant of β-blockade and have demonstrated reduction in gradients, improved diastolic filling, and reduction in subendocardial ischemia.[69-71] At higher doses, the vasodilatory effects might predominate over negative inotropic effects and should therefore be used with caution in patients with very high LVOT gradients. They should also be avoided in the presence of LV systolic dysfunction.

Disopyramide. This is a class 1A antiarrhythmic drug that has been the mainstay of HCM medical therapy for many years. Disopyramide has been shown to reduce gradients and decrease symptoms in patients with obstructive HCM.[72,73] Its use might

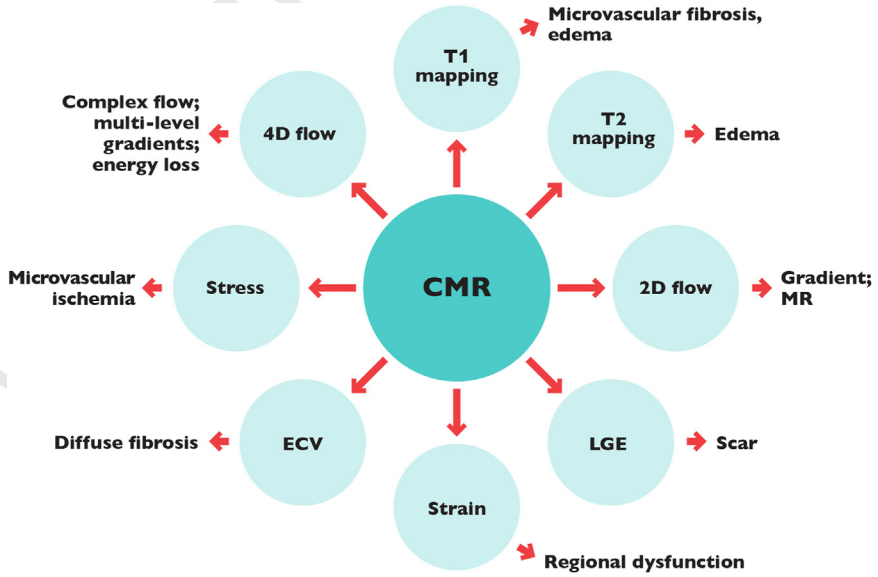


Figure 8. Beyond anatomy: the multiple applications of cardiac magnetic resonance (MR) imaging (CMR) in patients with hypertrophic cardiomyopathy. ECV, extracellular volume; LGE, late gadolinium enhancement.

Table 1. Questions to address in the evaluation of obstruction in patients with hypertrophic cardiomyopathy

Question	Comment
Is there clinical evidence of obstruction at rest?	– Physical examination, including Valsalva or squat to stand manoeuvre where possible
Is there imaging evidence of left ventricular outflow obstruction?	– Flow acceleration predominantly at outflow level – Associated SAM of anterior mitral leaflet or chordal structures – Associated posteriorly directed mitral regurgitation – Anomalous insertion of papillary muscle heads directly into mitral annulus – Normal aortic valve opening – Absence of subaortic membrane
Is there midventricular obstruction?	– Possible papillary muscle contribution to obstruction
Is there apical obstruction?	– Flow acceleration and measurable gradients at apex – Presence of early or established apical aneurysm
Is there multilevel obstruction?	– Outflow and midventricular obstruction might coexist – Determine dominant level of obstruction using cardiac magnetic resonance imaging and echocardiography as far as possible – When aortic valve and left ventricular outflow tract obstruction coexist, multimodality imaging and/or invasive hemodynamic study might be needed to determine relative contributions
Has a provocable outflow tract gradient been excluded?	– Valsalva – Exercise: bike or treadmill – Other provocation modalities (amyl nitrite, upright imaging, postprandial exercise echocardiography, pharmacological stress imaging) – Novel imaging (eg, computed tomography)
Does provocation testing indicate obstruction is principally at outflow level?	– Does SAM worsen? – Does mitral regurgitation worsen?

SAM, systolic anterior motion.

be limited by anticholinergic side effects (dry eyes/mouth, constipation, urinary retention); pyridostigmine may be coadministered to help mitigate these effects.[74] Monitoring for QT interval prolongation is advised, and treatment interrupted if QTc exceeds 500-525 ms.[75] Disopyramide is generally used in combination with either a β-blocker or nondihydropyridine calcium channel blocker. Unfortunately, many patients have reported reduction in efficacy over time.[74,75]

Cardiac myosin inhibitors. This is a new drug class. Mavacamten is the first CMI approved for treatment of adults with obstructive HCM. Pediatric trials have been launched or are in development. These drugs aim to decrease the excess availability of myosin heads to form cross-bridges with actin molecules, thereby reducing the excessive force of contraction and impaired relaxation that are hallmarks of HCM. By leaving more of these heads in the super-relaxed state, the drug also promotes a more energy-efficient environment at the sarcomere level. Recent mavacamten data are summarized in Table 2.

The results of CMI trials are encouraging, with several caveats. In EXPLORER-HCM, the efficacy end point was met in only 37% of participants, despite uptitration of the drug to as high as 15 mg from the 5 mg initial dose.[7] Some benefit was nonetheless reported in many of the remaining patients on the basis of gradient reduction, improvement in biomarkers, and better symptomatic status.

The other major issue to consider is one of LV systolic impairment. Because the drugs are designed to reduce excess cross-bridge formation, some reduction in LVEF is expected. However, the studies have shown that a small percentage of patients experienced an excessive reduction in LVEF. For this reason, beginning treatment with mavacamten currently includes echocardiographic surveillance every month for the first 3 months, and every 3 months thereafter. Mavacamten should not be used in patients with LVEF $< 55\%$ and should be temporarily discontinued if LVEF decreases to $< 50\%$ during follow-up (permanently if LVEF decreases to $< 30\%$).

Table 2. Key mavacamten phase 3 trials in patients with obstructive HCM

	EXPLORER-HCM[7]	VALOR-HCM[8]
Study design and sample size	• Double blind, randomized trial • Mavacamten 2.5-15 mg vs placebo for 30 weeks • N = 251	• Double blind, randomized trial • Mavacamten 2.5-15 mg vs placebo for 16 weeks • N = 112
Key inclusion criteria	HCM and NYHA classification 2 or 3 and LVOT gradient ≥ 50 mm Hg (at rest, Valsalva or exercise) and LVEF ≥ 55%	Patients with obstructive HCM referred for SRT
Key results	37% of patients who received mavacamten vs 17% of patients who received placebo ($P = 0.0005$) met the primary end point: 1) Increase in pVO_2 by 3 mL/kg/min without decrease in NYHA classification; *or* 2) Increase in pVO_2 by 1.5 mL/kg/min and improvement in NYHA classification by at least 1	18% of patients who received mavacamten vs 77% of patients who received placebo ($P < 0.001$) met the primary end point of SRT performed or SRT guidelines-eligible

EXPLORER-HCM, xxxx; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; pVO_2, peak oxygen consumption; SRT, septal reduction therapy; VALOR-HCM, xxxx.

