

AHA/ACC CLINICAL PRACTICE GUIDELINE

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

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Endorsed by The Pediatric & Congenital Electrophysiology Society

ACC/AHA Joint Committee Members, see page e608

Key Words: AHA Scientific Statements ■ guidelines ■ hypertrophic cardiomyopathy ■ sarcomeric genes ■ shared decision-making ■ echocardiography ■ cardiovascular magnetic resonance ■ exercise stress testing ■ left ventricular outflow tract obstruction ■ systolic dysfunction ■ diastolic dysfunction ■ genetics ■ family screening ■ sudden cardiac death ■ ventricular arrhythmias ■ atrial fibrillation ■ rhythm monitoring ■ risk stratification ■ implantable cardioverter defibrillator ■ septal reduction therapy ■ surgical myectomy ■ septal alcohol ablation ■ physical activity ■ pregnancy ■ occupation

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The American Heart Association requests that this document be cited as follows: Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Sorajja P. 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. *Circulation*. 2020;142:e558–e631. doi: 10.1161/CIR.0000000000000937

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<https://www.ahajournals.org/journal/circ>

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TOP 10 TAKE-HOME MESSAGES–2020 AHA/ACC GUIDELINE FOR THE DIAGNOSIS AND TREATMENT OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

1. Shared decision-making, a dialogue between patients and their care team that includes full disclosure of all testing and treatment options, discussion of the risks and benefits of those options and, importantly, engagement of the patient to express their own goals, is particularly relevant in the management of conditions such as hypertrophic cardiomyopathy (HCM).
2. Although the primary cardiology team can initiate evaluation, treatment, and longitudinal care, referral to multidisciplinary HCM centers with graduated levels of expertise can be important to optimizing care for patients with HCM. Challenging treatment decisions—where reasonable alternatives exist, where the strength of recommendation is weak (eg, any Class 2b decision) or is particularly nuanced, and for invasive procedures that are specific to patients with HCM—represent crucial opportunities to refer patients to these HCM centers.
3. Counseling patients with HCM regarding the potential for genetic transmission of HCM is one of the cornerstones of care. Screening first-degree family members of patients with HCM, using either genetic testing or an imaging/electrocardiographic surveillance protocol, can begin at any age and can be influenced by specifics of the patient/family history and family preference.

As screening recommendations for family members hinge on the pathogenicity of any detected variants, the reported pathogenicity should be reconfirmed every 2 to 3 years.

4. Optimal care for patients with HCM requires cardiac imaging to confirm the diagnosis, characterize the pathophysiology for the individual, and identify risk markers that may inform decisions regarding interventions for left ventricular outflow tract obstruction and sudden cardiac death (SCD) prevention. Echocardiography continues to be the foundational imaging modality for patients with HCM. Cardiovascular magnetic resonance imaging will also be helpful in many patients, especially those in whom there is diagnostic uncertainty, poor echocardiographic imaging windows, or where uncertainty persists regarding decisions around implantable cardioverter-defibrillator (ICD) placement.
5. Assessment of an individual patient's risk for SCD continues to evolve as new markers emerge (eg, apical aneurysm, decreased left ventricular systolic function, and extensive gadolinium enhancement). In addition to a full accounting of an individual's risk markers, communication with patients regarding not just the presence of risk markers but also the magnitude of their individualized risk is key. This enables the informed patient to fully participate in the decision-making regarding ICD placement, which incorporates their own level of risk tolerance and treatment goals.
6. The risk factors for SCD in children with HCM carry different weights than those observed in adult patients; they vary with age and must account for different body sizes. Coupled with the complexity of placing ICDs in young patients with anticipated growth and a higher risk of device complications, the threshold for ICD implantation in children often differs from adults. These differences are best addressed at primary or comprehensive HCM centers with expertise in children with HCM.
7. Septal reduction therapies (surgical septal myectomy and alcohol septal ablation), when performed by experienced HCM teams at dedicated centers, continue to improve in safety and efficacy such that earlier intervention may be possible in select patients with drug-refractory or severe outflow tract obstruction causing signs of cardiac decompensation. Given the data on the significantly improved outcomes at comprehensive HCM centers, these decisions represent an optimal referral opportunity.
8. Patients with HCM and persistent or paroxysmal atrial fibrillation have a sufficiently increased risk of stroke such that oral anticoagulation with direct oral anticoagulants (or alternatively warfarin) should be considered the default treatment

option independent of the CHA₂DS₂-VASc score. As rapid atrial fibrillation is often poorly tolerated in patients with HCM, maintenance of sinus rhythm and rate control are key pursuits in successful treatment.

9. Heart failure symptoms in patients with HCM, in the absence of left ventricular outflow tract obstruction, should be treated similarly to other patients with heart failure symptoms, including consideration of advanced treatment options (eg, cardiac resynchronization therapy, left ventricular assist device, transplantation). In patients with HCM, an ejection fraction <50% connotes significantly impaired systolic function and identifies individuals with poor prognosis and who are at increased risk for SCD.
10. Increasingly, data affirm that the beneficial effects of exercise on general health can be extended to patients with HCM. Healthy recreational exercise (moderate intensity) has not been associated with increased risk of ventricular arrhythmia events in recent studies. Whether an individual patient with HCM wishes to pursue more rigorous exercise/training is dependent on a comprehensive shared discussion between that patient and their expert HCM care team regarding the potential risks of that level of training/participation but with the understanding that exercise-related risk cannot be individualized for a given patient.

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA. For some guidelines, the ACC and AHA partner with other organizations.

INTENDED USE

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices

meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

CLINICAL IMPLEMENTATION

Management, in accordance with guideline recommendations, is effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

METHODOLOGY AND MODERNIZATION

The ACC/AHA Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine,^{1,2} and on the basis of internal reevaluation. Similarly, presentation and delivery of guidelines are reevaluated and modified in response to evolving technologies and other factors to optimally facilitate dissemination of information to healthcare professionals at the point of care.

Numerous modifications to the guidelines have been implemented to make them shorter and enhance “user friendliness.” Guidelines are written and presented in a modular, “knowledge chunk” format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review.

In recognition of the importance of cost–value considerations, in certain guidelines, when appropriate and feasible, an analysis of value for a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.³

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of “full revision” and “focused update” will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual⁴ and other methodology articles.^{5–7}

SELECTION OF WRITING COMMITTEE MEMBERS

The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise

and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators.

RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found at <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy>. Appendix 1 of the guideline lists writing committee members’ relevant RWI; for the purposes of full transparency, their comprehensive disclosure information is available [online](https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces). Comprehensive disclosure information for the Joint Committee is also available at <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces>.

EVIDENCE REVIEW AND EVIDENCE REVIEW COMMITTEES

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.^{4–5} Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee is commissioned when there are ≥ 1 questions deemed of utmost clinical importance and merit formal systematic review to determine which patients are most likely to benefit from a drug, device, or treatment strategy, and to what degree. Criteria for commissioning an evidence review committee and formal systematic review include absence of a current authoritative systematic review, feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline, relevance to a substantial number of patients, and likelihood that the findings can be translated into actionable recommendations. Evidence review committee members may include methodologists, epidemiologists, clinicians, and biostatisticians. Recommendations developed by the writing committee on the basis of the systematic review are marked “SR.”

GUIDELINE-DIRECTED MANAGEMENT AND THERAPY

The term guideline-directed management and therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments. For these and all recommended drug treatment regimens, the reader should confirm dosage with product insert material and evaluate for contraindications and interactions. Recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

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1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected

databases relevant to this guideline, was conducted from January 1, 2010, to April 30, 2020. Key search words included but were not limited to the following: hypertrophic cardiomyopathy, coronary, ischemia, systole, atrial fibrillation, exercise, stroke volume, transplant, magnetic resonance imaging, sudden death, sudden cardiac death, left ventricular hypertrophy, subvalvular stenosis, echocardiography, nuclear magnetic resonance imaging, computed tomographic angiography, genetic testing, and diagnostic imaging. Additional relevant studies, published through April 2020 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables are included in the [Online Data Supplement](#) and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are representative and not all-inclusive.

1.2. Organization of the Writing Committee

The writing committee consisted of clinicians, cardiologists, interventionalists, cardiovascular surgeons, and a lay/patient representative. The writing committee included representatives from the ACC, AHA, American

Table 1. Associated Guidelines

Title	Organization	Publication Year (Reference)
Guidelines		
Hypertrophic cardiomyopathy	ACCF/AHA/ESC	2011 ¹ 2014 ²
Atrial fibrillation	AHA/ACC/HRS	2014 ³ 2019 ⁴
Heart failure	ACC/AHA	2013 ⁵ 2017 ⁶
Primary prevention	AHA/ACC	2019 ⁷
Management of overweight and obesity in adults	AHA/ACC/TOS	2014 ⁸
Device-based therapy for cardiac rhythm abnormalities	ACC/AHA/HRS	2013 ⁹
Ventricular arrhythmias and sudden cardiac death	AHA/ACC/HRS	2017 ¹⁰
Bradycardia	ACC/AHA/HRS	2018 ¹¹
Prevention of cardiovascular disease in women	AHA/ACC	2011 ¹²
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACC	2011 ¹³
Assessment of cardiovascular risk in asymptomatic adults	ACC/AHA	2010 ¹⁴
Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure	NHLBI	2003 ¹⁵
VHD statement on comprehensive centers	AATS/ACC/ASE/SCAI/STS	2019 ¹⁶
Federal Aviation Association Medical CertificationFederal Motor Carrier Safety Administration Regulations	https://www.faa.gov/pilots/medical / https://www.fmcsa.dot.gov/regulations/medical	17,18

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; AHA, American Heart Association; ASE, American Society of Echocardiography; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; NHLBI, National Heart, Lung, and Blood Institute; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; TOS, The Obesity Society; and VHD, valvular heart disease.

Table 2. ACC/AHA Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)*

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE†
CLASS 1 (STRONG) Benefit >>> Risk Suggested phrases for writing recommendations: - Is recommended - Is indicated/useful/effective/beneficial - Should be performed/administered/other - Comparative-Effectiveness Phrases‡: - Treatment/strategy A is recommended/indicated in preference to treatment B - Treatment A should be chosen over treatment B	LEVEL A - High-quality evidence‡ from more than 1 RCT - Meta-analyses of high-quality RCTs - One or more RCTs corroborated by high-quality registry studies
CLASS 2a (MODERATE) Benefit >> Risk Suggested phrases for writing recommendations: - Is reasonable - Can be useful/effective/beneficial - Comparative-Effectiveness Phrases‡: - Treatment/strategy A is probably recommended/indicated in preference to treatment B - It is reasonable to choose treatment A over treatment B	LEVEL B-R (Randomized) - Moderate-quality evidence‡ from 1 or more RCTs - Meta-analyses of moderate-quality RCTs
CLASS 2b (WEAK) Benefit ≥ Risk Suggested phrases for writing recommendations: - May/might be reasonable - May/might be considered - Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	LEVEL B-NR (Nonrandomized) - Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies - Meta-analyses of such studies
CLASS 3: No Benefit (MODERATE) Benefit = Risk (Generally, LOE A or B use only) Suggested phrases for writing recommendations: - Is not recommended - Is not indicated/useful/effective/beneficial - Should not be performed/administered/other	LEVEL C-LD (Limited Data) - Randomized or nonrandomized observational or registry studies with limitations of design or execution - Meta-analyses of such studies - Physiological or mechanistic studies in human subjects
Class 3: Harm (STRONG) Risk > Benefit Suggested phrases for writing recommendations: - Potentially harmful - Causes harm - Associated with excess morbidity/mortality - Should not be performed/administered/other	LEVEL C-EO (Expert Opinion) Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Association for Thoracic Surgery, American Society of Echocardiography, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. Appendix 1 lists writing committee members' relevant RWI. For the purposes of full transparency, the writing committee members' comprehensive disclosure information is available [online](#).

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC and AHA, 1 reviewer each from the American Association for Thoracic Surgery, American

Society of Echocardiography, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance, and 26 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by all collaborators and The Pediatric & Congenital Electrophysiology Society.

1.4. Scope of the Guideline

The purpose of this new guideline is to commission a full guideline revision of the previous "2011 ACCF/

AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy.”¹ The current version will replace the 2011 guideline and addresses comprehensive evaluation and management of adults and children with hypertrophic cardiomyopathy (HCM). Diagnostic modalities such as electrocardiography, imaging and genetic testing, and management of patients include medical therapies, septal reduction therapies, sudden cardiac death (SCD) risk assessment/prevention, and lifestyle considerations such as participation in activities/sports, occupation, and pregnancy. Table 1 lists other guidelines and pertinent documents that the writing committee considered for this guideline. The listed documents contain relevant information for the management of patients with hypertrophic cardiomyopathy.

1.5. Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention

Abbreviation	Meaning/Phrase
AF	atrial fibrillation
CAD	coronary artery disease
CMR	cardiovascular magnetic resonance
CPET	cardiopulmonary exercise test
CRT	cardiac resynchronization therapy
DOAC	direct-acting oral anticoagulants
EF	ejection fraction
GDMT	guideline-directed management and therapy
HCM	hypertrophic cardiomyopathy
HF	heart failure
ICD	implantable cardioverter-defibrillator
LAMP2	lysosome-associated membrane protein-2
LBBS	left bundle branch block
LGE	late gadolinium enhancement
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
MET	metabolic equivalent
MR	mitral regurgitation

NSVT	nonsustained ventricular tachycardia
NYHA	New York Heart Association
RCT	randomized controlled trial
RV	right ventricular
SAM	systolic anterior motion
SCAF	subclinical AF
SCD	sudden cardiac death
SRT	septal reduction therapy
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
VF	ventricular fibrillation
VT	ventricular tachycardia

on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 2).¹

1.6. Abbreviations

2. DEFINITION, ETIOLOGY, CLINICAL COURSE, AND NATURAL HISTORY

2.1. Prevalence

HCM is a common genetic heart disease reported in populations globally. Inherited in an autosomal dominant pattern, the distribution of HCM is equal by sex, although women are diagnosed less commonly than men. The prevalence of HCM depends on whether subclinical or clinically evident cases are being considered, is age dependent, and may have racial/ethnic differences.¹ The prevalence of unexplained asymptomatic hypertrophy in young adults in the United States has been reported to range from 1:200 to 1:500.² Symptomatic hypertrophy based on medical claims data has been estimated at <1:3000 adults in the United States; however, the true burden is much higher when unrecognized disease in the general population is considered.³ Clinical evaluation for HCM may be triggered by occurrence of symptoms, a cardiac event, detection of a heart murmur, an abnormal 12-lead ECG identified on routine examination, or through cardiac imaging during family screening studies.

2.2. Nomenclature/Differential Diagnosis

Since the original clinical description of HCM >60 years ago, various names have been used to describe this disease, including idiopathic hypertrophic subaortic stenosis and hypertrophic obstructive cardiomyopathy. Because left ventricular (LV) outflow tract obstruction (LVOTO) is present or develops over time in most patients with HCM, yet one-third remain nonobstructive, the

writing committee recommends the term HCM (with or without outflow tract obstruction).

In some areas, the use of HCM to describe the increased LV wall thickness associated with systemic disorders or secondary causes of LV hypertrophy (LVH) can lead to confusion. Systemic disorders include various metabolic and multiorgan syndromes such as RASopathies (variants in several genes involved in RAS-MAPK signaling), mitochondrial myopathies, glycogen/lysosomal storage diseases in children, and Fabry, amyloid, sarcoid, hemochromatosis, Danon cardiomyopathy in adults. In these diseases, although the magnitude and distribution of increased LV wall thickness can be similar to that of isolated HCM caused by variants in sarcomeric genes, the pathophysiologic mechanisms responsible for hypertrophy, natural history, and treatment strategies are not the same.¹⁻⁵ For these reasons, other cardiac or systemic diseases capable of producing LVH should not be labeled as HCM and will not be addressed in this document.

In addition, other scenarios can arise that present diagnostic challenges, including conditions that produce secondary LVH, which can also overlap phenotypically with HCM, including remodeling secondary to athletic training (ie, “athletes heart”) as well as morphologic changes related to long-standing systemic hypertension (ie, hypertensive cardiomyopathy). Similarly, hemodynamic obstruction caused by left-sided obstructive lesions (valvular or subvalvular stenosis) or obstruction after antero-apical infarction and stress cardiomyopathy can cause diagnostic dilemmas.^{6,7} Although HCM cannot be definitely excluded in such situations, a number of clinical markers and testing strategies can be used to help differentiate between HCM and conditions of physiologic LVH.

2.3. Definition, Clinical Diagnosis, and Phenotype

For the purposes of this guideline, we have considered the clinical definition of HCM as a disease state in which morphologic expression is confined solely to the heart. It is characterized predominantly by LVH in the absence of another cardiac, systemic, or metabolic disease capable of producing the magnitude of hypertrophy evident in a given patient and for which a disease-causing sarcomere (or sarcomere-related) variant is identified, or genetic etiology remains unresolved.

A clinical diagnosis of HCM in adult patients can therefore be established by imaging (Section 6.1), with 2D echocardiography or cardiovascular magnetic resonance (CMR) showing a maximal end-diastolic wall thickness of ≥ 15 mm anywhere in the left ventricle, in the absence of another cause of hypertrophy in adults.¹⁻⁴ More limited hypertrophy (13–14 mm) can be diagnostic when present in family members of a patient with HCM or in conjunction with a positive genetic test.

For children, the diagnostic criteria are confounded by needing to adjust for body size and growth. Traditionally, a body surface area adjusted z-score of ≥ 2 standard deviations above the mean has been used. This cut-off represents a significantly lower threshold than the 15-mm absolute value used in adults. For reference, 15 mm represents a z-score of approximately 6 standard deviations above the mean in adults. We propose that the diagnosis of HCM in children should therefore consider the circumstances of screening and the pretest probability of disease: a threshold of $z > 2.5$ may be appropriate to identify early HCM in asymptomatic children with no family history, whereas for children with a definitive family history or a positive genetic test, a threshold of $z > 2$ may suffice for early diagnosis. The emergence of the HCM phenotype in younger family members who carry a pathogenic sarcomere variant without previously evident LVH at initial screening (ie, genotype-positive/previously phenotype-negative) is well recognized and underscores the principle that normal or mildly increased LV wall thicknesses will be encountered in individuals with genetically affected status, as the disease manifests. In the absence of increased wall thickness, such individuals should be considered at risk for subsequent development of, but not yet having, clinically evident HCM.

Nearly any pattern and distribution of LV wall thickening can be observed in HCM, with the basal anterior septum in continuity with the anterior free wall the most common location for LVH. In a subset of patients, hypertrophy can be limited and focal, confined to only 1 or 2 LV segments with normal LV mass. Although common in HCM, neither systolic anterior motion (SAM) of the mitral valve nor hyperdynamic LV function is required for a clinical diagnosis. A number of other morphologic abnormalities are also not diagnostic of HCM but can be part of the phenotypic expression of the disease, including hypertrophied and apically displaced papillary muscles, myocardial crypts, anomalous insertion of the papillary muscle directly in the anterior leaflet of the mitral valve (in the absence of chordae tendinae), elongated mitral valve leaflets, myocardial bridging, and right ventricular (RV) hypertrophy.

2.4. Etiology

In the early 1990s, the DNA sequencing of HCM pedigrees led to the discovery that damaging variants in genes coding for sarcomere proteins segregated (or were co-inherited) with LVH identified by echocardiographic assessment, abnormal ECGs, and physical findings. HCM thereby became regarded as a monogenic cardiac disease, helping to consolidate a clinically heterogeneous disease into a single entity based on genetic substrate.¹

Currently, variants in 1 of 8 or more genes encoding proteins of the cardiac sarcomere (or sarcomere-related structures) have been implicated in causing LVH, the *sine qua non* of HCM. Among patients with HCM, ~30% to 60% have an identifiable pathogenic or likely

pathogenic genetic variant. A substantial proportion of patients with HCM are currently without any evidence of a genetic etiology to their disease, including a subgroup (up to 40% of patients in 1 study) who also have no other affected family members (ie, “non-familial” HCM).² These observations suggest that other novel pathophysiologic mechanisms may be responsible or contribute to phenotypic expression in these affected patients with HCM.

Among patients with HCM and a pathogenic sarcomeric gene variant, the 2 most common genes are beta myosin heavy chain 7 (*MYH7*) and myosin-binding protein C3 (*MYBPC3*), identified in 70% of variant-positive patients, while other genes (*TNNI3*, *TNNT2*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*) each account for a small proportion of patients (1% to 5%). Within these genes, >1500 variants have been recognized, the majority of which are “private” (unique to the individual family). Each offspring of an affected family member has a 50% chance of inheriting the variant.³ Although the likelihood of developing clinical HCM is high in family members with a pathogenic variant, the age at which disease expression occurs in a given individual is variable.

The precise mechanisms by which sarcomere variants result in the clinical phenotype have not been fully elucidated. Mutant sarcomere genes trigger myocardial changes, leading to hypertrophy and fibrosis, which ultimately results in a small, stiff ventricle with impaired systolic and diastolic performance despite a preserved LVEF. Similarly, abnormal sarcomeric proteins may not be solely responsible for all of the clinical characteristics observed in patients with HCM. Diverse disease features including abnormal intramural coronary arteries responsible for small vessel ischemia, elongated mitral valve leaflets, and congenital anomalies of the sub-mitral valve apparatus, which are widely recognized components of the HCM phenotype, appear to have no known direct association with sarcomere variants.

2.5. Natural History/Clinical Course

Although HCM can be compatible with normal life expectancy without limiting symptoms or the need for major treatments in most patients, other patients can experience significant consequences that are attributable to the disease. To this point, there is increasing recognition of patients with HCM identified clinically at advanced ages of >60 years with little to no disability. Yet, a multi-center registry report has suggested that the lifelong risk of adverse events (eg, mortality, HF, stroke, ventricular arrhythmia, AF) caused by HCM may be greater among patients with pathogenic sarcomeric gene variants or those diagnosed early in life.¹ The large number and diversity of the HCM-associated variants does not allow the specific genotype to be used to inform the anticipated outcomes in individual patients.

Among referral-based cohorts of patients with HCM, 30% to 40% will experience adverse events, including: 1) sudden death events; 2) progressive limiting symptoms because of LVOTO or diastolic dysfunction; 3) HF symptoms associated with systolic dysfunction; and 4) AF with risk of thromboembolic stroke. Nevertheless, studies reporting relatively long-term HCM patient outcomes have demonstrated that for patients at risk for, or who develop one of these, disease-related complications, the application of contemporary cardiovascular therapies and interventions has lowered HCM mortality rates to <1.0%/year.^{2,3} One of the major treatment initiatives responsible for lowering mortality has been the evolution of SCD risk stratification strategies based on a number of major noninvasive risk markers, which can identify adult patients with HCM at greatest risk for sudden death who are then candidates for implantable cardioverter-defibrillator (ICD) placement. The decrease in sudden death rates in HCM appears now to have shifted focus to heart failure (HF) as the predominant cause of disease-related morbidity and mortality and, therefore, greatest unmet treatment need in adults.

3. PATHOPHYSIOLOGY

The pathophysiology of HCM consists of dynamic LVOTO, mitral regurgitation (MR), diastolic dysfunction, myocardial ischemia, arrhythmias, and autonomic dysfunction. For a given patient with HCM, the clinical outcome may be dominated by one of these components or may be the result of a complex interplay. Thus, it is prudent to consider the potential presence of such abnormalities in a comprehensive clinical evaluation and address their impact in the management of these patients.

3.1. LVOT Obstruction

LVOTO, either at rest or with provocation, is present in ~75% of patients with HCM.¹ Two principal mechanisms are responsible for LVOTO: 1) septal hypertrophy with narrowing of the LVOT, leading to abnormal blood flow vectors that dynamically displace the mitral valve leaflets anteriorly; and 2) anatomic alterations in the mitral valve and apparatus, including longer leaflets as well as anterior displacement of the papillary muscles and mitral valve apparatus, which makes the valve more susceptible to the abnormal flow vectors. Consequently, there is systolic anterior motion of the mitral valve leaflets, which leads to LVOTO, high intracavitary pressures, and MR from the loss of leaflet coaptation.^{2–5} By causing increased LV systolic pressure, LVOTO also may exacerbate LVH, myocardial ischemia, and prolong ventricular relaxation. LVOTO is associated with impaired stroke volume and an increased risk of HF and poorer survival.^{6,7} The presence of a peak LVOT gradient of ≥ 30 mm Hg is considered to be indicative of obstruction, with resting or provoked gradients ≥ 50

mm Hg generally considered to be the threshold for septal reduction therapy (SRT) in those patients with drug-refractory symptoms.

LVOTO in HCM is dynamic and sensitive to ventricular load and contractility.⁸ Increased myocardial contractility, decreased preload, or lower afterload will increase the LVOT gradient. Subtle changes in these conditions may be noted and can lead to large variations in LVOT gradients and obstruction. Spontaneous variability in the LVOT gradient can occur with daily activities, food and alcohol intake, or even with quiet respiration.^{9,10} Thus, provocative maneuvers may be necessary in patients with low or absent peak resting gradients (ie, <30 mm Hg) to elicit the presence of LVOTO, particularly in patients with symptoms. Such maneuvers include standing, Valsalva strain, amyl nitrite inhalation, or exercise (fasted or postprandial), with simultaneous echocardiography performed to document the relation of the gradient to occurrence of systolic anterior motion of the mitral valve.^{11–15} Because of the lack of specificity, the use of dobutamine for determination of provocative LVOTO and eligibility for SRT is not advised.¹⁶

The diagnosis of LVOTO is made most commonly with echocardiography and, in some experienced centers (Table 3), with CMR imaging when echocardiographic imaging is suboptimal. The site and characteristics of the obstruction should be located, such as valvular, dynamic LVOTO, fixed subvalvular, midcavitary gradients associated with hypertrophied papillary muscles, anomalous papillary muscle insertion, or muscular obstruction caused by compensatory mid-ventricular hyperkinesis after apical infarction. In some instances, there is discordant information between the clinical findings and echocardiography in a symptomatic patient in whom SRT is being contemplated. Invasive assessment for LVOTO may be helpful in these circumstances.¹⁷

3.2. Diastolic Dysfunction

Altered ventricular load with high intracavitary pressures, nonuniformity in ventricular contraction and relaxation, and delayed inactivation from abnormal intracellular calcium reuptake are common abnormalities in HCM, and each contribute to the presence of diastolic dysfunction.^{1–3} Chamber stiffness can arise from myocardial hypertrophy, ischemia, and replacement or interstitial fibrosis. In some patients, the severity of hypertrophy also significantly compromises ventricular cavity size and stroke volume. Altered systolic-diastolic coupling and impaired cardiac cellular energetics are also causes of decreased exercise capacity in HCM, which carries prognostic impact independent of LVOTO.^{2,4,5} CMR imaging with late gadolinium-enhancement (LGE) can be used to detect and quantify myocardial fibrosis and scarring, which contributes to diastolic dysfunction as well as future left ventricular remodeling.^{6,7} Finally, an association between left atrial fibrosis, HCM, and atrial fibrillation (AF) has been reported.⁸

Exercise intolerance or symptoms of HF can occur from diastolic dysfunction in the absence of LVOTO and may require invasive testing with or without exercise testing to detect. With impairment in ventricular myocardial relaxation, greater dependency on the atrial systole for ventricular filling may occur, leading to poor tolerance of AF or similar arrhythmias in some patients.

