

**CLINICAL PRACTICE GUIDELINES**

# 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines

*Developed in Collaboration With and Endorsed by the American Medical Society for Sports Medicine, the Heart Rhythm Society, Pediatric & Congenital Electrophysiology Society, and the Society for Cardiovascular Magnetic Resonance*

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**AIM:** The “2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy” provides recommendations to guide clinicians in the management of patients with hypertrophic cardiomyopathy.

**METHODS:** A comprehensive literature search was conducted from September 14, 2022, to November 22, 2022, encompassing studies, reviews, and other evidence on human subjects that were published in English from PubMed, EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline. Additional relevant studies, published through May 23, 2023, during the guideline writing process, were also considered by the writing committee and added to the evidence tables, where appropriate.

**STRUCTURE:** Hypertrophic cardiomyopathy remains a common genetic heart disease reported in populations globally. Recommendations from the “2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy” have been updated with new evidence to guide clinicians.

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

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**WHAT IS NEW**

Table 1 reflects recommendations that are substantially revised from the 2020 Hypertrophic Cardiomyopathy Guidelines or were drafted as new recommendations in the 2024 Hypertrophic Cardiomyopathy Guidelines.

**Table 1. What Is New: New and Substantially Revised Recommendations in the 2024 HCM Guideline\***

New or Revised	2024 Section Title	Recommendation in 2020 HCM Guideline	COR in 2020 Guideline	Recommendation in 2024 HCM Guideline	COR in 2024 Guideline
Revised	6.5 Heart Rhythm Assessment	In patients with HCM who have additional risk factors for AF, such as left atrial dilatation, advanced age, and NYHA functional 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.	2a	In patients with HCM who are deemed to be at high risk for developing AF based on the presence of risk factors or as determined by a validated risk score, and who are eligible for anticoagulation, extended ambulatory monitoring is recommended to screen for AF as part of initial evaluation and annual follow-up.	1
New	6.7 Exercise Stress Testing	N/A	N/A	In pediatric patients with HCM, regardless of symptom status, exercise stress testing is recommended to determine functional capacity and to provide prognostic information.	1
Revised	7.2 Patient Selection for ICD Placement	For patients $\geq 16$ years of age with HCM and with $\geq 1$ 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.	2a	For patients with HCM with $\geq 1$ major SCD risk factor, discussion of the estimated 5-year sudden death risk and mortality rates can be useful during the shared decision-making process for ICD placement.	2a
Revised	8.1.1 Pharmacological Management of Symptomatic Patients with Obstructive HCM	For patients with obstructive HCM who have persistent severe symptoms attributable to LVOTO despite beta blockers or nondihydropyridine calcium channel blockers, either adding disopyramide in combination with 1 of the other drugs, or SRT performed at experienced centers, is recommended.	1	For patients with obstructive HCM who have persistent symptoms attributable to LVOTO despite beta blockers or nondihydropyridine calcium channel blockers, adding a myosin inhibitor (adult patients only), or disopyramide (in combination with an atrioventricular nodal blocking agent), or SRT performed at experienced centers, is recommended.	1
New	8.2 Management of Patients With Nonobstructive HCM With Preserved EF	N/A	N/A	For younger (eg, $\leq 45$ years of age) patients with nonobstructive HCM due to a pathogenic or likely pathogenic cardiac sarcomere genetic variant, and a mild phenotype, valsartan may be beneficial to slow adverse cardiac remodeling.	2b
New	8.3 Management of Patients With HCM and Advanced HF	N/A	N/A	In patients with HCM who develop persistent systolic dysfunction (LVEF $< 50\%$ ), cardiac myosin inhibitors should be discontinued.	1
Revised	9.1 Recreational Physical Activity and Competitive Sports	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.	2b	For patients with HCM, participation in vigorous recreational activities is reasonable after an annual comprehensive evaluation and shared decision-making with an expert professional who balances potential benefits and risks.  For patients with HCM who are capable of a high level of physical performance, participation in competitive sports may be considered after review by an expert provider with experience managing athletes with HCM who conducts an annual comprehensive evaluation and shared decision-making that balances potential benefits and risks.	2a  2b
New	9.1 Recreational Physical Activity and Competitive Sports	N/A	N/A	For most patients with HCM, universal restriction from vigorous physical activity or competitive sports is not indicated.	3: No Benefit
New	9.3 Pregnancy in Patients With HCM	N/A	N/A	In pregnant women, use of mavacamten is contraindicated due to potential teratogenic effects.	3: Harm

\*Table 1 highlights new and substantially revised practice-changing recommendations since 2020 and is not a comprehensive list of all updates in this guideline.

AF indicates atrial fibrillation; COR, Class of Recommendation; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; N/A, not applicable; NYHA, New York Heart Association; SCD, sudden cardiac death; and SRT, septal reduction therapy.

## TOP 10 TAKE-HOME MESSAGES

1. Shared decision-making is essential to provide the best clinical care. This involves thoughtful dialogue among patients, families, and their care team in which health care professionals present all available testing and treatment options; discuss the risks, benefits, and applicability of those options to the individual patient; and ensure the patient expresses their personal preferences and goals to develop their treatment plan.
2. Although the primary cardiology team can initiate evaluation, treatment, and longitudinal care, referral to multidisciplinary hypertrophic cardiomyopathy (HCM) centers with appropriate 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 decision relying on a Class of Recommendation 2b) or is particularly nuanced (eg, interpretation of genetic testing; primary prevention implantable cardioverter-defibrillator decision-making), and for HCM-specific invasive procedures—may critically benefit from involving specialized HCM centers.
3. Careful ascertainment of family history, counseling patients with HCM about the potential for genetic transmission of HCM, and options for genetic testing are cornerstones of care. Screening first-degree family members of patients with HCM, using either genetic testing, serial imaging, or electrocardiographic surveillance as appropriate, can begin at any age and can be influenced by specifics of the patient and family history and family preference. Because screening recommendations for family members hinge on the pathogenicity of any detected variants, the reported pathogenicity should be reconfirmed every 2 to 3 years, and input from specialized HCM centers with genetics expertise may be valuable.
4. Assessing a patient's risk for sudden cardiac death is an important component of management. Integrating the presence or absence of established risk markers with tools to estimate individual risk score will facilitate the patient's ability to participate in decision-making regarding implantable cardioverter-defibrillator placement. These discussions should incorporate a patient's personal level of risk tolerance and their specific treatment goals.
5. The risk factors for sudden cardiac death in children with HCM carry different weights and components than those used in adult patients. Pediatric risk stratification also varies with age and must account for different body sizes. Coupled with the complexity of placing implantable cardioverter-defibrillators in young patients with anticipated growth and a higher risk of device complications, the threshold for implantable cardioverter-defibrillator implantation in children often differs from adults. These differences are best addressed at comprehensive HCM centers with expertise in caring for children with HCM. New risk calculators, specific to children and adolescents, have been validated and can help young patients and their families contextualize their estimated risk of sudden cardiac death.
6. Cardiac myosin inhibitors are now available to treat patients with symptomatic obstructive HCM. This new class of medication inhibits actin-myosin interaction, thus decreasing cardiac contractility and reducing left ventricular outflow tract obstruction. Mavacamten is currently the only US Food and Drug Administration–approved agent. These agents can be beneficial for patients with obstructive HCM who do not derive adequate symptomatic relief from first-line drug therapy.
7. Invasive septal reduction therapies (surgical septal myectomy and alcohol septal ablation), when performed by experienced HCM teams at dedicated centers, can provide safe and effective symptomatic relief for patients with drug-refractory or severe outflow tract obstruction. Given the data on the significantly improved outcomes at comprehensive HCM centers, these decisions represent an optimal opportunity for referral.
8. Patients with HCM and persistent or paroxysmal atrial fibrillation have a sufficiently increased risk of stroke such that oral anticoagulation with direct-acting oral anticoagulants (or alternatively warfarin) should be considered the default treatment option irrespective of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. New tools to stratify risk for incident atrial fibrillation have been developed and may assist in determining the frequency of screening patients with ambulatory telemetry. Because rapid atrial fibrillation is often poorly tolerated in patients with HCM, maintenance of sinus rhythm and rate control are key treatment goals.
9. Exercise stress testing is particularly helpful in determining overall exercise tolerance and for latent exercise provoked left ventricular outflow tract obstruction. Because children may not describe symptoms readily, routine exercise testing can be particularly important for young patients.
10. Increasingly, data affirm that the beneficial effects of exercise on general health are extended to patients with HCM. Healthy recreational exercise (light [ $<3$  metabolic equivalents], moderate [ $3$ – $6$  metabolic equivalents], and vigorous [ $>6$  metabolic equivalents] intensity levels) has not been associated with increased risk of ventricular arrhythmia events in short-term studies. If patients pursue rigorous exercise training for the purpose of performance or competition, it is important to engage in

a comprehensive discussion and seek input from expert HCM professionals regarding the potential risks and benefits, to develop an individualized training plan, and to establish a regular schedule for reevaluation.

## 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 the 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.

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,<sup>1,2</sup> 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 health care 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.<sup>3</sup>

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 manual<sup>4</sup> and other methodology articles.<sup>5–7</sup>

## 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 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 [online](#). Appendix 1 of the guideline lists writing committee members' comprehensive and relevant RWI; for the purposes of full transparency, comprehensive and relevant disclosure information for the Joint Committee is also available [online](#).

## Evidence Review and Evidence Review Committees

In developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.<sup>4,5</sup> 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  $\geq 1$  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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Chair, ACC/AHA Joint Committee on  
Clinical Practice Guidelines*

## 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 September 14, 2022, to November 2022, and included literature published between 2013 and 2022. Various published search hedges were used to eliminate animal studies and to locate relevant material that may not have been retrievable using existing database study type filters at the time the searches were performed.<sup>1–6</sup> 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, left ventricular hypertrophy, subvalvular stenosis, echocardiography, nuclear magnetic resonance imaging, computed

tomographic angiography, genetic testing, and diagnostic imaging. Additional relevant studies, published through May 23, 2023, 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. Composition of the Writing Committee

The writing committee consisted of clinicians, adult cardiologists, pediatric cardiologists, interventionalists, a cardiac surgeon, and 2 lay/patient representatives. The writing committee included representatives from the ACC, AHA, American Medical Society for Sports Medicine, Heart Rhythm Society, Pediatric & Congenital Electrophysiology Society, and Society for Cardiovascular Magnetic Resonance. Appendix 1 of the current document lists writing committee members' comprehensive and relevant RWI.

### 1.3. Document Review and Approval

The Joint Committee appointed a peer review committee to review the document. The peer review committee was composed of individuals nominated by ACC, AHA, and the collaborating organizations. Reviewers' RWI information was distributed to the writing committee and is published in Appendix 2.

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by American Medical Society for Sports Medicine, Heart Rhythm Society, Pediatric & Congenital Electrophysiology Society, and Society for Cardiovascular Magnetic Resonance.

### 1.4. Scope of the Guideline

In developing the "2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy" (2024 HCM guideline), the writing committee reviewed previously published guidelines. Table 2 contains a list of these publications and statements deemed pertinent to this writing effort and is intended for use as a resource, thus obviating the need to repeat existing guideline recommendations.

### 1.5. Class of Recommendations 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

**Table 2. Associated Guidelines and Statements**

Title	Organization	Publication Year (Reference)
<b>Guidelines</b>		
Hypertrophic cardiomyopathy	ACC/AHA ESC	2011 <sup>1</sup> 2014 <sup>2</sup> 2020 <sup>3</sup>
Atrial fibrillation	AHA/ACC	2014 <sup>4</sup> 2019 <sup>5</sup> 2023 <sup>6</sup>
Heart failure	ACC/AHA	2013 <sup>7</sup> 2016 <sup>8</sup> 2022 <sup>9</sup>
Primary prevention	AHA/ACC	2019 <sup>10</sup>
Management of overweight and obesity in adults	AHA/ACC/TOS	2014 <sup>11</sup>
Device-based therapy for cardiac rhythm abnormalities	ACC/AHA/HRS	2013 <sup>12</sup>
Ventricular arrhythmias and sudden cardiac death	AHA/ACC/HRS	2017 <sup>13</sup>
Bradycardia	ACC/AHA/HRS	2018 <sup>14</sup>
Prevention of cardiovascular disease in women	AHA/ACC	2011 <sup>15</sup>
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACC	2011 <sup>16</sup>
Assessment of cardiovascular risk in asymptomatic adults	ACC/AHA	2010 <sup>17</sup>
Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure	NHLBI	2003 <sup>18</sup>
VHD statement on comprehensive centers	AATS/ACC/ ASE/SCAI/STS	2019 <sup>19</sup>

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.

risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 3).