Mavacamten has the potential for teratogenicity and is not recommended for use during pregnancy or when the possibility of pregnancy exists. An effective form of contraception is required not only for the duration of treatment but is advised for at least 4 months after cessation of treatment as well. It is recommended that women of childbearing age check pregnancy status periodically during treatment.

A phase 3 randomized controlled trial for the next-in-class CMI, aficamten, (**S**afety, **E**fficacy, and **Q**uantitative **U**nderstanding of **O**bstruction **I**mpact of **A**ficamten in **HCM** [SEQUOIA-HCM]), has been completed and results have been recently published.[76] Aficamten has a shorter half-life than mavacamten. Aficamten is not yet approved in Canada.

CMIs may be used in addition to β-blockade or non-dihydropyridine calcium channel blockers, however, concomitant use with disopyramide is presently unclear. The use of CMIs as first-line agents is not currently recommended. A randomized control trial to compare aficamten with metoprolol in patients with obstructive HCM is currently ongoing (**M**etoprolol vs **A**ficamten in **P**atients With **L**VOT Obstruction on **E**xercise Capacity in **HCM** [MAPLE-HCM; NCT05767346]).

CMI pharmacogenetics and drug interactions. Mavacamten is extensively metabolized through cytochrome CYP2C19 (74%) and to a lesser extent through CYP3A4 (18%) and CYP2C9 (8%).[77] A proportion of patients are poor CYP2C19 metabolizers, and this is more common in patients of East Asian ancestry (13%) compared with African (4%) or European (2%) ancestries. Poor metabolizers have significantly higher peak concentrations and area under the curve for concentration after an administered dose. This might explain why some patients experience an exaggerated response to mavacamten. Pharmacogenotype status might therefore affect maintenance dose requirements. Importantly, the half-life of mavacamten is long (6-9 days) in normal metabolizers and very long (23 days) in CYP2C19 poor metabolizers. As a consequence, dose up-titration should be done slowly (over 12 weeks after initiation of therapy) with monitoring of LVEF in accordance with the product monograph.

Finally, it should be noted that there is the potential also to elevate plasma levels of mavacamten by other drugs that affect CYP2C19 and CYP3A4. Mavacamten is contraindicated with concomitant use of moderate or strong CYP2C19 inhibitors or strong CYP3A4 inhibitors. Diltiazem, which is a moderate CYP3A4 inhibitor, might also increase plasma levels of mavacamten in patients who happen also to be poor CYP2C19 metabolizers, and caution with this combination of drugs is warranted. Examples of possible drug interactions are given in Supplemental Appendix S7. For complete interaction data, see https://www.drugs.com/drug-interactions/mavacamten.html.

For an in-depth review of the use of this drug class and an up-to-date summary of all relevant trials, see a recent review by Ostrominski et al.[78]

Where CMI drugs fit on the therapeutic ladder. All trials to date have used mavacamten as a second-line agent used in combination with either a β-blocker or a calcium channel blocker. Therefore, currently, it is most appropriate to reserve a CMI for patients in whom there is an insufficient symptomatic response to first-line agents (Fig. 9). In most cases, a β-blocker will be used as primary therapy. If this is insufficient (there are no data yet as to the superiority of one over the other), then it is reasonable to use in addition either disopyramide or mavacamten. Mavacamten appears from early reports to have a more favourable side effect profile. Studies on long-term efficacy are under way.

When medical therapy fails. A proportion of patients will not experience an adequate response to any form of medical therapy. Some might decide that they can operate within their daily limitations, but most will seek symptom relief with surgical myectomy (adults or children) or alcohol septal reduction (adults only).

Alcohol septal ablation. For patients with obstructive HCM and persistent symptoms despite use of optimal medical therapy, an invasive approach to septal reduction might be indicated. There is no experience for alcohol septal ablation in pediatric patients. Alcohol septal ablation should be conducted at experienced centres by expert operators.

Coronary anatomy must be favourable and usually requires the presence of a dominant septal perforator that perfuses the hypertrophied septal segment. Patients in whom the septum is perfused by multiple small arteries are not candidates. Furthermore, because of the risk of development of a ventricular septal defect from tissue necrosis, septal ablation is generally reserved for patients with septal thickness > 16 mm.[79]

There is a significant risk of AV block due to the proximity of the septal target to the AV node. Patients with baseline conduction delay are particularly prone. The overall incidence of intraprocedural pacing is 45%, whereas for permanent pacing this is 5%-10%.[80,81] Data from a large European registry of 1275 septal ablation patients, with median follow-up of almost 6 years, have shown durable relief of symptoms with a low rate of adverse events.[82]

Surgical myectomy. Surgery is usually the most effective therapy for obstruction (and in children, the only approved septal reduction therapy), with low risk of adverse outcomes. Myectomy should be reserved for severe cases in which patient comorbidities are not prohibitive, and conducted within experienced centres by expert operators. The perioperative risk of mortality within high-volume centres is approximately 1% with approximately 90% of patients achieving long-term symptomatic improvement. Focusing only on the septum might be insufficient in patients with only mild thickening, and concomitant mitral valve intervention might be required.

There are relatively few experienced HCM surgical centres.[83] New centres might require recruitment of experienced physicians and surgeons trained in high-volume myectomy centres with the intention that surgical outcomes within new centres will be comparable with those in well established programs.[84]

Percutaneous intramyocardial septal radiofrequency ablation. Percutaneous intramyocardial septal radiofrequency ablation is a specialized technique that involves insertion of a radiofrequency electrode needle into the hypertrophied ventricular septum percutaneously via the transapical intramyocardial approach with real-time imaging guidance. The needle tip is used to emit high-frequency alternating current to generate heat, causing irreversible coagulation necrosis. The safety and effectiveness of the early procedures using this technique was described over a series of studies.[85-87]

Pictorial approach to management of symptomatic obstruction in HCM. Figure 9 shows a summary of the approach to managing symptomatic obstruction, and highlights first-line therapy and options for second-line therapies with their advantages and disadvantages. Figure 10 provides guidance for patient selection for alcohol septal ablation vs surgical myectomy.

Management of symptoms in patients with nonobstructive HCM with preserved ejection fraction. At least one-third of patients with HCM do not have resting or inducible LVOT obstruction. Although patients with nonobstructive HCM are more likely to be asymptomatic, long-term mortality and rates of serious adverse outcomes might be similar to that in patients with obstructive disease.[88,89] Morbidity in patients with nonobstructive HCM reflects diastolic dysfunction, a hallmark of HCM, as well as ischemia with no obstructive arteries.