3.3. Mitral Regurgitation

Mitral regurgitation (MR) can occur secondarily from LVOTO or from primary leaflet abnormalities and contributes to symptoms of dyspnea. In MR caused by LVOTO, SAM of the mitral valve leads to loss of leaflet coaptation, and the jet is predominantly mid-to-late systolic and posterior or lateral in orientation.¹ A posteriorly directed jet of MR in obstructive HCM correlates with SAM of the mitral valve as the underlying pathophysiologic mechanism. However, central and anterior jets may also result from SAM of the mitral valve (ie, these jets do not reliably predict primary mitral leaflet abnormalities), and caution is necessary in using the jet direction of MR on preoperative transthoracic echocardiogram (TTE) to guide the decision for concomitant mitral valve surgery during septal myectomy for HCM. Factors that affect the severity of LVOTO also may affect the degree of MR. Thus, significant MR may not be evident without provocation for LVOTO and SAM of the mitral valve. Primary abnormalities of the mitral valve and its apparatus are also common, including excessive leaflet length, anomalous papillary muscle insertion, and anteriorly displaced papillary muscles.^{2–4} In some patients, these primary mitral valve abnormalities may be the principal cause of symptoms. For patients in whom SRT is being contemplated, close examination for mitral valve abnormalities should be performed to determine the optimal invasive approach.^{5,6}

3.4. Myocardial Ischemia

Patients with HCM are susceptible to myocardial ischemia attributable to a mismatch between myocardial oxygen supply and demand. Myocardial hypertrophy, microvascular dysfunction with impaired coronary flow reserve, and medial hypertrophy of the intramural arterioles and their reduced density are common findings.^{1,2} These abnormalities are worsened by the presence of hyperdynamic systolic function and LVOTO with high intracavitary pressures.^{3,4} Blunted coronary flow reserve occurs even without epicardial stenosis, although the presence of concomitant severe coronary atherosclerosis exacerbates mismatch and is associated with a poorer prognosis.⁵ The presence of myocardial ischemia may lead to infarction, which may be evident as LGE on CMR imaging.⁶ Apical myocardial ischemia and infarction (with or without midventricular obstruction)

Table 3. Suggested Competencies of Comprehensive and Primary HCM Centers

Potential HCM Care Delivery Competencies	Comprehensive HCM Center	Primary HCM Center	Referring Centers/Physicians
Diagnosis	X	X	X
Initial and surveillance TTE	X	X	X
Advanced echocardiographic imaging to detect latent LVOTO	X	X	
Echocardiography to guide SRT	X	*	
CMR imaging for diagnosis and risk stratification	X	X	
Invasive evaluation for LVOTO	X	*	*
Coronary angiography	X	X	X
Stress testing for elicitation of LVOTO or consideration of advanced HF therapies/transplant	X	X	
Counseling and performing family screening (imaging and genetic)	X	X	X
Genetic testing/counseling	X	X	*
SCD risk assessment	X	X	X
Class 1 and Class 2a ICD decision-making with adult patients	X	X	X
Class 2B ICD decision-making with adult patients	X		
ICD implantation (adults)	X	X	*
ICD decision-making and implantation with children/adolescents and their parents	X	*	
Initial AF management and stroke prevention	X	X	X
AF catheter ablation	X	X	*
Initial management of HFrEF and HFpEF	X	X	X
Advanced HF management (eg, transplantation, CRT)	X	*	
Pharmacologic therapy for symptomatic obstructive HCM	X	X	X
Invasive management of symptomatic obstructive HCM	X	†	
Counseling occupational and healthy living choices other than high-intensity or competitive activities	X	X	X
Counseling options on participation in high-intensity or competitive athletics	X		
Managing women with HCM through pregnancy	X	*	
Management of comorbidities	X	X	X

*Optional depending on the core competencies of the institution.

†If these procedures are performed, adequate quality assurance should be in place to demonstrate outcomes consistent with that achieved by comprehensive centers.

AF indicates atrial fibrillation; CMR, cardiovascular magnetic resonance; CRT, cardiac resynchronization therapy; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; LVOTO, left ventricular outflow tract obstruction; SCD, sudden cardiac death; and TTE, transthoracic echocardiography.

may be one of the mechanisms that contributes to the development of LV aneurysms, which carry increased risk of HF and ventricular arrhythmias.^{7,8} Myocardial bridging, a congenital anomaly whereby a bridge of overlying myocardium causes systolic compression of an epicardial coronary artery that can persist into diastole, may impair blood flow and is a rare cause of myocardial ischemia in a subset of patients.^{9–13}

3.5. Autonomic Dysfunction

Patients with HCM can have autonomic dysfunction, with impaired heart rate recovery and inappropriate

vasodilatation.^{1–4} The prevalence of autonomic dysfunction in HCM is uncertain, although studies have described an abnormal blood pressure response to exercise in ~25% of patients.^{2–4} An abnormal blood pressure response to exercise, defined as failure to increase systolic blood pressure by at least 20 mm Hg, or a drop in systolic blood pressure during exercise of >20 mm Hg from the peak value obtained, has been associated with a poorer prognosis. However, this blood pressure response may be attributable to autonomics, diastolic filling abnormalities, or LVOTO. This implies that the abnormal blood

pressure response may be modifiable with medical and surgical therapy.

4. SHARED DECISION-MAKING

Recommendation for Shared Decision-Making Referenced studies that support the recommendation are summarized in Online Data Supplement 1.		
COR	LOE	Recommendation
1	B-NR	1. For patients with HCM or at risk for HCM, shared decision-making is recommended in developing a plan of care (including but not limited to decisions regarding genetic evaluation, activity, lifestyle, and therapy choices) that includes a full disclosure of the risks, benefits, and anticipated outcomes of all options, as well the opportunity for the patient to express their goals and concerns. ¹⁻⁶

Synopsis

Shared decision-making is a dialogue that allows patients and providers to work together to select options that fully consider the input, values, and preferences of the patient (or their families in the case of an affected minor). This approach has been shown to improve confidence in clinical decisions and improved health outcomes.⁷ Although shared decision discussions should be the default interaction between patients (or their families in the case of an affected minor) and their care teams, the biggest opportunities are those areas where there are complex pathways that vary by the individual patient. In the management of HCM, decisions around genetic testing, ICD implantation, invasive therapies for relief of LVOTO, and participation in competitive or high-intensity exercise are particularly ripe for these crucial dialogues. Some of these discussions and decisions could also represent opportunities where referral to centers with more comprehensive experience are most appropriate and highly impactful.

5. MULTIDISCIPLINARY HCM CENTERS

Recommendations for Multidisciplinary HCM Centers		
COR	LOE	Recommendations
1	C-LD	1. In patients with HCM in whom SRT is indicated, the procedure should be performed at experienced centers (comprehensive or primary HCM centers) with demonstrated excellence in clinical outcomes for these procedures ¹⁻³ (Table 3 and Table 4).
2a	C-LD	2. In patients with HCM, consultation with or referral to a comprehensive or primary HCM center is reasonable to aid in complex disease-related management decisions ⁴⁻¹³ (Table 3).

Synopsis

The specialized needs, complex and evolving clinical management, and the relatively uncommon prevalence of HCM in many clinical practices have created a greater demand and need for clinical HCM centers with HCM-specific competencies similar to that proposed for the management of patients with valvular heart disease.^{5-7,14} These competencies often require specialized training and sufficient volumes to maintain desired outcomes. The main goal of the HCM centers' framework is to optimize care and counseling of patients with HCM and their families. It is recognized that care necessarily involves healthcare teams whose expertise falls along a spectrum rather than as a binary (present/absent) condition. The proposed approach recognizes that spectrum and is inclusive of roles for cardiologists working outside of HCM centers, those working in primary HCM centers that offer many or most HCM-specific services, and those working at fully comprehensive HCM centers. Participation in quality assessment and research to advance the understanding of HCM also falls more squarely in the realm of the HCM centers. Cardiologists practicing outside of HCM centers have a critical role in many aspects of HCM management (Table 3) including, but not limited to, providing ready access for initial and surveillance testing, treatment recommendations, and availability for rapid assessment when a patient's disease course changes.

Referral to HCM centers can help to confirm diagnosis, provide genetic counseling and testing, advise regarding more advanced treatment decisions, and provide patients with access to the highest level of longitudinal care possible for their disease.⁷ It is the expectation that primary and comprehensive HCM centers provide direct communication along established referral lines between programs themselves as well as the community of referring providers/centers in an effort to improve the quality of care in all settings and meet the needs of the individual patient.

A dedicated, multidisciplinary primary HCM center should be composed of a team with a high level of competence in treating patients with HCM, including the skills suggested in Table 3. Primary HCM centers that perform invasive SRTs should ensure reasonable outcomes for safety and benefit, commensurate with that reported from comprehensive HCM centers (Table 3 and Table 4). If only one of the invasive SRT options is available at a given center, patients should be fully informed of alternative options, including the pros and cons of both procedures and the possibility for referral to a comprehensive center that offers all treatment options to ensure appropriate patient participation in the decision-making.

A comprehensive HCM center comprises a similar organizational structure as a primary HCM center but has demonstrated graduated levels of expertise and

Table 4. Example Targets for Invasive Septal Reduction Therapies Outcomes

	Rate	
	Myectomy	Alcohol Septal Ablation
30-d mortality	≤1%	≤1%
30-d adverse complications (tamponade, LAD dissection, infection, major bleeding)	≤10%	≤10%
30-d complete heart block resulting in need for permanent pacemaker	≤5%	≤10%
Mitral valve replacement within 1 y	≤5%	
More than moderate residual mitral regurgitation	≤5%	≤5%
Repeat procedure rate	≤3%	≤10%
Improvement ≥ NYHA class	>90%	>90%
Rest and provoked LVOT gradient <50 mm Hg	>90%	>90%

LAD indicates left anterior descending; LVOT, left ventricular outflow tract; and NYHA, New York Heart Association.

resources specific for HCM that include additional competencies (Table 3). Referral to a comprehensive HCM center should specifically be considered for those patients with HCM who are candidates for any procedure specific to, or which requires specialized expertise to perform in, HCM, including particularly complex invasive SRTs,^{3,8,9} catheter ablation for ventricular and complex atrial tachyarrhythmias,^{10,11} and advanced HF therapies, including transplant.^{12,13} In addition, referral to a comprehensive HCM center can aid in complex disease-related management decisions including, but not limited to, particularly challenging primary prevention ICD decision-making as well as counseling patients with HCM on the potential risks associated with participating in competitive sports.⁴

Table 5. Clinical Features in Patients With “HCM Phenocopies (Mimics)”

Typical Presentation Age	Systemic Features	Possible Etiology	Diagnostic Approach
Infants (0–12 mo) and toddlers	Dysmorphic features, failure to thrive, metabolic acidosis	RASopathies Glycogen storage diseases, other metabolic or mitochondrial diseases Infant of a mother with diabetes	Geneticist assessment Newborn metabolic screening Specific metabolic assays Genetic testing
Early childhood	Delayed or abnormal cognitive development, visual or hearing impairment	RASopathies Mitochondrial diseases	Biochemical screening Genetic testing
School age and adolescence	Skeletal muscle weakness or movement disorder	Friedrich ataxia, Danon disease Mitochondrial disease	Biochemical screening Neuromuscular assessment Genetic testing
Adulthood	Movement disorder, peripheral neuropathy, renal dysfunction	Anderson-Fabry disease, Friedrich ataxia, infiltrative disorders (eg, amyloidosis), glycogen storage diseases	Biochemical screening Neuromuscular assessment Genetic testing

HCM indicates hypertrophic cardiomyopathy.

Recommendation-Specific Supportive Text

1. When performed in centers with limited experience and low procedural volume, invasive SRTs for relief of LVOTO are associated with increased mortality and morbidity, as well as mitral valve replacement.^{1–3,15,16} Strong consideration should therefore be given to referral of patients with obstructive HCM who are candidates for invasive SRTs to established high-volume primary or comprehensive HCM centers, which can perform these procedures with optimal safety and benefit outcomes.
2. Given the unique needs of HCM in clinical cardiovascular practice, as well as the specialized training and interpretation associated with many of the procedures and testing that are now routinely applied to this complex genetic heart disease, challenging management decision-making can arise for which it would be reasonable to offer patients referral to or consultation with an HCM center.^{4–13}

6. DIAGNOSIS, INITIAL EVALUATION, AND FOLLOW-UP

6.1. Clinical Diagnosis

Recommendation for Diagnosis, Initial Evaluation, and Follow-up
Referenced studies that support the recommendation are summarized in Online Data Supplement 2.

COR	LOE	Recommendation
1	B-NR	1. In patients with suspected HCM, comprehensive physical examination and complete medical and 3-generation family history is recommended as part of the initial diagnostic assessment ^{1–6} (Table 5 and Table 6).

Table 6. Screening With Electrocardiography and 2D Echocardiography in Asymptomatic Family Members*

Age of First-Degree Relative	Initiation of Screening	Repeat ECG, Echo
Pediatric		
Children and adolescents from genotype-positive families, and families with early onset disease	At the time HCM is diagnosed in another family member	Every 1-2 y
All other children and adolescents	At any time after HCM is diagnosed in a family member but no later than puberty	Every 2-3 y
Adults	At the time HCM is diagnosed in another family member	Every 3-5 y

*Includes all asymptomatic, phenotype-negative first-degree relatives deemed to be at-risk for developing HCM based on family history or genotype status and may sometimes include more distant relatives based on clinical judgment. Screening interval may be modified (eg, at onset of new symptoms or in families with a malignant clinical course or late-onset HCM).

ECG indicates electrocardiogram; Echo, echocardiogram; and HCM, hypertrophic cardiomyopathy.

Synopsis

Clinical evaluation for HCM may be triggered by the identification of a family history of HCM, symptoms including a cardiac event, a heart murmur during physical examination, during echocardiography performed for other indications, or an abnormal 12-lead ECG. A proper clinical evaluation should start with a comprehensive cardiac history, a family history including 3 generations, and a comprehensive physical examination (including maneuvers such as Valsalva, squat-to-stand, passive leg raising, or walking). This should be followed by an ECG and cardiac imaging to identify LVH when clinical findings are suggestive.

Recommendation-Specific Supportive Text

- Many patients with HCM are asymptomatic and identified incidentally or as a result of screening. Clinical history includes a detailed cardiac history and family history (3 generations) to identify relatives with HCM or with unexpected/sudden death. Assessment of overall fitness and functional capacity, with emphasis on training regimen and symptoms in response to exertion—chest pain, dyspnea, palpitations, and syncope. Associated syndromic or systemic/extracardiac symptoms or organ involvement are also documented (eg, ataxia, hearing, visual, or cognitive impairment, failure to thrive, neurodevelopmental abnormalities). Alternative etiologies to be considered include physiologic remodeling of the athlete, long-standing systemic hypertension, renal disease, or infiltrative diseases (amyloid cardiomyopathy).

In neonates, a history of maternal gestational diabetes is sought, and in infants <1 year of age, a systemic disease is important to exclude. Table 5 lists other causes of LVH that may mimic HCM but are not the subject of this guideline.

Classically, patients with HCM have a systolic murmur, prominent apical point of maximal impulse, abnormal carotid pulse, and a fourth heart sound. SAM of the mitral valve leads to LVOTO and resultant harsh crescendo-decrescendo systolic murmur best heard over the lower left sternal border. Physical findings of outflow tract obstruction should be sought both at rest and with provocative maneuvers (Valsalva maneuver, standing from the squatting position), although this may not be feasible in young children. SAM related to an elongated anterior mitral valve leaflet and papillary muscle abnormalities may result in leaflet separation/poor coaptation with posteriorly directed mitral regurgitation in late systole over the mitral position. A prominent point of maximal impulse is usually present, shifted laterally and either bifid or trifid. A carotid double pulsation, known as pulsus bisferiens, and an S4 from a noncompliant left ventricle may be present. Those without LVOTO (provocable or resting) may have a normal physical examination.

6.2. Echocardiography

Recommendations for Echocardiography

Referenced studies that support the recommendations are summarized in Online Data Supplement 3.

COR	LOE	Recommendations
1	B-NR	1. In patients with suspected HCM, a TTE is recommended in the initial evaluation. ¹⁻⁶
1	B-NR children	2. In patients with HCM with no change in clinical status or events, repeat TTE is recommended every 1 to 2 years to assess the degree of myocardial hypertrophy, dynamic LVOTO, MR, and myocardial function ⁷⁻¹⁴ (Figure 1).
	C-LD adults	
1	B-NR	3. For patients with HCM who experience a change in clinical status or a new clinical event, repeat TTE is recommended. ^{7,10,15-18}
1	B-NR	4. For patients with HCM and resting LVOT gradient <50 mm Hg, a TTE with provocative maneuvers is recommended. ¹⁹⁻²²
1	B-NR	5. For symptomatic patients with HCM who do not have a resting or provocable outflow tract gradient ≥50 mm Hg on TTE, exercise TTE is recommended for the detection and quantification of dynamic LVOTO. ²¹⁻²⁶
1	B-NR	6. For patients with HCM undergoing surgical septal myectomy, intraoperative transesophageal echocardiogram (TEE) is recommended to assess mitral valve anatomy and function and adequacy of septal myectomy. ²⁷⁻³⁰

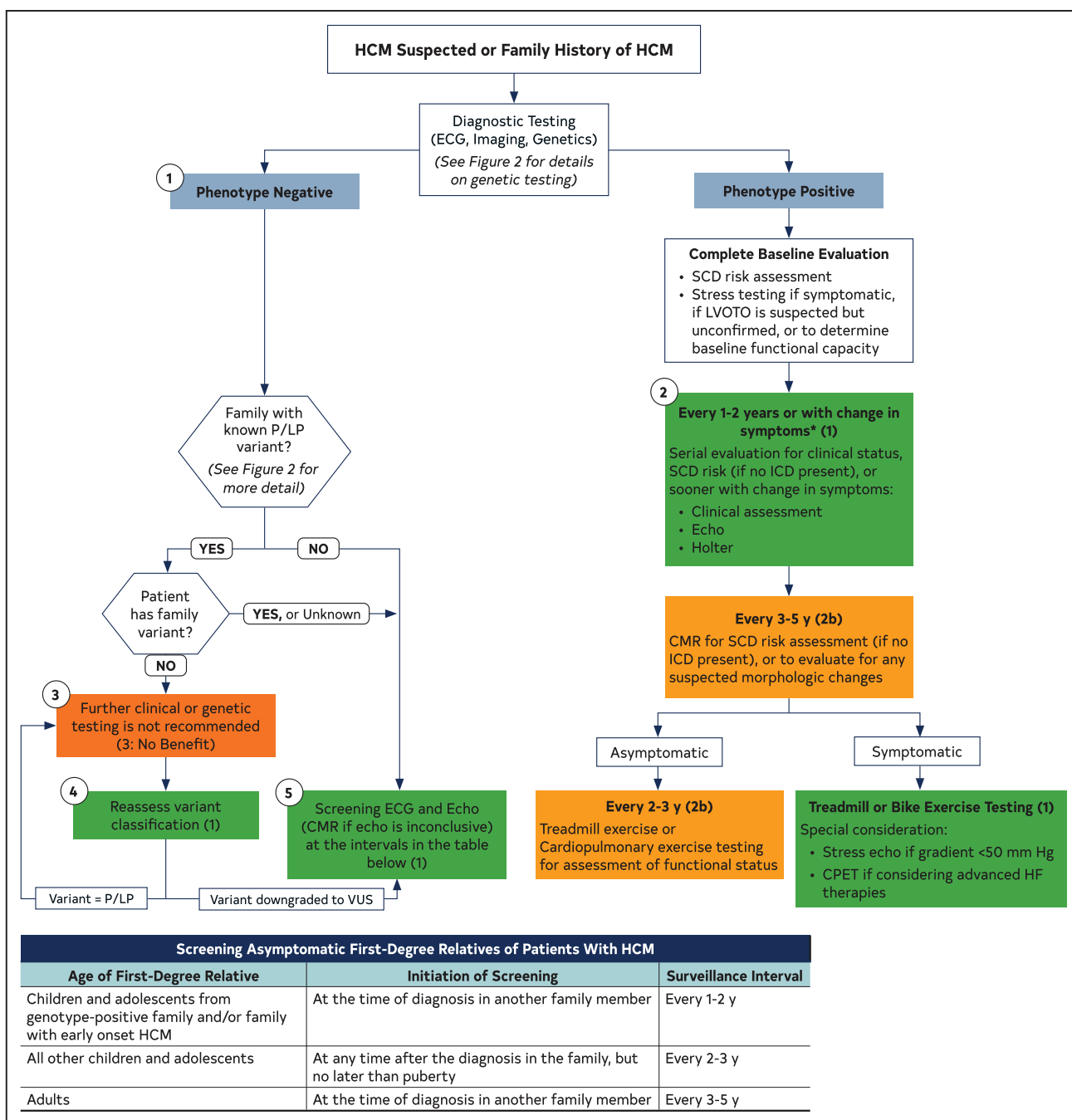


Figure 1. Recommended evaluation and testing for HCM.

Colors correspond to the Class of Recommendation in Table 2. *The interval may be extended, particularly in adult patients who remain stable after multiple evaluations. CMR indicates cardiovascular magnetic resonance; CPET, cardiopulmonary exercise test; ECG, electrocardiography/electrocardiogram; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVOTO, left ventricular outflow tract obstruction; P/LP, pathogenic or likely pathogenic variant; SCD, sudden cardiac death; and VUS, variant of unknown significance.

Recommendations for Echocardiography (Continued)		
COR	LOE	Recommendations
1	B-NR	7. For patients with HCM undergoing alcohol septal ablation, TTE or intraoperative TEE with intracoronary ultrasound-enhancing contrast injection of the candidate's septal perforator(s) is recommended. ^{3,31–35}

1	B-NR	8. For patients with HCM who have undergone SRT, TTE within 3 to 6 months after the procedure is recommended to evaluate the procedural results. ^{36–39}
1	B-NR	9. Screening: In first-degree relatives of patients with HCM, a TTE is recommended as part of initial family screening and periodic follow-up ^{3–5,7,8,33} (Figure 1, Table 6).

1	B-NR	10. Screening: In individuals who are genotype-positive or phenotype-negative, serial echocardiography is recommended at periodic intervals depending on age (1 to 2 years in children and adolescents, 3 to 5 years in adults) and change in clinical status ^{40–44} (Figure 1, Table 6).
2a	C-LD	11. For patients with HCM, TEE can be useful if TTE is inconclusive in clinical decision-making regarding medical therapy, and in situations such as planning for myectomy, exclusion of subaortic membrane or MR secondary to structural abnormalities of the mitral valve apparatus, or in the assessment of the feasibility of alcohol septal ablation. ^{27–30}
2a	B-NR	12. For patients with HCM in whom the diagnoses of apical HCM, apical aneurysm, or atypical patterns of hypertrophy is inconclusive on TTE, the use of an intravenous ultrasound-enhancing agent is reasonable, particularly if other imaging modalities such as CMR are not readily available or contraindicated. ^{45,46}
2a	C-LD	13. For asymptomatic patients with HCM who do not have a resting or provokable outflow tract gradient ≥ 50 mm Hg on standard TTE, exercise TTE is reasonable for the detection and quantification of dynamic LVOTO. ^{15,20,21,23–26}

Synopsis

Cardiac imaging plays an essential role in diagnosis and clinical decision-making for patients with HCM. Echocardiography is the primary imaging modality in most patients, with CMR imaging offering complementary information and as an alternative to echocardiography for selected patients in whom the echocardiogram is inconclusive. Important information to be gained from imaging includes establishing the diagnosis (or excluding alternative diagnoses), evaluating the severity of the phenotype, and evaluating for concomitant structural and functional cardiac abnormalities (eg, systolic, diastolic, valvular function). Characterization of dynamic LVOTO, including the integral role of the mitral valve, is a key strength of echocardiography. Documentation of the maximal wall thickness, cardiac chamber dimensions, systolic function, and the presence of LV apical aneurysm all inform phenotype severity and SCD risk stratification.

Recommendation-Specific Supportive Text

1. Comprehensive 2D echocardiography plays a primary role in establishing the diagnosis of HCM, determining hypertrophy pattern, presence of LV apical aneurysms, LV systolic and diastolic function, mitral valve function, and presence and severity of LVOTO.
2. Routine follow-up of patients with HCM is an important part of optimal care. In asymptomatic patients, serial TTE, performed every 1 to 2 years,

can help assess for changes in LV systolic and diastolic function, wall thickness, chamber size, LVOTO, and concomitant valvular disease. This interval may be extended in patients who remain clinically stable after multiple evaluations.

3. Changes in signs or symptoms in patients with HCM are often attributable to progression of the hemodynamics of HCM, or the development of new concomitant cardiovascular abnormalities, such as valvular heart disease. Echocardiography is the primary imaging modality to assess for these changes in patients with new or worsening symptoms.^{7,10,15–18}
4. LVOT gradients are dynamic, influenced by loading conditions, and recumbent resting echocardiography tends to underestimate the presence and severity of ambulatory LVOTO, with up to 50% of patients with obstructive physiology being identified on resting echocardiography. If the resting gradient is < 50 mm Hg, it is essential to perform provocative maneuvers such as Valsalva or squat-to-stand (or simply standing) maneuvers to uncover the presence of LVOTO, which may inform the care of the individual.^{15,19–21} Provocative maneuvers may not be as helpful in children, who often cannot cooperate with these maneuvers.
5. In general, to attribute effort-related symptoms to LVOTO, the resting or provoked gradient would need to be > 50 mm Hg. LVOT gradients can be dynamic, can be missed on resting echocardiography in up to 50% of patients with obstructive physiology,¹⁶ and maneuvers performed during a resting TTE to provoke an LVOT gradient (such as Valsalva) can be variable because of inconsistencies in instruction and patient effort. Stress echocardiography, representing the most physiologic form of provocation, can be most helpful for those patients where the presence or severity of LVOTO is uncertain after the baseline echocardiogram.^{21,23–26} Postprandial exercise may also be useful, particularly if the patient expresses increased symptoms after meals.⁴⁷ Exercise testing is only useful in older children, typically > 7 to 8 years of age, because young children are often unable to cooperate with exercise testing.
6. Intra-operative TEE is a standard part of surgical myectomy and adjunctive repairs for patients with HCM. TEE can assess mitral valve abnormalities and MR and extent of septal hypertrophy, as well as provide assessment of residual SAM of the mitral valve and LVOTO, and occurrence of a ventricular septal defect or new aortic insufficiency.^{27–30}
7. TTE or TEE imaging helps guide alcohol septal ablation, particularly in localizing the appropriate

left anterior descending septal perforator by intracoronary contrast injection as well as monitoring of LVOT gradient reduction during the procedure. The use of transthoracic guidance with ultrasound-enhancing agents has resulted in greater procedural success, decreased intervention time, smaller infarct size, and lower heart block rates.^{6,31–35} In cases where transthoracic image quality is suboptimal, intraprocedural TEE with ultrasound-enhancing agents can be used to guide septal ablation therapy.^{6,35}

8. Following SRT, efficacy of therapy, particularly evidence of septal thinning and LVOT gradient decrease, should be assessed. Residual SAM of the mitral valve and MR, aortic insufficiency, LV systolic and diastolic function, and ventricular septal defect should also be assessed. Although these results are usually apparent immediately after surgical septal myectomy, changes in LVOTO and formation of a myocardial septal scar may evolve over time (typically complete in 3 months but in some patients may persist for a year) after septal ablation.^{36,38,39,48,49}
9. When a diagnosis of HCM is made in a proband, echocardiographic screening of first-degree relatives is offered to identify affected relatives. In 2 large pediatric studies, yield on echocardiographic screening for clinical HCM in first-degree relatives was 10% to 15% throughout childhood and adolescence with similar disease rates of penetrance across age range.^{39,43,50} The median age at HCM onset was 8.9 (4.7 to 13.4) years, with earlier onset in males, those with family history of SCD, and pathogenic variants in *MYH7*/*MYBPC3*.³⁹ Likewise, the median time from HCM onset to a major cardiac event, including death, SCD, or cardiac intervention (myectomy, ICD), was 1.5 years.^{39,49–51} Taken together, these data support family screening initiated in childhood and repeated on a periodic basis as outlined in Table 6 in children and adults. It is also important to note that changes in LV systolic strain and diastolic function can precede definitive hypertrophy.^{52–54} Family members with these abnormalities likely warrant closer follow-up.
10. The ongoing screening of genotype-positive, phenotype-negative family members of all ages is important. Previous small studies reported onset of clinical HCM in adolescence or young adulthood for most genotype-positive cases.^{2,55} However, recent large studies suggest that clinical HCM can develop in younger family members, with 5% to 10% being phenotype-positive at first screening and another 3% to 5% before 18 years of age. Phenotype conversion can occur in young adults and therefore continued screening

into adulthood is warranted, although frequency of screening can be lowered because disease penetrance is lower in individuals who are >18 years of age.^{41–44,56} Although there is an absence of systematic evidence, most physicians continue clinical screening until midlife (age 50s) because disease can manifest in adults albeit at a lower frequency.