1.6. Abbreviations

Abbreviation	Meaning/Phrase
AF	atrial fibrillation
CAD	coronary artery disease
CMR	cardiovascular magnetic resonance
CPET	cardiopulmonary exercise test
CRT	cardiac resynchronization therapy

Abbreviation	Meaning/Phrase
DOAC	direct-acting oral anticoagulants
EF	ejection fraction
ESM	extended septal myectomy
GDMT	guideline-directed management and therapy
HCM	hypertrophic cardiomyopathy
HF	heart failure
ICD	implantable cardioverter-defibrillator
LBBB	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 atrial fibrillation
SCD	sudden cardiac death
SRT	septal reduction therapy
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
VF	ventricular fibrillation
VT	ventricular tachycardia
VUS	variant of uncertain significance

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

2.1. Prevalence

HCM is a common inherited heart disease reported in populations globally. The estimated prevalence of HCM varies depending on whether subclinical or clinically evident cases are being considered, how or if the diagnosis is adjudicated, and age of the sample studied.<sup>1</sup> The prevalence of unexplained asymptomatic hypertrophy in young adults in the United States has been reported in the range of 1:500.<sup>2</sup> 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.<sup>3</sup> HCM is often inherited in an autosomal dominant pattern but does not require a family history of HCM. There

**Table 3. Applying American College of Cardiology/American Heart Association 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†‡
<b>CLASS 1 (STRONG)</b> Benefit >>> Risk <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>Is recommended</li><li>Is indicated/useful/effective/beneficial</li><li>Should be performed/administered/other</li><li>Comparative-Effectiveness Phrases†:<ul style="list-style-type: none"><li>Treatment/strategy A is recommended/indicated in preference to treatment B</li><li>Treatment A should be chosen over treatment B</li></ul></li></ul>	<b>LEVEL A</b> <ul style="list-style-type: none"><li>High-quality evidence‡ from more than 1 RCT</li><li>Meta-analyses of high-quality RCTs</li><li>One or more RCTs corroborated by high-quality registry studies</li></ul>
<b>CLASS 2a (MODERATE)</b> Benefit >> Risk <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>Is reasonable</li><li>Can be useful/effective/beneficial</li><li>Comparative-Effectiveness Phrases†:<ul style="list-style-type: none"><li>Treatment/strategy A is probably recommended/indicated in preference to treatment B</li><li>It is reasonable to choose treatment A over treatment B</li></ul></li></ul>	<b>LEVEL B-R (Randomized)</b> <ul style="list-style-type: none"><li>Moderate-quality evidence‡ from 1 or more RCTs</li><li>Meta-analyses of moderate-quality RCTs</li></ul>
<b>CLASS 2b (WEAK)</b> Benefit ≥ Risk <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>May/might be reasonable</li><li>May/might be considered</li><li>Usefulness/effectiveness is unknown/unclear/uncertain or not well-established</li></ul>	<b>LEVEL B-NR (Nonrandomized)</b> <ul style="list-style-type: none"><li>Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li><li>Meta-analyses of such studies</li></ul>
<b>CLASS 3: No Benefit (MODERATE)</b> Benefit = Risk (Generally, LOE A or B use only) <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>Is not recommended</li><li>Is not indicated/useful/effective/beneficial</li><li>Should not be performed/administered/other</li></ul>	<b>LEVEL C-LD (Limited Data)</b> <ul style="list-style-type: none"><li>Randomized or nonrandomized observational or registry studies with limitations of design or execution</li><li>Meta-analyses of such studies</li><li>Physiological or mechanistic studies in human subjects</li></ul>
<b>Class 3: Harm (STRONG)</b> Risk > Benefit <b>Suggested phrases for writing recommendations:</b> <ul style="list-style-type: none"><li>Potentially harmful</li><li>Causes harm</li><li>Associated with excess morbidity/mortality</li><li>Should not be performed/administered/other</li></ul>	<b>LEVEL C-EO (Expert Opinion)</b> <ul style="list-style-type: none"><li>Consensus of expert opinion based on clinical experience</li></ul>

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.

is equal distribution of HCM by sex, although women are diagnosed less commonly than men. Differences in prevalence have been reported by race and ethnicity. Whether this difference is due to social disparities resulting in less access to specialists for diagnosis is unclear. As a result, these differences likely reflect underlying differences in social determinants of health, such as structural inequities in access to care leading to differences in diagnosis and awareness. Patients who self-identified as Black individuals (8.3%, N=205) compared with White individuals had a younger mean age at diagnosis (40 years versus 45.5 years), were more likely to have symptomatic heart failure (HF), and were less likely to undergo genetic testing.<sup>4</sup> Epidemiologic

studies of diverse samples are needed to better understand the interplay between genetic and social factors in the prevalence of HCM.

2.2. Nomenclature and Differential Diagnosis

Since the original clinical description of HCM was presented >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 not invariably present, 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 and lysosomal storage diseases in children; and Fabry, amyloid, sarcoid, and Danon cardiomyopathies. In these syndromic or infiltrative diseases, although the magnitude and distribution of increased LV wall thickness can be similar to that of HCM, the pathophysiologic mechanisms responsible for hypertrophy, natural history, and treatment strategies are not the same.<sup>1–5</sup> For these reasons, other cardiac or systemic diseases capable of producing LVH (ie, HCM mimics) will not be addressed in this document.

In addition, other scenarios can arise that present diagnostic challenges. These include conditions that produce secondary LVH, which can also overlap phenotypically with HCM, including remodeling secondary to athletic training (ie, “athlete’s 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.<sup>6,7</sup> 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, the clinical definition of HCM is considered 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 (see **Section 6.1, “Clinical Diagnosis”**), typically with 2D echocardiography or cardiovascular magnetic resonance (CMR) showing a maximal end-diastolic wall thickness of  $\geq 15$  mm anywhere in the left ventricle, in the absence of another cause of hypertrophy in adults.<sup>1–4</sup> 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 identifying a pathogenic or likely pathogenic variant often in a sarcomere gene.

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  $\geq 2$  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 a z-score  $>2.5$  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 a z-score  $>2$  may suffice for early diagnosis. The emergence of the HCM phenotype in younger family members who carry a pathogenic or likely pathogenic variant without previously evident LVH at initial screening (ie, genotype-positive/previously phenotype-negative) is well recognized and underscores the principle that, as the disease manifests, normal or mildly increased LV wall thicknesses will be encountered in individuals with genetically affected status. 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, systolic anterior motion (SAM) of the mitral valve and hyperdynamic LV function are not pathognomonic and are not required for a clinical diagnosis. Several 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 tendineae), elongated mitral valve leaflets, myocardial bridging, and right ventricular (RV) hypertrophy.

### 2.4. Etiology

In the early 1990s, the DNA sequencing from families with HCM led to the discovery that damaging variants in genes coding for sarcomere proteins segregated (or were coinherited) with LVH identified by echocardiographic assessment, abnormal electrocardiograms (ECGs), and physical findings. HCM thereby became regarded as a potentially monogenic disease, helping to consolidate a clinically heterogeneous disease into a single entity based on genetic substrate.<sup>1</sup>

Currently, variants in 1 of  $\geq 8$  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, approximately 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, “nonfamilial” HCM).<sup>2</sup> These observations suggest that other novel pathophysiologic mechanisms may be responsible for, or contribute to, phenotypic expression in these affected patients with HCM. Although HCM appears to be a monogenic disease in some cases, common genetic variants have also been identified as genetic modifiers of disease penetrance and -associated with risk for LVH and HCM, which suggests both monogenic and polygenic susceptibility.<sup>3</sup>

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 most patients who are variant positive, while other genes (*TNNI3*, *TNNT2*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*) each account for a small proportion of patients (1%-5%). Within these genes, most rare variants identified are “private” (unique to the individual family). Each offspring of an affected family member has a 50% chance of inheriting the variant.<sup>4</sup> 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 as well as the degree of expression is variable.

The precise mechanisms by which sarcomere variants result in the clinical phenotype have not been fully elucidated. Alterations in the sarcomere gene 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 left ventricular ejection fraction (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 submitral 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 and Clinical Course

Although HCM can be compatible with normal life expectancy without limiting symptoms or the need for major treatments in most patients, many patients can experience significant consequences that are attribut-

able to the disease. To this point, there is increasing recognition of patients with HCM identified clinically at  $>60$  years of age with little to no disability. Yet, a multicenter registry report has suggested that the life-long risk of adverse events (eg, mortality, HF, stroke, ventricular arrhythmia, atrial fibrillation [AF]) caused by HCM may be greater among patients with pathogenic or likely pathogenic sarcomeric gene variants or those diagnosed early in life.<sup>1</sup> The large number and diversity of the HCM-associated variants do not allow the specific genotype to be used to inform the anticipated outcomes in individual patients.

Among referral-based cohorts of patients with HCM, many 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 outcomes in patients with HCM 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 significantly lowered HCM mortality rates.<sup>2,3</sup> One of the major treatment initiatives responsible for lowering the mortality rate has been the evolution of sudden cardiac death (SCD) risk stratification strategies based on several major noninvasive risk markers that 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 HF and complications of AF as the predominant cause of disease-related morbidity and mortality and, therefore, the greatest unmet treatment need in adults. Risk for adverse events in HCM, particularly for HF, are likely due to the complex interplay of genetics with environmental factors, such as obesity, hypertension, sleep apnea, and diabetes.<sup>4</sup> Among patients with HCM, cardiometabolic risk factors (eg, obesity, hypertension, diabetes, obstructive sleep apnea) are highly prevalent and are associated with poorer prognosis, highlighting the importance of intensive risk factor modification of traditional risk factors.

## 3. PATHOPHYSIOLOGY

The pathophysiology of HCM consists of dynamic LVOTO, mitral regurgitation (MR), diastolic dysfunction, myocardial ischemia, arrhythmias, metabolic and energetic abnormalities, and potentially 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, the potential presence of such abnormalities should be considered with comprehensive clinical evaluation

and their impact addressed in the management of these patients.

### 3.1. Left Ventricular Outflow Tract Obstruction

LVOTO, either at rest or with provocation, is present in a significant proportion of patients with HCM<sup>1</sup> and primarily caused by SAM of the mitral valve. Obstruction is considered present if peak LVOT gradient is  $\geq 30$  mm Hg. Resting or provoked gradients  $\geq 50$  mm Hg are generally considered capable of causing symptoms and, therefore, are the threshold for contemplating advanced pharmacological or invasive therapies if symptoms are refractory to standard management.

LVOTO in HCM is dynamic and sensitive to ventricular preload, afterload, and contractility.<sup>2</sup> Thus, gradients vary with heart rate, blood pressure, volume status, activity, medications, food, and alcohol intake.<sup>3,4</sup> Provocative maneuvers are recommended if minimal gradients (ie,  $< 30$  mm Hg) are observed at rest. Maneuvers include standing, Valsalva strain, or exercise with simultaneous auscultation or echocardiography.<sup>5–9</sup> Using dobutamine to identify latent LVOTO and eligibility for advanced therapies is not advised due to lack of specificity.<sup>10</sup>

The site and characteristics of obstruction should be identified. Management will change depending on whether the obstruction is deemed to be valvular, dynamic LVOTO, fixed subvalvular, or midcavitary due to hypertrophied/anomalous papillary muscles and/or hyperdynamic LV function with systolic cavity obliteration. If clinical and echocardiographic findings are discordant, invasive assessment for LVOTO may be helpful.<sup>11</sup>

### 3.2. Diastolic Dysfunction

Altered ventricular load with high intracavitary pressures, impaired LV compliance from hypertrophy and fibrosis, altered energetics, microvascular ischemia, and delayed inactivation from abnormal intracellular calcium reuptake are features of HCM that contribute to diastolic dysfunction.<sup>1–3</sup> Additionally, impaired relaxation can be identified in young sarcomere gene variant carriers with normal LV wall thickness, suggesting that diastolic abnormalities can be an early manifestation of pathogenic sarcomere variants.<sup>4</sup> In some patients, increased stiffness and severe hypertrophy significantly compromise ventricular cavity size and stroke volume and may result in restrictive physiology. Diastolic dysfunction can contribute to decreased exercise capacity and adverse prognosis independent of LVOTO.<sup>2,5,6</sup> Determining if exercise intolerance or symptoms are due to diastolic dysfunction may require invasive testing. With impaired 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

MR can occur secondarily from SAM or primarily from leaflet abnormalities and, regardless of etiology, can contribute to symptom burden. Common primary abnormalities of the mitral valve in patients with HCM include excessive leaflet length, anomalous papillary muscle insertion, and anteriorly displaced papillary muscles.<sup>1–3</sup> MR jet characteristics can provide insight to etiology as MR caused by SAM is typically mid-to-late systolic in timing and posterior or lateral in orientation, owing to the anterior distortion of the mitral valve and compromised leaflet coaptation.<sup>4</sup> However, central and anterior jets may also result from SAM of the mitral valve. For patients in whom invasive septal reduction therapy (SRT) is being contemplated, close examination of the mitral valve is required to determine the optimal invasive approach and potential need for concomitant mitral valve intervention.<sup>5,6</sup>

Factors that affect the severity of LVOTO may also affect the degree of MR, thus imaging should be performed at rest and with provocation. Additionally, variation in the degree of MR may underlie some of the variation in symptoms reported by patients.