Although few randomized studies exist for medical management of symptomatic nonobstructive HCM with preserved ejection fraction, β-blockade followed by non-dihydropyridine calcium channel blockers are often used as first-line therapy because of observational and experiential data in patients with HCM.[13,14] In patients with symptomatic HCM and established microvascular dysfunction nonresponsive to β-blockade, additional antianginal therapies,[90] including nitrates or ranolazine (available through the Special Access Program in Canada), might be considered. Patients with clinical and/or biochemical evidence of congestion might benefit from careful diuretic use. There is no evidence to support one class of diuretic over another; specifically, spironolactone was shown to have no additional benefit in limiting myocardial fibrosis.[91] Currently, the role of SGLT2 inhibitors is ill-defined in patients with HCM with preserved LVEF but are often prescribed when systolic function is reduced. Clinical trials with CMIs in patients with nonobstructive HCM are ongoing.

Management of HCM with systolic dysfunction. Systolic dysfunction affects a small percentage of patients and, when it develops, occurs in adults at a median of 15 years after initial diagnosis of HCM (Table 3). When LV systolic dysfunction develops, mean time to death, transplantation, or need for implantation of an LV assist device is 8.4 years.[27,92] Compared with patients with HCM and preserved LVEF, those with LV systolic dysfunction have a substantially worse prognosis.[27,92] Serial exercise testing might be a useful monitoring tool to objectively chart functional decline in this population.[93] Reduced exercise capacity is a prognostic marker of heart failure and transplant-free survival in children and adults.[93] Rapid heart failure progression is not inevitable in patients with HCM with systolic dysfunction,[92] and some patients have a stable trajectory and remain minimally symptomatic for years.

Guideline-directed heart failure therapies might be poorly tolerated because of the restrictive hemodynamics in patients with HCM and the low contractile reserve in advanced disease. HCM patients should start treatment with low doses with careful titration, and referred for advanced heart failure management as appropriate.

VII. Risk Stratification and Prevention of SCD

Practical Tips

- An ICD for secondary prevention is recommended for patients with HCM and sustained ventricular tachycardia or aborted cardiac arrest.
- Risk stratification of SCD in HCM relies on:
  - the presence of stand-alone high-risk clinical features, and
  - estimated high risk using validated calculators.
- Referral for shared decisions regarding primary prevention ICD implantation should be considered in the setting of any of the following:
  - Maximal wall thickness ≥ 30 mm
  - Recent unexplained syncope
  - LVEF < 50%
  - Apical aneurysm
  - Extensive fibrosis defined as LGE involving ≥ 15% of the left ventricle
  - Presence of any NSVT in children and young adults, or NSVT with high-risk features in older patients (eg, frequent, fast, and/or long duration)
  - Strong family history for SCD
  - Adults with estimated 5-year risk of SCD events ≥ 4% on the basis of the HCM Risk-SCD score[9]: https://qxmd.com/calculate/calculator_303/hcm-risk-scd
  - Children with high risk of arrhythmic events on the basis of validated scores using:
  - **Pre**cision **M**edicine for **C**ardiomyopath**y** (PRIMaCY):[11] https://primacycalculator.com
  - HCM Risk-Kids:[10] https://hcmriskkids.org
- Recent data support the safety of mild-moderate exercise in patients with HCM with regard to the risk of SCD. Patients wishing to engage in vigorous/competitive exercise should be referred for expert HCM consultation.

Indications for ICD implantation

ICD insertion for secondary prevention is recommended for patients with documented sustained ventricular tachycardia or those resuscitated from cardiac arrest presumed to be of arrhythmogenic origin. For all other HCM patients, SCD risk stratification is recommended as part of ongoing surveillance (Fig. 11) to assess risk and determine if benefit from ICD insertion for primary prevention outweighs risk of device-related complications. Two risk stratification strategies are currently accepted for this purpose in adults. The first uses independent risk markers, each one of which might lead to consideration of ICD insertion. The second, the HCM Risk-SCD calculator, uses a formula that incorporates different risk markers to provide a 5-year risk of SCD or life-threatening arrhythmic events.[9] The latter strategy simplifies the complex process of risk stratification in patients with HCM and provides clearer recommendations and a more standardized approach. It might, however, result in under- or overestimation of risk in some patients. SCD risk stratification in patients with HCM requires knowledge of the strengths and limitations of the