11. TEE can be particularly useful if there is uncertainty regarding mitral valve structural abnormalities, mechanism of MR, or suspicion of alternate causes of outflow obstruction (discrete subaortic stenosis, valvular stenosis) on TTE or suspected or by other clinical parameters.³⁰
12. In patients with HCM, LVH can be localized to any segment of the LV wall, and care should be taken to completely image all LV wall segments. In cases where the LV apex is suboptimally visualized, use of ultrasound-enhancing agent or CMR imaging can aid in detection of apical hypertrophy, aneurysm, and thrombus.^{45,57,58}
13. In patients who are asymptomatic, understanding whether they have LVOTO at rest or provocation is important in understanding the potential pathophysiology. Even in asymptomatic patients, knowing that they have provokable obstruction can influence health advice (eg, regarding hydration) or choice of therapies for concomitant conditions (eg, diuretics or vasodilators for patients with hypertension).^{21,23–26}

6.3. Cardiovascular Magnetic Resonance Imaging

Recommendations for CMR Imaging

Referenced studies that support the recommendations are summarized in Online Data Supplement 4.

COR	LOE	Recommendations
1	B-NR	1. For patients suspected to have HCM in whom echocardiography is inconclusive, CMR imaging is indicated for diagnostic clarification. ^{1–7}
1	B-NR	2. For patients with LVH in whom there is a suspicion of alternative diagnoses, including infiltrative or storage disease as well as athlete's heart, CMR imaging is useful ^{1–7} (Figure 1).
1	B-NR	3. For patients with HCM who are not otherwise identified as high risk for SCD, or in whom a decision to proceed with ICD remains uncertain after clinical assessment that includes personal/family history, echocardiography, and ambulatory electrocardiographic monitoring, CMR imaging is beneficial to assess for maximum LV wall thickness, ejection fraction (EF), LV apical aneurysm, and extent of myocardial fibrosis with LGE. ^{1–15}

Table 7. Established Clinical Risk Factors for HCM Sudden Death Risk Stratification

Family history of sudden death from HCM	Sudden death judged definitively or likely attributable to HCM in ≥ 1 first-degree or close relatives who are ≤ 50 y of age. Close relatives would generally be second-degree relatives; however, multiple SCDs in tertiary relatives should also be considered relevant.
Massive LVH	Wall thickness ≥ 30 mm in any segment within the chamber by echocardiography or CMR imaging; consideration for this morphologic marker is also given to borderline values of ≥ 28 mm in individual patients at the discretion of the treating cardiologist. For pediatric patients with HCM, an absolute or z-score threshold for wall thickness has not been established; however, a maximal wall that corresponds to a z-score ≥ 20 (and >10 in conjunction with other risk factors) appears reasonable.
Unexplained syncope	≥ 1 Unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic (vasovagal) etiology, nor attributable to LVOTO, and especially when occurring within 6 mo of evaluation (events beyond 5 y in the past do not appear to have relevance).
HCM with LV systolic dysfunction	Systolic dysfunction with EF $<50\%$ by echocardiography or CMR imaging.
LV apical aneurysm	Apical aneurysm defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the LV chamber; independent of size.
Extensive LGE on CMR imaging	Diffuse and extensive LGE, representing fibrosis, either quantified or estimated by visual inspection, comprising $\geq 15\%$ of LV mass (extent of LGE conferring risk has not been established in children).
NSVT on ambulatory monitor	It would seem most appropriate to place greater weight on NSVT as a risk marker when runs are frequent (≥ 3), longer (≥ 10 beats), and faster (≥ 200 bpm) occurring usually over 24 to 48 h of monitoring. For pediatric patients, a VT rate that exceeds the baseline sinus rate by $>20\%$ is considered significant.

CMR indicates cardiovascular magnetic resonance; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; NSVT, nonsustained ventricular tachycardia; and SCD, sudden cardiac death.

1	B-NR	4. For patients with obstructive HCM in whom the anatomic mechanism of obstruction is inconclusive on echocardiography, CMR imaging is indicated to inform the selection and planning of SRT. ^{16–20}
2b	C-EO	5. For patients with HCM, repeat contrast-enhanced CMR imaging on a periodic basis (every 3 to 5 years) for the purpose of SCD risk stratification may be considered to evaluate changes in LGE and other morphologic changes, including EF, development of apical aneurysm, or LV wall thickness (Figure 1, Table 7).

may impact management strategies.^{7–9,16–19} Additionally, extensive LGE (ie, myocardial fibrosis) represents a noninvasive marker for increased risk for potentially life-threatening ventricular tachyarrhythmias and HF progression with systolic dysfunction.^{11–14} It is recognized that CMR imaging may not be feasible in certain patients because of availability, cost, contraindications attributable to pacemakers or ICDs, severe renal insufficiency, and patient factors (pediatric age and a requirement for general anesthesia, or sedation, claustrophobia, or body habitus).

Synopsis

CMR imaging provides high spatial resolution and fully tomographic imaging of the heart, as well as assessment of myocardial fibrosis after injection of contrast with LGE.^{1,2} These attributes of CMR imaging are well-suited for characterizing the diverse phenotypic expressions of HCM, providing diagnosis, risk prediction, and preprocedural planning for septal reduction.^{1,7} For these reasons, CMR imaging is an important complementary imaging technique in the evaluation of patients with HCM.

CMR imaging has the distinct advantage, by virtue of producing images with sharp contrast between the blood pool and myocardium, to provide highly accurate LV wall thickness measurements, robust quantification of LV and RV chamber size, LV mass, systolic function, and can identify areas of LVH not well visualized by echocardiography.^{1–7} CMR imaging has also expanded our appreciation for the diversity in morphologic abnormalities, including LV apical aneurysms as well as structural abnormalities of the mitral valve and subvalvular apparatus that contribute to LVOTO, findings which

Recommendation-Specific Supportive Text

1. For patients in whom HCM is suspected based on cardiac symptoms, an abnormal 12-lead ECG, or family history of inherited heart disease, and in whom echocardiographic examination is non-diagnostic or inconclusive, CMR imaging is an important adjunctive test to clarify diagnosis.^{1–7} In such clinical situations, CMR imaging can identify focal areas of LVH, particularly when hypertrophy is confined to certain regions of the LV wall, including the anterolateral wall, posterior septum, and apex. This increased sensitivity in detecting LVH by CMR imaging is attributable to high spatial resolution and the fact that CMR imaging is not encumbered by poor acoustic windows caused by pulmonary or thoracic parenchyma.^{4–6}
2. Important differences in the pattern and location of LVH, cavity dimensions, and the pattern and distribution of LGE can aid in the differentiation of HCM from other cardiovascular diseases associated with LVH, including other inherited

cardiomyopathies (eg, lysosomal or glycogen storage diseases), infiltrative cardiomyopathies (eg, amyloid), or conditions with secondary hypertrophy attributable to pressure overload (eg, hypertension or athletic conditioning).⁷

3. In some patients with HCM, maximal LV wall thickness measurements can be underestimated (or overestimated) with echocardiography compared with CMR imaging.¹⁻⁷ This observation can have direct management implications for SCD risk assessment, because LV wall thickness is one of the major risk markers for SCD.^{4-6,10} In addition, apical aneurysms may not always be detected by echocardiography.^{8,9} Extensive LGE, often occupying multiple LV segments, is associated with increased risk for future potentially life-threatening ventricular arrhythmias, independent of location or pattern within the LV wall.¹¹⁻¹³ Some studies have promoted a threshold for extensive LGE of $\geq 15\%$ of the LV mass as representing a significant (2-fold) increase in SCD risk.¹² However, there is no consensus on the optimal quantification technique(s) that can yield varying results. The absence of (or minimal) LGE is associated with lower risk for SCD.^{12,13,21} LGE can serve as an arbitrator to aid in decision-making when the decision on whether to pursue ICD placement remains ambiguous after standard risk stratification.¹²

Patients with HCM and systolic dysfunction (EF $< 50\%$), a phenotype characterized by adverse LV remodeling with ventricular cavity enlargement and wall thinning because of scarring, are associated with increased risk for potentially lethal ventricular tachyarrhythmias as well as advanced HF symptoms.^{14,15} CMR imaging can provide quantitative EF assessment in patients with HCM in whom determination of systolic function remains uncertain with echocardiography.

4. Because of specific anatomic features of the LVOT, some patients with HCM will be more suitable candidates for septal myectomy than percutaneous alcohol ablation.¹⁶⁻²⁰ CMR imaging can reliably characterize specific features of the LVOT anatomy that may be contributing to SAM-septal contact and obstructive physiology and, therefore, are relevant to strategic planning for septal reduction procedures, including precise distribution of septal hypertrophy, abnormalities of the mitral valve and subvalvular apparatus, including abnormally positioned papillary muscles, anomalous papillary muscle insertion directly into mitral valve, accessory muscle bundles, and abnormal chordal connections, particularly

if these morphologic features are not clearly identified with echocardiography.¹⁶⁻²⁰

5. The progression of high-risk morphologic features, including apical aneurysm, extensive LGE, systolic dysfunction, and massive LVH is not well-defined. Nevertheless, given the importance of these in management considerations, including SCD prevention with ICD therapy, periodic longitudinal evaluation with CMR imaging to detect development or progression in ≥ 1 of these issues may be informative.^{8,10,15,22,23}

6.4. Cardiac Computed Tomography

Recommendation for Cardiac Computed Tomography (CT)		
COR	LOE	Recommendation
2b	C-LD	1. In adult patients with suspected HCM, cardiac CT may be considered for diagnosis if the echocardiogram is not diagnostic and CMR imaging is unavailable. ¹⁻³

Synopsis

Cardiac CT provides excellent spatial resolution allowing for clear definition of LV structure (including hypertrophy pattern, wall thickness measurement, detection of subaortic membrane and intracardiac thrombus) and function. Small studies have demonstrated ability of CT to assess myocardial fibrosis, although this adds further radiation exposure and needs further validation. In addition to myocardial structure, CT can provide an assessment of coronary anatomy, including stenosis and anomalous origin of coronary arteries. Disadvantages of CT are the use of radiation and radioiodine contrast and inferior temporal resolution compared with echocardiography. CT angiography is discussed in Section 6.6.

Recommendation-Specific Supportive Text

1. Although not used commonly, CT can provide important insights when echocardiography is technically limited and CMR imaging is contraindicated or unavailable and is one of the tools that can be used to define coronary anatomy.¹⁻³

6.5. Heart Rhythm Assessment

Recommendations for Heart Rhythm Assessment		
Referenced studies that support the recommendations are summarized in Online Data Supplement 5.		
COR	LOE	Recommendations

1	B-NR	1. In patients with HCM, a 12-lead ECG is recommended in the initial evaluation and as part of periodic follow-up (every 1 to 2 years) ¹⁻³ (Figure 1, Table 6).
1	B-NR	2. In patients with HCM, 24- to 48-hour ambulatory electrocardiographic monitoring is recommended in the initial evaluation and as part of periodic follow-up (every 1 to 2 years) to identify patients who are at risk for SCD and guide management of arrhythmias ⁴⁻⁶ (Figure 1).
1	B-NR	3. In patients with HCM who develop palpitations or lightheadedness, extended (>24 hours) electrocardiographic monitoring or event recording is recommended, which should not be considered diagnostic unless patients have had symptoms while being monitored. ⁷
1	B-NR	4. In first-degree relatives of patients with HCM, a 12-lead ECG is recommended as a component of the screening algorithm ¹⁻³ (Figure 1, Table 6).
2a	B-NR	5. In patients with HCM who have additional risk factors for AF, such as left atrial dilatation, advanced age, and New York Heart Association (NYHA) class III to class IV HF, and who are eligible for anticoagulation, extended ambulatory monitoring is reasonable to screen for AF as part of initial evaluation and periodic follow-up (every 1 to 2 years) ⁸⁻¹² (Figure 1).
2b	B-NR	6. In adult patients with HCM without risk factors for AF and who are eligible for anticoagulation, extended ambulatory monitoring may be considered to assess for asymptomatic paroxysmal AF as part of initial evaluation and periodic follow-up (every 1 to 2 years). ⁸⁻¹²

Synopsis

Both 12-lead electrocardiographic and ambulatory monitoring are necessary for patients with HCM. A 12-lead ECG can convey information about LVH and repolarization abnormalities as well as arrhythmias, including bradycardia and tachycardia. It also provides information about conduction abnormalities that may be present at initial evaluation or in followup. Ambulatory monitoring is necessary in the evaluation for SCD risk. Historically this has been 24 to 48 hours. Extended monitoring is most useful for the determination of the cause of symptoms or to diagnose AF.

Recommendation-Specific Supportive Text

1. The 12-lead ECG is abnormal in 75% to 95% of patients with phenotypic HCM, including but not limited to evidence for LVH and repolarization changes. However, these abnormalities do not reliably correlate with the severity or pattern of hypertrophy. The 12-lead ECG is also useful in identifying Wolff-Parkinson-White pattern, which may suggest certain phenocopies of HCM.¹⁻³

Alternative diagnoses may also be suggested, such as amyloidosis in the presence of low-voltage and conduction delays. In addition, a pseudo-myocardial infarction pattern may be present in young individuals before there is manifest evidence of wall thickening on echocardiography. A12-lead ECG is commonly used in the screening for HCM, including family members without LVH. There is considerable debate regarding the utilization of the 12-lead ECG in screening healthy adolescents for HCM as part of preparticipation athletic screening.¹³

2. Ambulatory electrocardiographic monitoring for detection of ventricular tachyarrhythmias has historically played an important role in risk stratification of patients with HCM. Episodes of nonsustained ventricular tachycardia (NSVT) may identify patients at significantly higher risk of subsequent SCD.⁴⁻⁶ There is increasing evidence that NSVT in young patients with HCM is more prognostic for SCD than in patients >35 years of age, and also that longer and faster NSVT is associated with greater incidence of ICD-treated arrhythmias.¹⁴ There is also evidence that longer periods of monitoring will diagnose more episodes of NSVT¹⁵; however, NSVT as a risk factor for SCD has historically been based on a 24- to 48-hour monitor. The optimal time frame of monitoring is not yet established and, thus, at this time, it is reasonable to perform serial ambulatory electrocardiographic monitoring every 1 to 2 years in patients who do not have ICDs.
3. In the presence of symptoms, ambulatory electrocardiographic monitoring should be continued until a patient has symptoms while wearing the monitor. In some patients with infrequent symptoms, portable event monitors or implantable monitors may be warranted.⁷
4. ECGs are considered to be a standard part of the initial screening of relatives of patients with HCM.
5. AF is associated with adverse outcomes (including stroke) in patients with HCM. Although several studies show that asymptomatic AF is present is up to 50% of patients,⁸⁻¹² it is unclear that asymptomatic episodes, especially if short in duration, contribute to adverse outcomes. Predictors of AF include left atrial dilatation, advanced age, and NYHA class III to class IV HF. Thus, patients with these characteristics should be assessed more frequently and possibly including extended ambulatory electrocardiographic screening.
6. AF is associated with adverse outcomes (including stroke) in patients with HCM. Although several studies show that asymptomatic AF is present is up to 50% of patients,⁸⁻¹² it is unclear that

asymptomatic episodes, especially if short in duration, contribute to adverse outcomes. Predictors of AF include left atrial dilatation, advanced age, and NYHA class III to class IV HF. Thus, patients with these characteristics should be assessed more frequently and possibly including extended ambulatory electrocardiographic screening.

6.6. Angiography and Invasive Hemodynamic Assessment

Recommendations for Angiography and Invasive Hemodynamic Assessment Referenced studies that support the recommendations are summarized in Online Data Supplement 8.		
COR	LOE	Recommendations
1	B-NR	1. For patients with HCM who are candidates for SRT and for whom there is uncertainty regarding the presence or severity of LVOTO on noninvasive imaging studies, invasive hemodynamic assessment with cardiac catheterization is recommended. ¹⁻⁴
1	B-NR	2. In patients with HCM with symptoms or evidence of myocardial ischemia, coronary angiography (CT or invasive) is recommended. ⁵
1	B-NR	3. In patients with HCM who are at risk of coronary atherosclerosis, coronary angiography (CT or invasive) is recommended before surgical myectomy. ⁶

Synopsis

Over the past 60 years, the hemodynamic profile and assessment of patients with obstructive HCM has been well established. Echocardiography remains the gold standard for the reliable, noninvasive assessment of dynamic outflow tract obstruction in HCM. For this reason, there is no compelling rationale to consider invasive hemodynamic evaluation in the routine assessment of patients with obstructive HCM or routine coronary angiography in the general population who has HCM. Invasive hemodynamic assessment should be undertaken only when the diagnostic information cannot be obtained from the clinical and noninvasive imaging examinations and when such information will alter patient management. Consequently, selected patient subsets will benefit from these evaluations. It is crucial that the operator who performs the assessment be experienced in such cases and use appropriate catheters while avoiding pitfalls such as catheter entrapment.

Recommendation-Specific Supportive Text

1. In patients with a clinical history of significant limiting HF symptoms (NYHA class II to class IV) but in whom there is ambiguity regarding presence

or magnitude of an LVOT gradient on cardiac imaging, invasive hemodynamic studies can clarify the presence of resting or latent outflow tract obstruction as well as provide information on cardiac output and filling pressures. Such circumstances may arise if the reliability of echocardiographic imaging is limited by poor acoustic windows, or if the Doppler profile cannot be reliably distinguished between increased velocity from outflow tract obstruction versus contamination of the profile by MR or reflect the fact that outflow gradients can be extremely dynamic, with spontaneous variability influenced by altered myocardial contractility and loading conditions at the time of cardiac imaging testing.

A number of provocative maneuvers have been used in the catheterization laboratory to identify the presence of a latent gradient, including Valsalva maneuver, inducing a premature ventricular contraction to assess for the Brockenbrough-Braunwald-Morrow sign (post-extrasystolic augmentation in LVOT gradient and reduction in aortic pulse pressure), upper or lower extremity exercise, and inhalation of amyl nitrate. Low-dose isoproterenol infusion may be used to assess for latent obstruction as its use is generally limited to those invasive cardiologists with expertise in the hemodynamic evaluation of HCM. Dobutamine has previously been used for this purpose; however, the dosing protocols used for dobutamine stress studies can induce gradients even in patients without HCM, leading to a significant false-positive rate.⁷

Another common clinical scenario that may support invasive hemodynamic assessment in a patient with obstructive HCM is coexistent valvular aortic stenosis. In clinical situations such as those noted previously, it is crucial that the operator performing the assessment be experienced in such cases and use appropriate catheters (eg, endhole pigtail, halo) while avoiding pitfalls such as catheter entrapment. Documentation of the LVOT gradient at rest and, if not severe (≥ 50 mm Hg), after provocative maneuvers helps guide clinical care.

2. Chest discomfort is a common symptom in patients with HCM. For those patients with atherosclerotic coronary risk factors or in whom chest pain does not respond to medical therapy, the possibility of epicardial coronary artery disease (CAD) needs to be considered. Epicardial CAD may also be suspected based on noninvasive testing, although high false-positive rates are associated with nuclear stress testing. Coronary angiography is useful in patients with

HCM when findings of CAD could aid in patient management.

- Coronary angiography is usually performed in patients who are scheduled for surgical myectomy and have risk factors for coronary atherosclerosis. Findings of extensive CAD would inform decision-making regarding altering the strategy to surgical myectomy combined with coronary bypass surgery. Coronary angiography is a requisite component of alcohol septal ablation, to assess septal anatomy and for the presence of CAD that can be addressed at the time of septal ablation.

6.7. Exercise Stress Testing

Recommendations for Exercise Stress Testing Referenced studies that support the recommendations are summarized in Online Data Supplement 7.		
COR	LOE	Recommendations
1	B-NR	1. For symptomatic patients with HCM who do not have resting or provokable outflow tract gradient ≥ 50 mm Hg on TTE, exercise TTE is recommended for the detection and quantification of dynamic LVOTO. ^{1,2}
1	B-NR	2. In patients with nonobstructive HCM and advanced HF (NYHA functional class III to class IV despite GDMT), cardiopulmonary exercise stress testing should be performed to quantify the degree of functional limitation and aid in selection of patients for heart transplantation or mechanical circulatory support. ^{3,4}
2a	B-NR	3. In patients with HCM, exercise stress testing is reasonable to determine functional capacity and to provide prognostic information as part of initial evaluation. ^{3,4}
2a	C-LD	4. For asymptomatic patients with HCM who do not have a resting or provokable outflow tract gradient ≥ 50 mm Hg on standard TTE, exercise TTE is reasonable for the detection and quantification of dynamic LVOTO. ⁵⁻¹⁰
2b	C-EO	5. In patients with obstructive HCM who are being considered for SRT and in whom functional capacity or symptom status is uncertain, exercise stress testing may be reasonable (Figure 1).
2b	C-EO	6. In patients with HCM in whom functional capacity or symptom status is uncertain, exercise stress testing may be considered every 2 to 3 years (Figure 1).

Synopsis

There is evidence to show that exercise stress testing, particularly when combined with simultaneous analysis of respiratory gases (ie, cardiopulmonary exercise test [CPET]), is safe in patients with HCM and provides information on the severity and mechanism of functional limitation. The value of exercise testing in assessing myocardial ischemia is limited because of resting ECG and wall motion abnormalities. Myocardial perfusion imaging using single-photon or positron emission

tomography shows perfusion abnormalities in $>50\%$ of patients, most of whom have no significant epicardial CAD.

Recommendation-Specific Supportive Text

- LVOT gradients can be dynamic, and maneuvers performed during a resting TTE to provoke an LVOT gradient (such as Valsalva) can be variable because of inconsistencies in instruction and patient effort. Stress echocardiography, representing the most physiologic form of provocation, can be most helpful for those patients where the presence or severity of LVOTO is uncertain after the baseline echocardiogram.⁵⁻⁹ LV outflow gradients in the postprandial state are higher than when fasting,¹¹ and treatment with beta-blockers often reduces the severity of exercise-induced LVOTO. Although there are few data comparing treadmill and bicycle ergometry, both are acceptable when performed in experienced laboratories. Exercise testing is only useful in older children, typically >7 to 8 years of age, because young children are often unable to cooperate with exercise testing.
- CPET is a standard part of the evaluation for patients with severe symptoms, including those being considered for cardiac transplantation.^{3,4} CPET can be helpful in differentiating HCM from other causes of ventricular hypertrophy, for example, athletic adaptation.
- CPET, with simultaneous measurement of respiratory gases, provides objective data on the severity and mechanism of functional limitation.^{3,4} Data from >3000 patients show that reduced peak oxygen consumption and submaximal exercise parameters, such as ventilatory efficiency and anaerobic threshold, are associated with progression to advanced HF and all-cause mortality.
- In patients who are asymptomatic, understanding whether they have LVOTO at rest or provocation provides a comprehensive understanding their individual pathophysiology. Even in asymptomatic patients, knowing that they have provokable obstruction can influence health advice (eg, regarding hydration), or choices of therapies for concomitant conditions (eg, diuretics or vasodilators for patients with hypertension).⁵⁻¹⁰ Latent LVOTO, as an explanation for exertional or postural syncope, can be revealed by exercise stress echocardiography. Up to one-third of adults with HCM have hypotension or a failure to augment the systolic blood pressure during exercise caused by an inappropriate fall in systemic vascular resistance or low cardiac output reserve.

Recommendations for Genetics and Family Screening (Continued)

- | COR | LOE | Recommendations |
|-----|-----|---|
| | | An abnormal exercise blood pressure response (failure to increase systolic blood pressure by at least 20 mm Hg, or a drop in systolic blood pressure during exercise of >20 mm Hg from the peak value obtained) may be associated with a higher risk of SCD in patients ≤40 years of age. Its value as an independent marker of sudden death risk is confounded by the emergence of newer risk markers. |
| 5. | | CPET, with simultaneous measurement of respiratory gases, provides objective data on the severity and mechanism of functional limitation. ^{3,4} Data from >3000 patients show that reduced peak oxygen consumption and submaximal exercise parameters, such as ventilatory efficiency and anaerobic threshold, are associated with progression to advanced HF and all-cause mortality. |
| 6. | | Exercise testing can provide objective evidence regarding an individual patient's functional capacity. This information can impact decisions on whether to escalate therapies, particularly if the symptom status of the patient is unclear on the basis of clinical history. |

6.8. Genetics and Family Screening**Recommendations for Genetics and Family Screening**
Referenced studies that support the recommendations are summarized in Online Data Supplements 8 and 9.

COR	LOE	Recommendations
1	B-NR	1. In patients with HCM, evaluation of familial inheritance, including a 3-generation family history, is recommended as part of the initial assessment. ¹⁻⁷
1	B-NR	2. In patients with HCM, genetic testing is beneficial to elucidate the genetic basis to facilitate the identification of family members at risk for developing HCM (cascade testing). ⁸⁻¹¹
1	B-NR	3. In patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause, a work-up including genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy ("HCM phenocopies") is recommended. ¹²⁻¹⁴
1	B-NR	4. In patients with HCM who choose to undergo genetic testing, pre- and posttest genetic counseling by an expert in the genetics of cardiovascular disease is recommended so that risks, benefits, results, and their clinical significance can be reviewed and discussed with the patient in a shared decision-making process. ^{1-3,16}
1	B-NR	5. When performing genetic testing in an HCM proband, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM. ^{*8,11,17,18}

1	B-NR	6. In first-degree relatives of patients with HCM, both clinical screening (ECG and 2D echocardiogram) and cascade genetic testing (when a pathogenic/likely pathogenic variant has been identified in the proband) should be offered. ^{3,7,12,19,20,22}
1	B-NR	7. In families where a sudden unexplained death has occurred with a postmortem diagnosis of HCM, postmortem genetic testing is beneficial to facilitate cascade genetic testing and clinical screening in first-degree relatives. ^{23,24}
1	B-NR	8. In patients with HCM who have undergone genetic testing, serial reevaluation of the clinical significance of the variant(s) identified is recommended to assess for variant reclassification, which may impact diagnosis and cascade genetic testing in family members ²⁵⁻²⁷ (Figure 1 and Figure 2).
1	B-NR	9. In affected families with HCM, preconception and prenatal reproductive and genetic counseling should be offered. ^{1-3,16}
2b	B-NR	10. In patients with HCM, the usefulness of genetic testing in the assessment of risk of SCD is uncertain. ^{10,27-29}
2b	B-NR	11. In patients with HCM who harbor a variant of uncertain significance, the usefulness of clinical genetic testing of phenotype-negative relatives for the purpose of variant reclassification is uncertain. ^{4,7,8,30}
3: No benefit	B-NR	12. For patients with HCM who have undergone genetic testing and were found to have no pathogenic variants (ie, harbor only benign/likely benign variants), cascade genetic testing of the family is not useful. ^{4,8-10}
3: No benefit	B-NR	13. Ongoing clinical screening is not indicated in genotype-negative relatives in families with genotype-positive HCM, unless the disease-causing variant is downgraded to variant of uncertain significance, likely benign, or benign variant during follow-up. ^{25,31,32,34,35}

*Strong evidence HCM genes include, at the time of this publication: MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1.