### 3.4. Myocardial Ischemia

Patients with HCM may be susceptible to myocardial ischemia due to potential mismatch between myocardial oxygen supply and demand. Myocardial hypertrophy, microvascular dysfunction with impaired coronary flow reserve, and medial hypertrophy and reduced density of the intramural arterioles are common findings in HCM.<sup>1,2</sup> These abnormalities may be exacerbated by the presence of hyperdynamic systolic function and LVOTO with high intracavitary pressures.<sup>3,4</sup> 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.<sup>5</sup> Apical myocardial ischemia and injury (with or without midventricular obstruction) may be one of the mechanisms that contributes to the development of LV apical aneurysms, which may carry increased risk of HF, stroke, and ventricular arrhythmias.<sup>6,7</sup> 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 may rarely cause myocardial ischemia in a subset of patients.<sup>8–12</sup>

### 3.5. Autonomic Dysfunction

Patients with HCM may have autonomic dysfunction, with impaired heart rate recovery and inappropriate vasodilatation.<sup>1–4</sup> The prevalence of autonomic dysfunction in HCM is uncertain, although studies have described an abnormal blood pressure response to exercise in approximately 25% of patients.<sup>2–4</sup> Whether these findings were due to pure autonomic dysfunction, LVOTO, or other

conditions is unclear. Currently, no specific recommendations exist for assessment or treatment of autonomic dysfunction in patients with HCM.

#### 4. SHARED DECISION-MAKING

Recommendation for Shared Decision-Making Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
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 and caregivers to express their goals and concerns. <sup>1-5</sup>

##### Synopsis

Shared decision-making is a dialogue that allows patients, families, and health care professionals to work together to select options that fully consider the input, values, and preferences for the patient. This approach has been shown to improve confidence in clinical decisions and improved health outcomes.<sup>6</sup> Although shared decision-making 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.

##### Recommendation-Specific Supportive Text

1. In the management of HCM, decisions around genetic testing, ICD implantation, advanced therapies for relief of LVOTO, and participation in competitive or high-intensity exercise are particularly critical 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 (as described in detail in **Section 5, “Multidisciplinary HCM Centers”**).

#### 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 (Tables 4 and 5). <sup>1-3</sup>
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 (Table 4). <sup>4-14</sup>

##### 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.<sup>5-7,15</sup> The main goal of the HCM centers' framework is to optimize care and counseling of patients with HCM and their families. The proposed approach recognizes that a spectrum of expertise exists and is inclusive of roles for cardiologists working outside of HCM centers, those working in primary HCM centers, and those working at fully comprehensive HCM centers. Cardiologists practicing outside of HCM centers have a critical role in many aspects of HCM management (Table 4) 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.<sup>7</sup>

##### 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 rates, as well as mitral valve replacement.<sup>1-3,16,17</sup> 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. Primary HCM centers that perform invasive SRTs should ensure outcomes for safety and benefit, commensurate with that reported from comprehensive HCM centers (Tables 4 and 5). 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 HCM center that offers all treatment options to ensure appropriate patient participation in the decision-making.
2. Given the unique needs of patients with HCM in clinical cardiovascular practice, as well as the specialized training and interpretation associated with many of the procedures and testing for this complex condition, challenging management decision-making can arise for which referral to or



**Table 4. Suggested Competencies of Comprehensive and Primary HCM Centers**

Potential HCM Care Delivery Competencies	Comprehensive HCM Center	Primary HCM Center	Referring Centers and 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 and transplant	X	X	
Counseling and performing family screening (imaging and genetic)	X	X	X
Genetic testing and counseling	X	X	*
SCD risk assessment	X	X	X
COR 1 and COR 2a ICD decision-making with adult patients	X	X	X
COR 2b ICD decision-making with adult patients	X		
ICD implantation (adults)	X	X	*
ICD decision-making and implantation with children and adolescents and their parents and caregivers	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	*	
Pharmacological therapy for 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; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LVOTO, left ventricular outflow tract obstruction; SCD, sudden cardiac death; SRT, septal reduction therapy; and TTE, transthoracic echocardiography.

**Table 5. 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)	≤5	≤5
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
Symptomatic improvement (eg, ≥1 NYHA functional 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.

consultation with an HCM center would be reasonable.<sup>4–13</sup> Referral to a comprehensive HCM center should specifically be considered for those patients with HCM who are candidates for any procedure that requires specialized expertise, including complex invasive SRTs,<sup>3,8,9</sup> catheter ablation for ventricular and complex atrial tachyarrhythmias,<sup>10,11</sup> and advanced HF therapies, including transplant.<sup>12,13</sup> In addition, referral to a comprehensive HCM center can aid in complex disease-related management decisions including, but not limited to, genetic counseling, challenging primary prevention ICD decision-making, as well as counseling patients with HCM on sports participation.<sup>4</sup>

6. DIAGNOSIS, INITIAL EVALUATION, AND FOLLOW-UP

6.1. Clinical Diagnosis

Recommendation for Clinical Diagnosis		
Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
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 (Tables 6 and 7). <sup>1–6</sup>

Synopsis

Clinical evaluation for HCM may be triggered by the identification of a family history of HCM; by symptoms including a cardiac event; by detection of a heart murmur



**Table 6. 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
Youth and adolescence	Skeletal muscle weakness or movement disorder	Friedreich's ataxia Danon disease Mitochondrial disease	Biochemical screening Neuromuscular assessment Genetic testing
Adulthood	Movement disorder, peripheral neuropathy, renal dysfunction	Anderson-Fabry disease Friedreich's ataxia infiltrative disorders (eg, amyloidosis) Glycogen storage diseases Mitochondrial disease	Biochemical screening Neuromuscular assessment Genetic testing

HCM indicates hypertrophic cardiomyopathy.

during physical examination; during an echocardiographic examination performed for other indications; or by abnormal results on a 12-lead ECG. A proper clinical evaluation should begin 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.

**Table 7. 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.

Recommendation-Specific Supportive Text

1. Many patients with HCM are asymptomatic and are 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 unexpected or sudden death. Assessment of overall fitness and functional capacity, and symptoms in response to exertion—chest pain, dyspnea, palpitations, and syncope—should also be performed. Associated syndromic or systemic and extracardiac symptoms or organ involvement are also documented. Alternative etiologies should be excluded, including athletic remodeling, uncontrolled hypertension, renal disease, or infiltrative diseases. In neonates, a history of maternal gestational diabetes should be considered and, in infants <1 year of age, exclude systemic disease (Table 6).

Classically, patients with HCM have a harsh crescendo-decrescendo systolic murmur often due to SAM of the mitral valve with LVOTO, prominent apical point of maximal impulse, abnormal carotid pulse, and a fourth heart sound. Presence of out-flow tract obstruction should be sought at rest and with provocative maneuvers when possible (Valsalva maneuver, standing from the squatting position). SAM related to an elongated anterior mitral valve leaflet and papillary muscle abnormalities may result in leaflet separation or poor coaptation with posteriorly directed MR in late systole over the mitral position. Those without LVOTO (provocable or resting) may have a normal physical examination.<sup>1-6</sup>

6.2. Echocardiography

Recommendations for Echocardiography Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. In patients with suspected HCM, a transthoracic echocardiogram (TTE) is recommended in the initial evaluation. <sup>1-6</sup>
1	B-NR (children)	2. In patients with HCM who have 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 (Figure 1). <sup>7-14</sup>
	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. <sup>9,14-17</sup>
1	B-NR	4. For patients with HCM and resting peak LVOT gradient <50 mm Hg, a TTE with provocative maneuvers is recommended. <sup>18-21</sup>
1	B-NR	5. For symptomatic patients with HCM who do not have a resting or provokable outflow tract peak gradient ≥50 mm Hg on TTE, exercise TTE is recommended for the detection and quantification of dynamic LVOTO. <sup>20-25</sup>
1	B-NR	6. For patients with HCM who are undergoing surgical septal myectomy, intraoperative transesophageal echocardiogram (TEE) is recommended to assess mitral valve anatomy and function and adequacy of septal myectomy. <sup>26-29</sup>
1	B-NR	7. For patients with HCM who are undergoing alcohol septal ablation, TTE or intraoperative TEE with intracoronary ultrasound-enhancing contrast injection of the candidate's septal perforator(s) is recommended. <sup>30-34</sup>
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. <sup>35-38</sup>
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 (Figure 1, Table 7). <sup>9-57,14,32</sup>
1	B-NR	10. Screening: In individuals who are genotype-positive, phenotype-negative, echocardiography is recommended at periodic intervals depending on age (1-2 years in children and adolescents, 3-5 years in adults) and change in clinical status (Figure 1, Table 7). <sup>39-43</sup>
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. <sup>26-29</sup>
2a	B-NR	12. For patients with HCM in whom the diagnosis 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 are contraindicated. <sup>44,45</sup>
2a	C-LD	13. For asymptomatic patients with HCM who do not have a resting or provokable outflow tract peak gradient ≥50 mm Hg on standard TTE, exercise TTE is reasonable for the detection and quantification of dynamic LVOTO. <sup>15,19,20,22-25</sup>

Synopsis

Cardiac imaging has an essential role in the 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 has 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.<sup>1-6</sup>
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.<sup>7-14</sup>
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 these changes in patients with new or worsening symptoms.<sup>9,14-17</sup>
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 sustained Valsalva or squat-to-stand (or simply standing) maneuvers to uncover the presence of LVOTO, which may inform the care of the individual.<sup>15,18-21</sup> 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 and can be missed on resting echocardiography in up to 50% of patients with obstructive physiology.<sup>16</sup> Maneuvers performed during a resting TTE to provoke an LVOT gradient (eg, Valsalva) can be variable because of inconsistencies in instruction and patient effort. Stress echocardiography (focusing on LVOTO rather than regional wall motion), 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.<sup>20,22–25</sup> Postprandial exercise may also be useful, particularly if the patient expresses increased symptoms after meals.<sup>46</sup> Exercise testing is only useful in older children, typically  $>7$  to 8 years of age, or when the child is able to cooperate with testing, because young children are often unable to cooperate with exercise testing.
6. Intraoperative 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.<sup>26–29</sup>
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.<sup>6,30–34</sup> In cases where transthoracic image quality is suboptimal, intraprocedural TEE with ultrasound-enhancing agents can be used to guide septal ablation therapy.<sup>6,34</sup>
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.<sup>35,37,38,47,48</sup>
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.<sup>12,39,40</sup> The median age at HCM onset was 8.9 (4.7–13.4) years, with earlier onset in male individuals, those with family history of SCD, and pathogenic variants in *MYH7/MYBPC3*.<sup>39</sup> Likewise, the median time from HCM onset to a major cardiac event, including death, SCD, or cardiac intervention (eg, myectomy, ICD), was 1.5 years.<sup>39,40,49</sup> Taken together, these data support family screening initiated in childhood and repeated on a periodic basis in children and adults (Table 7). Changes in LV systolic strain and diastolic function can precede definitive hypertrophy.<sup>50–52</sup> 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.<sup>2,53</sup> However, 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; therefore, continued screening into adulthood is warranted, although frequency of screening can be lowered because the penetrance rate is lower in individuals who are  $>18$  years of age.<sup>39–43</sup> Although an absence of systematic evidence is observed, most physicians continue clinical screening until midlife (approximately 50 years of age) 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.<sup>29</sup>
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 an ultrasound-enhancing agent or CMR imaging can aid in detection of apical hypertrophy, aneurysm, and thrombus.<sup>44,45</sup>
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).<sup>20,22–25</sup>

6.3. CMR Imaging

Recommendations for CMR Imaging Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. For patients suspected of having HCM in whom echocardiography is inconclusive, CMR imaging is indicated for diagnostic clarification. <sup>1-7</sup>
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 (Figure 1). <sup>1-7</sup>
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 or 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 replacement fibrosis with late gadolinium enhancement (LGE). <sup>1-15</sup>
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. <sup>16-20</sup>
2b	C-EO	5. For patients with HCM, repeat contrast-enhanced CMR imaging on a periodic basis (every 3-5 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 8).