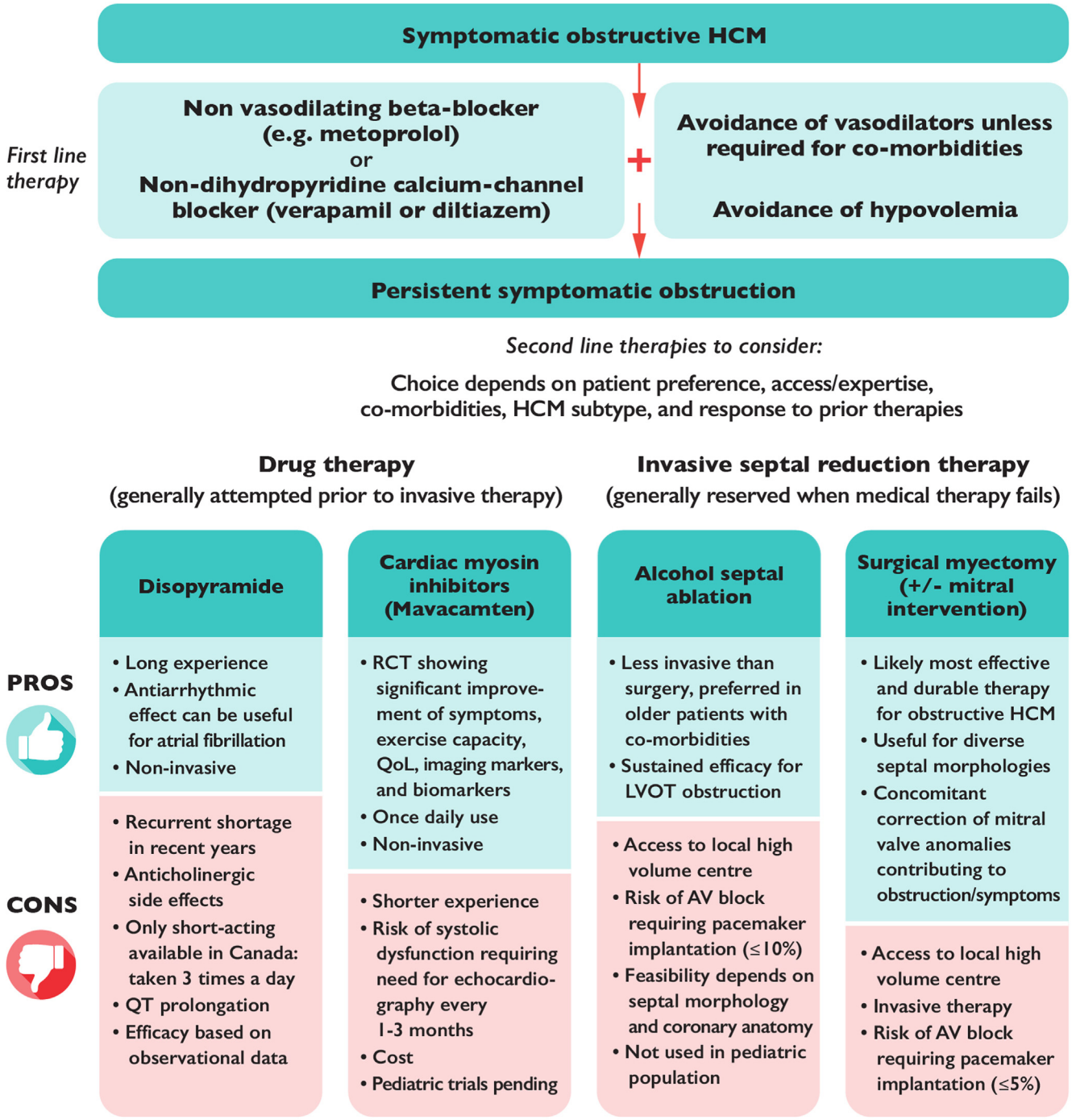


Figure 9. Management of symptomatic obstruction in patients with hypertrophic cardiomyopathy (HCM). Note that mavacamten and alcohol septal ablation are not approved for use in pediatric HCM. AV, atrioventricular; LVOT, left ventricular outflow tract; QoL, quality of life; RCT, randomized controlled trial.

HCM Risk-SCD calculator and of the individual risk markers (Table 4, Supplemental Appendix S8 and Fig. 11).

SCD risk stratification in pediatric patients with HCM

Similar to adults, SCD risk stratification in pediatric patients requires an integrated assessment of risk factors. However, unlike young adults, the presence of a single risk factor is usually not sufficient to recommend ICD implantation for primary prevention because of the greater risk of ICD complications in young children. There are differences in factors associated with SCD risk in pediatric compared with adult patients. In recent years, SCD risk calculators have been developed and validated that incorporate pediatric-specific risk factors into a single prediction model.[10,11] Unexplained syncope (sevenfold higher risk), NSVT (twofold higher risk), and

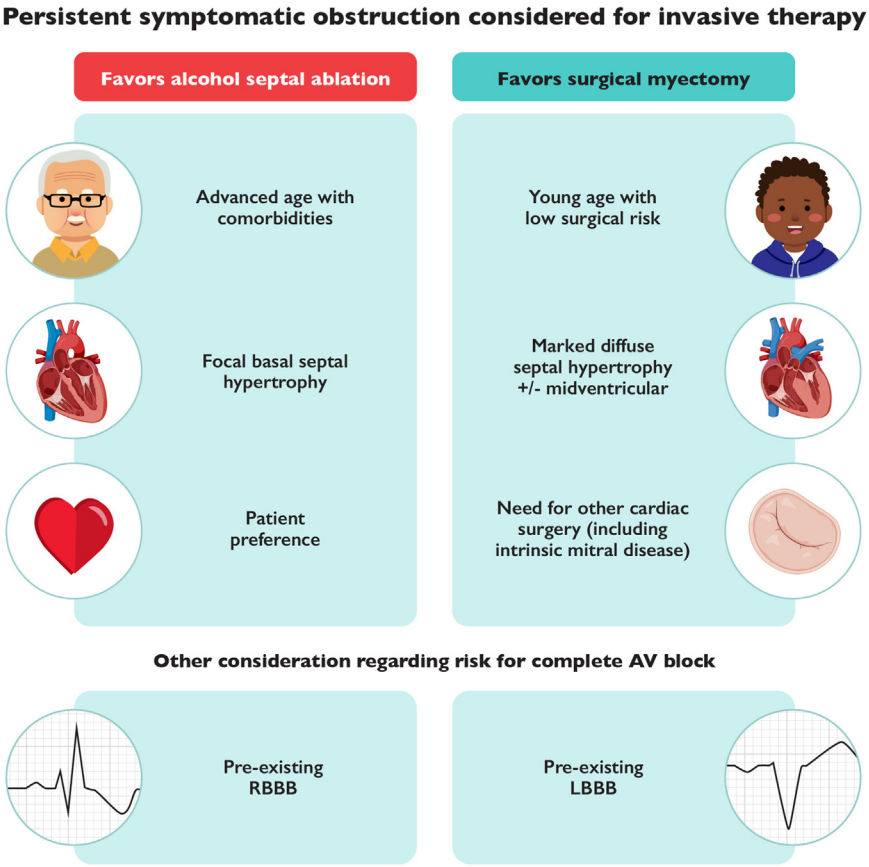


Figure 10. Selection of optimal invasive septal reduction therapy. AV, atrioventricular; LBBB, left bundle branch block; RBBB, right bundle branch block. Q22

presence of a pathogenic/likely pathogenic HCM-causing variant (1.3-fold greater risk) are binary factors associated with SCD. A caveat is that a rate of 120 beats per minute might be too low to count as NSVT in young children considering their high baseline heart rates, hence, it is important to define NSVT as a ventricular rate that exceeds 20% of baseline-adjusted sinus rate.

Echocardiographic measures of LV hypertrophy (ie, septal and LV posterior wall diameter *z*-scores each of which have an independent predictive value), as well as left atrial diameter *z*-scores show a nonlinear association with SCD risk.[11] The caveat is that unlike in adults, there is no absolute cutoff for LV wall thickness *z*-score above which an ICD is recommended although risk increases at *z*-scores of 10 and higher.[10,11] Age is also associated with SCD risk with greater frequency of events in preadolescents, adolescents, and teenagers.

There are 2 risk prediction models currently in use. Although PRIMaCY includes all the previously mentioned risk factors, the HCM-Risk Kids calculator includes a subset of these factors. Of note, peak LVOT gradient is not associated with SCD risk; in fact very high gradients (> 100 mm Hg) are associated with lower SCD risk rates.[10,11,95] Also, unlike in adults, family history of SCD is not associated with SCD risk.[11,95] This is probably because older relatives of pediatric patients might not yet have manifested SCD events. Also, similar to adults, a blunted blood pressure response on exercise stress testing is associated with future heart failure but not with SCD.[93] However, in post hoc analysis, exercise-induced ischemia was associated with SCD risk although it is not

Table 3. Risk markers for—and consequences of—developing HCM with systolic dysfunction

Risk factors for systolic dysfunction in patients with HCM
• Younger age at diagnosis
• Increased wall thickness
• Borderline left ventricular ejection fraction (50%-59%)
• Increased burden of LGE on CMR
• Family history of HCM, particularly end-stage HCM
• Pathogenic sarcomeric variants, particularly in the thin filament genes (*TNNT2*, *TNNI3*, *TPM1*, *ACTC1*)[94]
Risk factors for unfavourable outcomes
• Left ventricular ejection fraction < 35%
• Increased burden of LGE on CMR
• Development of atrial fibrillation
• Multiple pathogenic/likely pathogenic sarcomeric gene variants
Outcomes of patients with the most risk factors
• Two- to 10-fold greater risk of mortality (2%-11% per year vs 0.2% per year in those without risk factors)
• Fivefold more frequent arrhythmic sudden death events (2.4% per year vs 0.5% per year in those without risk factors)
• Greater need for cardiac transplantation (> 11-fold higher) or left ventricular assist device implantation (26-fold higher)
• Advanced New York Heart Association classification III-IV

CMR, cardiac magnetic resonance imaging; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement.