Synopsis

Genetic testing plays an important role in the diagnosis and management of HCM in patients and their families. HCM is inherited as an autosomal dominant trait in most cases, with offspring having a 50% chance of inheriting the same disease-causing genetic variant.³ A discussion about the role of genetic testing is considered a standard part of the clinical engagement of patients with HCM, including appropriate pre- and posttest genetic counseling performed either by a trained cardiac genetic counselor or by someone knowledgeable in the genetics of cardiovascular disease. It is essential to take a multigenerational (preferably at least 3 generations) family history of HCM and suspected SCD events. The importance of potential psychological, social, legal, ethical, and professional implications of having a genetic disease³⁶ should be conveyed. Genetic assessment should ideally be performed in a specialized

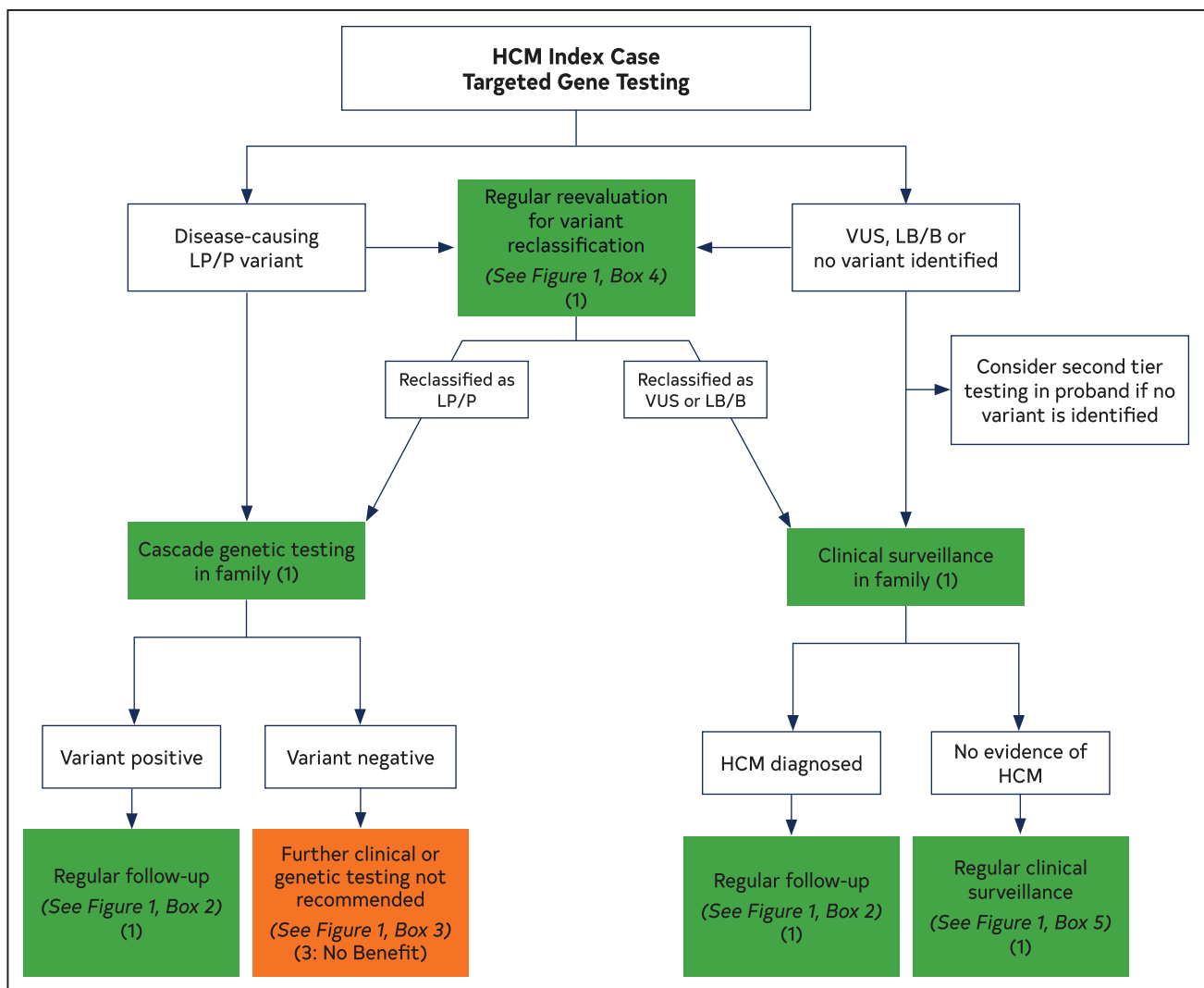


Figure 2. Genetic testing process in HCM.

Colors correspond to the Class of Recommendation in Table 2. HCM indicates hypertrophic cardiomyopathy; LB/B, likely benign/benign; LP/P, likely pathogenic or pathogenic; and VUS, variant of unknown significance.

multidisciplinary HCM center with experience in all aspects of the genetic counseling and testing process.¹

Recommendation-Specific Supportive Text

1. Taking a family history facilitates the identification of other clinically affected and at-risk family members, patterns of disease transmission, consanguinity within the family, and a history of SCD in a relative. These findings may be relevant to both the diagnosis and management of individuals with HCM in the family and subsequent clinical and genetic screening of at-risk family members.^{25–27}
2. Genetic testing in HCM has several clinical benefits, including confirmation of the diagnosis, preclinical diagnosis, cascade genetic testing in the

family, and in guiding reproductive decisions.^{8–11} Cascade genetic testing in the family identifies those who carry the disease-causing variant and require ongoing surveillance, while those who do not carry the variant can be released from lifelong clinical surveillance.

3. Genes associated with HCM phenocopies may be included in first-tier genetic testing if there is clinical suspicion based on phenotype evaluation of a systemic disorder, including *PRKAG2* (glycogen storage disease), *LAMP2* (Danon disease),¹³ *GLA* (Fabry disease),³⁹ transthyretin amyloid cardiomyopathy, and disease genes related to RASopathies. In some circumstances, the genetic test result may alter the management of the index case, such as enzyme replacement therapy in patients with Fabry disease or more aggressive clinical management of patients with Danon disease.

4. Pretest genetic counseling is important to ensure the patient undergoing genetic testing fully understands and is informed of the benefits and potential harms (including psychosocial, ethical, and insurability) of finding a genetic cause of disease. Posttest genetic counseling allows a clear explanation to be provided for the genetic testing findings, regardless of whether a pathogenic or likely pathogenic variant is identified and the implications of both a positive and a negative result for the individual and for the family.^{1–3,16}
5. HCM is predominantly a disease of the sarcomere and, therefore, first-line genetic testing primarily includes panel testing for genes with strong evidence for being disease-causing in HCM.¹¹ Genetic testing can be performed using various technological platforms, including gene panels, exome sequencing, or whole genome sequencing.⁹ Gene panels generally include 8 sarcomere genes, including *MYH7*, *MYBPC3*, *TNNI3*, *TNNT2*, *TPM1*, *MYL2*, *MYL3*, and *ACTC1*, and typically identify a disease-causing variant in approximately 30% of sporadic and 60% of familial cases.^{4,8–10} At this time, expanding to larger panels usually does not add diagnostic value.^{8,18} Initial genetic testing is usually performed in the index case (proband).⁸ If targeted gene panel testing does not reveal a causal variant, exome sequencing may provide a second-tier test on a clinical or research basis with genetic counseling that explains the often low diagnostic yield on exome sequencing at this time and the chance of incidental finding of susceptibility variants for diseases other than the disorder under study. In up to 40% of patients with HCM, no sarcomere variant is identified, and there is no family history of disease.²⁸ Identification of a variant of uncertain significance (VUS) is not a clinically actionable result but can be investigated further at either a clinical or research level, to further clarify variant pathogenicity (eg, through cosegregation analysis in family members, DNA testing in parents to determine whether the VUS is de novo, functional studies) (Figure 1 and Figure 2).
6. After genetic testing, a clinically actionable result (ie, likely pathogenic or pathogenic) can provide diagnostic clarification in the proband and offers the potential for cascade (predictive) testing of at-risk family members.^{3,7,12,19,20} Cascade testing involves targeted testing of first-degree relatives for the pathogenic or likely pathogenic variant found in the proband. When cascade testing is performed in an at-risk relative, those who are found not to carry the disease-causing gene variant can be released from further (lifelong) clinical surveillance. Those who are found to carry the disease-causing gene variant should undergo clinical screening at regular intervals (Table 6). Family members of a patient where genetic testing is not done or is negative (ie, no likely pathogenic or pathogenic variant is identified) also require clinical screening at regular intervals because there is considerable phenotypic heterogeneity in age of onset and disease progression within members of the same family.
7. Postmortem testing for HCM-associated variants using blood or tissue collected at autopsy has been reported, particularly in instances where the family variant is unknown and no other affected family members are still living.^{23,41,42} Access to a molecular autopsy as well as considerations related to costs and insurance coverage for this testing can vary between jurisdictions. Nevertheless, identification of a likely pathogenic or pathogenic variant not only confirms the diagnosis of HCM but allows cascade genetic testing of other at-risk relatives as outlined previously (Figure 1 and Figure 2).
8. Determining pathogenicity of variants relies on a weight of collective evidence based on American College of Medical Genetics and Genomics criteria¹⁷ and may change over time. In particular, there are fewer high-quality genetic data in a non-White HCM population. This highlights the importance of periodic reevaluation of variants every few years in case the variant has been reclassified (ie, either upgraded to likely pathogenic or pathogenic), in which case family cascade genetic testing can be initiated, or downgraded to a VUS, likely benign, or benign variant, whereby family screening would revert to regular clinical surveillance.^{25–27} In 1 report, 11% of HCM variants were either downgraded or upgraded over 6 years into a category that would necessitate a change in cascade screening of family members.³¹ This highlights the importance of having the necessary expertise within a specialized multidisciplinary clinic setting to not only perform genetic testing and interpret the genetic information but to continue to reevaluate the pathogenicity of variants during follow-up.^{25,26} The American College of Medical Genetics and Genomics published guidelines for clinical laboratories to implement policies to reevaluate variants based on new information about the variant and the patient or family phenotype.³⁵ The American College of Medical Genetics and Genomics also stressed the importance of notifying a patient undergoing genetic testing that the genetic interpretation may change over time, and that recontacting the patient with updated results is a shared responsibility of the healthcare provider, clinical geneticist, clinical laboratory, patient, and family, while acknowledging that laboratories

currently do not have a mechanism to receive reimbursement for such efforts.³⁴

9. In autosomal dominant HCM, there is a 1 in 2 (50%) chance of passing on the disease-causing gene variant to an affected individual's offspring, although variable penetrance can result in differences in onset and severity of clinical manifestations.⁴³ Prenatal genetic counseling is helpful in explaining the risk of transmission of disease, as well as discussing potential reproductive options.^{1-3,16} These options include in vitro fertilization with preimplantation genetic diagnosis, prenatal genetic screening, and postnatal genetic testing. The benefits and potential harms can be discussed for each of these options, such that the individual or couple can make a fully informed decision.
10. Although there is some evidence that individuals who carry >1 likely pathogenic or pathogenic variant may have more severe disease, including SCD, the role of the genetic test result in the determination of risk in SCD remains uncertain and is therefore not clinically used for this purpose. Similarly, a genetic result in isolation does not influence decisions related to implanting an ICD in patients with HCM. Several studies have reported that patients with HCM who carry pathogenic/likely pathogenic sarcomere variants have a worse prognosis compared to sarcomere variant-negative patients with HCM. This includes earlier onset of disease, higher incidence of SCD, higher incidence of AF and ventricular arrhythmias, HF, and overall mortality.^{10,12,27,29,44} However, there remains considerable heterogeneity within and between families with variants in the same gene that currently limits the application of genetic information for clinical decision-making, including risk stratification for SCD in the proband.
11. Genetic testing for HCM is first performed in an individual in the family with clear phenotypic evidence of HCM, usually the proband (index case). If a definitive likely pathogenic or pathogenic variant is identified, then cascade genetic testing in at-risk relatives can be offered (Figure 1 and Figure 2). Genetic testing in a phenotype-negative relative without a known genetic diagnosis in the proband has a very low yield of identifying a genetic cause of HCM, and a negative test in this situation will not change recommendations for ongoing clinical screening.^{4,7,8,30} Identification of a VUS in a proband is not a clinically actionable result. In select circumstances only, family member testing may be offered at either a clinical or research level to further clarify the pathogenicity of the variant (eg, through cosegregation analysis in family members, determine de novo status

through parental testing, functional studies). However, this is most appropriate in the setting of guidance from a cardiovascular genetics expert (Figure 1 and Figure 2).

12. If genetic testing does not identify a pathogenic variant in a patient with HCM (ie, only identifies benign/likely benign variants), there is no indication to do genetic testing in family members as the identification of such variants will not change clinical management, including the need for continued clinical screening.^{4,8-10}
13. In genotype-negative relatives of individuals with genotype-positive HCM, no further clinical follow-up is required (Figure 1 and Figure 2). Over time, as more knowledge is gained, some variants previously thought to be likely pathogenic or pathogenic may be downgraded to a VUS or benign category.^{25,31,32} In such instances, family relatives who were released from clinical surveillance on the basis of the previous gene result need to be notified and regular clinical screening recommenced.^{34,35}

6.9. Genotype-Positive, Phenotype-Negative

Recommendations for Individuals Who Are Genotype-Positive, Phenotype-Negative

Referenced studies that support the recommendations are summarized in Online Data Supplement 10.

COR	LOE	Recommendations
1	B-NR	1. In individuals who are genotype-positive, phenotype-negative for HCM, serial clinical assessment, electrocardiography, and cardiac imaging are recommended at periodic intervals depending on age (every 1 to 2 years in children and adolescents, and every 3 to 5 years in adults) and change in clinical status ¹⁻⁵ (Figure 1 and Figure 2, Table 6).
2a	C-LD	2. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive athletics of any intensity is reasonable. ⁶
3: No benefit	B-NR	3. In individuals who are genotype-positive, phenotype-negative for HCM, ICD is not recommended for primary prevention. ³⁻⁸

Synopsis

Genotype-positive, phenotype-negative individuals are those who carry a pathogenic or likely pathogenic HCM-causing variant but are asymptomatic without evidence of LVH on cardiac imaging. These individuals are also described as having preclinical HCM. They need ongoing cardiac surveillance for development of clinical HCM, although the time from genetic diagnosis to clinical HCM varies considerably within and between families.^{1,5,7} Studies have reported alterations in myocardial strain, LV

relaxation abnormalities, myocardial crypts, mitral valve leaflet abnormalities, abnormal trabeculae, myocardial scarring, electrocardiographic abnormalities, and abnormal serum NT-proBNP concentrations even in the absence of LVH.^{9–12} However, the clinical significance of these subclinical structural and functional abnormalities is unclear and, therefore, treatment decisions are usually not made based on these findings alone.

Recommendation Specific Supportive Text

1. The ongoing screening of genotype-positive, phenotype-negative family members of all ages is important. Previous small studies reported onset of clinical HCM in adolescence or young adulthood for most genotype-positive cases.^{1,5} However, recent large studies suggest that clinical HCM can develop in younger family members, with 5% to 10% being phenotype-positive at first screening and another 3% to 5% before 18 years of age.^{2,4,7} A third of patients who developed clinical HCM required medical, surgical, or device therapy before 18 years of age.⁴ Phenotype conversion can occur in young adults and, therefore, continued screening into adulthood is warranted,¹ although frequency of screening can be lowered because disease penetrance is lower in individuals who are >18 years of age.³ Although there is an absence of systematic evidence, most physicians continue clinical screening until mid-life (age 50s) because disease can manifest in adults, albeit at a lower frequency.
2. Sudden death in genotype-positive, phenotype-negative individuals is rare.⁶ There are no accurate risk prediction models for SCD in genotype-positive, phenotype-negative individuals at this time. Decisions about participation in competitive sports are usually made jointly with the patient and family taking into consideration family history of SCD, type of sports activity, and patient and family risk tolerance. Because of the low risk of sudden death, phenotype-negative individuals are not restricted from competitive sports and are not routinely monitored with ambulatory electrocardiography and exercise stress testing unless the family history indicates a high risk for SCD or as part of precompetitive athletic screening (eg, athletics involving intense, burst-sprint activity). This is appropriate every 1 to 2 years to assess safety of ongoing competitive athletics participation.
3. ICDs are not offered for primary prevention in genotype-positive, phenotype-negative individuals given low risk of SCD. Similarly, preemptive medical therapy is not offered in genotype-positive, phenotype-negative individuals. In a small pilot

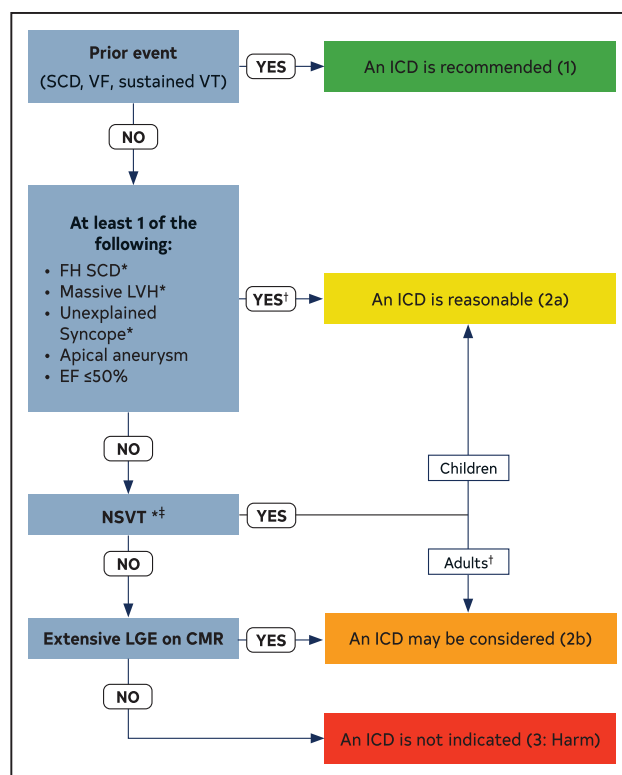


Figure 3. ICD patient selection.

Colors correspond to the Class of Recommendation in Table 2. *ICD decisions in pediatric patients with HCM are based on ≥1 of these major risk factors: family history of HCM SCD, NSVT on ambulatory monitor, massive LVH, and unexplained syncope. †In patients >16 years of age, 5-year risk estimates can be considered to fully inform patients during shared decision-making discussions. ‡It would seem most appropriate to place greater weight on frequent, longer, and faster runs of NSVT. CMR indicates cardiovascular magnetic resonance; EF, ejection fraction; FH, family history; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

randomized trial, preemptive treatment of sarcomere variant-positive, phenotype-negative individuals with diltiazem was associated with a small improvement in LV diastolic function and thickness: dimension ratio on 3-year follow-up.¹³ However, the trial was not powered to detect effects on clinical outcomes.

7. SCD RISK ASSESSMENT AND PREVENTION

7.1. SCD Risk Assessment

Recommendations for SCD Risk Assessment

Referenced studies that support the recommendations are summarized in Online Data Supplement 11.

COR	LOE	Recommendations
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1	B-NR	- In patients with HCM, a comprehensive, systematic noninvasive SCD risk assessment at initial evaluation and every 1 to 2 years thereafter is recommended and should include evaluation of these risk factors¹⁻²⁵ (Figure 1 and Figure 3, Table 7): - Personal history of cardiac arrest or sustained ventricular arrhythmias - Personal history of syncope suspected by clinical history to be arrhythmic - Family history in close relative of premature HCM-related sudden death, cardiac arrest, or sustained ventricular arrhythmias - Maximal LV wall thickness, EF, LV apical aneurysm - NSVT episodes on continuous ambulatory electrocardiographic monitoring
1	B-NR	For patients with HCM who are not otherwise identified as high risk for SCD, or in whom a decision to proceed with ICD placement remains uncertain after clinical assessment that includes personal/family history, echocardiography, and ambulatory electrocardiographic monitoring, CMR imaging is beneficial to assess for maximum LV wall thickness, EF, LV apical aneurysm, and extent of myocardial fibrosis with LGE^{1,11,12,15-20} (Table 7).
2a	B-NR	For patients who are ≥ 16 years of age with HCM, it is reasonable to obtain echocardiography-derived left atrial diameter and maximal LVOT gradient to aid in calculating an estimated 5-year sudden death risk that may be useful during shared decision-making for ICD placement^{2,22} (Table 7).

Synopsis

HCM has been regarded as the most common cause of SCD in young people in North America, a highly visible and devastating complication of this genetic heart disease.^{1,2,21,22,26-32} Among patients with HCM, younger patients are at higher risk for SCD than older patients.^{6,26-30,33,34} The 5-year cumulative proportion of SCD events in childhood HCM from diagnosis was 8% to 10% for SCD events in childhood.^{35,36} There appears to be no sex- or race-based differences in SCD risk.^{28,29}

Over several decades, a multitude of studies have focused on identification of major clinical risk markers that stratify patients according to level of risk to identify high-risk patients who may be candidates for SCD prevention with ICDs.^{1-22,26-33,37-61} This risk stratification strategy and the penetration of ICDs into clinical practice has substantially reduced disease-related mortality rates.^{31,32} A predictive risk score is also available that can derive individualized estimated 5-year SCD risk to aid in risk stratification and ICD decision-making in adult patients.^{2,22} The evolution of SCD risk assessment, including the addition of new risk markers, has resulted in the removal of abnormal blood pressure response to exercise as a routine part of the SCD risk evaluation.

The current conventional noninvasive SCD risk markers (Table 7) used to estimate increased risk level

in individual patients with HCM, and to identify those patients most likely to benefit from primary prevention ICD therapy,^{1,26,27,30-32} are based on personal and family history,^{1,3,5,6} noninvasive testing including echocardiography,^{1,7-9} ambulatory electrocardiographic monitoring,^{13,14} and CMR imaging.¹⁵⁻²⁰ Given that the risk of SCD extends over many decades of life, periodic reassessment of SCD risk is an integral component of the longitudinal evaluation of most patients with HCM.^{1,2,6,22,31,32}

Risk Stratification Considerations in Pediatric Patients

Historically, risk stratification for SCD in children has been based on risk markers derived from adult HCM studies. Several studies suggest that adult risk factors have limited ability to predict SCD in pediatric patients.^{35,44,46,59,60} More recent collaborative studies suggest some, but not all, of the adult risk factors are important in pediatric patients with HCM.^{35,54,57,59,60} Risk prediction models for children with HCM have been developed but have not yet been used widely in clinical practice.^{35,36} The risk factors proposed in these guidelines remain based on adult risk factors and current available pediatric specific information.^{33,36-64} Ultimately, decisions regarding ICD placement must be based on individual judgment for each patient, taking into account all age-appropriate risk markers, strength of the risk factor(s) identified, the overall clinical profile, the level of risk acceptable to the patient and family, and the potential complications related to device implants, including psychological impact and inappropriate ICD shock.

Recommendation-Specific Supportive Text

- Over the past several decades, numerous retrospective observational studies of patients with HCM have identified components of personal and family history as well as results from cardiovascular imaging and ambulatory monitoring to be associated with increased risk for future potentially life-threatening ventricular tachyarrhythmias.¹⁻²² For this reason, SCD risk assessment at the initial visit and repeated every 1 to 2 years^{1,2,31} is a critical part of the evaluation of patients with HCM and includes: 1) previous history of cardiac arrest or sustained (>30 seconds or associated with hemodynamic compromise) ventricular arrhythmias^{1,3}; 2) family history of sudden death, cardiac arrest, or sustained ventricular arrhythmias judged definitively or likely

- attributable to HCM in ≥ 1 first-degree or other close family members ≤ 50 years of age^{1,2,5,6}; 3) continuous (24- to 48-hour) ambulatory electrocardiographic monitoring to detect NSVT or sustained VT^{1,2,6,13,14,22}; 4) history of recent episode(s) of syncope (transient loss of consciousness) considered likely to be caused by arrhythmia (eg, episodes occurring in the previous 6 months because they carry the most prognostic importance, whereas those occurring >5 years in the past have little significance)^{1,2,4,22}; and 5) cardiac imaging that helps determine maximal LV wall thickness in all segments of the LV chamber,^{7,9} EF,^{10,21,24,25} and presence of apical aneurysm.^{11,12} In pediatric patients, LV wall thickness is commonly reported both as an absolute measurement and standardized z-score adjusted for body surface area. As data suggest a lower SCD event rate in stable, older patients with HCM (>60 years of age),³² the decision regarding ongoing risk assessment is individualized in this subset of patients.
2. Compared with CMR imaging, echocardiography can underestimate maximal LV wall thickness and may not detect LV apical aneurysm in some patients with HCM.^{11,12,15–17} In addition, extensive myocardial fibrosis, as detected by CMR-derived LGE, is associated with increased risk for potentially life-threatening ventricular arrhythmias.^{18–20} For these reasons, if a patient with HCM does not have evidence of increased SCD risk after assessment with family/personal history, echocardiography, and ambulatory monitoring, or risk stratification otherwise remains uncertain, contrast-enhanced CMR imaging can provide further characterization of maximum LV wall thickness measurement in any segment, EF, presence of LV apical aneurysm, and presence/extent of LGE.^{1,10–12,15–21,24,25,31} Although CMR imaging may be helpful in pediatric patients with HCM, this may require sedation, the risk of which may outweigh the benefits in an otherwise asymptomatic child. The use of CMR imaging should be determined by the physician and family after evaluating the child's individual risk.
 3. To calculate estimated SCD 5-year risk estimates for adults with HCM, echocardiographic left atrial diameter and maximal instantaneous LVOT gradient with continuous-wave Doppler technique are needed.^{2,22} The SCD risk estimate does not take into account the impact of newer markers of SCD risk, including systolic dysfunction (EF $<50\%$), apical aneurysm, and LGE. The impact of ≥ 1 of these newer risk markers on an individual patient with HCM whose 5-year risk estimate is undetermined.

7.2. Patient Selection for ICD Placement

Recommendations for ICD Placement in High-Risk Patients With HCM

Referenced studies that support the recommendations are summarized in Online Data Supplement 12.

COR	LOE	Recommendations
1	C-EO	1. In patients with HCM, application of individual clinical judgment is recommended when assessing the prognostic strength of conventional risk marker(s) within the clinical profile of the individual patient, as well as a thorough and balanced discussion of the evidence, benefits, and estimated risks to engage the fully informed patient's active participation in ICD decision-making. ^{1–5}
1	B-NR	2. For patients with HCM, and previous documented cardiac arrest or sustained VT, ICD placement is recommended ^{2–6} (Figure 3, Table 7).
2a	B-NR	3. For adult patients with HCM with ≥ 1 major risk factors for SCD, it is reasonable to offer an ICD. These major risk factors include ^{2,3,7–21} (Figure 3, Table 7): a. Sudden death judged definitively or likely attributable to HCM in ≥ 1 first-degree or close relatives who are ≤ 50 years of age; b. Massive LVH ≥ 30 mm in any LV segment; c. ≥ 1 Recent episodes of syncope suspected by clinical history to be arrhythmic (ie, unlikely to be of neurocardiogenic [vasovagal] etiology, or related to LVOTO); d. LV apical aneurysm, independent of size; e. LV systolic dysfunction (EF $<50\%$).
2a	B-NR	4. For children with HCM who have ≥ 1 conventional risk factors, including unexplained syncope, massive LVH, NSVT, or family history of early HCM-related SCD, ICD placement is reasonable after considering the relatively high complication rates of long-term ICD placement in younger patients ^{22–29} (Figure 3, Table 7).
2a	B-NR	5. For patients ≥ 16 years of age with HCM and with ≥ 1 major SCD risk factors, discussion of the estimated 5-year sudden death risk and mortality rates can be useful during the shared decision-making process for ICD placement ^{3,19} (Figure 3, Table 7).
2b	B-NR	6. In select adult patients with HCM and without major SCD risk factors after clinical assessment, or in whom the decision to proceed with ICD placement remains otherwise uncertain, ICD may be considered in patients with extensive LGE by contrast-enhanced CMR imaging or NSVT present on ambulatory monitoring ^{2,3,16,19,28,30–32} (Figure 3, Table 7).
2b	C-LD	7. In select pediatric patients with HCM in whom risk stratification is otherwise less certain, it may be useful to consider additional factors such as extensive LGE on contrast-enhanced CMR imaging and systolic dysfunction in risk stratification ^{33,34} (Figure 3, Table 7).
3: Harm	B-NR	8. In patients with HCM without risk factors, ICD placement should not be performed. ^{2,30}
3: Harm	B-NR	9. In patients with HCM, ICD placement for the sole purpose of participation in competitive athletics should not be performed. ³⁵

Synopsis

In patients with HCM, risk stratification and selection of patients for prophylactic ICD therapy continues to evolve, including novel risk markers and predictive scoring strategies.^{1–28,30–34,36} The proven efficacy of the ICD in aborting potentially life-threatening ventricular tachyarrhythmias and saving lives in patients with HCM has placed increasing weight on the importance of accurate selection of patients for device therapy.^{4,5,28,37} Over the past several decades, retrospective observational studies have identified a number of noninvasive clinical risk markers associated with increased risk for sudden death events in HCM.^{2–28,30–32} In association with clinical judgment and shared decision-making, patients with HCM are considered potential candidates for primary prevention ICDs by virtue of ≥ 1 major risk markers which, together, have a high sensitivity in predicting those patients with HCM at greatest future risk for sudden death events.^{1,2,4,37}

More recently, other approaches to risk stratification in HCM have emerged. By incorporating a number of disease-related features into a logistic regression equation, a 5-year sudden death risk can be estimated.^{3,19,29} This risk score in HCM may help patients understand a quantified estimate of their SCD risk that can be used during shared decision-making discussions.^{3,19} Because individual patients may consider the impact of SCD risk estimates differently, it is the consensus of this committee that prespecified management recommendations should not be assigned to calculated risk estimates as the sole arbiter of the decision to insert an ICD. Contemporary SCD risk markers in HCM, including LV apical aneurysm, LGE, and systolic dysfunction (EF $< 50\%$), are not included in the risk calculator, and their impact on the calculated 5-year risk estimate is uncertain.