Synopsis

CMR imaging provides high spatial resolution and tomographic imaging of the heart and assessment of myocardial replacement fibrosis (LGE) after contrast administration.<sup>1,2</sup> These attributes make CMR imaging well-suited for characterizing the diverse phenotypic expressions of HCM. CMR imaging is therefore a complementary imaging technique in the evaluation of HCM patients for diagnosis, risk prediction, and preprocedural planning for SRT.<sup>1,7</sup>

CMR imaging produces images with sharp contrast between the blood pool and myocardium. This allows for accurate LV wall thickness measurements, quantification of LV and RV chamber size, LV mass, systolic function, and identification of LVH not well visualized by echocardiography.<sup>1-7</sup> In addition, optimal images of LV apical aneurysms and structural abnormalities of the mitral valve and subvalvular apparatus that contribute to LVOTO are produced, which may impact management strategies.<sup>7-9,16-19</sup> Extensive LGE (ie, myocardial replacement fibrosis) represents a noninvasive marker for increased risk for potentially life-threatening ventricular tachyarrhythmias and progression to systolic dysfunction.<sup>11-14</sup> 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).

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 nondiagnostic or inconclusive, CMR imaging is an important adjunctive test to clarify diagnosis.<sup>1-7</sup> 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.<sup>4-6</sup>
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).<sup>7</sup>
3. Maximal LV wall thickness measurements can be underestimated (or overestimated) with echocardiography compared with CMR imaging.<sup>1-7</sup> This can have direct management implications for diagnosis and SCD risk assessment, because LV wall thickness is a major risk marker for SCD.<sup>4-6,10</sup> In addition, apical aneurysms may not always be detected by echocardiography.<sup>8,9</sup> Extensive LGE, often occupying multiple LV segments, is associated with increased risk for life-threatening ventricular arrhythmias, independent of location or pattern within the LV wall.<sup>11-13</sup> 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.<sup>12</sup> However, no consensus on the optimal quantification technique(s) has been determined. LGE can serve as an arbiter in decision-making on whether to pursue ICD placement when risk remains ambiguous after standard risk stratification.<sup>12</sup> Patients with HCM and systolic dysfunction (EF  $< 50\%$ ), adverse LV remodeling with ventricular cavity enlargement and wall thinning because of scarring, are at increased risk for lethal ventricular tachyarrhythmias and increased HF symptoms.<sup>14,15</sup> CMR can provide quantitative



EF assessment in whom determination of systolic function remains uncertain with echocardiography. Absence of (or minimal) LGE is associated with lower risk of SCD.<sup>12,13,21</sup>

4. Because of specific anatomic features of the LVOT, some patients with HCM will be more suitable candidates for septal myectomy than for percutaneous alcohol ablation.<sup>16–20</sup> 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.<sup>16–20</sup>
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.<sup>8,10,15,22,23</sup>

6.4. Cardiac CT

Recommendation for Cardiac 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. <sup>1–3</sup>

Synopsis

Cardiac CT provides excellent spatial resolution that allows 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 the ability of CT to assess myocardial fibrosis, although this adds further radiation exposure and needs further validation.<sup>2,3</sup> 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 (“Angiography and Invasive Hemodynamic Assessment”).**

Recommendation-Specific Supportive Text

1. Although not commonly used, 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.<sup>1–3</sup>

6.5. Heart Rhythm Assessment

Recommendations for Heart Rhythm Assessment Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
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 1-2 years) (Figure 1, Table 7). <sup>1–3</sup>
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 1-2 years) to identify patients who are at risk for SCD and to guide management of arrhythmias (Figure 1). <sup>4–6</sup>
1	B-NR	3. In patients with HCM who develop palpitations or lightheadedness, extended (>24 hours) electrocardiographic monitoring or event recording is recommended for arrhythmia diagnosis and clinical correlation. <sup>6</sup>
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 (Figure 1, Table 7). <sup>1–3</sup>
1	B-NR	5. In patients with HCM who are deemed to be at high risk for developing AF based on the presence of risk factors or as determined by a validated risk score, and who are eligible for anticoagulation, extended ambulatory monitoring is recommended to screen for AF as part of initial evaluation and annual follow-up (Figure 1). <sup>7–12</sup>
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 1-2 years). <sup>7–12</sup>

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 follow-up. Ambulatory monitoring is necessary in the evaluation of 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. In patients with additional risk factors, periodic screening of AF may be necessary in order to intervene promptly.



### 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.<sup>13</sup> The 12-lead ECG is also useful in identifying other abnormalities, such as Wolff-Parkinson-White pattern, which may suggest certain phenocopies of HCM.<sup>1-3</sup> 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.<sup>13</sup> A 12-lead ECG is commonly used in the screening for HCM, including family members without LVH.<sup>1-3</sup> There is considerable debate regarding the utilization of the 12-lead ECG in screening healthy adolescents for HCM as part of preparticipation athletic screening.<sup>14</sup>
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.<sup>4-6</sup> 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.<sup>15</sup> There is also evidence that longer periods of monitoring will diagnose more episodes of NSVT<sup>16</sup>; 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, such that the proper diagnosis is made. Clinical studies have shown a broad spectrum of arrhythmias in patients with HCM, most of them not lethal; thus, clinical correlation of symptoms with monitor findings is essential.<sup>6</sup> In some patients with infrequent symptoms, portable event monitors or implantable monitors may be warranted.
4. ECGs are considered to be a standard part of the initial screening of relatives of patients with HCM.<sup>1-3</sup> Electrocardiographic abnormalities may precede the development of LVH in children who are gene carriers; thus, ECG is considered more sensitive than echocardiography as a screening tool in families with HCM.<sup>13</sup>

5. AF is associated with adverse outcomes (including stroke) in patients with HCM. Although several studies show that asymptomatic AF is present in up to 50% of patients,<sup>7-11</sup> it is unclear that asymptomatic episodes, especially if short in duration (<30 seconds) and low burden (<1%), contribute to adverse outcomes. Predictors of clinically important AF include left atrial dilatation, increasing age, duration of disease, and NYHA functional class III to IV HF. Thus, patients with these characteristics should be assessed more frequently and possibly including extended (duration determined by clinical circumstances) ambulatory electrocardiographic screening to provide prompt intervention when AF is detected. To facilitate identifying patients who would benefit the most from screening, a risk score (the HCM-AF score) was developed that includes the aforementioned risk factors and allows prognostic estimation of the risk of developing AF. The model was developed from a cohort of 1900 patients with HCM and subsequently validated; in the development cohort, 17.2% of high-risk patients developed AF (rate 3.4% per year), whereas in the external validation cohort, 13.3% of high-risk patients developed AF (rate 2.7% per year).<sup>12</sup> In the HCM-AF score study, AF was defined as ≥1 clinically overt episodes documented by ECG or telemetry, requiring medical attention and consideration for treatment within 10 years of initial visit.<sup>12</sup>
6. AF is associated with adverse outcomes (including stroke) in patients with HCM. Although several studies show that asymptomatic AF is present in up to 50% of patients,<sup>7-11</sup> it is unclear whether asymptomatic episodes, especially if short in duration, contribute to adverse outcomes. Predictors of AF include left atrial dilatation, advanced age, and NYHA functional class III to class IV HF. Yet, in patients without risk factors, the risk of developing AF is low, although not zero: approximately 3.3% at 5 years.<sup>12</sup>

### 6.6. Angiography and Invasive Hemodynamic Assessment

Recommendations for Angiography and Invasive Hemodynamic Assessment		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. For patients with symptomatic HCM for whom there is uncertainty regarding the presence or severity of LVOTO on noninvasive imaging studies, invasive hemodynamic assessment with cardiac catheterization is recommended. <sup>1-4</sup>
1	B-NR	2. In patients with HCM who have symptoms or evidence of myocardial ischemia, coronary angiography (CT or invasive) is recommended. <sup>5</sup>
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. <sup>6</sup>

Synopsis

Echocardiography remains the gold standard for the reliable, noninvasive assessment of dynamic outflow tract obstruction in 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. In addition, invasive hemodynamic assessment can be useful to guide management in carefully selected patients with HCM who have persistent symptoms despite optimal medical therapy to more fully characterize the hemodynamic profile, presence or absence of LVOTO, and contribution of other disease states, such as chronic primary or secondary pulmonary hypertension or concomitant valve disease. It is crucial that the operator performing the assessment be experienced in such cases and use appropriate catheters (eg, end-hole pigtail, halo), while avoiding pitfalls such as catheter entrapment.

Recommendation-Specific Supportive Text

1. In patients with a clinical history of significant, limiting HF symptoms (NYHA functional class II to 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.<sup>1,2</sup> 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. Outflow gradients can be extremely dynamic, with spontaneous variability influenced by altered myocardial contractility and loading conditions at the time of cardiac imaging testing.<sup>2</sup> Several 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), or upper or lower extremity exercise.<sup>3,4</sup> Documentation of the LVOT gradient at rest and, if not severe ( $\geq 50$  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 and false-negative rates are associated with nuclear and echocardiographic stress testing. Coronary angiography is useful in patients with HCM when findings of CAD could aid in patient management.<sup>6</sup>

3. Coronary angiography is usually performed in patients who are scheduled for surgical myectomy and have risk factors for coronary atherosclerosis and significant myocardial bridging. Findings of extensive CAD would inform decision-making regarding altering the strategy to surgical myectomy combined with coronary bypass surgery.<sup>6</sup> 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 the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. For symptomatic patients with HCM who do not have resting or provokable outflow tract peak gradient $\geq 50$ mm Hg on TTE, exercise TTE is recommended for the detection and quantification of dynamic LVOTO. <sup>1-6</sup>
1	B-NR	2. In patients with nonobstructive HCM and advanced HF (NYHA functional class III to class IV), 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. <sup>7-9</sup>
1	B-NR	3. In pediatric patients with HCM, regardless of symptom status, exercise stress testing is recommended to determine functional capacity and to provide prognostic information. <sup>10</sup>
2a	B-NR	4. In adult patients with HCM, exercise stress testing is reasonable to determine functional capacity and to provide prognostic information as part of initial evaluation. <sup>9,11,12</sup>
2a	C-LD	5. For asymptomatic patients with HCM who do not have a resting or provokable outflow tract peak gradient $\geq 50$ mm Hg on standard TTE, exercise TTE is reasonable for the detection and quantification of dynamic LVOTO. <sup>1,3-6,13,14</sup>
2b	C-LD	6. In patients with obstructive HCM and ambiguous functional capacity, exercise stress testing may be reasonable to guide therapy (Figure 1). <sup>15,16</sup>
2b	C-EO	7. In patients with HCM for whom it is unclear if their functional capacity has declined, exercise stress testing may be considered every 2 to 3 years (Figure 1).

Synopsis

In patients with HCM, exercise stress testing is safe and provides information on the severity and mechanism of functional limitation. Particularly when combined with

simultaneous analysis of respiratory gases (ie, cardiopulmonary exercise test [CPET]), lower exercise capacity is strongly prognostic of adverse events, including death, HF, and ventricular arrhythmias in both adults and children. The accuracy of exercise testing in assessing myocardial ischemia can be limited if there are resting ECG and/or wall motion abnormalities. Conversely, myocardial perfusion imaging using single-photon or positron emission tomography has a high rate of false-positive findings for epicardial CAD, with perfusion abnormalities detectable in >50% of patients, most of whom have no significant epicardial CAD. In patients with HCM with a high clinical suspicion for myocardial ischemia, coronary angiography (CT or invasive) should be considered. Dobutamine is not recommended because diagnostic accuracy for ischemia is limited and induction of intracavitary gradients is nonphysiologic. This section focuses only on the modality of exercise stress testing for its utility in detecting latent LVOT obstruction and exercise capacity as it relates to prognosis and treatment recommendations.