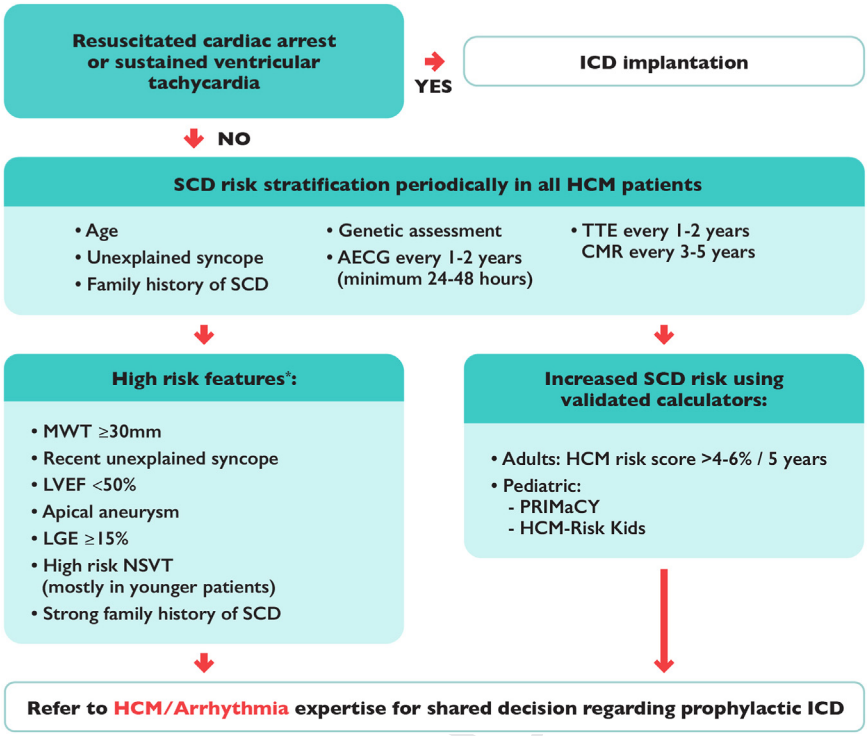


Figure 11. Approach to sudden cardiac death (SCD) risk stratification in patients with hypertrophic cardiomyopathy (HCM) and indications for implantable cardiac defibrillator (ICD) implantation. AECG, ambulatory electrocardiogram (Holter); CMR, cardiac magnetic resonance imaging; ICD, implantable cardiac defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MWT, maximal left ventricular wall thickness; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; TTE, transthoracic echocardiography.
* See Table 4 and Supplemental Appendix S8 for details regarding specific risk factors. In pediatric patients, primary prevention ICD implantation is usually only considered in the presence of > 1 risk factor. Although the illustration only shows possible indications for ICD implantation, the management of HCM and potential SCD risk mitigation should also include therapy for heart failure and obstructive physiology as discussed in other sections of this CPU. Validated risk scores include the HCM Risk-SCD score for patients older than 16 years (https://qxmd.com/calculate/calculator_303/hcm-risk-scd),[9] the **Pre**cision **M**edicine for **C**ardiomyopath**y** (PRIMaCY) risk calculator for patients younger than 18 years (https://primacycalculator.com),[11] and the HCM-Risk Kids for patients aged 1-16 years (https://hcmriskkids.org).[10]

known if it is an independent risk factor. Finally, LGE presence and burden using CMR imaging has not been evaluated systematically in children with HCM and therefore is not included in the risk calculations. Nonetheless, extensive myocardial fibrosis may be considered a risk factor in pediatric patients.

Exercise recommendations

Because HCM is one of the leading causes of death in athletes, patients with HCM have traditionally been instructed to restrict their physical activity to nonvigorous exercise and to refrain from participation in most competitive sports.[13,96,97] However, the health benefits of exercise in the general population are well recognized. Specifically in patients with HCM in the RESET-HCM clinical trial 136 patients were randomized to 16 weeks of moderate-intensity exercise training (n = 67) or usual activity (n = 69); moderate-intensity training improved exercise capacity assessed according to peak oxygen consumption.[98] This study was not powered to assess safety and excluded higher-risk patients, such as those with exercise-induced syncope or ventricular arrhythmias, medically refractory LVOT obstruction, history of hypotensive response with exercise test, and/or LVEF < 55%.

More recently, the LIVE-HCM prospective observational cohort study reported on the safety of vigorous exercise in patients with HCM.[12] A total of 1660 patients with either HCM (n = 1534) or carriers of HCM-causing genetic variants with no HCM (genotype positive phenotype negative; n = 126) were enrolled and followed for a median of 38 months. Participants were categorized on the basis of self-reported physical activity into sedentary, moderate, or vigorous-intensity exercise. A total of 77 individuals (4.6%) reached the composite end point of death, resuscitated sudden cardiac arrest, arrhythmic syncope, or appropriate ICD shock. Individuals who engaged in vigorous exercise (n = 699, of whom 259 participated competitively) did not experience a higher rate of the composite end point compared with the others (hazard ratio, 1.01; 95% CI, 0.68-1.48). Competitive athletes with HCM who exercised vigorously also did not experience a greater risk of events compared with patients who did not exercise vigorously (hazard ratio, 0.71; 95% CI, 0.39-1.32).

Considering the mounting evidence suggestive of the safety of vigorous exercise and potential benefit of exercise training, a more permissive approach to exercise is recommended for patients with HCM. Moderate exercise (as defined in RESET-HCM[98] or LIVE-HCM[12]) should be recommended for all