Recommendation-Specific Supportive Text

1. Primary prevention ICD decision-making in HCM can often be complex and challenging, because of the low SCD event rates observed in this disease. In addition, the relatively young age of patients with HCM considered for SCD prevention means risk periods can often extend over many years and decades of an individual patient's life. For these reasons, decisions regarding primary prevention ICD therapy should incorporate a discussion with patients that includes risk for SCD and the benefit that ICD therapy provides in protecting against life-threatening ventricular tachyarrhythmias balanced with the understanding that long-term device therapy can be associated with complications.^{1,4,5}
2. Patients with HCM who have experienced a previous documented cardiac arrest or hemodynamically significant VT/ventricular fibrillation (VF)

remain at significantly increased risk for future life-threatening ventricular tachyarrhythmias and should therefore be considered for secondary prevention ICD therapy.^{2–6}

3. Identification of adult patients with HCM at high risk for SCD should be guided by the presence of a number of acknowledged noninvasive SCD risk factors (Table 7). Because each of these major risk factors individually is associated with increased risk, it would be reasonable to consider primary prevention ICD for patients with ≥ 1 SCD risk factor(s) (Figure 3 and Table 7).^{2,4,5,7–18,20,21,30–32} This risk stratification strategy provides high sensitivity for identifying at-risk patients who may benefit from life-saving ICD therapy and the opportunity to fully incorporate a shared-decision making process that takes into consideration the complete clinical profile of the patient as well as physician judgment and patient preference.^{1,2,37} Given the very low SCD event rate observed in patients of advanced age (> 60 years) with HCM, the risk stratification strategy with major markers is most applicable to young adults and middle-aged patients with HCM.^{2,4,5,36,37}
4. Risk stratification in children with HCM requires evaluation of multiple age-appropriate risk factors.^{22–29,38} Although unexplained syncope, NSVT, LV wall thickness, and left atrial diameter z-scores have a similar relationship with SCD risk in children as in adults (Table 7), the relationship of age, LVOT gradient, and family history of SCD differs compared with adults.²⁹ On the basis of the totality of available data and expert opinion, we recommend a strategy of considering primary prevention ICD for children with HCM with ≥ 1 of these major SCD risk factor(s) with the understanding that the magnitude of increase in risk with a single risk factor in isolation is unclear and risk may be higher when multiple risk factors coexist in a patient (Figure 3 and Table 7).

Massive LVH: There is an association between increasing LV posterior wall thickness and septal thickness (z-scores) with risk for SCD in children.^{29,39} Although an absolute wall thickness is associated with increased SCD risk, the association is curvilinear, and risk appears to be maximized at approximately a z-score of 20.^{22–28} Studies that reported a lower z-score cut-off of > 6 as representing higher risk were based on association with a composite endpoint of cardiac death or transplant rather than SCD alone.⁴⁰ It is therefore the consensus of this writing committee that a z-score of only 6 is inappropriately low and would overclassify children as high risk for SCD.

Unexplained syncope: Judged by history as unlikely to be neurocardiogenic (vasovagal),

unexplained syncope has a strong association with SCD risk in pediatric patients with HCM.^{7,22–24,28,29}

Family history of early SCD related to HCM: In pediatric patients, data regarding family history of SCD are conflicting, with many studies not finding an association with SCD in children.^{8,22,23,27–29} However, data from these studies may be confounded by incomplete ascertainment of genetic risk profile (de novo versus familial variant), relationship to the patients, and age of SCD in family members. SCD in a family member may be more relevant if the death occurred at a very young age (ie, during childhood or teenage years), or if SCD has occurred in multiple family members.

NSVT: NSVT, identified on ambulatory monitoring performed over 24 to 48 hours, is associated with an increase in SCD risk, with stronger association as an independent risk factor in younger patients with HCM.^{2,4,5,16,17,19,22,23,25,28,29} As normal sinus rates in children can exceed adult proposed VT rate guidelines, VT is typically defined when the ventricular rate exceeds 20% of the baseline age-adjusted sinus rate.

Other considerations: Recent multicenter studies report that left atrial diameter z-score is positively associated,^{27,37} while resting LVOT gradient is not associated with SCD risk in children.^{29,39} Risk estimate scores that incorporate several of these risk factors along with left atrial diameter z-score have been developed in children with HCM but have not yet been used prospectively in clinical ICD decision-making. Although LV systolic dysfunction and apical aneurysms are uncommon in children, it would seem prudent based on adult evidence to consider these as potentially increasing SCD risk in children but should be considered in the context of the entire risk profile of the individual patient. Finally, the complexity and potential psychological impact of ICD decision-making in this age group must be underscored, given the long periods of time with exposure to ICD therapy in young patients, and the relatively higher complication rates of long-term device therapy in this subgroup of patients.^{2,4,5,13,14,17,18,22,28}

5. In patients with HCM who are ≥ 16 years of age with ≥ 1 major SCD risk factors, estimating 5-year SCD risk may aid patients in understanding the magnitude of their individual risk for SCD to further assist in ICD decision-making.^{3,19} Because individual patients may consider the impact of SCD risk estimates differently, it is the consensus of this writing committee that prespecified risk thresholds should not be the sole arbiter of the decision to insert an ICD. Contemporary SCD risk markers in HCM, including LV apical aneurysm, LGE, and systolic dysfunction (EF $< 50\%$), are not

included in the risk calculator, and their impact on 5-year risk estimates is uncertain. Children who are 16 to 18 years of age accounted for 2% of the cohort used for the adult-based risk calculator. The low representation of this age group should be considered if calculating risk estimates for patients in this age range.

6. Extensive LGE often occupying multiple LV segments is associated with increased risk for future potentially life-threatening ventricular arrhythmias in adults, independent of location or pattern within the LV wall.^{30–32} Some studies have promoted a threshold for extensive LGE of $\geq 15\%$ of the LV mass as representing a significant increase in SCD risk^{30,32}; however, there are several methods used to quantify LGE, which can yield different results, and no consensus has been achieved on which is optimal. The strong cross-sectional relationship between LGE and NSVT in patients with HCM provides further support for LGE as representing the structural nidus for ventricular tachyarrhythmias in HCM. In addition, bursts of NSVT identified on ambulatory monitoring performed over 24 to 48 hours is also associated with some increase in SCD risk,^{2,4,5,16,17,19} with greatest weight as an independent risk factor given to adult patients with HCM with particularly frequent, long, and fast runs of NSVT.¹⁷ In the absence of other major risk markers, the impact of short, isolated bursts of NSVT on SCD risk is less certain.^{14,17,37} The benefit of extended monitoring period with longer-term ambulatory monitoring devices for the purpose of risk stratification in HCM remains uncertain.
7. The association between SCD risk and LGE in children with HCM is not well defined. Although nearly half of older children and adolescents have LGE, the extent of LGE that constitutes high risk in children has not been established.^{33,34} However, given that LGE represents a structural nidus for VT that can increase risk of SCD outcomes in adult patients with HCM^{30–32} it would seem appropriate to consider extensive LGE as potentially increasing SCD risk in children. LV systolic dysfunction is uncommon in children but likely also increases risk for adverse events, including SCD. Sedation or general anesthesia may be required for CMR imaging in young patients.
8. Given the long-term complications associated with ICD placement, device therapy should not be offered to patients with HCM without evidence of increased risk based on the proposed risk factor algorithm^{4,5} (Figure 3).
9. It is inappropriate to recommend ICD therapy to patients with HCM whose clinical profile is otherwise low risk for SCD, for the sole purpose of permitting return to organized competitive sports.³⁵

7.3. Device Selection Considerations

Recommendations for Selection of ICD Device Type Referenced studies that support the recommendations are summarized in Online Data Supplement 13.		
COR	LOE	Recommendations
1	B-NR	1. In patients with HCM who are receiving an ICD, either a single chamber transvenous ICD or a subcutaneous ICD is recommended after a shared decision-making discussion that takes into consideration patient preferences, life-style, and expected potential need for pacing for bradycardia or VT termination. ^{1–16}
1	B-NR	2. In patients with HCM who are receiving an ICD, single-coil ICD leads are recommended in preference to dual-coil leads. ¹³
2a	B-NR	3. In patients with HCM who are receiving an ICD, dual-chamber ICDs are reasonable for patients with a need for atrial or atrioventricular sequential pacing for bradycardia/conduction abnormalities, or as an attempt to relieve symptoms of obstructive HCM (most commonly in patients >65 years of age). ^{17–24}
2a	C-LD	4. In selected adult patients with nonobstructive HCM receiving an ICD who have NYHA class II to ambulatory class IV HF, left bundle branch block (LBBB), and LV ejection fraction (LVEF) <50%, cardiac resynchronization therapy (CRT) for symptom reduction is reasonable. ^{25–29}
2b	C-LD	5. In patients with HCM in whom a decision has been made for ICD implantation and who have paroxysmal atrial tachycardias or AF, dual-chamber ICDs may be reasonable, but this decision must be balanced against higher complication rates of dual-chamber devices. ^{17–24}

Synopsis

The decision of which type of ICD to implant is very important and nuanced. There are risks and benefits to consider. Considerations include transvenous versus subcutaneous ICD, single-chamber versus dual-chamber versus CRT devices, and number of defibrillation coils when using a transvenous approach. Patients with HCM receiving ICDs are usually younger than those with ischemic and even nonischemic cardiomyopathies who receive a device and, thus, life-long complications are likely to be higher in those with HCM.

Pediatric Concerns

ICD implantation in children raises additional concerns and challenges.^{30–32} Although selection for who should receive ICDs is discussed in the preceding section, the approach to implantation will vary based on body size. Epicardial leads will often be necessary in smaller children, usually <30 kg, and for children requiring an LV/CRT lead. Complications of ICDs may be higher in children and adolescents because of higher baseline heart rates, which can lead to inappropriate shocks,

somatic growth that increases risk of lead fracture, and the need for multiple device replacements/extractions over a lifetime.³⁰ In younger patients, transvenous leads have shown higher rates of failure compared with older patients. Smaller individuals with subcutaneous ICDs may also be at risk for higher complication rates, including device erosion.^{31–33}

Recommendation-Specific Supportive Text

1. The decision to implant an ICD includes additional considerations, including transvenous versus subcutaneous ICD, single-chamber versus dual-chamber versus CRT devices, and number of defibrillation coils.^{1–16} Benefits of transvenous devices include the ability to pace for bradycardia, and potential RV apical pacing for reduction of symptoms, antitachycardia pacing for VT, smaller size, extended battery longevity, and longer experience with use. The disadvantage is the lead, which may fail over time, necessitating additional leads and removal of older leads, which is associated with significant risk. In addition, device and lead infections may lead to endocarditis. Advantages of the subcutaneous ICD include the lack of a transvenous lead, potentially fewer lead failures, and ease of removal. Disadvantages include the larger size of the device, the shorter battery longevity, potentially increased inappropriate shocks because of T-wave oversensing and myopotentials, and shorter history of use. Patients with HCM undergoing subcutaneous ICD implantation should be screened for potential oversensing after exercise and even potentially on a treadmill after implantation.

Shared decision-making conversations should incorporate patient preferences, lifestyle, and expected potential need for pacing for bradycardia or VT termination. Providers should consider the age of the patient, potential need for pacing, and concerns about inappropriate shock and lead longevity.

Single-chamber systems have fewer complications, both in the short-term and long-term follow-up compared with dual-chamber transvenous systems.^{15–20} Thus, single-chamber devices are generally preferred over dual-chamber systems.

2. Single-coil ICD leads are less complicated to remove but carry the risk of elevated defibrillation thresholds. However, most individuals, both with and without HCM, have an adequate safety margin with single-coil leads.^{11–14} Single-coil leads have almost exclusively been implanted with left-sided implants, and data from populations without HCM suggest that dual-coil leads are necessary for right-sided implants. Thus, the recommendation

for single-coil leads should be applied only to left-sided implants. Finally, strong consideration should be given to defibrillation threshold testing in those patients with single-coil leads, right-sided implants, and massive hypertrophy.

3. In patients with HCM with a need for atrial pacing, a dual-chamber system would be needed. There have been 4 RCTs with consistent findings on the benefit of RV pacing in patients with HCM with LVOT gradients ≥ 30 mm Hg. Acutely, RV apical pacing reduces the LVOT gradient, but the long-term clinical benefits have not been consistently beneficial.^{21–25,34} However, in subgroup analysis, there is some evidence that RV pacing may benefit some individuals who are ≥ 65 years of age. This potential advantage must be weighed against the higher complication risk with dual-chamber devices.
4. Although most of the evidence supporting the benefit of CRT is derived from studies with minimal or no patients with HCM, it would be reasonable to offer this therapy to patients with HCM who meet current recommendations for the implantation of a CRT-defibrillator in accordance with the HF guidelines,³⁵ including patients with NYHA class II to ambulatory class IV HF, LVEF $\leq 35\%$, and widened QRS. Those with an LBBB and QRS duration ≥ 150 ms receive a class 1 recommendation, while those with LBBB and QRS between 120 and 149 ms receive a 2a recommendation, and those with non-LBBB and QRS between 120 and 149 ms receive a 1b recommendation. In addition to those patients, there have been a number of small case series of CRT-defibrillator in patients with HCM and LVEF $>35\%$.^{25–29} Approximately half of patients will clinically respond to CRT with an improvement in their NYHA functional class or evidence of reverse LV remodeling. The benefit appears to be greater in those with LBBB and very prolonged QRS duration. Responders show a modest improvement in LVEF. One study found a significantly longer time to the combined endpoint of LVAD, heart transplantation, or death,²⁷ while 2 other studies did not identify a survival benefit.^{25,29} RV pacing shares a similar physiology to LBBB so that this recommendation may be extended to those with LVEFs between 35% and 50% and expected to be paced $>40\%$ of the time, similar to the recommendation in the 2018 AHA/ACC/HRS pacing guidelines.³⁶
5. An atrial lead may provide better discrimination between ventricular and supraventricular arrhythmias, although data are modest regarding reduced inappropriate therapy in those with dual-chamber devices, and there are data that the complication rate is higher with dual-chamber devices.^{15–20} However, in pediatric patients with atrial

tachyarrhythmias, the rates of which can approach typical VT rates, a dual-chamber device may aid in distinguishing supraventricular tachycardia from VT. This potential advantage must be weighed against the higher complication risk with the additional hardware.

8. MANAGEMENT OF HCM

8.1. Management of Symptomatic Patients With Obstructive HCM

8.1.1. Pharmacologic Management of Symptomatic Patients With Obstructive HCM

Recommendations for Pharmacologic Management of Patients With Obstructive HCM

Referenced studies that support the recommendations are summarized in Online Data Supplement 14.

COR	LOE	Recommendations
1	B-NR	1. In patients with obstructive HCM and symptoms* attributable to LVOTO, nonvasodilating beta-blockers, titrated to effectiveness or maximally tolerated doses, are recommended. ^{1–3}
1	Verapamil B-NR Diltiazem C-LD	2. In patients with obstructive HCM and symptoms* attributable to LVOTO, for whom beta-blockers are ineffective or not tolerated, substitution with non-dihydropyridine calcium channel blockers (eg, verapamil, diltiazem) is recommended. ^{4–6}
1	B-NR	3. For patients with obstructive HCM who have persistent severe symptoms* attributable to LVOTO despite beta-blockers or non-dihydropyridine calcium channel blockers, either adding disopyramide in combination with 1 of the other drugs, or SRT performed at experienced centers,† is recommended. ^{7–12}
1	C-LD	4. For patients with obstructive HCM and acute hypotension who do not respond to fluid administration, intravenous phenylephrine (or other vasoconstrictors without inotropic activity), alone or in combination with beta-blocking drugs, is recommended. ¹³
2b	C-EO	5. For patients with obstructive HCM and persistent dyspnea with clinical evidence of volume overload and high left-sided filling pressures despite other HCM GDMT, cautious use of low-dose oral diuretics may be considered.
2b	C-EO	6. For patients with obstructive HCM, discontinuation of vasodilators (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers) or digoxin may be reasonable because these agents can worsen symptoms caused by dynamic outflow tract obstruction.
3: Harm	C-LD	7. For patients with obstructive HCM and severe dyspnea at rest, hypotension, very high resting gradients (eg, >100 mm Hg), as well as all children <6 weeks of age, verapamil is potentially harmful. ^{4,14}

*Symptoms include effort-related dyspnea or chest pain; and occasionally other exertional symptoms (eg, syncope, near syncope) that are attributed to LVOTO and interfere with everyday activity or quality of life.

†Comprehensive or primary HCM centers with demonstrated excellence in clinical outcomes for these procedures (Table 3 and Table 4).

Synopsis

The principal role of pharmacologic therapy targeted at the dynamic left ventricular obstruction is that of symptom relief, because there are not convincing data to suggest that pharmacologic therapy alters the natural history of HCM. Because the outflow tract obstruction is remarkably variable throughout daily life, the success of a given medication is determined by the patient's symptom response and not the measured gradient. In general, nonvasodilating beta-blockers are considered first-line therapy. The calcium channel blockers, verapamil, or diltiazem are reasonable alternatives to beta-blocker therapy. For patients who do not respond to trials of ≥ 1 of these drugs, advanced therapies with disopyramide or septal reduction are often the next step. One of the other key steps in managing symptomatic, obstructive HCM is to eliminate medications that may promote outflow tract obstruction, such as pure vasodilators (eg, dihydropyridine class calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) and high-dose diuretics. Low-dose diuretics, when added to other first-line medications, are sometimes useful for patients with persistent dyspnea or congestive symptoms. The principles of pharmacologic management outlined here also apply to patients with obstruction at the midventricular level.

Recommendation-Specific Supportive Text

1. Beta-blockers were the first studied medication for treatment of dynamic outflow tract obstruction and are generally considered the first-line agent for most patients with obstructive HCM. Medications should be titrated to a dose where there is symptom benefit but not declare failure of beta-blockade until there is demonstrated physiologic evidence of beta-blockade (ie, suppression of resting heart rate).^{1–3}
2. Diltiazem and verapamil have both been demonstrated to provide relief of symptoms in patients with obstructive HCM. Both of these agents can have vasodilating properties, in addition to the negative inotropic and negative chronotropic effects, which can be limiting. The use of calcium channel blockers in combination with beta-blockers, as therapy directed at HCM, is unsupported by evidence^{4–6}; however, these may have a role in management of concomitant hypertension.

3. Patients with HCM who did not respond to beta-blockers or non-dihydropyridine calcium channel blockers are candidates for more advanced therapies, including disopyramide and SRT when performed by experienced operators in comprehensive centers (Table 3 and Table 4). The choice among these options should be approached through a comprehensive shared discussion with the patient that includes the success rates, benefits, and risks of each of the options. Disopyramide has been shown to provide symptomatic benefit in patients with obstructive HCM who have failed first-line therapy with beta-blockers, verapamil, or diltiazem.^{7–9} This agent is an important option, particularly in those patients who are not candidates for SRTs. As disopyramide can enhance conduction through the atrioventricular node, which could lead to rapid conduction with the onset of AF, this medication should be used in combination with another medication that has atrioventricular nodal blocking properties (eg, beta-blocker, verapamil, or diltiazem). The anticholinergic side effects that can be seen with disopyramide can be mitigated with pyridostigmine. In patients with obstructive HCM who remain severely symptomatic despite optimal medical therapy, SRT, when performed by experienced operators in comprehensive centers (Table 3 and Table 4), is very effective for relieving LVOTO.¹⁰ Survival of patients with LVOTO is reduced compared with those without obstruction, and relief of obstruction may mitigate this incremental risk.^{11,12}
4. Acute hypotension in patients with obstructive HCM is a medical urgency. Maximizing preload and afterload, while avoiding increases in contractility or heart rate, is the critical focus in treating acute hypotension. Intravenous vasoconstrictors, such as phenylephrine, can also reverse this dangerous situation. Beta blockade can also be useful in combination with the vasoconstrictor as it dampens contractility and improves preload by prolonging the diastolic filling period.
5. In the presence of signs or symptoms of congestion, cautious use of low-dose diuretics may provide some symptom relief. Aggressive diuresis can be problematic, as decreasing the preload can augment LVOTO.
6. Caution should be exercised when introducing therapies in patients with HCM who will be treated for coexisting conditions. Some medications can cause or worsen symptoms related to LVOTO. Examples include the use of diuretics and vasodilators to treat hypertension or protect renal function. Those medications can be used in asymptomatic patients. However, if symptoms are present, or emerge after the initiation of the medication, it may be necessary

Recommendations for Invasive Treatment of Symptomatic Patients With Obstructive HCM (Continued)

COR	LOE	Recommendations
		to up-titrate medications being used for obstructive HCM or consider alternative therapies for the comorbid condition. As a result, positive inotropic agents, pure vasodilators, and high-dose diuretics can be considered relatively contraindicated in patients with symptomatic obstructive HCM.
7.		Although verapamil and diltiazem can be very effective medications to relieve symptoms attributable to LVOTO, in some patients, they have been reported to have a more prominent vasodilatory action. This afterload-reducing effect can be particularly dangerous in patients with very high resting gradients (>80 to 100 mm Hg) and signs of congestive heart failure. There are several reports of life-threatening bradycardia and hypotension in newborns of <6 weeks of age who have received intravenous verapamil for supraventricular tachycardia. ¹⁴ However, verapamil has been found to be efficacious and well tolerated when administered to older infants and children with HCM in controlled conditions. ¹⁵

8.1.2. Invasive Treatment of Symptomatic Patients With Obstructive HCM**Recommendations for Invasive Treatment of Symptomatic Patients With Obstructive HCM**

Referenced studies that support the recommendations are summarized in Online Data Supplement 15.

COR	LOE	Recommendations
1	B-NR	1. In patients with obstructive HCM who remain severely symptomatic despite GDMT, SRT in eligible patients,* performed at experienced centers,† is recommended for relieving LVOTO ¹⁻³ (Table 3 and Table 4).
1	B-NR	2. In symptomatic patients with obstructive HCM who have associated cardiac disease requiring surgical treatment (eg, associated anomalous papillary muscle, markedly elongated anterior mitral leaflet, intrinsic mitral valve disease, multivessel CAD, valvular aortic stenosis), surgical myectomy, performed at experienced centers,† is recommended ⁴⁻⁷ (Table 3 and Table 4).
1	C-LD	3. In adult patients with obstructive HCM who remain severely symptomatic, despite GDMT and in whom surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation in eligible patients,* performed at experienced centers,† is recommended ⁸⁻¹⁰ (Table 3 and Table 4).

2b	B-NR	4. In patients with obstructive HCM, earlier (NYHA class II) surgical myectomy performed at comprehensive HCM centers (Table 3 and Table 4) may be reasonable in the presence of additional clinical factors, including ^{3,11-22} : a. Severe and progressive pulmonary hypertension thought to be attributable to LVOTO or associated MR. b. Left atrial enlargement with ≥1 episodes of symptomatic AF. c. Poor functional capacity attributable to LVOTO as documented on treadmill exercise testing. d. Children and young adults with very high resting LVOT gradients (>100 mm Hg).
2b	C-LD	5. For severely symptomatic patients with obstructive HCM, SRT in eligible patients,* performed at experienced centers† (Table 3 and Table 4), may be considered as an alternative to escalation of medical therapy after shared decision-making including risks and benefits of all treatment options. ^{1,10,23-25}
3: Harm	C-LD	6. For patients with HCM who are asymptomatic and have normal exercise capacity, SRT is not recommended. ^{13,21}
3: Harm	B-NR	7. For symptomatic patients with obstructive HCM in whom SRT is an option, mitral valve replacement should not be performed for the sole purpose of relief of LVOTO. ^{26,27}

*General eligibility criteria for septal reduction therapy: a) Clinical: Severe dyspnea or chest pain (usually NYHA functional class III or class IV), or occasionally other exertional symptoms (eg, syncope, near syncope), when attributable to LVOTO, that interferes with everyday activity or quality of life despite optimal medical therapy. b) Hemodynamic: Dynamic LVOT gradient at rest or with physiologic provocation with approximate peak gradient of ≥50 mm Hg, associated with septal hypertrophy and SAM of mitral valve. c) Anatomic: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

†Comprehensive or primary HCM centers with demonstrated excellence in clinical outcomes for these procedures (Table 3 and Table 4).

Synopsis

SRT is generally reserved for patients whose symptoms are not relieved by medical therapy and impair quality of life, usually consistent with NYHA functional class III or class IV.

Transaortic extended septal myectomy is an appropriate treatment for the broadest range of symptomatic patients with obstructive HCM. Techniques of myectomy have evolved and allow gradient relief at any level of obstruction within the ventricle,²⁸⁻³⁰ with demonstrated mortality <1% and clinical success >90% to 95%.^{1,24,31-33} Although some centers achieve these results with isolated extended septal myectomy, other centers have found value in including revision of the anterior mitral leaflet or apparatus.^{27,34-39} Successful myectomy eliminates or reduces SAM-mediated MR and leads to a reduction in left atrial size and a small degree of LV reverse remodeling.^{27,31,40,41} Long-term survival after surgical myectomy is similar to an age-matched general population, and recurrent outflow tract obstruction is rare.⁴²⁻⁴⁴ Septal myectomy is especially advantageous in patients who have associated cardiac disease requiring surgical correction

and in patients with associated papillary muscle abnormalities that contribute to outflow tract obstruction.^{4,39,45}

Similarly, techniques of alcohol septal ablation have been refined, and in centers with experienced interventional teams, procedural mortality is low (<1%). Alcohol septal ablation requires appropriate coronary anatomy, and the procedure may be less effective with high resting gradients (≥ 100 mm Hg) and extreme septal thickness (≥ 30 mm).^{9,46} Earlier concerns regarding late ventricular arrhythmias related to septal scar are not substantiated in more recent series, and intermediate-term survival is generally similar to that of patients who have undergone surgical myectomy.^{8,9,47,48} Alcohol septal ablation is associated with greater risk of conduction block requiring a permanent pacemaker compared with surgical myectomy and greater need for repeat intervention because of residual obstruction; repeat alcohol septal ablation or myectomy is reported in 7% to 20% of patients after alcohol septal ablation.^{8–10} Septal reduction by alcohol septal ablation avoids sternotomy and, generally, patients experience less pain. Septal reduction by alcohol septal ablation is advantageous in patients whose frailty or comorbid conditions increase the risk of surgical myectomy.