Recommendation-Specific Supportive Text

1. 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 and can be missed on resting echocardiography in up to 50% of patients with obstructive physiology,<sup>17</sup> and maneuvers performed during a resting TTE to provoke an LVOT gradient (eg, 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.<sup>1,3–6</sup> Postprandial exercise may also be useful, particularly if the patient expresses increased symptoms after meals.<sup>18</sup> Exercise testing is only useful in older children, typically >7 to 8 years of age, or when able to cooperate with the testing protocol.
2. CPET is a standard part of the evaluation for patients with severe symptoms, including those being considered for cardiac transplantation.<sup>7–9</sup>
3. In pediatric patients with HCM, there is a strong association of exercise-induced ischemic electrocardiographic changes and abnormal blood pressure response with lower transplant-free survival.<sup>10</sup> Exercise-induced ischemia in pediatric patients is also independently associated with a higher risk of SCD. Exercise testing is only useful in older children, typically >7 to 8 years of age, or when able to cooperate with the testing protocol.
4. Exercise stress testing provides information on the severity and mechanism of functional limitation (eg, provokable LVOTO, abnormal blood pressure

response, chronotropic incompetence, arrhythmias, ischemia, and/or reduced heart rate reserve). When available, the use of CPET, with simultaneous measurement of respiratory gases, is preferred. Data from >9000 patients show that reduced peak oxygen consumption and submaximal exercise parameters, such as ventilatory efficiency and anaerobic threshold, are associated with a higher rate of ventricular arrhythmias, progression to advanced HF, and higher all-cause mortality.<sup>9,11,12</sup>

5. 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).<sup>1,3–6</sup>
6. In patients with symptomatic LVOTO who are undergoing septal myectomy, lower preoperative peak VO<sub>2</sub> and lack of improvement in peak VO<sub>2</sub> postoperatively despite resolution of LVOTO are associated with higher mortality.<sup>15,16</sup> Therefore, significantly reduced exercise capacity measured with or without use of CPET compared with the norm for the patient's age and sex may prompt earlier consideration for advanced therapies to alleviate LVOTO.
7. A decline in exercise capacity relative to the norm for a patient's age and sex can impact decisions on whether to escalate therapies, particularly if the patient's functional capacity is ambiguous based on their clinical history.

6.8. Genetics and Family Screening

Recommendations for Genetics and Family Screening Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
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. <sup>1–7</sup>
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). <sup>8–11</sup>
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 workup including genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy (“HCM phenocopies”) is recommended. <sup>12–14</sup>
1	B-NR	4. In patients with HCM, genetic counseling by an expert in the genetics of cardiovascular disease is recommended so that risks, benefits, test results, and their clinical significance can be reviewed and discussed with the patient in a shared decision-making process. <sup>1–3,15</sup>

Recommendations for Genetics and Family Screening (Continued)		
COR	LOE	Recommendations
1	B-NR	5. When performing genetic testing in a proband with HCM, the initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM.* <sup>8,11,16,17</sup>
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. <sup>3,7,12,18–20</sup>
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. <sup>21,22</sup>
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. <sup>23–25</sup> (Figures 1 and 2).
1	B-NR	9. In affected families with HCM, preconception and prenatal reproductive and genetic counseling should be offered. <sup>1–3,15</sup>
2b	B-NR	10. In adult patients with HCM, the usefulness of genetic testing in the assessment of risk of SCD is uncertain. <sup>10,25–27</sup>
2b	B-NR	11. In patients with HCM who have a variant of uncertain significance (VUS), the usefulness of clinical genetic testing of phenotype-negative relatives for the purpose of variant reclassification is uncertain. <sup>4,7,8,28</sup>
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 or likely benign variants), cascade genetic testing of the family is not useful. <sup>4,8–10</sup>
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 a VUS, likely benign, or benign variant during follow-up. <sup>23,29–32</sup>

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

Synopsis

Genetic testing has 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. 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 obtain 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 impli-

cations of having a genetic disease<sup>33</sup> should be conveyed. Genetic assessment should ideally be performed in a specialized multidisciplinary HCM center with experience in all aspects of the genetic counseling and testing process.<sup>1</sup>

Recommendation-Specific Supportive Text

- Obtaining 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 the diagnosis and management of individuals with HCM in the family and subsequent clinical and genetic screening of at-risk family members.<sup>23–25</sup>
- 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.<sup>8–11</sup> 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.
- 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),<sup>13</sup> *GLA* (Fabry disease),<sup>34</sup> 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.
- 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.<sup>1–3,15</sup>
- HCM is predominantly a disease of the sarcomere, and first-line genetic testing primarily includes panel testing for genes with strong evidence for being disease-causing.<sup>11</sup> Genetic testing can be performed using various platforms, including gene panels, exome sequencing, or genome sequencing.<sup>9</sup> Gene panels include 8 sarcomere genes, including *MYH7*, *MYBPC3*, *TNNI3*, *TNNT2*, *TPM1*, *MYL2*, *MYL3*, and *ACTC1*, and identify a disease-causing variant in approximately 30% of sporadic and 60% of familial cases.<sup>4,8–10</sup> Expanding to larger panels usually does



not add diagnostic value.<sup>8,17</sup> Initial genetic testing is usually performed in the index case (proband).<sup>8</sup> 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, recognizing the chance of incidental findings. In up to 40% of patients with HCM, no sarcomere variant is identified, and there is no family history of disease.<sup>26</sup> Identification of a 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 VUS is *de novo*, functional studies) (Figures 1 and 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.<sup>3,7,12,18,19</sup> 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 7). 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.<sup>21,35,36</sup> 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 (Figures 1 and 2).
8. Determining pathogenicity of variants relies on a weight of collective evidence based on American College of Medical Genetics and Genomics criteria<sup>16</sup> and may change over time. 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.<sup>23–25</sup> 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.<sup>29</sup> This highlights the importance of having the necessary expertise within a specialized multidisciplinary clinic setting to not only perform genetic testing and interpret the results but to reevaluate the pathogenicity of variants during follow-up.<sup>23,24</sup> The American College of Medical Genetics and Genomics guidelines recommend clinical laboratories implement policies to reevaluate variants based on new information about the patient or family phenotype.<sup>32</sup> The American College of Medical Genetics and Genomics also highlights the importance of notifying a patient undergoing genetic testing that the genetic interpretation may change over time, and that the patient may be recontacted with updated results.<sup>31</sup>

9. In autosomal dominant HCM, there is a 1 in 2 (50%) chance of passing on the disease-causing gene variant to each offspring of an affected individual, although variable penetrance can result in differences in onset and severity of clinical manifestations.<sup>37</sup> Prenatal genetic counseling is helpful in explaining the risk of transmission of disease, as well as discussing potential reproductive options.<sup>1–3,15</sup> 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 some evidence exists that adults 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 adult patients with HCM. Several studies have reported that patients with HCM who carry pathogenic or likely pathogenic sarcomere variants have a worse prognosis compared with patients with HCM who are sarcomere variant-negative.<sup>10,12,25,27,38</sup> This includes earlier onset of disease, higher incidence of SCD, higher incidence of AF and ventricular arrhythmias, HF, and overall mortality.<sup>10,12,25,27,38</sup> In pediatric patients, the presence of sarcomeric variants is more closely associated with SCD and has been incorporated into one of the SCD risk tools.<sup>38</sup>
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 (Figures 1 and 2). Genetic testing in a

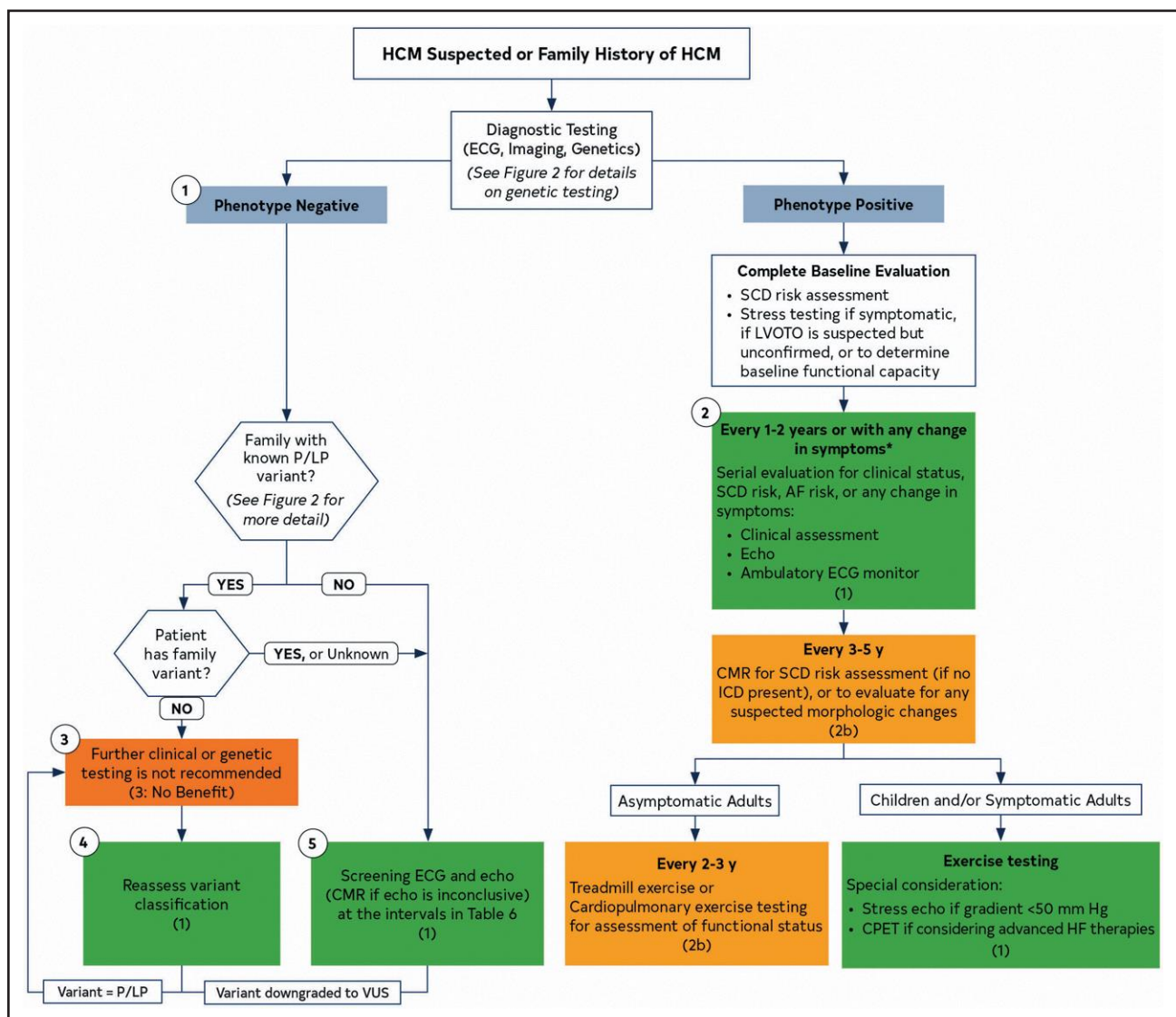


phenotype-negative relative without a known genetic diagnosis in the proband has a very low yield of identifying a genetic cause of HCM, and a negative test in this situation will not change recommendations for ongoing clinical screening.<sup>4,7,8,28</sup> Identification of a VUS in a proband is not 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 (Figures 1 and 2).