Table 4. Risk factors for SCD in HCM

Risk marker	Definition	Comments	Pediatric-specific comments Q19
Age	Continuous variable	– Lower SCD risk in patients diagnosed after 60 years of age – Best integrated in risk calculator	– Included in pediatric SCD risk calculator[10,11]
Unexplained syncope	Syncope unlikely to be neurocardiogenic (vagal) and not attributable to LV obstruction	– Recent episodes (eg, < 6 months) are most predictive – Remote episodes (eg, > 5 years) may be disregarded in most cases. Consider exercise-triggered severe LV obstruction as an alternative cause of exertional syncope	– Strong association with SCD – Included in pediatric SCD risk calculator[10,11]
Extreme hypertrophy	MWT ≥ 30 mm (in adults) measured using TTE or CMR	– MWT is a continuous variable: ICD insertion may be considered with wall thickness approaching 30 mm – In the HCM Risk-SCD calculator, risk peaks at 27 mm and decreases at higher MWT. A biological explanation for this observation remains unknown	– LV hypertrophy is nonlinearly associated with SCD – Pediatric measures use wall thickness *z*-scores rather than an absolute cutoff for extreme hypertrophy – IVST and LVPWT *z*-scores should be analyzed as independent factors. – Included in pediatric SCD risk calculator[10,11]
Systolic dysfunction	LVEF < 50%	– Consider confirming dysfunction with different imaging modalities if LVEF is between 45% and 50% – Consider alternative causes of dysfunction, especially if LGE extent is low – Not included in HCM Risk-SCD calculator	– Not evaluated as a risk factor for SCD because systolic dysfunction is rare in a pediatric population
Increased LA diameter	Anteroposterior diameter measured on TTE	– Included in the SCD risk calculator – Not regarded as an isolated risk marker sufficient for consideration of ICD insertion	– LA diameter *z*-score is associated with SCD risk – Included in pediatric SCD risk calculator[10,11]
LVOT obstruction	Dynamic gradient ≥ 30 mm Hg in the LVOT	– Included in the SCD risk calculator – Not regarded as an isolated risk marker sufficient for consideration of ICD insertion	– Not associated with increased SCD risk – Included in pediatric SCD risk calculators with appropriate weighting
Family history of SCD	SCD at young age or with known HCM	– ICD implantation might not be indicated if HCM is very mild, in the absence of other risk markers, and if risk is estimated as low using the HCM Risk-SCD calculator	– Although not included in risk calculators because of lack of statistical association, remains a potential risk factor
NSVT	Ventricular rhythm ≥ 3 beats at ≥ 120 beats per minute (in adults)	– Frequency of occurrence, rate, and duration should be taken into account in risk stratification – Predictive ability is greater in younger patients – Has the largest coefficient in the SCD risk calculator and therefore might overestimate risk, especially in older patients and if NSVT is short, slow, or low frequency	– Strong association with SCD – In younger children, the higher baseline sinus rates should be taken into account when determining if NSVT is fast

Continued

Table 4. Continued.

Risk marker	Definition	Comments	Pediatric-specific comments Q19
Genotype positive	Pathogenic or likely pathogenic HCM-causing variant	– Associated with SCD risk but limited data on whether it is an independent risk factor	– Associated with SCD risk – Included in pediatric SCD risk calculator[11]
Apical aneurysm	Discrete thin-walled dyskinetic or akinetic segment of the LV apex	– SCD risk might correlate with aneurysm size – Confirming aneurysm anatomy with CMR or contrast TTE is recommended – ICD implantation indication is on the basis of limited data – Not included in SCD risk calculator	– Not evaluated as a risk factor for SCD because LV aneurysm is rare in the pediatric population
Extensive LGE	> 15% of LV mass	– Semiautomated threshold techniques for quantification – Should be conducted at experienced centres because of interobserver variability – SCD risk correlates with LGE extent – Not included in SCD risk calculator	– Not currently defined as a risk factor for SCD because CMR imaging is routinely done only in older children where it can be performed without need for sedation – Extensive LGE should, however, be considered as a risk factor similar to as considered in adults – Not included in risk calculator

CMR, cardiac magnetic resonance imaging; HCM, hypertrophic cardiomyopathy; ICD, implantable cardiac defibrillator; IVST, interventricular septal thickness; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVPWT, left ventricular posterior wall thickness; MWT, maximal wall thickness; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; TTE, transthoracic echocardiography.

stable HCM patients. Patients who wish to engage in vigourous exercise, especially those contemplating competitive sports participation, should be referred to specialized HCM experts.

Closing Remarks

The view of the writing group is that this document is intended to be a helpful review of highly relevant, recent, and practical clinical aspects of the management of patients with HCM, particularly for physicians for whom HCM is not the primary focus of their practice. There remain numerous grey areas in the management of HCM and we have tried to explore these and provide some level of consensus, while recognizing that each patient must be considered in their own unique context. We are at a particularly interesting juncture in the history of HCM with potentially rapidly evolving novel therapies. Some aspects were believed to be beyond the scope of this document. No doubt future updates will be important for reevaluation of the rapidly evolving landscape of HCM.

We acknowledge that this document reflects the consensus opinion of the writing committee on the basis of published evidence as well as our collective experiences and should therefore be viewed as guidance rather than recommendations.

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References

1. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol 2015;65:1249-54.
2. Tadros R, Francis C, Xu X, et al. Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect. Nat Genet 2021;53:128-34.
3. Harper AR, Goel A, Grace C, et al. Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity. Nat Genet 2021;53:135-42.

4. Ingles J, Goldstein J, Thaxton C, et al. Evaluating the clinical validity of hypertrophic cardiomyopathy genes. Circ Genom Precis Med 2019;12:e002460.

5. Neubauer S, Kolm P, Ho CY, et al. Distinct subgroups in hypertrophic cardiomyopathy in the NHLBI HCM registry. J Am Coll Cardiol 2019;74:2333-45.

6. Canepa M, Fumagalli C, Tini G, et al. Temporal trend of age at diagnosis in hypertrophic cardiomyopathy: an analysis of the International Sarcomeric Human Cardiomyopathy Registry. Circ Heart Fail 2020;13:e007230.

7. Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;396:759-69.

8. Desai MY, Owens A, Geske JB, et al. Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy. J Am Coll Cardiol 2022;80:95-108.

9. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010-20.

10. Norrish G, Ding T, Field E, et al. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM Risk-Kids). JAMA Cardiol 2019;4:918-27.

11. Miron A, Lafreniere-Roula M, Steve Fan CP, et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. Circulation 2020;142:217-29.

12. Lampert R, Ackerman MJ, Marino BS, et al. Vigorous exercise in patients with hypertrophic cardiomyopathy. JAMA Cardiol 2023;8:595-605.

13. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.

14. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2020;76:e159-240.

15. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC guidelines for the management of cardiomyopathies. Eur Heart J 2023;44:3503-626.

16. Garcia-Hernandez S, de la Higuera Romero L, Ochoa JP, McKenna WJ. Emerging themes in genetics of hypertrophic cardiomyopathy: current status and clinical application. Can J Cardiol 2024;40:742-53.

17. Ho CY, Day SM, Ashley EA, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation 2018;138:1387-98.

18. Mathew J, Zahavich L, Lafreniere-Roula M, et al. Utility of genetics for risk stratification in pediatric hypertrophic cardiomyopathy. Clin Genet 2018;93:310-9.

19. de Feria AE, Kott AE, Becker JR. Sarcomere mutation negative hypertrophic cardiomyopathy is associated with ageing and obesity. Open Heart 2021;8:e001560.

20. Hathaway J, Helio K, Saarinen I, et al. Diagnostic yield of genetic testing in a heterogeneous cohort of 1376 HCM patients. BMC Cardiovasc Disord 2021;21:126.

21. Christian S, Cirino A, Hansen B, et al. Diagnostic validity and clinical utility of genetic testing for hypertrophic cardiomyopathy: a systematic review and meta-analysis. Open Heart 2022;9:e001815.

22. Gruner C, Care M, Siminovitch K, et al. Sarcomere protein gene mutations in patients with apical hypertrophic cardiomyopathy. Circ Cardiovasc Genet 2011;4:288-95.