Recommendation-Specific Supportive Text

1. Generally, SRT performed by experienced operators in comprehensive centers (Table 3 and Table 4) is contemplated when patients continue to have severe symptoms despite optimal medical therapy.¹ SRT with either surgical myectomy or alcohol septal ablation is rarely indicated for the asymptomatic patient. Survival of patients with LVOTO is reduced compared with those without obstruction, and relief of obstruction may mitigate this incremental risk.^{2,3} Currently, however, there is insufficient evidence to recommend SRT to improve patient survival as the sole indication for the procedures. Highly symptomatic patients should be able to participate in a full discussion of all of the treatment options, including the success rates, benefits, and risks. If either of the procedures is unavailable for the patient at their primary cardiology practice, referral to more comprehensive HCM centers is encouraged. The classic approach of transaortic septal myectomy is potentially limited in infants and young children, in whom the aortic annulus is small. In such instances, the modified Konno procedure has been reported to provide equally satisfactory long-term results.⁴⁹
2. In patients with symptomatic obstructive HCM who have associated cardiac disease requiring surgical treatment (eg, associated anomalous papillary muscle, markedly elongated anterior mitral

leaflet, intrinsic mitral valve disease, CAD, valvular aortic stenosis), surgical myectomy performed by experienced operators provides the opportunity to correct all of the structural/anatomic issues with a single procedure. Similarly, for patients with paroxysmal AF, intraoperative pulmonary vein isolation or maze procedure can also be added to septal myectomy.^{50,51} Transaortic septal myectomy adds little to the risk of other cardiac procedures, and relief of LVOTO will minimize the risk of hemodynamic instability early postoperatively.^{4–7}

3. In adult patients with symptomatic obstructive HCM in whom surgery is contraindicated or the risk is considered unacceptably high because of serious comorbidities or advanced age, alcohol septal ablation when feasible and performed in experienced centers (Table 3 and Table 4) becomes the preferred invasive strategy for relief of LVOTO.
4. Although most patients who undergo invasive therapy are those with advanced symptoms (NYHA class III to class IV), select patients who report fewer symptoms but who have other evidence of significant hemodynamic impairment may be eligible for surgical myectomy at comprehensive HCM centers (Table 3 and Table 4) to relieve the LVOTO and minimize the chances for long-term sequelae. Data suggest that surgical myectomy can reverse severe progressive pulmonary hypertension,^{11,12,52} improve outcomes of those with objective evidence of marked exercise impairment,¹³ reverse left atrial enlargement,^{14,15,53} ameliorate occult gastrointestinal bleeding caused by shear stress-mediated changes in von Willebrand factor,^{41,42} and decrease rates of subsequent ventricular arrhythmias.^{3,18,19} Similar to the recommendations regarding surgery for patients with asymptomatic mitral valve disease, earlier surgery in patients with HCM should be limited to those comprehensive HCM centers with documented evidence of the highest success rates and lowest complication rates (ie, durable success is >90% with an expected mortality rate <1%) (Table 4).²⁰ Although successful ablation could be reasonably expected to offer the same benefits, the risks are higher (particularly need for permanent pacemaker or need for reintervention to achieve success).
5. Some patients with obstructive HCM and severe symptoms might choose SRT as an alternative to escalation of medical management after being fully informed through shared decision-making about risks/benefits. Previously, SRT was reserved, appropriately, for the most symptomatic patients because procedural mortality was 5% to 10%. Indeed, this high mortality has been observed in the recent era in centers with minimal experience with the operation.²³ In comprehensive HCM centers,

procedural complication rates are very low, offering septal reduction to patients with significant limiting HF symptoms without waiting for progression to marked disability (ie, traditional NYHA class III and class IV) and can be seen as similar to offering early intervention in valvular heart disease in centers with demonstrated excellent outcomes.^{1,10,24,25} However, symptoms and impaired quality of life may be perceived very differently by individual patients with HCM, underscoring the importance of shared decision-making in establishing the optimal timing for intervention.

6. There are no definitive data to suggest benefit for SRT in adult patients with HCM who are asymptomatic with normal exercise tolerance or those whose symptoms are easily minimized on optimal medical therapy.
7. Mitral valve replacement is more common in generalized centers than in specialized centers, and while valve replacement eliminates SAM and associated MR as well as the outflow tract gradient, the addition of mitral valve replacement to myectomy increases hospital mortality (>10-fold) and length of hospitalization compared with patients undergoing isolated septal myectomy.²⁶ Further, when intervention on the valve at the time of myectomy is needed because of intrinsic mitral disease, every effort should be made to repair the valve as long-term mortality is worse in patients with prosthetic replacement compared with patients who have septal myectomy and mitral valve repair.²⁷

8.2. Management of Patients With Nonobstructive HCM With Preserved EF

Recommendations for Management of Patients With Nonobstructive HCM With Preserved EF		
Referenced studies that support the recommendations are summarized in Online Data Supplement 15.		
COR	LOE	Recommendations
1	C-LD	1. In patients with nonobstructive HCM with preserved EF and symptoms of exertional angina or dyspnea, beta-blockers or non-dihydropyridine calcium channel blockers are recommended. ¹⁻¹⁰
2a	C-EO	2. In patients with nonobstructive HCM with preserved EF, it is reasonable to add oral diuretics when exertional dyspnea persists despite the use of beta-blockers or non-dihydropyridine calcium channel blockers.
2b	C-LD	3. In patients with nonobstructive HCM with preserved EF, the usefulness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the treatment of symptoms (angina and dyspnea) is not well established. ¹¹

2b	C-LD	4. In highly selected patients with apical HCM with severe dyspnea or angina (NYHA class III or class IV) despite maximal medical therapy, and with preserved EF and small LV cavity size (LV end-diastolic volume <50 mL/m ² and LV stroke volume <30 mL/m ²), apical myectomy by experienced surgeons at comprehensive centers may be considered to reduce symptoms. ¹²
2b	C-EO	5. In asymptomatic patients with nonobstructive HCM, the benefit of beta-blockers or calcium channel blockers is not well established.

Synopsis

Symptomatic, nonobstructive HCM is a diagnostic and therapeutic challenge. This is related to differences in disease onset, severity, and risk for adverse outcomes.¹³ The overall risk for HCM-related death appears similar between patients with and without obstructive physiology.¹⁴ Dyspnea and chest discomfort are common symptoms in patients with nonobstructive HCM. These can be a result of increased LV filling pressures related to diastolic dysfunction (including restrictive physiology) or decompensated HF, increased myocardial oxygen demand, impaired microvascular function, or coincidental CAD. The presence of restrictive physiology in association with HCM has been described in children and appears to confer higher risk of adverse outcomes.¹⁵ In patients with angina or CAD risk factors, obstructive CAD should be excluded.¹⁶ Comorbid conditions including hypertension, diabetes, obesity, and physical inactivity are often major contributors to reduced fitness and symptoms in patients with nonobstructive HCM. Control of these comorbid conditions in combination with pharmacologic therapies for HCM can provide optimal reduction of symptom burden. No trials have prospectively evaluated the long-term outcomes with medications in patients with nonobstructive HCM.

Recommendation-Specific Supportive Text

1. In patients with nonobstructive HCM without obstructive CAD, pharmacologic management of chest discomfort is similar to that of dyspnea. Beta-blockers and non-dihydropyridine calcium channel blockers are first-line agents. Both therapies aim to slow the heart rate, improve diastolic function, reduce LV filling pressures, and reduce myocardial oxygen demand. These agents have only been evaluated in a few small trials, with most of the trials having a mix of patients with obstructive and nonobstructive HCM. In patients without LVOTO, verapamil or diltiazem are effective at reducing chest pain and improving exercise capacity and may improve stress myocardial perfusion defects.^{1,3,4,6,7} Alternatively, beta-blockers are used in symptomatic

patients based on clinical experience and extrapolation from obstructive HCM, rather than trial data.^{8,9} Isolated refractory chest pain is uncommon but may be difficult to manage without aggressive use of high doses of non-dihydropyridine calcium blockers or beta-blockers. The medication doses should be titrated to effectiveness with monitoring for bradycardia or atrioventricular conduction block, especially if the calcium channel blockers and beta-blockers are used in combination. Beta-blockers should be the primary medical therapy in neonates and children. Limited data suggest verapamil (in patients >6 months of age) can be used safely as an alternative to beta-blockers.¹⁰

2. Loop or thiazide diuretics may be used to improve dyspnea and volume overload in nonobstructive HCM when volume overload is present. Aldosterone antagonists are also used in some patients. Cautious use of any of these diuretics is needed, usually as intermittent dosing as needed or chronic low-dose therapy, to prevent symptomatic hypotension and hypovolemia.^{17,18}
3. Although several pilot trials suggested that angiotensin receptor blockers and angiotensin-converting enzyme inhibitors may have benefits on myocardial structure and function, a larger placebo-controlled trial of 124 patients with non-obstructive and obstructive HCM (112 with LVOT gradient <30 mm Hg) did not show any benefit of losartan versus placebo on LV mass, fibrosis, or functional class.¹¹ However, treatment with losartan was without clinical adverse consequences and could be used for other indications, if needed.
4. Patients with extensive apical hypertrophy extending to the midventricle may have severely reduced LV end-diastolic volume and severe diastolic dysfunction. This often leads to refractory angina, dyspnea, and ventricular arrhythmias with very limited medical options. Transapical myectomy to augment LV cavity size with an aim to increase stroke volume and decrease LV end-diastolic pressure has been recently found to be safe and reduced symptoms.¹² Although experience of only a single center has been published, this surgical approach may be an option for this rare subgroup of severely symptomatic patients with nonobstructive HCM who have a small LV cavity size refractory to routine therapy. Practically, small cavity size has evolved to be defined as LV end-diastolic volume <50 mL/m² and LV stroke volume <30 mL/m². This surgical approach requires extensive surgical experience with HCM and should be limited to centers of excellence with the highest volumes, surgical experience, and expertise.
5. The aim of beta-blockers and non-dihydropyridine calcium channel blockers is to reduce

symptoms by lowering LV diastolic pressures and improve LV filling with a slower heart rate. In the absence of symptoms, there are no data indicating benefit, although the use of these agents may paradoxically lead to chronotropic incompetence. Iatrogenic chronotropic incompetence should be considered in patients with symptoms and no identified obstructive physiology at rest or with provocation. Assessment may include an ambulatory ECG to look for a heart rate plateau or a stress test to look for an inappropriate heart rate response. There are no prospective data demonstrating benefit of these agents on long-term outcomes in patients with nonobstructive HCM.

8.3. Management of Patients With HCM and Atrial Fibrillation

Recommendations for Management of Atrial Fibrillation Referenced studies that support the recommendations are summarized in Online Data Supplement 16.		
COR	LOE	Recommendations
1	B-NR	1. In patients with HCM and clinical AF, anticoagulation is recommended with direct-acting oral anticoagulants (DOAC) as first-line option and vitamin K antagonists as second-line option, independent of CHA ₂ DS ₂ -VASC score. ¹⁻⁵
1	C-LD	2. In patients with HCM and subclinical AF detected by internal or external cardiac device or monitor of >24 hours' duration for a given episode, anticoagulation is recommended with DOAC as first-line option and vitamin K antagonists as second-line option, independent of CHA ₂ DS ₂ -VASC score. ^{1,6-8}
1	C-LD	3. In patients with AF in whom rate control strategy is planned, either beta-blockers, verapamil, or diltiazem are recommended, with the choice of agents according to patient preferences and comorbid conditions. ^{9,10}
2a	C-LD	4. In patients with HCM and subclinical AF detected by internal or external device or monitor, of >5 minutes' but <24 hours' duration for a given episode, anticoagulation with DOAC as first-line option and vitamin K antagonists as second-line option can be beneficial, taking into consideration duration of AF episodes, total AF burden, underlying risk factors, and bleeding risk. ^{1,6-8,11}
2a	B-NR	5. In patients with HCM and poorly tolerated AF, a rhythm control strategy with cardioversion or antiarrhythmic drugs can be beneficial with the choice of an agent according to AF symptom severity, patient preferences, and comorbid conditions. ^{10,12-24}
2a	B-NR	6. In patients with HCM and symptomatic AF, as part of a AF rhythm control strategy, catheter ablation for AF can be effective when drug therapy is ineffective, contraindicated, or not the patient's preference. ^{12,25,26}

2a	B-NR	7. In patients with HCM and AF who require surgical myectomy, concomitant surgical AF ablation procedure can be beneficial for AF rhythm control. ^{10,13,27–29}
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Synopsis

AF, commonly observed in patients with HCM, is associated with significant morbidity, impaired quality of life, and substantial stroke risk. Therapy includes prevention of thromboembolic events and controlling symptoms. Traditional stroke risk scoring systems used in the general population are not predictive in patients with HCM. Vitamin K antagonists are effective for stroke prevention, and recent studies support the use of DOACs as well. In view of the substantial stroke risk, periodic AF surveillance would allow for early intervention with anticoagulants in high-risk patients. Asymptomatic AF detected by cardiac devices or monitors also increases risk of stroke, so the decision to anticoagulate should take into considerations the duration of episodes as well as underlying risk factors. When a rhythm control strategy is needed, a number of antiarrhythmic drugs have been shown to be safe and effective, allowing for individualization according to underlying substrate and patient preference. Catheter ablation is also an important option, although the procedure is less effective than in the general population, and there is a more frequent need of repeat procedures and concomitant use of antiarrhythmic drugs. Surgical AF ablation, often with atrial appendage removal, is a potential rhythm management option in patients undergoing surgical myectomy. Surgical AF ablation or maze is not frequently pursued as an isolated surgical indication. Other supraventricular arrhythmias and atrial flutter are likely not increased in incidence in patients with HCM, and treatment is usually similar to populations without HCM.

Recommendation-Specific Supportive Text

1. Clinical AF is AF that causes symptoms for which patients seek medical attention. Although there are no RCTs, the risk of systemic embolization is high in patients with HCM with AF. A meta-analysis that included 33 studies and 7381 patients revealed an overall prevalence of thromboembolism in patients with HCM with AF of 27.09% and incidence of 3.75 per 100 patients.¹ The stroke risk is independent of CHA₂DS₂-VASc score,³⁰ with a significant number of strokes observed in patients with a score of 0. A number of studies have shown that anticoagulation, particularly warfarin with target international normalized ratio 2 to 3, reduces the stroke risk in this population,^{2,30} whereas more recent publications have shown DOACs to be at least as effective as warfarin, with additional advantages reported, such as improved patient satisfaction and long-term outcomes.^{3–5}

Although left atrial appendage occlusion devices have been evaluated in populations, the number of patients with HCM in these trials was limited. Thus, the role of left atrial appendage occlusion devices in HCM remains untested. The recommendations for anticoagulation of patients with atrial flutter are the same as those for patients with AF.¹⁴

2. Similar to patients without HCM, subclinical or asymptomatic AF (SCAF) is detected by cardiac devices in patients with HCM as well. SCAF was reported in 16 of 30 patients with HCM (53%) after a median follow-up of 595 days.⁷ Device-detected AF was identified in 29 out of 114 patients with HCM (25%), resulting in an annualized incidence of 4%/year.⁶ In patients without HCM, SCAF has been associated with an increased risk of thromboembolism, albeit lower than risk described for clinical AF.⁸ Considerable debate exists regarding the AF duration threshold for initiating anticoagulation in SCAF because the duration used to define and quantify AF varied significantly between different studies. Nevertheless, the data increasingly show that longer duration episodes are associated with greatest risk. An ASSERT (Atrial Fibrillation Reduction Atrial Pacing Trial) substudy suggested only episodes >24 hours were associated with increased risk.¹⁵ Also influencing risk are the total AF burden¹¹ and the presence of traditional risk factors, whereas very short episodes lasting a few seconds do not appear to increase risk.^{16,17} When making the diagnosis of device-detected AF, review of stored intracardiac electrograms is essential to exclude artifact or false-positives.
3. Given the poor tolerance of AF in patients with HCM, a rhythm-control strategy is often preferred, because more recent data support improved outcomes with a rhythm-control strategy compared with historical controls.^{9,10} For those patients for whom a rate-control strategy is chosen (eg, because of patient choice, antiarrhythmic drug failure, or intolerance), a non-dihydropyridine calcium channel blocker, a beta-blocker, or a combination of the two is preferable. There is a theoretical concern that digoxin could exacerbate LVOTO attributable to a positive inotropic effect. However, in the absence of a gradient, digoxin is a potential option although data on efficacy in this population are lacking. The choice of medication should be individually determined according to age, underlying substrate, and comorbidities, as well as severity of symptoms. Dose adjustments are based on the balance between adequate rate control versus side effects, including excessive bradycardia. In patients with hypotension, dyspnea at rest and very high resting gradients (eg, >100 mm Hg), verapamil should be avoided. Atrioventricular node ablation with pacemaker implantation can be a last option in refractory cases.

Table 8. Antiarrhythmic Drug Therapy Options for Patients With HCM and AF

Antiarrhythmic Drug	Efficacy for AF	Side Effects	Toxicities	Use in HCM
Disopyramide	Modest	Anticholinergic HF	Prolonged QTc	Particularly with early onset AF
Flecainide and propafenone	?		Proarrhythmia	Not generally recommended in the absence of an ICD
Sotalol	Modest	Fatigue Bradycardia	Prolonged QTc Prolonged QTc Proarrhythmia	Reasonable
Dofetilide	Modest	Headache	Proarrhythmia	Reasonable
Dronedarone	Low	HF	Prolonged QTc	?
Amiodarone	Modest-high	Bradycardia	Liver, lung, thyroid, skin, neurologic	Reasonable

AF indicates atrial fibrillation; HCM, hypertrophic cardiomyopathy; HF, heart failure; and ICD, implantable cardioverter-defibrillator.

4. SCAF is often observed in patients with HCM and implanted cardiac devices^{6,7} and has been associated with an increased risk of thromboembolism.⁸ Yet, the minimum duration of SCAF that confers increased risk has not been precisely defined, because there appears to be a gradient of risk depending on underlying substrate. Although ASSERT data suggested only episodes >24 hours increased stroke risk,¹⁵ other evidence suggests that shorter duration episodes may pose risk in patients with traditional risks factors.¹⁶ In ASSERT, the absolute stroke risk increased with increasing CHADS₂ score, reaching a rate of 3.78 per year in those with score >2.¹⁸ Botto stratified risk according to AF duration and CHADS₂ score, with a CHADS₂ score of 1 increasing the risk only if AF duration was >24 hours, whereas for CHADS₂ scores ≥2, episodes >5 minutes increased risk.¹⁹ Similar risk stratification is unavailable in HCM, yet risk factors for stroke in the population with HCM have been identified and include advancing age, previous embolic events, NYHA functional class, left atrial diameter, vascular disease, and maximal LV wall thickness.³⁰ When very short AF duration is observed, continued surveillance should be maintained as the burden of AF is likely to progress.
5. Recent studies suggest that with current therapies, AF in patients with HCM can be managed effectively, leading to low morbidity and mortality compared with historical controls.^{9,10} In general, drug selection for rhythm control in patients with HCM is based on extrapolation from studies of the AF population at large. Yet, reports suggest several drugs are safe and effective in a population with HCM (Table 8). Amiodarone has been used over many years and is generally deemed a favored option.^{10,20} Disopyramide has been safely prescribed for reduction of LVOTO, but its efficacy in AF is not well established.^{21,31} Data on NYHA class IC antiarrhythmic agents are limited because of concerns regarding

Recommendations for the Management of Patients With HCM and Ventricular Arrhythmias (Continued)

COR	LOE	Recommendations
		their use in patients with structural heart disease. When used, therapy with class IC agents is safest in the presence of an ICD. ¹⁰ Class III agents have been used as well. A recent report in 25 patients with HCM showed dofetilide to be well tolerated and facilitated AF management. ¹³ Sotalol has also been shown to be safe and is commonly used in pediatric patients as well, either in oral or intravenous forms. ^{23,32–34} The US Food and Drug Administration–mandated safety precautions should be adopted when prescribing antiarrhythmic drugs.
6.		Catheter ablation plays an important role in the management of AF and typical atrial flutter. Although no RCTs exist in this area, a number of meta-analyses have been published in patients with HCM undergoing catheter ablation for drug refractory AF, including one that compared catheter ablation between patients with HCM versus a cohort without HCM. ^{12,25} In general, the procedure is safe and remains an important tool. However, the results seem less favorable compared with patients without HCM, with a 2-fold higher risk of relapse, more frequent need of repeat procedures, and higher use of concomitant antiarrhythmic drugs. This is attributed to the fact that patients with HCM have a greater degree of electrophysiologic and structural remodeling than the population without HCM. ²⁵ Contributing factors for atrial remodeling include LVOTO, diastolic impairment, MR, and other factors. It can be postulated that aggressive intervention in the earlier stages of disease would be more effective, but this is unproven, and ongoing remodeling is expected. With that in mind, some authors have suggested the need for a more extensive ablation approach, with linear lesions and ablation of triggers

not associated with the pulmonary veins often required to improve the long-term durability of the procedure.²⁶

7. AF in patients with HCM is often poorly tolerated; therefore, aggressive rhythm control strategies are at times required. In view of the lower success rate of catheter ablation in HCM compared with the general AF population, surgical AF ablation is a potential rhythm management option, especially in patients already undergoing open heart surgery for a surgical myectomy. In combination with surgical relief of the LVOT gradient and MR, which can limit or even reverse negative atrial remodeling, concomitant surgical AF ablation may be successful in decreasing AF burden. Several studies have reported satisfactory midterm efficacy, yet these reports universally include a small number of patients, and the durability of the procedure appears to decrease with time.^{27,29} In a recent study that represents the largest series of patients with AF treated surgically, freedom from AF recurrence at 1 year was 44% for ablation patients (n=49) and 75% with the maze procedure (n=72) ($P<0.001$).¹⁰ In this study, with concomitant surgical ablation, freedom from AF at 3 years was 70%, left atrial size being a predictor of recurrence.¹⁰ Data on the stand-alone surgical AF ablation are scant but have been reported in a limited number of patients.

8.4. Management of Patients With HCM and Ventricular Arrhythmias

Recommendations for the Management of Patients With HCM and Ventricular Arrhythmias Referenced studies that support the recommendations are summarized in Online Data Supplement 17.		
COR	LOE	Recommendations
1	B-NR	1. In patients with HCM and recurrent poorly tolerated life-threatening ventricular tachyarrhythmias refractory to maximal antiarrhythmic drug therapy and ablation, heart transplantation assessment is indicated in accordance with current listing criteria. ^{1,2}
1	Amiodarone, B-NR Dofetilide, C-LD1 Mexiletine, C-LD2 Sotalol, C-LD3	2. In adults with HCM and symptomatic ventricular arrhythmias or recurrent ICD shocks despite beta-blocker use, antiarrhythmic drug therapy listed is recommended, with the choice of agent guided by age, underlying comorbidities, severity of disease, patient preferences, and balance between efficacy and safety. ³⁻⁶

1	C-LD	3. In children with HCM and recurrent ventricular arrhythmias despite beta-blocker use, antiarrhythmic drug therapy (amiodarone, ^{3,4} mexiletine, ⁶ sotalol ^{3,4}) is recommended, with the choice of agent guided by age, underlying comorbidities, severity of disease, patient preferences, and balance of efficacy and safety.
1	C-LD	4. In patients with HCM and pacing-capable ICDs, programming antitachycardia pacing is recommended to minimize risk of shocks. ^{7,8}
2a	C-LD	5. In patients with HCM and recurrent symptomatic sustained monomorphic VT, or recurrent ICD shocks despite optimal device programming, and in whom antiarrhythmic drug therapy is either ineffective, not tolerated, or not preferred, catheter ablation can be useful for reducing arrhythmia burden. ⁹⁻¹¹

Synopsis

In patients with HCM and ICDs, preventing recurrent VT is an important goal of therapy, because ICD shocks have been associated with impaired quality of life and worse outcomes.¹² Most studies on secondary prevention of VT are extrapolated from studies in patients without HCM because data on VT management in patients with HCM are scant. The choice of pharmacologic therapy should be individualized according to individual substrate, but amiodarone is generally considered superior, albeit at the expense of increased side effects and with no effect on overall survival. Programming ICDs with antitachycardia pacing may minimize risk of shocks because monomorphic VT and ventricular flutter are common. In cases refractory to antiarrhythmic drugs and to optimal ICD programming, catheter ablation is an option.

Recommendation-Specific Supportive Text

1. Referral for transplantation should be in accordance with current guidelines.¹³ Transplant referral does not absolutely require reduced EF, because patients with preserved EF may also develop advanced HF with restrictive physiology or intractable ventricular arrhythmias.^{1,2}
2. Most patients with HCM and VT are likely already receiving beta-blockers, generally the first treatment option. Because no study has looked into pharmacologic therapies for preventing ICD shocks specifically in the population with HCM, recommendations are extrapolated from studies that enrolled different disease substrates. In the OPTIC (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients) trial, 412 patients with documented ventricular arrhythmias were randomized to amiodarone plus beta-blocker, sotalol, or

beta-blocker alone. At 1 year, shocks occurred in 38.5% assigned to beta-blocker alone, 24.3% assigned to sotalol, and 10.3% assigned to amiodarone plus beta-blocker.³ Thus, amiodarone was most effective but at the expense of increased side effects.³ In an observational study that included 30 patients, dofetilide, a class III agent, was found to decrease the number of ICD therapies even after other agents were ineffective.⁵ Proof of efficacy for mexiletine is scant but is often adjunctive to amiodarone.⁶ A meta-analysis that involved 8 studies and 2268 patients confirmed that the benefit of antiarrhythmic drug therapy was driven mainly by amiodarone, with no effect on overall survival.⁴ The safety and efficacy of class IC drugs, propafenone and flecainide, is uncertain, in addition to safety concerns when used in patients with ischemic heart disease.¹⁴ Drugs with risk for proarrhythmia are often initiated in the hospital.

3. In pediatric patients with HCM, recurrent episodes of VT are generally treated with beta-blockers as first-line therapy. If VT is recurrent (with greater emphasis placed on episodes that are faster or longer and those that may trigger ICD shocks among patients with ICDs), additional antiarrhythmic agents may be used either to address symptoms, suppress recurrent life-threatening events, or to prevent unnecessary ICD shocks. ICD shocks, even when appropriate, have been linked to psychologic trauma in pediatric patients, and thus it is reasonable to consider management options that minimize shocks. For children with recurrent ICD shocks despite maximal antiarrhythmic therapy, data regarding alternative therapies such as catheter ablation are limited. Sympathetic denervation has been reported, although data are limited to case reports.¹⁵
4. ICD therapy has been shown to prevent SCD and improve survival in patients with HCM.¹⁶ Historically, it has been the general belief that the mechanism of SCD in this population was VF. Yet, it appears that ventricular arrhythmias amenable to termination by antitachycardia pacing, including monomorphic VT and ventricular flutter, are more common than previously thought. Among 71 patients with HCM and ICDs who received appropriate therapies, 74 were VF, 18 ventricular flutter, and 57 were for monomorphic VT. Further, when antitachycardia pacing was available, it was successful in 74% of episodes.⁷ This is especially important in those at risk for monomorphic VT, such as those with apical aneurysms, although patients with fast ventricular arrhythmias may benefit as well.
5. In patients with HCM and recurrent ventricular arrhythmias, despite pharmacologic therapy, additional therapies are required. Of 22 patients

who underwent ablation, there was a 73% success rate with no major complications; of note, epicardial ablation was required in 58%.⁹ Freedom from VT 12 months' postablation was found in 11 out of 14 patients with VT and apical aneurysms, which is a common source of sustained monomorphic VT in this population,¹⁰ and 78% VT-free survival was reported after combined epicardial and endocardial ablation in 9 patients with sustained monomorphic VT.¹¹ Therefore, it appears that in selected patients with HCM, combined epicardial and endocardial ablation is a reasonably safe and effective option for treating monomorphic VT refractory to antiarrhythmic drugs and to optimal ICD programming. In 1 case series, surgical aneurysmectomy proved effective in 3 patients with apical aneurysms and incessant ventricular arrhythmias as an alternative to ablation.¹⁷ For patients with apical aneurysm who are not having surgery, anticoagulation can also be considered because there may be increased risk of thromboembolic events.¹⁸ In pediatric patients, age and heart size must be taken into account when considering ablation. An additional option in cases of refractory VT/VF is left cardiac sympathetic denervation, which has efficacy in individual case reports.¹⁵

8.5. Management of Patients With HCM and Advanced HF

Recommendations for Patients With HCM and Advanced HF
Referenced studies that support the recommendations are summarized in Online Data Supplement 18.