12. If genetic testing does not identify a pathogenic variant in a patient with HCM (ie, only identifies

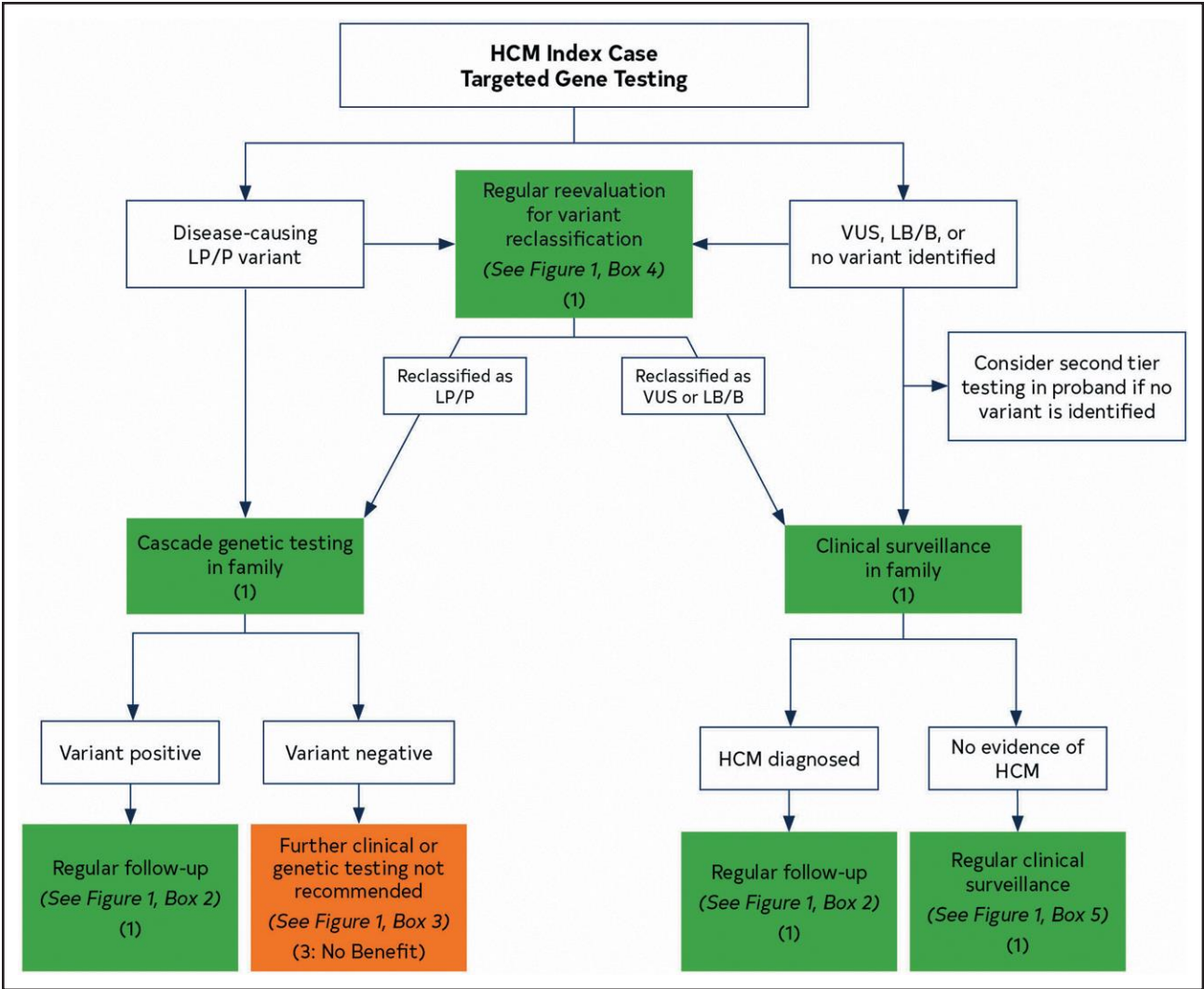
benign or likely benign variants), there is no indication to do genetic testing in family members as the identification of such variants will not change clinical management, including the need for continued clinical screening.<sup>4,8–10</sup>

13. In genotype-negative relatives of individuals with genotype-positive HCM, no further clinical follow-up is required (Figures 1 and 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.<sup>23,29,30</sup> 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.<sup>31,32</sup>



**Figure 1. Recommended Evaluation and Testing for HCM.**

Colors correspond to Table 3. \*The interval may be extended, particularly in adult patients who remain stable after multiple evaluations. AF indicates atrial fibrillation; CMR, cardiovascular magnetic resonance; CPET, cardiopulmonary exercise test; ECG, electrocardiography/electrocardiogram; echo, echocardiography/echocardiogram; 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.



**Figure 2. Genetic Testing Process in HCM.** Colors correspond to Table 3. HCM indicates hypertrophic cardiomyopathy; LB/B, likely benign/benign; LP/P, likely pathogenic or pathogenic; and VUS, variant of unknown significance.

6.9. Individuals Who Are Genotype-Positive, Phenotype-Negative

Recommendations for Individuals Who Are Genotype-Positive, Phenotype-Negative		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
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 1-2 years in children and adolescents and every 3-5 years in adults) and change in clinical status (Figures 1 and 2, Table 7). <sup>1-5</sup>
2a	B-NR	2. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive sports of any intensity is reasonable. <sup>6,7</sup>
3: No benefit	B-NR	3. In individuals who are genotype-positive, phenotype-negative for HCM, ICD is not recommended for primary prevention. <sup>2-6,8</sup>

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.<sup>1,5,8</sup> 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.<sup>9-12</sup> 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.<sup>1,5</sup> However, 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.<sup>2,4,8</sup> A third of patients who developed clinical HCM required medical, surgical, or device therapy before 18 years of age.<sup>4</sup> Phenotype conversion can occur in young adults and, therefore, continued screening into adulthood is warranted,<sup>1</sup> although frequency of screening can be lowered because disease penetrance is lower in individuals who are >18 years of age.<sup>3</sup> Although there is an absence of systematic evidence, most physicians continue clinical screening until midlife (approximately 50 years of age) because disease can manifest in adults, albeit at a lower frequency.
2. Sudden death in genotype-positive, phenotype-negative individuals is rare.<sup>6</sup> No accurate risk prediction models for SCD exist in genotype-positive, phenotype-negative individuals currently. In a recent prospective registry, no arrhythmic events in genotype-positive, phenotype-negative individuals (total of 126) were observed, including those exercising vigorously or participating in competitive athletics.<sup>7</sup> 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. This is appropriate every 1 to 2 years to assess the safety of ongoing competitive athletics participation.
3. ICDs are not offered for primary prevention in genotype-positive, phenotype-negative individuals given the low risk of SCD. Similarly, preemptive medical therapy is not offered in genotype-positive, phenotype-negative individuals. In a small pilot 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.<sup>13</sup> However, the trial was not powered to detect effects on clinical outcomes.

7. SCD RISK ASSESSMENT AND PREVENTION

7.1. SCD Risk Assessment

7.1.1. SCD Risk Assessment in Adults With HCM

Recommendations for SCD Risk Assessment in Adults With HCM Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. In adult 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 factors (Figures 1 and 3, Table 8) <sup>1–25</sup> : a. Personal history of cardiac arrest or sustained ventricular arrhythmias; b. Personal history of syncope suspected by clinical history to be arrhythmic; c. Family history in close relative of premature HCM-related sudden death, cardiac arrest, or sustained ventricular arrhythmias; d. Maximal LV wall thickness, EF, LV apical aneurysm; e. NSVT episodes on continuous ambulatory electrocardiographic monitoring.
1	B-NR	2. For adult 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 (Table 8). <sup>1,11,12,15–20</sup>
2a	B-NR	3. 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 (Table 8). <sup>2,22</sup>

Synopsis

HCM has been regarded as one of the most common causes of SCD in young people in North America.<sup>1,2,21,22,26–32</sup> Among patients with HCM, younger patients are at higher risk for SCD than older patients.<sup>6,26–30,33–36</sup> There appears to be no sex- or race-based differences in SCD risk.<sup>28,29</sup> 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 (Table 8).<sup>1–22,26–33,37–61</sup> This risk stratification strategy and the penetration of ICDs into clinical practice has substantially reduced disease-related mortality rates.<sup>31,32</sup>

Predictive risk scores are also available that can derive individualized estimated 5-year SCD risk to aid in risk stratification and ICD decision-making in adults and children.<sup>2,22,35,62,63</sup> 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.<sup>1,2,6,22,31,32</sup>

Recommendation-Specific Supportive Text

1. Numerous observational studies of patients with HCM have identified variables associated with increased risk for potentially life-threatening ventricular tachyarrhythmias.<sup>1–22</sup> For this reason, SCD risk assessment at the initial visit and repeated every 1 to 2 years<sup>1,2,31</sup> 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<sup>1,3</sup>; (2) family history of SCD, or sustained ventricular arrhythmias judged definitively or likely attributable to HCM in ≥1 first-degree or other close family members ≤50 years of age<sup>1,2,5,6</sup>; (3) continuous (24- to 48-hour) ambulatory electrocardiographic monitoring to detect NSVT or sustained VT<sup>1,2,6,13,14,22</sup>; (4) history of syncope 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)<sup>1,2,4,22</sup>; and (5) cardiac imaging that helps determine maximal LV wall thickness,<sup>7,9</sup> EF,<sup>10,21,24,25</sup> and presence of apical aneurysm with transmural scar or LGE.<sup>11,12</sup> Because data suggest a lower SCD event rate in stable, older patients with HCM (>60 years of age),<sup>32</sup> the decision regarding ongoing risk assessment is individualized in this subset of patients.
2. CMR imaging may more accurately measure maximal LV wall thickness and detect LV apical aneurysm in some patients with HCM.<sup>11,12,15–17</sup> In addition, extensive myocardial replacement fibrosis, as detected by CMR-derived LGE, is associated with increased risk for potentially life-threatening ventricular arrhythmias.<sup>18–20</sup> For these reasons, if a patient with HCM does not have evidence of increased SCD risk after assessment with family and 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 and extent of LGE.<sup>1,10–12,15–21,24,25,31</sup>

Table 8. Clinical Sudden Death Risk Factors for Adults and Children With HCM

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. <sup>30,31</sup>
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 thickness that corresponds to a z-score ≥20 (and >10 in conjunction with other risk factors) appears reasonable. <sup>32,33</sup>
Unexplained syncope	≥1 unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic (vasovagal) etiology, not 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). <sup>34</sup>
HCM with LV systolic dysfunction	Systolic dysfunction with EF <50% by echocardiography or CMR imaging. <sup>24,27</sup>
LV apical aneurysm	Apical aneurysm defined as a discrete thin-walled dyskinetic or akinetic segment with transmural scar or LGE of the most distal portion of the LV chamber, independent of size. (In children, apical aneurysm is uncommon, and the risk has not been studied.) <sup>15,16</sup>
Extensive LGE on CMR imaging	Extensive LGE, representing replacement fibrosis, either quantified or estimated by visual inspection, comprising ≥15% of LV mass (extent of LGE conferring risk has not been defined in children). <sup>9–11,20–22,25</sup>
NSVT on ambulatory monitor	≥3 beats at ≥120 bpm has generally been used in studies. It would seem most appropriate to place greater weight on NSVT as a risk marker when runs are frequent (eg, ≥3), longer (eg, ≥10 beats), or faster (eg, ≥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. <sup>35–37</sup>
Genotype status	Genotype-positive status (ie, harboring a putatively disease-causing pathogenic/likely pathogenic variant) is associated with higher SCD risk in pediatric patients with HCM. <sup>12,14</sup>

bpm indicates beats/min; CMR, cardiovascular magnetic resonance; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; and VT, ventricular tachycardia.



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.<sup>2,22</sup> 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 the 5-year risk estimate for an individual patient with HCM is undetermined.

7.1.2. SCD Risk Assessment in Children and Adolescents With HCM

Recommendations for SCD Risk Assessment in Children and Adolescents With HCM		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. For children and adolescents 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 factors (Figures 1 and 3, Table 8) <sup>1–8</sup> : a. Personal history of cardiac arrest or sustained ventricular arrhythmias; b. Personal history of syncope suspected by clinical history to be arrhythmic; c. Family history in close relative of premature HCM-related sudden death, cardiac arrest, or sustained ventricular arrhythmias; d. Maximal LV wall thickness, EF, LV apical aneurysm; e. NSVT episodes on continuous ambulatory electrocardiographic monitoring.
1	C-LD	2. For children and adolescents with HCM who have a borderline risk for SCD, or in whom a decision to proceed with ICD placement remains uncertain after clinical assessment that includes personal and family history, echocardiography, and ambulatory electrocardiographic monitoring, CMR imaging is beneficial to assess for extent of myocardial fibrosis with LGE (Table 8). <sup>9–11</sup>
2a	B-NR	3. For patients <16 years of age with HCM, it is reasonable to calculate an estimated 5-year sudden death risk that includes echocardiographic parameters (interventricular septal thickness in diastole, LV posterior wall thickness in end-diastole, left atrial diameter, maximal LVOT gradient) and genotype, which may be useful during shared decision-making for ICD placement (Table 8). <sup>1,12</sup>

Synopsis

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.<sup>1–8,13,14</sup> More recent collaborative studies suggest some, but not all, of the adult risk factors are important in pediatric patients with HCM.<sup>1,4,5</sup> Two risk prediction models for children with HCM have been developed and are being used in clinical practice.<sup>1,12</sup> The risk factors proposed in these guidelines include a combination of adult risk

factors and currently available pediatric-specific information. 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