23. Bean LJH, Funke B, Carlston CM, et al. Diagnostic gene sequencing panels: from design to report-a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2020;22:453-61.

24. Wilde AAM, Semsarian C, Marquez MF, et al; European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS). expert consensus statement on the state of genetic testing for cardiac diseases. Europace 2022;24:1307-67.

25. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.

26. Wilde AAM, Semsarian C, Marquez MF, et al; European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS). expert consensus statement on the state of genetic testing for cardiac diseases. Heart Rhythm 2022;19:e1-60.

27. Marstrand P, Han L, Day SM, et al. Hypertrophic cardiomyopathy with left ventricular systolic dysfunction: insights from the SHaRe Registry. Circulation 2020;141:1371-83.

28. Tower-Rader A, Betancor J, Popovic ZB, et al. Incremental prognostic utility of left ventricular global longitudinal strain in hypertrophic obstructive cardiomyopathy patients and preserved left ventricular ejection fraction. J Am Heart Assoc 2017;6:e006514.

29. Saito M, Okayama H, Yoshii T, et al. Clinical significance of global two-dimensional strain as a surrogate parameter of myocardial fibrosis and cardiac events in patients with hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging 2012;13:617-23.

30. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-9.

31. Hughes RK, Shiwani H, Rosmini S, et al. Improved diagnostic criteria for apical hypertrophic cardiomyopathy. JACC Cardiovasc Imaging 2024;17:501-12.

32. Reant P, Dufour M, Peyrou J, et al. Upright treadmill vs. semi-supine bicycle exercise echocardiography to provoke obstruction in symptomatic hypertrophic cardiomyopathy: a pilot study. Eur Heart J Cardiovasc Imaging 2017;19:31-8.

33. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. Circulation 2007;116:2702-8.

34. Feiner E, Arabadjian M, Winson G, Kim B, Chaudhry F, Sherrid MV. Post-prandial upright exercise echocardiography in hypertrophic cardiomyopathy. J Am Coll Cardiol 2013;61:2487-8.

35. Turvey L, Augustine DX, Robinson S, et al. Transthoracic echocardiography of hypertrophic cardiomyopathy in adults: a practical guideline from the British Society of Echocardiography. Echo Res Pract 2021;8:G61-86.

36. Abbasi MA, Ong KC, Newman DB, Dearani JA, Schaff HV, Geske JB. Obstruction in hypertrophic cardiomyopathy: many faces. J Am Soc Echocardiogr 2024;37:613-25.

37. Spirito P, Binaco I, Poggio D, et al. Role of preoperative cardiovascular magnetic resonance in planning ventricular septal myectomy in patients with obstructive hypertrophic cardiomyopathy. Am J Cardiol 2019;123: 1517-26.

38. Amano Y, Takayama M, Kumita S, Kumazaki T. MR imaging evaluation of regional, remote, and global effects of percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy. J Comput Assist Tomogr 2007;31:600-4.

39. Moon JC, Fisher NG, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. Heart 2004;90:645-9.

40. Wu B, Lu M, Zhang Y, et al. CMR assessment of the left ventricle apical morphology in subjects with unexplainable giant T-wave inversion and without apical wall thickness > / = 15 mm. Eur Heart J Cardiovasc Imaging 2017;18:186-94.

41. Rowin EJ, Maron BJ, Maron MS. The hypertrophic cardiomyopathy phenotype viewed through the prism of multimodality imaging: clinical and etiologic implications. JACC Cardiovasc Imaging 2020;13:2002-16.

42. Olivotto I, Maron BJ, Appelbaum E, et al. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol 2010;106:261-7.

43. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484-95.

44. Balaram SK, Sherrid MV, Derose JJ Jr, Hillel Z, Winson G, Swistel DG. Beyond extended myectomy for hypertrophic cardiomyopathy: the resection-plication-release (RPR) repair. Ann Thorac Surg 2005;80: 217-23.

45. Lipshultz SE, Law YM, Asante-Korang A, et al. Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American Heart Association. Circulation 2019;140:e9-68.

46. Papanastasiou CA, Zegkos T, Karamitsos TD, et al. Prognostic role of left ventricular apical aneurysm in hypertrophic cardiomyopathy: a systematic review and meta-analysis. Int J Cardiol 2021;332:127-32.

47. Zhang Y, Zhu Y, Zhang M, et al. Implications of structural right ventricular involvement in patients with hypertrophic cardiomyopathy. Eur Heart J Qual Care Clin Outcomes 2022;9:34-41.

48. Maron MS, Rowin EJ, Wessler BS, et al. Enhanced American College of Cardiology/American Heart Association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. JAMA Cardiol 2019;4:644-57.

49. Rowin EJ, Maron MS, Adler A, et al. Importance of newer cardiac magnetic resonance-based risk markers for sudden death prevention in hypertrophic cardiomyopathy: an international multicenter study. Heart Rhythm 2022;19:782-9.

50. Du D, Li COY, Ong K, et al. Arrhythmia monitoring for risk stratification in hypertrophic cardiomyopathy. CJC Open 2022;4:406-15.

51. Debonnaire P, Joyce E, Hiemstra Y, et al. Left atrial size and function in hypertrophic cardiomyopathy patients and risk of new-onset atrial fibrillation. Circ Arrhythm Electrophysiol 2017;10:e004052.

52. Guttmann OP, Pavlou M, O'Mahony C, et al. Predictors of atrial fibrillation in hypertrophic cardiomyopathy. Heart 2017;103:672-8.

53. Nasser MF, Gandhi S, Siegel RJ, Rader F. Anticoagulation for stroke prevention in patients with hypertrophic cardiomyopathy and atrial fibrillation: a review. Heart Rhythm 2021;18:297-302.

54. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol 2003;42:873-9.

55. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society comprehensive guidelines for the management of atrial fibrillation. Can J Cardiol 2020;36: 1847-948.

56. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 2001;104:2517-24.

57. Lee HJ, Kim HK, Jung JH, et al. Novel oral anticoagulants for primary stroke prevention in hypertrophic cardiomyopathy patients with atrial fibrillation. Stroke 2019;50:2582-6.

58. Dominguez F, Climent V, Zorio E, et al. Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation. Int J Cardiol 2017;248:232-8.

59. Santangeli P, Di Biase L, Themistoclakis S, et al. Catheter ablation of atrial fibrillation in hypertrophic cardiomyopathy: long-term outcomes and mechanisms of arrhythmia recurrence. Circ Arrhythm Electrophysiol 2013;6:1089-94.

60. Castagno D, Di Donna P, Olivotto I, et al. Transcatheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy: long-term results and clinical outcomes. J Cardiovasc Electrophysiol 2021;32:657-66.

61. Rozen G, Elbaz-Greener G, Marai I, et al. Utilization and complications of catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. J Am Heart Assoc 2020;9:e015721.

62. Faraz F, Rehman MEU, Sabir B, et al. Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis. Curr Probl Cardiol 2023;48:101524.