COR	LOE	Recommendations
1	C-LD	1. In patients with HCM who develop systolic dysfunction with an LVEF <50%, guideline-directed therapy for HF with reduced EF is recommended. ¹⁻³
1	C-LD	2. In patients with HCM and systolic dysfunction, diagnostic testing to assess for concomitant causes of systolic dysfunction (such as CAD) is recommended. ⁴⁻⁶
1	B-NR	3. In patients with nonobstructive HCM and advanced HF (NYHA functional class III to class IV despite guideline-directed therapy), CPET should be performed to quantify the degree of functional limitation and aid in selection of patients for heart transplantation or mechanical circulatory support. ^{7,8}
1	B-NR	4. In patients with nonobstructive HCM and advanced HF (NYHA class III to class IV despite guideline-directed therapy) or with life-threatening ventricular arrhythmias refractory to maximal guideline-directed therapy, assessment for heart transplantation in accordance with current listing criteria is recommended. ⁹⁻¹²

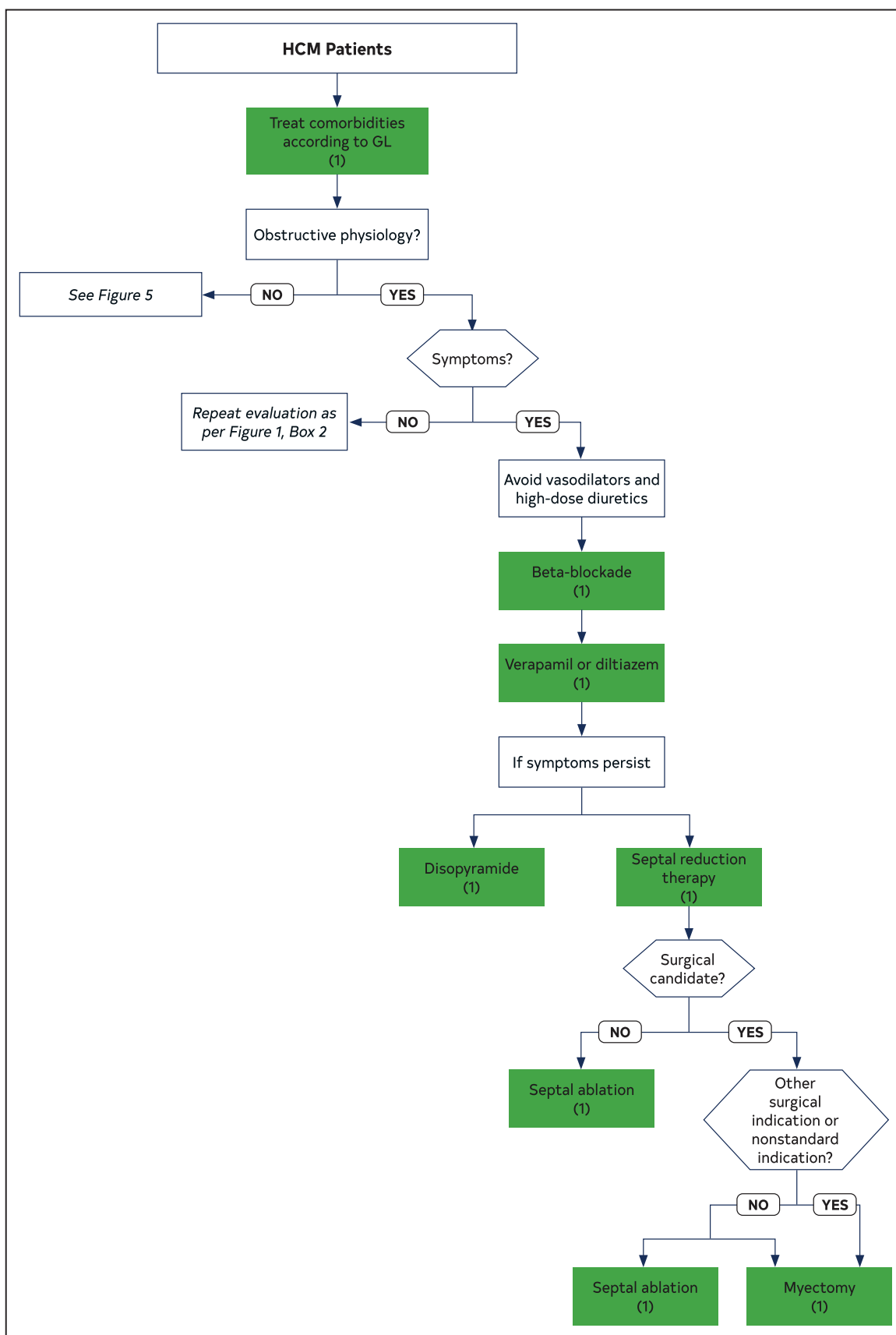


Figure 4. Management of symptoms in patients with HCM.

Colors correspond to the Class of Recommendation in Table 2. GL indicates guideline; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and SRT, septal reduction therapy.

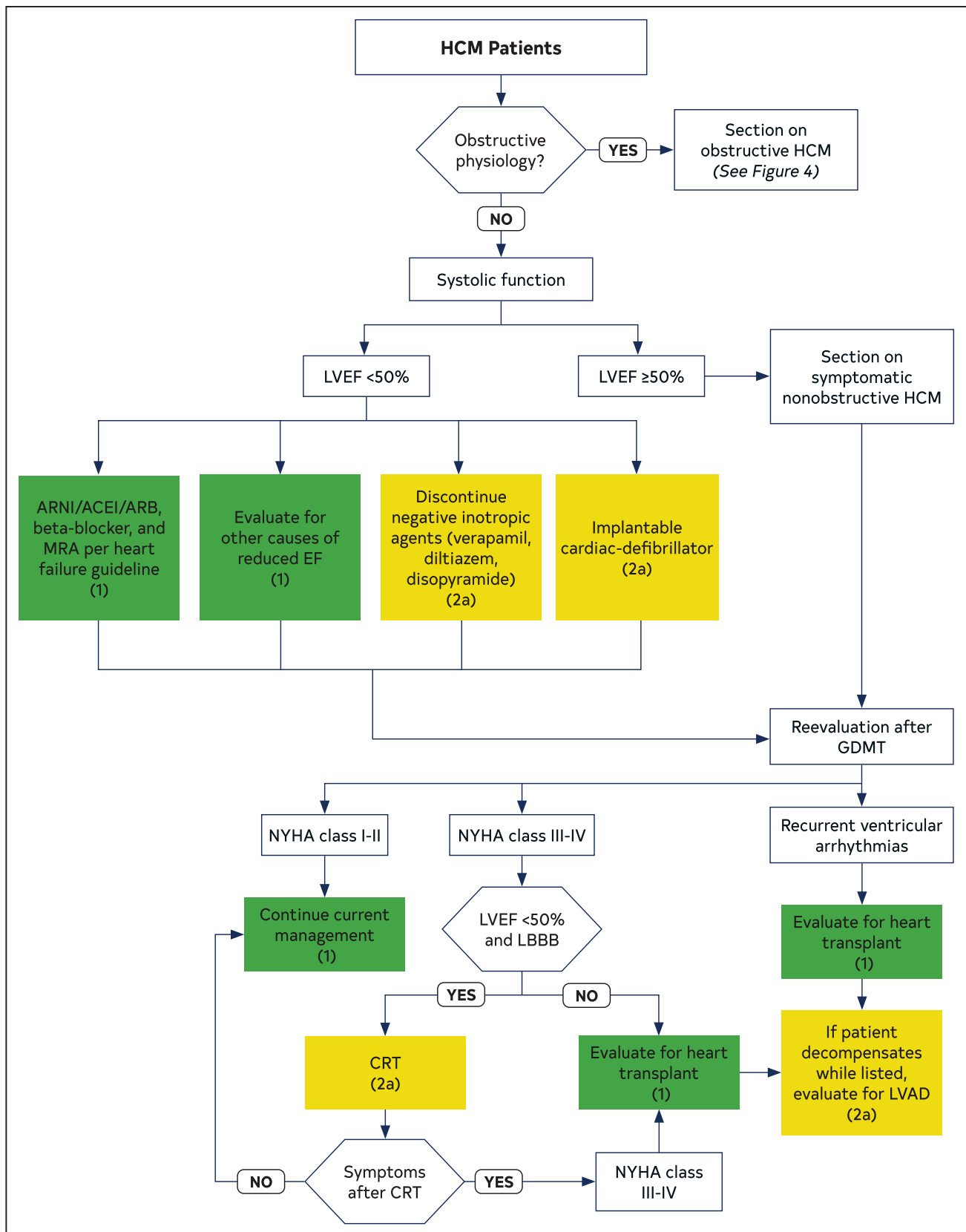


Figure 5. Heart failure algorithm.

Colors correspond to the Class of Recommendation in Table 2. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitors; CRT, cardiac resynchronization therapy; EF, ejection fraction; GDMT, guideline-directed management and therapy; HCM, hypertrophic cardiomyopathy; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and NYHA, New York Heart Association.

2a	C-EO	5. For patients with HCM who develop systolic dysfunction (LVEF <50%), it is reasonable to discontinue previously indicated negative inotropic agents (specifically, verapamil, diltiazem, or disopyramide).
2a	B-NR	6. In patients with nonobstructive HCM and advanced HF (NYHA functional class III to class IV despite GDMT) who are candidates for heart transplantation, continuous-flow LVAD therapy is reasonable as a bridge to heart transplantation. ^{13–16}
2a	C-LD	7. In patients with HCM and LVEF <50%, ICD placement can be beneficial. ³
2a	C-LD	8. In patients with HCM and LVEF <50%, NYHA functional class II to class IV symptoms despite guideline-directed therapy, and LBBB, CRT can be beneficial to improve symptoms. ^{17–21}

Synopsis

A general approach to the management of heart failure symptoms is shown in Figures 4 and 5. As EF often overestimates myocardial systolic function in patients with HCM, by convention, an EF <50% is associated with worse outcomes, and therefore is considered to represent significantly reduced systolic function. As such, in patients with HCM, guideline-directed medical therapy for heart failure with reduced ejection fraction is initiated for EF <50% (as opposed to <40% in other heart failure populations) and otherwise is generally based on the Heart Failure Guidelines.^{1,2,22–28} ICD for the primary prevention of SCD, or CRT in patients with EF <50% and NYHA class III to class IV symptoms who meet other criteria for CRT are also used.¹ Regardless of LVEF, if patients experience recurrent ventricular arrhythmias or severe (NYHA class III to class IV) symptoms despite optimization of medical therapy and SRT is not an option, heart transplant evaluation is warranted, and CPET plays a role in risk stratification. For patients with NYHA class III to class IV symptoms, an LVAD is sometimes used.

Recommendation-Specific Supportive Text

1. No RCTs have been performed in patients with HCM and HF. When tested in RCTs in patients with HCM and normal EF, neither losartan³¹ nor spironolactone³² had any effect on markers of fibrosis, LV dimensions, EF, or symptoms. Observational studies of patients with HCM and EF <50% indicate worse survival than that of patients with HCM and preserved EF,^{2,3,33} might be worse than that of patients with dilated cardiomyopathy,³⁴ and does not vary based on the presence or absence of LV dilation.³⁵ Thus, although HCM has typically been excluded from RCTs in HF, there is no compelling reason to believe that HCM with reduced EF differs sufficiently to disqualify

- many highly effective, evidence-based, guideline-directed therapies for HF with reduced EF as tolerated in the presence of restrictive physiology.^{1,22,26}
2. The discovery of reduced EF in the setting of HCM is uncommon (approximately 5%) and should prompt an appropriate search for other potential contributing causes of LV dysfunction.^{2,4–6,25,35} Those causes should include, but are not limited to, CAD, valvular heart disease, and metabolic disorders as outlined in guidelines for the management of HF with reduced EF.¹
3. CPET provides a noninvasive method for assessing the cardiovascular, pulmonary, and skeletal muscle components of exercise performance. In patients with HCM, exercise parameters such as peak oxygen consumption, minute ventilation to CO₂ production, and ventilatory anaerobic threshold predict death from HF and need for heart transplantation.^{7,8}
4. Advanced HF, commonly associated with but not

Table 9. Lifestyle Considerations for Patients With HCM

Lifestyle Considerations*	
Sports/activity	For most patients with HCM, mild- to moderate-intensity recreational exercise is beneficial to improve cardiorespiratory fitness, physical functioning, and quality of life, and for their overall health in keeping with physical activity guidelines for the general population
Pregnancy	For women with clinically stable HCM who wish to become pregnant, it is reasonable to advise that pregnancy is generally safe as part of a shared discussion regarding potential maternal and fetal risks, and initiation of guideline-directed therapy.
Comorbidities	The clinician should monitor and counsel patients on prevention and treatment of comorbid conditions that can worsen severity of HCM (atherosclerotic cardiovascular disease, obesity, hypertension, sleep-disordered breathing)

*Shared decision-making is an important component of counseling and lifestyle modifications.

HCM indicates hypertrophic cardiomyopathy.

limited to those with a reduced EF, arises in a small subset (3% to 5%) of patients with nonobstructive HCM.^{5,6,36} Referral for transplantation should be in accordance with current guidelines.³⁷ Transplant referral does not absolutely require reduced EF, because patients with preserved EF may also develop advanced HF with restrictive physiology.^{11,12} However, patients with HCM, particularly those with LVOTO whose symptoms respond to medical, interventional, surgical, or device therapy as indicated would not warrant evaluation for transplantation. Once listed for transplantation, patients with HCM can possibly have a higher wait list mortality compared with patients with dilated cardiomyopathy, related in part to lower usage of mechanical circulatory support attributable to smaller left ventricular size

Recommendations for Sports and Activity (Continued)

- | COR | LOE | Recommendations |
|-----|-----|--|
| | | and differing hemodynamic profiles. ^{11,38–40} The revised 2018 United Network for Organ Sharing Heart Transplant Allocation Policy addresses this disparity with separate listing criteria and priority specific to patients with HCM. ⁴¹ Posttransplant survival in patients with HCM is comparable, and in some studies superior, to that of patients with other forms of heart disease. ^{9–11,40,42} Children with HCM also warrant consideration for transplantation if they are not responsive to or appropriate candidates for other therapeutic interventions. ⁴³ |
| | | 5. Despite the absence of RCTs or observational data, negative inotropic agents (specifically, verapamil, diltiazem, and disopyramide) that are otherwise indicated for management of HCM may need to be discontinued in patients with worsening HF symptoms. However, these agents may be continued if needed for rate control of AF on a case-by-case basis. |
| | | 6. Patients with HCM have traditionally been ineligible for LVAD support because of small LV cavities and relatively preserved EF. However, a number of case series have demonstrated that support with continuous flow LVADs results in acceptable outcomes in patients with HCM, ^{13–16} with better increased post-LVAD survival in patients with HCM and larger LV cavities (>46 to 50 mm). ^{13,15} There are limited data on the role of biventricular assist devices in patients with HCM. Data on the role of mechanical circulatory support in children with HCM are similarly limited. One study of 20 children with advanced HF with preserved EF, including 3 with HCM, showed poor survival, with only 50% either successfully weaned or bridged to transplantation. ⁴⁴ |
| | | 7. Patients with HCM were not included in the primary prevention ICD trials for patients with HF. However, a retrospective study of 706 patients with HCM indicated a 68% reduction in mortality over 5 years in patients with nonobstructive HCM with ICDs. ³ Prophylactic ICD implantation is the generally accepted clinical practice for patients with HCM and systolic dysfunction (EF ≤50%). ¹ In the pediatric population, small body size may impact the feasibility, and risk of ICD implantation and should be taken into account when discussing ICD implantation. |
| | | 8. CRT is established to improve symptoms, reduce HF hospitalizations, and increase survival in patients with HF with EF ≤35% and LBBB with QRS duration ≥150 ms. ¹ Whether the same benefits apply to patients with HCM is unclear. Patients with HCM were specifically excluded from some RCTs of CRT in HF. ^{45–47} and, in others, |

the proportion of patients with HCM included was not clearly defined.^{48–51} Further, case series offer conflicting results on the effect of CRT on symptoms, EF, and survival.^{17–21} Future studies are needed to identify CRT responders and establish disease-specific eligibility criteria. Thus, the usefulness of CRT in patients with HCM and reduced EF is not well established, but CRT may improve symptoms and LV chamber dimensions in select patients.

9. LIFESTYLE CONSIDERATIONS FOR PATIENTS WITH HCM

Table 9 addresses lifestyle considerations for patients with HCM.

9.1. Sports and Activity

Recommendations for Sports and Activity Referenced studies that support the recommendations are summarized in Online Data Supplement 19.		
COR	LOE	Recommendations
1	B-NR	1. For most patients with HCM, mild- to moderate-intensity recreational* exercise is beneficial to improve cardiorespiratory fitness, physical functioning, and quality of life, and for their overall health in keeping with physical activity guidelines for the general population. ^{1–3}
1	C-EO	2. For athletes with HCM, a comprehensive evaluation and shared discussion of potential risks of sports participation by an expert provider is recommended. ⁴
2a	C-EO	3. For most patients with HCM, participation in low-intensity competitive sports is reasonable. ^{5,6}
2a	C-LD	4. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive athletics of any intensity is reasonable. ^{5–11}
2b	C-LD	5. For patients with HCM, participation in high-intensity recreational activities or moderate- to high-intensity competitive sports activities may be considered after a comprehensive evaluation and shared discussion, repeated annually with an expert provider who conveys that the risk of sudden death and ICD shocks may be increased, and with the understanding that eligibility decisions for competitive sports participation often involve third parties (eg, team physicians, consultants, and other institutional leadership) acting on behalf of the schools or teams. ^{4,7–11}
3: Harm	B-NR	6. In patients with HCM, ICD placement for the sole purpose of participation in competitive athletics should not be performed. ^{5,7,12}

*Recreational exercise is done for the purpose of leisure with no requirement for systematic training and without the purpose to excel or compete against others.

Synopsis

Although regular physical activity is well known to promote longevity and to reduce overall cardiovascular disease risk, recommendations for recreational exercise and competitive sports participation for patients with HCM have been challenging.^{5,6,12,13} Available data provide discordant information regarding the risk of SCD with participation in these activities and the proportion of these SCDs that are attributable to HCM.^{14–21} Although previous observational studies identify HCM as one of the most common causes of SCD among competitive athletes,^{14,15} SCD is overall a rare event in young people,^{17,22} including athletes.^{18,20,21,23} and in those with a diagnosis of HCM.^{24,25} Given these somewhat disparate findings and the enormous heterogeneity in HCM disease expression, it is not possible to reliably define for any individual patient with HCM the degree to which risk may be increased by participating in vigorous recreational or competitive sports. For these reasons, evaluation of athletes with HCM should incorporate a shared dialogue, with weight given to individual patient contribution/participation in a discussion balanced with an understanding of the potential risk of SCD associated with physical activity.^{4,26–28} Final decisions for eligibility for competitive sports participation often involve third parties acting on behalf of the schools or teams.

Recommendation-Specific Supportive Text

1. The cardiovascular and overall health benefits of regular physical activity are well-established. Yet, inactivity is prevalent among patients with HCM.^{29,30} “The Physical Activity Guidelines for Americans” recommend that adults engage in at least 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity aerobic exercise weekly, and that children engage in at least 60 minutes of moderate-to-vigorous exercise daily.³¹ In RESET-HCM (Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy), adult patients who followed prescriptions of moderate-intensity exercise, compared with those doing their usual activity, showed significant improvements in exercise capacity measured by peak oxygen consumption, as well as subjective improvements in physical functioning, after 4 months of training.¹ Although the study was underpowered for safety, there were no major adverse events and no increase in non-lethal arrhythmias in the exercise training group compared with the usual activity group. Increased physical activity has also been associated with

improved quality of life in patients with HCM.³² In devising exercise recommendations, exercise intensity can be gauged by metabolic equivalents of task with light <3 metabolic equivalents (METs), moderate 3 to 6 METs, and vigorous >6 METs as defined by the Compendium of Physical Activities,³³ by % maximum heart rate achieved (light 40% to 50%, moderate 50% to 70%, vigorous >70%), or by level of perceived exertion on the Borg scale (light 7 to 12, moderate 13 to 14, vigorous ≥15).³⁴ Some initial period of supervised exercise may be warranted in some patients, such as those excluded from RESET-HCM because of an abnormal blood pressure response to exercise, a history of ventricular arrhythmias triggered by exercise, or advanced HF. Children with HCM can typically participate in physical education at school, with an exception made that the child not be graded and not be timed or scored for performance. The presence of AEDs near playgrounds and/or facilities can provide a level of reassurance. Data are insufficient to make formal recommendations regarding isometric exercise, although it seems prudent to advise against Valsalva maneuver, which can acutely worsen LVOTO.

2. There is a level of uncertainty regarding the degree to which risk may be increased during sports participation in athletes with HCM. Expert providers will be familiar with the evidence and ongoing studies relevant to these discussions and, therefore, will be in the best position to provide guidance in the context of shared decision-making.⁴ Particularly for patients with obstructive physiology, advice to avoid dehydration or exposures to extreme environmental conditions (heat, humidity) is important.
3. Low-intensity sports are ones in which the aerobic component would not exceed 3 METs, heart rate would be <50% of maximum, or level of perceived exertion would be no higher than 12 on the Borg scale.³³
4. Available studies provide no evidence that genotype-positive individuals without LVH are at risk of SCD above that of the general population.^{5,6}
5. Previous AHA/ACC guidelines have recommended against participation in most competitive sports for patients with HCM on the basis of the complex interaction between the underlying abnormal electrophysiologic substrate in HCM, the physiologic alterations that occur during competition, and observational data that HCM is a common cause of SCD among athletes.^{5,12,13,35} More recently, data from a series of studies (total number of patients with HCM included is <500) have demonstrated a similar burden of ventricular arrhythmias in patients with HCM engaged in

competitive sports compared with those who are not.^{7–11} Although risk of SCD may be increased for patients with HCM participating in moderate- to high-intensity competitive sports, precisely defining this risk for any individual patient with HCM is not possible. Eligibility decisions for competitive athletes with HCM should not be based on the conventional risk stratification strategy (Section 7 of this document), nor should patients necessarily be reassured by certain aspects of morphologic expression, such as mild LV wall thickness or the absence of outflow tract obstruction. Although some advocate for prolonged event monitoring, there are no data to support this. Because precise risk for participation in sports for individuals with HCM is not easily quantifiable and likely differs across the enormous spectrum of physical activities demanded by different types of sports, there is the opportunity for some degree of flexibility, individual responsibility, and choice in making eligibility decisions for individual patient-athletes with HCM. Evaluations and shared discussions with athletes with HCM regarding sports participation should be undertaken by providers with expertise in HCM and be repeated on at least an annual basis or earlier if new symptoms arise.^{4,27}

6. Sudden death risk stratification and recommendations for ICD placement should be made in accordance with the algorithm put forth in this guideline document, independent of decisions regarding sports participation. Inappropriate ICD utilization would expose patients unnecessarily to device-related complications and should be avoided.^{5,7,12}

9.2. Occupation

Recommendations for Occupation in Patients With HCM		
COR	LOE	Recommendations
2a	C-EO	1. For patients with HCM, it is reasonable to follow Federal Motor Carrier Safety Administration cardiovascular disease guidelines that permit driving commercial motor vehicles, if they do not have an ICD or any major risk factors for SCD and are following a guideline-directed management plan. ¹
2a	C-EO	2. For pilot aircrew with a diagnosis of HCM, it is reasonable to follow Federal Aviation Administration guidelines that permit consideration of multicrew flying duties, provided they are asymptomatic, are deemed low risk for SCD, and can complete a maximal treadmill stress test at 85% peak heart rate. ²

2b	C-EO	3. Patients with HCM may consider occupations that require manual labor, heavy lifting, or a high level of physical performance after a comprehensive clinical evaluation, risk stratification for SCD, and implementation of guideline-directed management. Before a shared decision between a clinician and patient is reached, the clinician should convey that risks associated with the physical requirements of these occupations are uncertain.
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Synopsis

There are a number of occupational considerations for patients with HCM, particularly when there is potential for loss of consciousness that can place the patient or others in a harmful situation. For some occupations (commercial driving and piloting an aircraft), there are federal guidelines and restrictions that cannot be superseded by this guideline document.

Recommendation-Specific Supportive Text

1. The Federal Motor Carrier Safety Administration updated its guidelines in 2015.¹ A permit for driving a commercial vehicle can be obtained by patients with HCM who do not have an ICD and do not possess any of the major risk factors for SCD (Section 7 of this document).
2. The Federal Aviation Administration guidelines do not explicitly list HCM as a disqualifying diagnosis for piloting an aircraft. However, a recent report from an occupational aviation work group states that for patients with HCM who are asymptomatic, they may be considered for multicrew flying duties.² There are no restrictions for patients with HCM to be nonpilot aircrew.
3. Occupations that require considerable heavy manual labor (eg, construction work) or a high level of physical performance (eg, law enforcement, fire fighters) may impose some risk to patients with HCM but also potentially to a coworker or the public, in the event of loss of consciousness. Therefore, it is important to approach these decisions on an individual basis and in the context of shared decision-making.

9.3. Pregnancy

Recommendations for Pregnancy in Patients With HCM Referenced studies that support the recommendations are summarized in Online Data Supplement 20.		
COR	LOE	Recommendations
1	B-NR	1. For pregnant women with HCM and AF or other indications for anticoagulation, low-molecular-weight heparin or vitamin K antagonists (at maximum therapeutic dose of <5 mg daily) are recommended for stroke prevention. ^{1–3}

1	C-LD	2. In pregnant women with HCM, selected beta-blockers should be administered for symptoms related to outflow tract obstruction or arrhythmias, with monitoring of fetal growth. ^{4,5}
1	C-LD	3. In most pregnant women with HCM, vaginal delivery is recommended as the first-choice delivery option. ^{4,6}
1	B-NR	4. In affected families with HCM, preconceptual and prenatal reproductive and genetic counseling should be offered. ⁴⁻⁷
1	C-EO	5. For pregnant women with HCM, care should be coordinated between their cardiologist and an obstetrician. For patients with HCM who are deemed high risk, consultation is advised with an expert in maternal-fetal medicine.
2a	C-LD	6. For women with clinically stable HCM who wish to become pregnant, it is reasonable to advise that pregnancy is generally safe as part of a shared discussion regarding potential maternal and fetal risks, and initiation of guideline-directed therapy. ⁸⁻¹¹
2a	C-LD	7. In pregnant women with HCM, cardioversion for new or recurrent AF, particularly if symptomatic, is reasonable. ^{7,12}
2a	C-LD	8. In pregnant women with HCM, general or epidural anesthesia is reasonable, with precautions to avoid hypotension. ⁹
2a	C-EO	9. In pregnant women with HCM, it is reasonable to perform serial echocardiography, particularly during the second or third trimester when hemodynamic load is highest, or if clinical symptoms develop. ⁸
2b	C-EO	10. In pregnant women with HCM, fetal echocardiography may be considered for diagnosis of fetal HCM in the context of prenatal counseling.

Synopsis

Pregnancy in most women with HCM is well tolerated. Maternal mortality is very low, with only 3 sudden deaths reported in the literature, all in high-risk (and 1 undiagnosed) patients, over the past 17 years.⁸⁻¹¹ Symptoms (dyspnea, chest pain, palpitations) and complications (HF and arrhythmias) occur in ~25% of pregnant women with HCM, for whom most had symptoms preceding their pregnancy. There is no difference in outcomes reported for women with LVOTO compared with those without obstruction.