1. SCD risk assessment at the initial visit and repeated every 1 to 2 years is a critical part of the evaluation of patients with HCM<sup>1–8,13,14</sup> and includes: (1) previous history of cardiac arrest or sustained (>30 seconds or associated with hemodynamic compromise) ventricular arrhythmias; (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; (3) continuous (24- to 48-hour) ambulatory electrocardiographic monitoring to detect NSVT or sustained VT; (4) history of syncope considered likely to be caused by arrhythmia; and (5) cardiac imaging that helps determine maximal LV wall thickness, EF, and presence of apical aneurysm. In pediatric patients, LV wall thickness is commonly reported both as an absolute measurement and standardized z-score adjusted for body surface area. The presence of HCM-associated genetic variants is also included in one of the risk calculators.
2. CMR imaging may more accurately measure maximal LV wall thickness and detect LV apical aneurysm in some patients with HCM.<sup>15–19</sup> In addition, extensive myocardial replacement fibrosis, as detected by CMR-derived LGE, is associated with increased risk for potentially life-threatening ventricular arrhythmias.<sup>20–22</sup> For these reasons, if a patient with HCM does not have evidence of increased SCD risk after assessment with family and 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 and extent of LGE.<sup>15–28</sup> Although CMR imaging may be helpful in pediatric patients with HCM,<sup>9–11</sup> 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 5-year SCD risk estimates for children with HCM, age, echocardiographic LV wall



diameter z-scores, left atrial diameter z-score, maximal instantaneous LVOT gradient with continuous-wave Doppler technique, in addition to history of unexplained syncope, NSVT, with or without genotype status are used.<sup>1,12</sup> The SCD risk estimate does not account for systolic dysfunction (EF <50%), apical aneurysm, exercise-induced ischemia, or LGE.<sup>9–11,29</sup> The contribution of ≥1 of these newer risk markers on the 5-year risk estimate for an individual patient with HCM 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 the Online Data Supplement.		
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. <sup>1–5</sup>
1	B-NR	2. For patients with HCM and previous documented cardiac arrest or sustained VT, ICD placement is recommended (Figure 3, Table 8). <sup>2–6</sup>
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 (Figure 3, Table 8) <sup>2,37–21</sup> : 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 with transmural scar or LGE; 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 (Figure 3, Table 8). <sup>22–30</sup>
2a	B-NR	5. For patients with HCM 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 (Figure 3, Table 8). <sup>3,19,29,30</sup>
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 (Figure 3, Table 8). <sup>2,3,16,19,31–33</sup>
2b	B-NR	7. In pediatric patients with HCM, it can be useful to consider additional factors such as extensive LGE on contrast-enhanced CMR imaging and systolic dysfunction in risk stratification for ICD shared decision-making (Figure 3, Table 8). <sup>34,35</sup>

Recommendations for ICD Placement in High-Risk Patients With HCM (Continued)		
COR	LOE	Recommendations
3: Harm	B-NR	8. In patients with HCM without risk factors, ICD placement should not be performed. <sup>2</sup>
3: Harm	B-NR	9. In patients with HCM, ICD placement for the sole purpose of participation in competitive athletics should not be performed. <sup>36</sup>

Synopsis

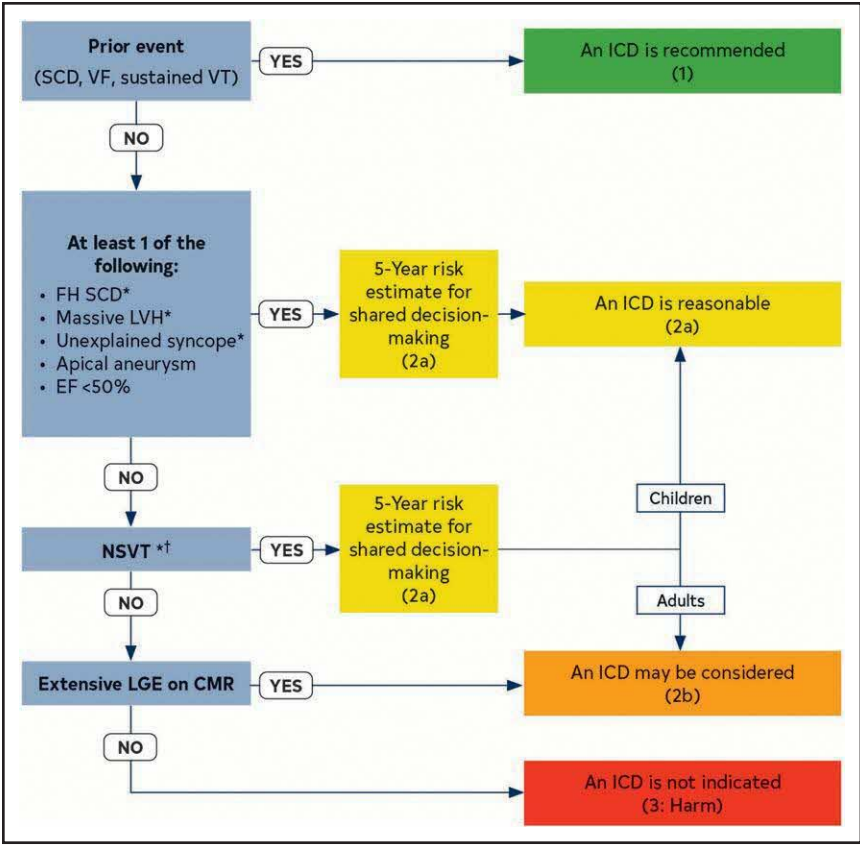
In patients with HCM, risk stratification and selection of patients for prophylactic ICD therapy continues to evolve.<sup>1–28,31–35,37</sup> The proven efficacy of the ICD has placed increasing weight on the importance of accurate selection of patients for device therapy.<sup>4,5,28,31–33,38</sup> In 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 that have a high sensitivity in predicting those patients with HCM at greatest risk SCD.<sup>1,2,4,38</sup> More recently, risk estimate calculators have been developed for adult and pediatric patients with HCM.<sup>3,19,29,37</sup> This 5-year risk estimate may help patients understand the magnitude of their SCD risk and can be used during shared decision-making discussions.<sup>3,19</sup> Because individual patients may consider the impact of SCD risk estimates differently, it is the consensus of the writing committee that management recommendations should not be assigned to prespecified risk estimates as the sole arbiter of the decision to recommend an ICD. Contemporary SCD risk markers in HCM, including LV apical aneurysm, LGE (with transmural scar), 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.<sup>1,4,5</sup>
2. Patients with HCM who have experienced a previously 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.<sup>2–6</sup>

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 8). 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  $\geq 1$  SCD risk factors (Figure 3, Table 8).<sup>2,4,5,7–18,20,21,31–33</sup> 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.<sup>1,2,38</sup> 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.<sup>2,4,5,37,38</sup>
4. Risk stratification in children with HCM requires evaluation of multiple age-appropriate risk factors.<sup>22–30,39</sup> It would be reasonable to consider primary prevention ICD for pediatric patients with  $\geq 1$  SCD risk factors with the understanding that the magnitude may be higher when multiple risk factors coexist in a patient (Figure 3, Table 8).<sup>22–29,37,40,41</sup> Risk estimate scores that incorporate risk factors relative to pediatric patients, along with left atrial diameter z-score and genotype status, have been developed in children with HCM.<sup>29,30</sup> Although LV systolic dysfunction and apical aneurysms are uncommon in children, it would seem prudent (based on adult evidence) to consider these 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.<sup>22–29</sup>
5. In patients with HCM with  $\geq 1$  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.<sup>19,29,30</sup> Because individual patients may consider the impact of SCD risk estimates differently, it is the consensus of the 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. There are separate risk calculations for adult patients<sup>19</sup> and children and adolescents.<sup>29,30</sup>
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.<sup>31–33</sup> Some studies have promoted a threshold for extensive LGE of  $\geq 15\%$  of the LV mass as representing a significant increase in SCD risk<sup>31,33</sup>; however, several methods are used to quantify LGE that can yield different results, and no consensus has been achieved about which method 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 are also associated with some increase in SCD risk,<sup>2,4,5,16,17,19</sup> with greatest weight as an independent risk factor given to adult patients with HCM with particularly frequent, long, and fast runs of NSVT.<sup>17</sup> In the absence of other major risk markers, the impact of short, isolated bursts of NSVT on SCD risk is less certain.<sup>14,17,38</sup> 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.<sup>34,35</sup> However, given that LGE represents a structural nidus for VT that can increase risk of SCD outcomes in adult patients with HCM,<sup>31–33</sup> 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 (Figure 3).<sup>4,5</sup>
9. Sudden death risk stratification and recommendations for ICD placement should be made in accordance with the algorithm put forth in this guideline, independent of decisions regarding sports participation. Inappropriate ICD utilization would expose patients unnecessarily to device-related complications and should be avoided.<sup>36</sup>



**Figure 3. Patient Selection for ICD Use.** Colors correspond to Table 3. \*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. †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.

### 7.3. ICD Device Selection Considerations

Recommendations for ICD Device Selection Considerations Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
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, age, lifestyle, and potential need for pacing for bradycardia or VT termination. <sup>1–6</sup>
1	B-NR	2. In patients with HCM who are receiving a transvenous ICD, single-coil ICD leads are recommended in preference to dual-coil leads, if defibrillation threshold is deemed adequate. <sup>7–9</sup>
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). <sup>10–13</sup>
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 LVEF <50%, cardiac resynchronization therapy (CRT) for symptom reduction is reasonable. <sup>14–18</sup>
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. <sup>19–24</sup>

### Synopsis

The decision of which type of ICD to implant is 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 with transvenous approach. Patients with HCM who receive 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.

ICD implantation in children raises additional concerns and challenges.<sup>1,25,26</sup> Although selection for whom should receive ICDs is discussed in **Section 7.2, “Patient Selection for ICD Placement,”** 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 or extractions over a lifetime.<sup>25</sup> In younger patients, transvenous leads have shown higher rates of failure compared with in older patients. Smaller individuals with subcutaneous ICDs may also be at risk for higher complication rates, including device erosion.<sup>1,26,27</sup>

Recommendation-Specific Supportive Text

1. The decision to implant an ICD includes additional considerations, including transvenous versus subcutaneous ICD.<sup>1–6</sup> 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, and extended battery longevity. The disadvantage is the lead, which may fail over time, necessitating additional leads and removal of older leads, which is associated with significant risk and the potential for lead infections. 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, inability to pace, and shorter history of use. Patients with HCM who undergo 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, because complications with transvenous systems are higher in young patients,<sup>25</sup> potential need for pacing, and concerns about inappropriate shock and lead longevity.
2. Single-coil ICD leads are less complicated to remove but carry the risk of elevated defibrillation thresholds.<sup>28</sup> However, most individuals, both with and without HCM, have an adequate safety margin with single-coil leads.<sup>7–9,29</sup> 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, epicardial systems, and massive hypertrophy.
3. In patients with HCM with a need for atrial pacing, a dual-chamber system would be needed. Four RCTs have shown consistent findings on the benefit of RV pacing in patients with HCM with LVOT gradients  $\geq 30$  mm Hg. Acutely, RV apical pacing reduces the LVOT gradient, but the long-term clinical benefits have not been consistently beneficial.<sup>10–14,30</sup> However, in subgroup analysis, some evidence has been seen that RV pacing may benefit some individuals who are  $\geq 65$  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 of a CRT-defibrillator in accordance with the AHA/ACC/HFSA HF guideline,<sup>31</sup> including patients with NYHA functional class II to ambulatory class IV HF, LVEF  $\leq 35\%$ , and QRS duration with LBBB. In addition to those patients, several small case series of CRT-defibrillator in patients with HCM and LVEF  $>35\%$  have been published.<sup>14–18</sup> Some 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 left ventricular assist device (LVAD) placement, heart transplantation, or death,<sup>16</sup> while 2 other studies did not identify a survival benefit.<sup>14,18</sup> 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 bradycardia and cardiac conduction delay guideline.<sup>32</sup>
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 data show that the complication rate is higher with dual-chamber devices.<sup>19–24</sup> 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. Pharmacological Management of Symptomatic Patients With Obstructive HCM

Recommendations for Pharmacological Management of Symptomatic Patients With Obstructive HCM Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
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. <sup>1–3</sup>



Recommendations for Pharmacological Management of Symptomatic Patients With Obstructive HCM (Continued)		
COR	LOE	Recommendations
1	B-NR†	2. In patients with obstructive HCM and symptoms* attributable to LVOTO, for whom beta blockers are ineffective or not tolerated, substitution with nondihydropyridine calcium channel blockers (eg, verapamil,‡ diltiazem‡) is recommended. <sup>4–6</sup>
	C-LD‡	
1	B-R	3. For patients with obstructive HCM who have persistent symptoms* attributable to LVOTO despite beta blockers or nondihydropyridine calcium channel blockers, adding a myosin inhibitor (adult patients only), or disopyramide (in combination with an atrioventricular nodal blocking agent), or SRT performed at experienced centers,§ is recommended. <sup>7–14</sup>
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. <sup>15</sup>
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. <sup>4,16</sup>

\*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.  
†Symbol corresponds to the Level of Evidence for verapamil.  
‡Symbol corresponds to the Level of Evidence for diltiazem.  
§Comprehensive or primary HCM centers with demonstrated excellence in clinical outcomes for these procedures (Tables 4 and 5).