63. Bogachev-Prokophiev AV, Afanasyev AV, Zheleznev SI, et al. Concomitant ablation for atrial fibrillation during septal myectomy in patients with hypertrophic obstructive cardiomyopathy. J Thorac Cardiovasc Surg 2018;155:1536-1542.e2.

64. Butcher C, Rajappan S, Wharmby AL, et al. Atrioventricular nodal ablation is an effective management strategy for atrial fibrillation in patients with hypertrophic cardiomyopathy. Heart Rhythm 2023;20: 1606-14.

65. McDonald M, Virani S, Chan M, et al. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. Can J Cardiol 2021;37: 531-46.

66. Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy: from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. J Am Coll Cardiol 2009;54:191-200.

67. Spoladore R, Maron MS, D'Amato R, Camici PG, Olivotto I. Pharmacological treatment options for hypertrophic cardiomyopathy: high time for evidence. Eur Heart J 2012;33:1724-33.

68. Dybro AM, Rasmussen TB, Nielsen RR, Andersen MJ, Jensen MK, Poulsen SH. Randomized trial of metoprolol in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2021;78:2505-17.

69. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med 1997;336:775-85.

70. Choudhury L, Elliott P, Rimoldi O, et al. Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. Basic Res Cardiol 1999;94:49-59.

71. Kaltenbach M, Hopf R, Kober G, Bussmann WD, Keller M, Petersen Y. Treatment of hypertrophic obstructive cardiomyopathy with verapamil. Br Heart J 1979;42:35-42.

72. Pollick C. Muscular subaortic stenosis: hemodynamic and clinical improvement after disopyramide. N Engl J Med 1982;307:997-9.

73. Pollick C, Kimball B, Henderson M, Wigle ED. Disopyramide in hypertrophic cardiomyopathy. I. Hemodynamic assessment after intravenous administration62. Am J Cardiol, 1988:1248-51.

74. Sherrid MV, Shetty A, Winson G, et al. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with beta-blockade or verapamil. Circ Heart Fail 2013;6:694-702.

75. Adler A, Fourey D, Weissler-Snir A, et al. Safety of outpatient initiation of disopyramide for obstructive hypertrophic cardiomyopathy patients. J Am Heart Assoc 2017;6:e005152.

76. Maron MS, Masri A, Nassif ME, et al. Aficamten for symptomatic obstructive hypertrophic cardiomyopathy. N Engl J Med 2024;390:1849-61.

77. Dalo JD, Weisman ND, White CM. Mavacamten, a first-in-class cardiac myosin inhibitor for obstructive hypertrophic cardiomyopathy. Ann Pharmacother 2023;57:489-502.

78. Ostrominski JW, Guo R, Elliott PM, Ho CY. Cardiac myosin inhibitors for managing obstructive hypertrophic cardiomyopathy: JACC: Heart Failure State-of-the-Art Review. JACC Heart Fail 2023;11:735-48.

79. Savarimuthu S, Harky A. Alcohol septal ablation: a useful tool in our arsenal against hypertrophic obstructive cardiomyopathy. J Card Surg 2020;35:2017-24.

80. Kashtanov M, Rzhannikova A, Chernyshev S, Kardapoltsev L, Idov E, Berdnikov S. Results of ten-year follow-up of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy. Int J Angiol 2018;27:202-7.

81. Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AF, Michels M, ten Berg JM. A systematic review and meta-analysis of long-term outcomes after septal reduction therapy in patients with hypertrophic cardiomyopathy. JACC Heart Fail 2015;3:896-905.

82. Veselka J, Jensen MK, Liebregts M, et al. Long-term clinical outcome after alcohol septal ablation for obstructive hypertrophic cardiomyopathy: results from the Euro-ASA registry. Eur Heart J 2016;37:1517-23.

83. Maron BJ, Dearani JA, Ommen SR, et al. Low operative mortality achieved with surgical septal myectomy: role of dedicated hypertrophic cardiomyopathy centers in the management of dynamic subaortic obstruction. J Am Coll Cardiol 2015;66:1307-8.

84. Crean AM, Gharibeh L, Saleem Z, Glineur D, Maharaj G, Grau JB. Extended myectomy for hypertrophic cardiomyopathy: early outcomes from a nascent centre of excellence in Canada. CJC Open 2022;4:921-8.

85. Qian D, Zhou X, Liu H, Cao L. Clinical value of 2D speckle tracking imaging in evaluating the effect of percutaneous intramyocardial septal radiofrequency ablation in patients with hypertrophic obstructive cardiomyopathy. J Clin Ultrasound 2021;49:554-62.

86. Liu L, Li J, Zuo L, et al. Percutaneous intramyocardial septal radiofrequency ablation for hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 2018;72:1898-909.

87. Zuo L, Hsi DH, Zhang L, et al. Electrocardiographic QRS voltage amplitude improvement by intramyocardial radiofrequency ablation in patients with hypertrophic obstructive cardiomyopathy and one year follow up. J Electrocardiol 2020;61:164-9.

88. Pelliccia F, Pasceri V, Limongelli G, et al. Long-term outcome of nonobstructive versus obstructive hypertrophic cardiomyopathy: a systematic review and meta-analysis. Int J Cardiol 2017;243:379-84.

89. Lu DY, Pozios I, Haileselassie B, et al. Clinical outcomes in patients with nonobstructive, labile, and obstructive hypertrophic cardiomyopathy. J Am Heart Assoc 2018;7:e006657.

90. Nagueh SF, Lombardi R, Tan Y, Wang J, Willerson JT, Marian AJ. Atorvastatin and cardiac hypertrophy and function in hypertrophic cardiomyopathy: a pilot study. Eur J Clin Invest 2010;40:976-83.

91. Maron MS, Chan RH, Kapur NK, et al. Effect of spironolactone on myocardial fibrosis and other clinical variables in patients with hypertrophic cardiomyopathy. Am J Med 2018;131:837-41.

92. Rowin EJ, Maron BJ, Carrick RT, et al. Outcomes in patients with hypertrophic cardiomyopathy and left ventricular systolic dysfunction. J Am Coll Cardiol 2020;75:3033-43.

93. Conway J, Min S, Villa C, et al. The prevalence and association of exercise test abnormalities with sudden cardiac death and transplant-free survival in childhood hypertrophic cardiomyopathy. Circulation 2023;147:718-27.

94. Coppini R, Ho CY, Ashley E, et al. Clinical phenotype and outcome of hypertrophic cardiomyopathy associated with thin-filament gene mutations. J Am Coll Cardiol 2014;64:2589-600.

95. Balaji S, DiLorenzo MP, Fish FA, et al. Risk factors for lethal arrhythmic events in children and adolescents with hypertrophic cardiomyopathy and an implantable defibrillator: an international multicenter study. Heart Rhythm 2019;16:1462-7.

96. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:e783-831.

97. Maron BJ, Udelson JE, Bonow RO, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. Circulation 2015;132:e273-80.

98. Saberi S, Wheeler M, Bragg-Gresham J, et al. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial. JAMA 2017;317:1349-57.

Supplementary Material

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