Recommendation-Specific Supportive Text

1. AF is associated with stroke in HCM and can be mitigated by anticoagulation.¹⁻³ Both low-molecular-weight heparin and low-dose warfarin carry acceptable risk during pregnancy and should be administered in accordance with the 2014 AHA/ACC valvular heart disease guidelines.¹³ Daily doses of warfarin >5 mg have been associated with increased teratogenicity in small

Recommendations for Patients With Comorbidities (Continued)

- | COR | LOE | Recommendations |
|-----|-----|--|
| | | observational studies. ¹⁴⁻¹⁹ There are insufficient safety data regarding DOACS in pregnancy. |
| 2. | | Most beta-blockers (ie, metoprolol, bisoprolol, labetalol, pindolol, propranolol) are generally considered safe to use during pregnancy; however, atenolol has some evidence of potential fetal risk. Closer monitoring of fetal growth and surveillance for fetal bradycardia may be considered for pregnant women on beta-blockers. ^{4,5} |
| 3. | | In pregnant women with cardiovascular disease, including cardiomyopathies, adverse outcomes during delivery are low (3% to 4%) and similar between vaginal delivery and cesarean section. ⁶ Valsalva during labor has also been shown to be well tolerated. Bleeding rates, including serious bleeding requiring transfusions, are higher in women who undergo cesarean section. Therefore, cesarean section should be reserved only for obstetric reasons or for emergency cardiac or other maternal health reasons. A delivery plan should ideally be established by the end of the second trimester. |
| 4. | | Prenatal genetic counseling is helpful in explaining the risk of transmission of disease, as well as discussing potential reproductive options. These reproductive options include preimplantation genetic diagnosis, fetal screening, prenatal testing, and postnatal genetic testing options. The benefits and potential harms can be discussed for each of these options, such that the individual or couple can make a fully informed decision about prenatal genetic testing and fetal screening. ⁴⁻⁷ |
| 5. | | A multidisciplinary care team that includes cardiologists and maternal-fetal medicine specialists can provide comprehensive management of pregnant women with HCM. |
| 6. | | Decisions regarding pregnancy in women with HCM include a shared discussion. This discussion conveys that maternal mortality with pregnancy is very low, and cardiac events occur primarily in those with preexisting symptoms and previous cardiac events. ⁸⁻¹¹ In those women who are very symptomatic, options for mitigating risk before conception are discussed. Depending on the individual circumstance, these options might include SRT for women with medically refractory symptomatic LVOTO, advanced HF therapies for women with HF, or ICD implantation for women with high-risk features for ventricular arrhythmias. |
| 7. | | Most antiarrhythmic agents are contraindicated during pregnancy because of the potential teratogenic effects, and many are not recommended |

for patients with HCM. Cardioversion during pregnancy can be performed with minimal risk to the fetus and is therefore preferred for restoring sinus rhythm in pregnant women with HCM, particularly if they are symptomatic.⁷ Anticoagulation to decrease the risk of thromboembolism associated with cardioversion would need to be individualized based on the trimester of pregnancy and the risk of anticoagulation to the fetus.

8. Epidural and general anesthesia are common modes of anesthesia to make the delivery more comfortable for the patient. There are generally no contraindications to either of these forms of anesthesia in pregnant patients with HCM as long as care is taken to avoid hypotension.⁹
9. Most complications that arise during pregnancy occur in the third trimester.⁸ Therefore, it would be reasonable to perform echocardiography in the latter stages of pregnancy, or if new symptoms arise.
10. Fetal echocardiography is available for prenatal diagnosis of HCM and is used in some select families, particularly if there is a history pediatric disease onset or severe disease manifestations in parents or other family members.⁴

9.4. Comorbidities

Recommendations for Patients With Comorbidities Referenced studies that support the recommendations are summarized in Online Data Supplement 21.		
COR	LOE	Recommendations
1	C-EO	1. In patients with HCM, adherence to the guidelines on the prevention of atherosclerotic cardiovascular disease is recommended to reduce risk of cardiovascular events. ¹
1	B-NR	2. In patients with HCM who are overweight or obese, counseling and comprehensive lifestyle interventions are recommended for achieving and maintaining weight loss ¹ and possibly lowering the risk of developing LVOTO, HF, and AF. ²⁻⁴
1	C-LD	3. In patients with HCM and hypertension, lifestyle modifications and medical therapy for hypertension are, ¹ with preference for beta-blockers and non-dihydropyridine calcium channel blockers in patients with obstructive HCM. ⁴⁻⁸
1	C-LD	4. In patients with HCM, assessment for symptoms of sleep-disordered breathing is recommended and, if present, referral to a sleep medicine specialist for evaluation and treatment. ⁹⁻¹²

Synopsis

Comorbid conditions, including hypertension, obesity, and sleep-disordered breathing, are common in patients

with HCM and may contribute to increased symptom burden, LVOTO, HF, and AF. Appropriate counseling and management of these conditions in patients with HCM is a critical component of their care.

Recommendation-Specific Supportive Text

1. Patients with HCM are frequently affected by other health conditions, including hypertension, diabetes, hyperlipidemia, and obesity and may also maintain unhealthy lifestyle practices, including inactivity and tobacco abuse, which together can compromise their overall cardiovascular health. In addition to treatment of their HCM, implementation of well-proven primary prevention strategies is warranted in both symptomatic and asymptomatic patients.¹
2. Excess weight is very common in adult patients with HCM, with >70% having a BMI >25 and >30% having a BMI >30.²⁻⁴ Obesity is also common in pediatric patients with HCM, with almost 30% having a BMI in the 99th percentile for age and sex.¹³ Patients who are obese have an increased burden of LVH and mass,^{2,3,13} are more symptomatic, are more likely to have LVOTO, and have reduced exercise capacity.²⁻⁴ In a large prospective, multicenter registry of patients with HCM, obesity was independently associated with a composite outcome of death, HF, AF, ventricular arrhythmias, and stroke, with hazard ratios ranging from 1.4 to 1.9.⁴ Although obese patients were less likely to carry a sarcomere gene variant, obesity increased risk in both genotype-positive and genotype-negative patients. Weight loss interventions in obese patients with HCM therefore have the potential to reduce symptoms and adverse outcomes, in addition to being an important component of primary prevention for overall cardiovascular health.
3. Hypertension is commonly coexistent in adult patients with HCM, with a prevalence of ~35% to 50%,⁴⁻⁶ and affects sarcomere variant-negative patients disproportionately.⁷ Intuitively, left ventricular pressure overload imposed by elevated systemic blood pressure could trigger the onset of, or exacerbate, LVH. Hypertension has been associated with increased penetrance in gene variant carriers.⁸ Target blood pressure should be in keeping with primary prevention guidelines. In patients with symptomatic obstructive HCM, beta-blockers or non-dihydropyridine calcium channel blockers are often used as first-line therapy.¹⁴ Low-dose diuretics may also be used as antihypertensive agents. Although some patients with obstructive physiology may tolerate

vasodilator therapy, these agents can exacerbate LVOTO and symptoms.

4. Sleep-disordered breathing is highly prevalent in patients with HCM, affecting 55% to 70%. Patients with obstructive sleep apnea are older, more often hypertensive, and have greater symptom burden and reduced exercise capacity.^{9,11} Obstructive sleep apnea has also been associated with a greater prevalence of AF¹⁰ and NSVT.¹² Diagnosis and treatment of obstructive sleep apnea could reduce symptoms and arrhythmic complications in patients with HCM but has not been systematically tested.

10. UNMET NEEDS

10.1. Limitations and Knowledge Gaps

10.1.1. Clinical Trials

There have been few clinical trials, particularly RCTs, in HCM. Thus, many of the recommendations put forth in this guideline are based on data from observational studies or expert opinion. More data are needed to identify strategies to improve functional capacity (particularly in symptomatic patients with nonobstructive HCM), to attenuate disease progression, and to reduce adverse outcomes. RCTs are challenging in this population, because of very low overall event rates and a slow rate of disease progression in most patients. As such, there is a clear need for novel trial designs and specific patient-reported outcome tools to rigorously assess impact of new therapies on meaningful endpoints, including quality of life- and sex-based differences among patients with HCM.

10.1.2. Prevent or Attenuate Disease Progression

There are currently no known preventive or disease-modifying therapies for HCM, in large part because of insufficient knowledge of the underlying biology that leads to disease emergence and progression. In a small RCT, diltiazem stabilized LV wall thickness: dimension ratio in gene variant carriers without LVH and decreased LV mass and diastolic filling in a subgroup.¹ Valsartan is currently being tested for its potential to attenuate disease progression in young gene variant carriers without LVH and in those with early manifestations of HCM.² Gene editing of underlying causal gene variants using technologies such as CRISPR/Cas9, gene replacement therapy, and allele-specific silencing are being investigated in preclinical studies, but are of uncertain clinical applicability at this time given unknown efficacy and concerns for off-target effects or toxicity.

10.1.3. Reduce Symptom Burden and Increase Functional Capacity, Particularly in Nonobstructive HCM

Although beta-blockers and non-dihydropyridine calcium channel blockers are the mainstay of medical therapy for patients with HCM, their use is largely empiric and predicated on a small number of studies. Other drugs that have been tested in RCTs in patients with HCM have not shown a benefit, demonstrated toxicity, or a signal for harm.^{3–5} An open-label, nonrandomized phase 2 trial of a small-molecule inhibitor of myosin showed decreased post-exercise LVOT gradients, improved exercise capacity, and lowered dyspnea scores.⁶ This is now being investigated in a phase 3 RCT.⁷ In patients with nonobstructive HCM, a phase 2 trial showed that treatment with the myosin inhibitor was associated with a reduction in NT-proBNP.⁸ Ongoing clinical trials are testing myosin inhibitors for efficacy in improving functional capacity in patients with both obstructive and nonobstructive HCM. Clinical trials that test lifestyle interventions to reduce symptom burden are also needed. Given the benefits of cardiopulmonary rehabilitation in other cardiac diseases, adding HCM to the list of reimbursable diagnoses would extend these benefits to this population.

10.1.4. Risk Stratification

Despite several large, prospective studies examining risk predictors of SCD, risk stratification algorithms still have low positive-predictive values such that many ICDs are placed unnecessarily. On the other hand, sudden cardiac arrest or SCD occurs in patients with no established risk factors, albeit rare. New risk factors and tools to enhance the power of risk stratification algorithms are needed, particularly in children. Similarly, the ability to predict which patients with HCM will suffer other adverse outcomes, such as HF and AF, is limited. These questions will benefit from continued assembly and growth of large, prospective registries that track clinical outcomes in well-genotyped and -phenotyped patients with HCM. Studies including larger numbers of pediatric and non-White populations with HCM are particularly needed.

10.1.5. Arrhythmia Management

AF affects a large proportion of adult patients with HCM, is often poorly tolerated, and may be more refractory to pharmacologic and catheter-based interventions than in patients without HCM.^{9–13} Technical advances in ablative therapy for AF may increase the success rate in patients with HCM.¹⁴ Prevention and treatment of ventricular arrhythmias in patients with ICDs and HCM can be problematic for a number of reasons. They include the often-young age at implantation and need for lifelong generator and lead revisions and high rate of inappropriate shocks for sinus tachycardia and

*Former Joint Committee on Clinical Practice Guidelines member; current member during the writing effort.

atrial arrhythmias. Advances in device technology, arrhythmia discrimination, and treatment algorithms may be of benefit to this population.

10.1.6. Genetics

Genetic testing services are not widely available outside of experienced centers. Greater access to genetic counseling and testing is needed for all patients with HCM. Improved algorithms for the interpretation of variants that are currently classified as variants of uncertain significance are also necessary. This will be greatly facilitated by efforts from the Clinical Genome Resource (ClinGen), a funded resource of the National Institutes of Health, in expert variant curation (<https://clinicalgenome.org/>).¹⁵

Approximately 50% of cases of HCM are genetically elusive. New gene discovery is needed to identify additional causal genes, recognizing that many of these cases may result from a combination of polygenic variants and environmental factors. Investigation into the phenotypic associations and clinical outcomes associated with individual variants should continue as well.

10.1.7. Exercise and Sports Participation

Data regarding potential risks of sports participation for patients with HCM are limited. Although this guideline document introduces the concept of a shared discussion regarding sports participation, more data are needed to frame these discussions and to inform patient decisions. A prospective, multicenter observational study to determine how exercise practices (including vigorous and competitive sports) impact patient outcomes and quality of life is ongoing. A randomized trial comparing the efficacy of high-intensity exercise versus moderate-intensity exercise to improve cardiorespiratory fitness and diastolic reserve in patients with HCM is also underway.

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ARTICLE INFORMATION

This document was approved by the American College of Cardiology Clinical Policy Approval Committee in August 2020, the American Heart Association Science Advisory and Coordinating Committee in August 2020, and the American Heart Association Executive Committee in October 2020.

Supplemental materials are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000937>

This article has been copublished in the *Journal of the American College of Cardiology*.

Copies: This document is available on the websites of the American College of Cardiology (www.acc.org) and the American Heart Association (professional.heart.org). A copy of the document is also available at <https://professional.heart.org/statements> by selecting the “Guidelines & Statements” button. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com.

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1. INTRODUCTION

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7. SCD RISK ASSESSMENT AND PREVENTION

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8. MANAGEMENT OF HCM

8.1. Management of Symptomatic Patients With Obstructive HCM

8.1.1. Pharmacologic Management of Symptomatic Patients With Obstructive HCM

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9. LIFESTYLE CONSIDERATIONS FOR PATIENTS WITH HCM

9.1. Sports and Activity

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Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Steve R. Ommen, Chair	Mayo Clinic—Professor of Medicine, Director of the Mayo Hypertrophic Cardiomyopathy Clinic	None	None	None	None	None	None	None
Seema Mital, Vice Chair	The Hospital for Sick Children—University of Toronto, Professor of Pediatrics, Staff Heart Function and Transplant Cardiologist	None	None	None	None	None	None	None
Michael A. Burke	Emory University School of Medicine and Emory Healthcare—Assistant Professor of Medicine, Emory Advanced Heart Failure Therapy Center	None	None	None	None	None	None	None
Sharlene M. Day	University of Pennsylvania—Associate Professor, Department of Medicine, Division of Cardiovascular Medicine, Center for Inherited Cardiac Diseases Director of Translational Research, Penn Cardiovascular Institute	None	None	None	None	• Share Registry (Myokardia)	None	8.1.1
Anita Deswal (HFSA)	The University of Texas MD Anderson Cancer Center—Department Chair, Medicine, Department of Cardiology, Division of Internal Medicine, Ting Tsung and Wei Fong Chao Distinguished Chair, Department of Cardiology, Division of Internal Medicine, Tenured Professor of Medicine, Department of Cardiology, Division of Internal Medicine	None	None	None	None	• Novartis Corporation	None	6.5, 8.5
Perry Elliott	Professor of Cardiovascular Medicine at UCL; Consultant Cardiologist Inherited Cardiovascular Disease Unit at St Bartholomew's Hospital; President of Cardiomyopathy UK	• 4DMT • Alnylam • AzaCor therapeutics • Genzyme Inc • Gilead • Pfizer • Sanofi/Genzyme	None	None	None	None	None	6.5, 8.5
Lauren L. Evanovich, PhD (Patient Representative)	University of South Florida—Assistant Professor	None	None	None	None	None	None	None
Judy Hung (ASE)	Massachusetts General Hospital—Cardiovascular Disease Internal Medicine	None	None	None	None	None	None	None
José A. Joglar	UT Southwestern Medical Center—Professor, Internal Medicine. Program Director, Clinical Cardiac Electrophysiology Fellowship Program Professor	None	None	None	None	None	None	None

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Paul Kantor	University of Southern California; Children's Hospital Los Angeles (CHLA)—Chief, Division of Cardiology, Co-Director of CHLA's Heart Institute	Novartis	None	None	None	None	None	6.5, 8.5
Carey Kimmelstiel	Tufts Medical Center—Professor of Medicine, Director, Interventional Cardiology Center	- Gilead - PLX Pharmaceuticals - Abbott† - Boston Scientific - Cardinal Health, Inc.†	Chiesi Pharmaceuticals	None	None	None	None	6.2, 6.3, 6.5, 6.9, 8.5
Michelle Kittleson	Cedars Sinai—Director, Heart Failure Research. Director, Post Graduate Medical Education in Heart Failure and Transplantation Professor of Medicine. Smidt Heart Institute Cedars-Sinai	None	None	None	None	None	None	None
Mark S. Link (HRS)	UT Southwestern Medical Center—Professor Director, Professor of Medicine, Director, Cardiac Electrophysiology	None	None	None	None	None	None	None
Martin S. Maron (SCMR)	Tufts Medical Center—Director of the Hypertrophic Cardiomyopathy Center and the Co-Director of the Cardiac CT and MRI program at Tufts Medical Center and Assistant Professor at Tufts University School of Medicine	- Cytokinetics - Takeda Pharmaceuticals	None	None	- Genzyme Corporation - Medtronic Vascular Inc.	- Celltrion - Genzyme Corporation - iRhythm - Medtronic Vascular Inc.	2018-Medical Malpractice (Plaintiff) 2018-Medical Malpractice (Plaintiff) 2018-Medical Malpractice (Defendant)	6.5, 6.6, 6.9, 7.3, 8.1.2, 8.3, 8.4, 8.5, 9.1, 9.2
Matthew W. Martinez	Co-Director Chanin T. Mast Hypertrophic Cardiomyopathy Center, Director, Sports Cardiology Morristown Medical Center/Atlantic Health System	None	None	None	None	None	None	None
Christina Y. Miyake	Texas Children's Hospital/ Baylor College of Medicine—Associate Professor Pediatrics-Pediatric Cardiology Baylor College of Medicine—Associate Professor Molecular Physiology and Biophysics	None	None	None	None	None	None	None
Hartzell V. Schaff (AATS)	Mayo Clinic—Professor of Surgery, Consultant, Department of Cardiovascular Surgery	None	None	None	Abbott†	None	None	7.3, 8.3
Christopher Semsarian	University of Sydney—Practitioner Fellow Professor of Medicine, Sydney Medical School Cardiologist, Royal Prince Alfred Hospital, Central Clinical School Head, Molecular Cardiology Program, Centenary Institute	None	None	None	None	Share Registry (Myokardia)	None	8.1.1

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Paul Sorajja (SCAI)	Minnesota Heart Institute—Interventional cardiologist at the Minneapolis Heart Institute at Abbott Northwestern Hospital, Director of the Center for Valve and Structural Heart Disease, Roger L. and Lynn C. Headrick Family Chair of the Valve Science Center for the Minneapolis Heart Institute Foundation	- Abbott Vascular - Boston Scientific - Edwards Lifesciences - Gore - Medtronic	- Abbott - Edwards Lifesciences - Medtronic	None	Medtronic Vascular	Abbott Laboratories	None	5, 6.2, 6.3, 6.5, 6.9, 7.1, 7.2, 7.3, 8.3, 8.4, 8.5, 9.1, 9.2

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of $\geq 5\%$ of the voting stock or share of the business entity, or ownership of $\geq \$5000$ of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to <https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy> for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

†Significant relationship.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; AHA, American Heart Association; ASE, American Society of Echocardiography; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; SCAI, Society for Cardiovascular Angiography and Interventions; SCMR, Society for Cardiovascular Magnetic Resonance; and UT, University of Texas.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)—2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Anastasia L. Armbruster	Joint Committee on Clinical Practice Guidelines content reviewer	St. Louis College of Pharmacy	None	AstraZeneca Pharmaceuticals	None	None	None	None
Andrew Wang	Official Reviewer - American Heart Association	Duke University Medical Center—Professor of Medicine	- American College of Physicians* - Cytokinetics - RioVant - UpToDate	None	None	Myokardia*	- Abbott Vascular - AHA, <i>Circulation</i>* - Medtronic - MyoKardia, Inc	Defendant, Diagnosis of Infective Endocarditis, 2019
Anjali T. Owens	AHA content reviewer	University of Pennsylvania, Perelman School of Medicine	- Cytokinetics - Myokardia	None	None	- Array Biopharma, PI, ARRY-797-301† - Myokardia, PI for MAVERICK trial and EXPLORER Trial†	None	None
Anna Woo	Official Reviewer - American Society of Echocardiography	Director, Echocardiography Laboratory, University Health Network, University of Toronto	None	None	None	None	None	None
Barry J. Maron	ACC/AHA content reviewer	Hypertrophic Cardiomyopathy Institute, Division of Cardiology, Tufts Medical Center, Boston, Massachusetts	None	None	None	None	None	None
Bulent Gorenek	Joint Committee on Clinical Practice Guidelines content reviewer	Eskisehir Osmangazi University School of Medicine – Professor of Cardiology	- AstraZeneca - Sandoz	None	None	None	None	None
Carmelo Milano	Official Reviewer - American Academy of Thoracic Surgeons	Duke University	Abbott Laboratories*	None	None	- Abbott Laboratories† - Medtronic† - NuPulse†	- Abiomed† - Allergant† - CryoLife† - Ethicon† - LivaNova†	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Daniel B. Mark	Joint Committee on Clinical Practice Guidelines content reviewer	Duke Clinical Research Institute—Professor of Medicine	None	None	None	- HeartFlow* - Merck & Co., Inc.*	Merck & Co., Inc.*	None
Dave L. Dixon	Joint Committee on Clinical Practice Guidelines content reviewer	Virginia Commonwealth University School of Pharmacy	None	None	None	- CDC* - Community Pharmacy Foundation*	- Accreditation Council for Clinical Lipidology† - American Pharmacists Association - American College of Pharmacy Cardiology Practice Research Network† - National Lipid Association†	None
Eugene Chung	ACC content reviewer	University of Michigan Medical School—Associate Professor of Medicine	None	None	None	None	None	None
Jacqueline E. Tamis-Holland	Joint Committee on Clinical Practice Guidelines content reviewer	Mount Sinai Saint Luke's Hospital	None	None	None	- Minneapolis Heart Institute, North American Covid STEMI Registry† - NIH, Ischemia Trial (DSMB)†	- Abbott Vascular† - AHA† - Bronx Lebanon Hospital, Cardiology Fellowship Program Director† - Medscape/Heart.org - The NGS Predict Study	None
James C. Lee	ACC content reviewer	Henry Ford Heart and Vascular Institute	Heartflow*	None	None	None	None	None
Jonathan L. Halperin	ACC/AHA content reviewer	Mount Sinai Medical Center—Professor of Medicine	- Abbott Laboratories† - ATLAS Group, University of Colorado, Colorado Prevention Center* - Boehringer Ingelheim* - Medtronic, Inc. - Ortho-McNeil Janssen	None	HWL, LLC†	Bayer Healthcare Pharmaceuticals (DSMB)†	None	None
Joseph E. Marine	Joint Committee on Clinical Practice Guidelines content reviewer	Johns Hopkins University School of Medicine—Associate Professor of Medicine	American College of Cardiology*	None	None	None	UpToDate	None
Y. Joseph Woo	Joint Committee on Clinical Practice Guidelines content reviewer	Stanford University School of Medicine	None	None	None	None	NIH*	None
Karine Guerrier	AHA content reviewer	Le Bonheur Children's Hospital, Memphis, Tennessee; University of Tennessee Health Sciences Center, Memphis, Tennessee	None	None	None	None	None	None
Kim K. Birtcher	Joint Committee on Clinical Practice Guidelines content reviewer	University of Houston College of Pharmacy	Jones & Bartlett Learning	None	None	None	None	None
Latha P. Palaniappan	Joint Committee on Clinical Practice Guidelines content reviewer	Stanford Medicine	23andme - National Minority Cardiovascular Alliance	None	None	NIH*	None	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Lisa de las Fuentes	Joint Committee on Clinical Practice Guidelines content reviewer	Washington University, School of Medicine, Department of Medicine, Cardiovascular Division	• Acceleron • Altavant • Arena • Bayer Healthcare Pharmaceuticals • Express Scripts • Johnson & Johnson • Mentor Planning and Consulting • Phase Bio • V-wave • WebMD, LLC*	• Bayer Healthcare Pharmaceuticals* • Simply Speaking*	None	• Acceleron* • Altavant* • Bayer Healthcare Pharmaceuticals • Complexa* • Johnson & Johnson* • Liquida*Medtronic* • National Institutes of Health (NIH)* • Reata • Trio Analytics* • United Therapeutics* • University of Kentucky (DSMB) • University of Toronto (DSMB)†	• ACC† • AHA† • <i>Circulation</i> Journals, Editorial Board • Ironwood • Pulmonary Hypertension Association*	None
Lynne W. Stevenson	ACC content reviewer	Vanderbilt University—Director, Cardiomyopathy Program	• ABIM • Novartis	None	None	• LivaNova (DSMB) • NHLBI* • PCORI	• Abbott† • Abbott • ACC* • Biotronik† • Biotronik • Boston Scientific • Endotronic† • Gore Medical† • Johnson & Johnson • NHLBI	None
Mariann R. Piano	Joint Committee on Clinical Practice Guidelines content reviewer	Vanderbilt University	None	None	None	None	None	None
N.A. Mark Estes III	ACC/AHA content reviewer	UPMC Heart and Vascular Institute—Professor of Medicine	• Boston Scientific* • Medtronic* • Saint Jude Medical*	None	None	None	• ABIM CCEP Test Writing Committee† • AHA† • IBHRE†	None
Mark V. Sherid	AHA content reviewer	NYU Langone Medical Center	• Celltrion*	None	None	None	• MyoKardia	None
Michael A. Fifer	ACC/AHA content reviewer	Massachusetts General Hospital—Director, Hypertrophic Cardiomyopathy Program	• Cytokinetics	None	None	• MyoKardia* • Novartis*	None	• Defendant, Various, 2020 • Plaintiff, Various, 2020
Nosheen Reza	AHA content reviewer	University of Pennsylvania	None	None	None	None	• Abbott Laboratories • Boston Scientific • Medtronic Vascular, Inc. • Zoll Services LLC	None
Patrick T. O'Gara	Joint Committee on Clinical Practice Guidelines content reviewer	Watkins Family Distinguished Chair in Cardiology, Brigham and Women's Hospital: Professor of Medicine Harvard Medical School	None	None	None	None	• Edwards Scientific† • Medtronic, Scientific Advisory Board† • Medtronic, Member of Executive Committee, Apollo Trial† • JAMA <i>Cardiology</i>* • NIH*	None
Robert B. Allen	Content Reviewer—ACC/AHA Lay Reviewer	Helis Oil & Gas Company, LLC—General Counsel	None	None	None	None	• AHA†	None
Scott Sample	Official Reviewer – American College of Cardiology Board of Governors	Carolina East Medical Center	None	None	None	None	• Boston Scientific*	• Third Party, Cardiac Risk Factors, 2020
Seshadri Balaji	Official Reviewer - Pediatric & Congenital Electrophysiology Society	Oregon Health & Science University	• Milestone Pharmaceuticals	None	None	None	• Yor Labs†	None
Shaun Rivers	Content Reviewer—ACC/AHA Lay Reviewer	Case Management Associates—co-owner	None	None	None	None	None	None

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Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Srihari S. Naidu	Official Reviewer - Society for Cardiovascular Angiography and Interventions	Westchester Medical Center—Director, Hypertrophic Cardiomyopathy Program; Director, Cardiac Catheterization Laboratories	• Cytokinetics • Myokardia	None	None	None	None	None
Tanveer Rab	ACC content reviewer	Emory University—Professor, Interventional Cardiology	None	None	None	None	None	None
Victoria N. Parikh	Official Reviewer - American Heart Association	Stanford Center for Inherited Cardiovascular Disease Stanford University School of Medicine	None	None	None	None	None	None
William Schuyler Jones	Joint Committee on Clinical Practice Guidelines content reviewer	Duke University Health System	• Bayer Healthcare Pharmaceuticals* • Janssen Pharmaceuticals, Inc.*	None	None	• Bristol Myers Squibb • PCORI	None	None
Yong-Mei Cha	Official Reviewer - Heart Rhythm Society	Mayo Clinic, Department of Cardiovascular Medicine	None	None	None	None	• Medtronic*	None

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*Significant relationship.

†No financial benefit.

ABIM indicates American Board of Internal Medicine; ACC, American College of Cardiology; AHA, American Heart Association; CCEP, Clinical Cardiac Electrophysiology; CDC, Centers for Disease Control and Prevention; Co-PI, co-principal investigator; DSMB, Data and Safety Monitoring Board; IBHRE, International Board of Heart Rhythm Examiners; *JAMA*, *Journal of the American Medical Association*; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; PCORI, Patient-Centered Outcomes Research Institute; PI, principal investigator; and VA, Veterans Affairs.