Synopsis

The principal role of pharmacological therapy targeted at the dynamic LV obstruction is that of symptom relief because no convincing data are available to suggest that pharmacological 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, mavacamten (a cardiac myosin inhibitor), 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 pharmacological 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 symptom benefit is observed, but failure of beta-blockade should not be declared until demonstrated physiologic evidence of beta-blockade (ie, suppression of resting heart rate) is reported.<sup>1–3</sup>
2. Diltiazem and verapamil both have been demonstrated to provide relief of symptoms in patients with obstructive HCM. 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<sup>4–6</sup>; however, these may have a role in management of concomitant hypertension.
3. Patients with HCM who do not respond to first-line therapy are candidates for escalation of therapy, including cardiac myosin inhibitors (eg, mavacamten) (in adult patients only), disopyramide, and SRT when performed by experienced operators in comprehensive HCM centers (Tables 4 and 5). The choice among these options should be approached through a comprehensive discussion with the patient that includes the success rates, benefits, and risks of each of the options. Mavacamten is a cardiac myosin inhibitor and has been shown to improve LVOT gradients, symptoms, and functional capacity in 30% to 60% of patients with obstructive HCM.<sup>13,14</sup> In the United States, a risk evaluation and mitigation strategy is required due to the observed decrease in LVEF <50% in 5.7% of patients attributable solely to the drug, but as high as 7% to 10% of patients when other extenuating clinical conditions are considered that nevertheless may also result in temporary discontinuation.<sup>14,17</sup> Disopyramide has also been shown to provide symptomatic benefit in patients with obstructive HCM who have failed

first-line therapy.<sup>7–9</sup> Because 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). SRT, when performed by experienced operators in comprehensive HCM centers (Tables 4 and 5), is very effective for relieving LVOTO and can be used instead of mavacamten or disopyramide.<sup>10–12</sup>

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.<sup>15</sup>
5. When signs or symptoms of congestion are observed, 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 used 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 to uptitrate 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 (>80–100 mm Hg) and signs of congestive HF. Several reports have been published of life-threatening bradycardia and hypotension in newborns of <6 weeks of age who have received intravenous verapamil for supraventricular tachycardia.<sup>16</sup> However, verapamil has been found to be efficacious and well tolerated when administered

to older infants and children with HCM in controlled conditions.<sup>18</sup>

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 the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. In patients with obstructive HCM who remain symptomatic despite GDMT, SRT in eligible patients,* performed at experienced HCM centers,† is recommended for relieving LVOTO (Tables 4 and 5). <sup>1–3</sup>
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 HCM centers,† is recommended (Tables 4 and 5). <sup>4–7</sup>
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 HCM centers,† is recommended (Tables 4 and 5). <sup>8–10</sup>
2b	B-NR	4. In patients with obstructive HCM, earlier (NYHA class II) surgical myectomy performed at comprehensive HCM centers (Tables 4 and 5) may be reasonable in the presence of additional clinical factors, including <sup>3,11–22</sup> : 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 symptomatic patients with obstructive HCM, SRT in eligible patients,* performed at experienced HCM centers† (Tables 4 and 5), may be considered as an alternative to escalation of medical therapy after shared decision-making including risks and benefits of all treatment options. <sup>1,10,23–25</sup>
3: Harm	C-LD	6. For patients with HCM who are asymptomatic and have normal exercise capacity, SRT is not recommended. <sup>13,21</sup>
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. <sup>26,27</sup>

\*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; and (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 (Tables 4 and 5).

## Synopsis

SRT is generally reserved for drug-refractory symptoms and should be performed in experienced HCM centers.<sup>28</sup> Transaortic extended septal myectomy (ESM) is an appropriate treatment for the broadest range of patients and allows gradient relief at any level within the ventricle,<sup>29–31</sup> with a mortality rate of <1% and clinical success >90% to 95%.<sup>1,24,27,32–39</sup> Successful ESM eliminates or reduces SAM-mediated MR and its consequences.<sup>27,32,40,41</sup> Long-term survival after ESM is similar to an age-matched general population. Recurrent outflow tract obstruction is rare after ESM.<sup>42–44</sup> ESM is especially advantageous when associated cardiac disease or associated papillary muscle abnormalities are present.<sup>4,37,45</sup> In HCM centers with experienced interventional teams, alcohol septal ablation is also associated with a low procedural mortality rate (<1%) but requires appropriate coronary anatomy. Alcohol septal ablation avoids sternotomy, has a shorter hospital stay, and is advantageous when frailty or comorbidities increase the risk of ESM. Alcohol septal ablation is less effective with gradients  $\geq 100$  mm Hg and septal thickness  $\geq 30$  mm<sup>9,46</sup> and is associated with greater risk of permanent pacemaker and greater need for repeat intervention for residual obstruction.<sup>8–10</sup> Although 5-year survival is similar between alcohol septal ablation and myectomy,<sup>8,9,47,48</sup> at 10 years of follow-up, survival is lower with alcohol septal ablation compared with ESM.

## Recommendation-Specific Supportive Text

1. Generally, SRT performed by experienced operators in comprehensive centers (Tables 4 and 5) is contemplated when patients continue to have severe symptoms despite optimal medical therapy or intolerant adverse effects from medical therapy.<sup>1</sup> 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.<sup>2,3</sup> Currently, however, insufficient evidence is available to recommend SRT to improve patient survival as the only indication for the procedures. Highly symptomatic patients should be able to participate in a full discussion of all 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 because the literature demonstrates a volume-outcome relationship. 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 for basal obstruction and a

- transapical approach (or combined transaortic and transapical) for midventricular obstruction.<sup>49</sup>
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 structural and 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.<sup>50,51</sup> 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.<sup>4–7</sup>
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 HCM centers (Tables 4 and 5) becomes the preferred invasive strategy for relief of LVOTO.<sup>8–10</sup>
4. Although most patients who undergo SRT are those with advanced symptoms (NYHA functional 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 (Tables 4 and 5) to relieve the LVOTO and its sequelae. Data suggest that surgical myectomy can improve progressive pulmonary hypertension,<sup>11,12,52</sup> improve outcomes of those with marked exercise impairment,<sup>13</sup> reverse left atrial enlargement,<sup>14,15,53</sup> ameliorate occult gastrointestinal bleeding,<sup>41,42</sup> and decrease rates of subsequent atrial<sup>54</sup> and ventricular arrhythmias.<sup>3,18,19</sup> Similar to the recommendations 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 5).<sup>20</sup> Although successful alcohol septal ablation has been shown to improve new onset AF burden and NYHA functional class in those presenting with NYHA functional class II symptoms and thereby could be reasonably expected to offer similar benefits at comprehensive HCM centers, this must be balanced against the higher pacemaker and reintervention rates in this lower risk cohort.<sup>8,9,55–58</sup>
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 and benefits. Previously, SRT was reserved, appropriately, for the most symptomatic patients because a procedural mortality rate was 5% to 10%. This high mortality rate has been observed in the recent era in HCM centers with less experience with the operation.<sup>23</sup> 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 functional 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.<sup>1,10,24,25</sup> 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. No definitive data have been published 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.<sup>13,21</sup>
7. Mitral valve replacement is more common in generalized HCM centers than in specialized HCM centers, and while valve replacement eliminates SAM and associated MR as well as the outflow tract gradient, the addition of mitral valve replacement with or without myectomy increases the hospital mortality rate (>10-fold) and length of hospitalization compared with patients undergoing isolated septal myectomy.<sup>26</sup> 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 because early and long-term mortality is worse in patients with prosthetic replacement compared with patients who have septal myectomy and mitral valve repair.<sup>27</sup>

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 the Online Data Supplement.		
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 nondihydropyridine calcium channel blockers are recommended. <sup>1-5</sup>
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 nondihydropyridine calcium channel blockers.

Recommendations for Management of Patients With Nonobstructive HCM With Preserved EF (Continued)		
COR	LOE	Recommendations
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. <sup>6</sup>
2b	C-LD	4. In highly selected patients with apical HCM with severe dyspnea or angina (NYHA functional 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 <sup>2</sup> and LV stroke volume <30 mL/m <sup>2</sup> ), apical myectomy by experienced surgeons at comprehensive centers may be considered to reduce symptoms. <sup>7</sup>
2b	C-EO	5. In asymptomatic patients with nonobstructive HCM, the benefit of beta blockers or calcium channel blockers is not well established.
2b	B-R	6. For younger (eg, ≤45 years of age) patients with nonobstructive HCM due to a pathogenic or likely pathogenic cardiac sarcomere genetic variant, and a mild phenotype,* valsartan may be beneficial to slow adverse cardiac remodeling. <sup>8</sup>

\*Mild phenotype indicates NYHA functional class I or II, maximal LV wall thickness 13 to 25 mm, no secondary prevention ICDs, no history of appropriate ICD shocks, and no AF.

Synopsis

Symptomatic, nonobstructive HCM is a diagnostic and therapeutic challenge. This is related to differences in disease onset, severity, and risk for adverse outcomes.<sup>9</sup> The overall risk for HCM-related death appears similar between patients with and without obstructive physiology.<sup>10</sup> 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.<sup>11</sup> In patients with angina or CAD risk factors, obstructive CAD should be excluded.<sup>12</sup> Comorbid conditions including hypertension, diabetes, obesity, obstructive sleep apnea, 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 pharmacological 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, pharmacological management of chest discomfort is similar to that of dyspnea.



Beta blockers and nondihydropyridine 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.<sup>1–5</sup> Alternatively, beta blockers are used in symptomatic patients based on clinical experience and extrapolation from obstructive HCM, rather than trial data.<sup>13,14</sup> 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.<sup>15</sup>

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.
3. Although several pilot trials suggested that angiotensin receptor blockers and angiotensin-converting enzyme inhibitors may have benefits on myocardial structure and function, a 12-month placebo-controlled trial of 124 patients with nonobstructive 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.<sup>6</sup> However, treatment with losartan was without clinically 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 found to be safe and reduced symptoms.<sup>7</sup> Although experience of only a single center has been published,<sup>7</sup> 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/m<sup>2</sup> and LV stroke volume <30 mL/m<sup>2</sup>. 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 nondihydropyridine 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, no data are available that indicate a 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. No prospective data are available that demonstrating benefit of these agents on long-term outcomes in patients with nonobstructive HCM.
6. A randomized, double-blind placebo controlled trial of valsartan, titrated to maximum US Food and Drug Administration–approved doses, in 178 patients who had nonobstructive HCM and were 8 to 45 years of age with pathogenic or likely pathogenic sarcomeric variants, NYHA functional class I to II symptoms, normal EF, no secondary prevention ICDs, no history of appropriate ICD shocks, and no prior SRT demonstrated an attenuation in a composite endpoint of LV wall thickness, LV mass, LV volume, left atrial size, diastolic parameters, and biomarkers.<sup>8</sup> Trials of other angiotensin receptor blockers tended to be smaller, included older patients with more advanced phenotypic expression, and/or those without sarcomeric variants.

8.3. Management of Patients With HCM and Advanced HF

Recommendations for Management of Patients With HCM and Advanced HF		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	C-LD	1. In patients with HCM who develop systolic dysfunction with an LVEF <50%, GDMT for HF with reduced EF is recommended. <sup>1–3</sup>
1	C-LD	2. In patients with HCM and systolic dysfunction, diagnostic testing to assess for concomitant causes of systolic dysfunction (eg, CAD) is recommended. <sup>4,5</sup>
1	B-NR	3. In patients with nonobstructive HCM and advanced HF (NYHA functional class III to class IV despite GDMT), CPET should be performed to quantify the degree of functional limitation and aid in selection of patients for heart transplantation or mechanical circulatory support. <sup>6,7</sup>

Recommendations for Management of Patients With HCM and Advanced HF (Continued)		
COR	LOE	Recommendations
1	B-NR	4. In patients with nonobstructive HCM and advanced HF (NYHA functional class III to class IV despite GDMT) or with life-threatening ventricular arrhythmias refractory to maximal GDMT, assessment for heart transplantation in accordance with current listing criteria is recommended. <sup>8–13</sup>
1	B-R	5. In patients with HCM who develop persistent systolic dysfunction (LVEF <50%), cardiac myosin inhibitors should be discontinued. <sup>14</sup>
2a	C-EO	6. 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	7. 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. <sup>15–19</sup>
2a	C-LD	8. In patients with HCM and persistent LVEF <50%, ICD placement can be beneficial. <sup>3,20</sup>
2a	C-LD	9. In patients with HCM and LVEF <50%, NYHA functional class II to class IV symptoms despite GDMT, and LBBB, CRT can be beneficial to improve symptoms. <sup>21–25</sup>

Synopsis

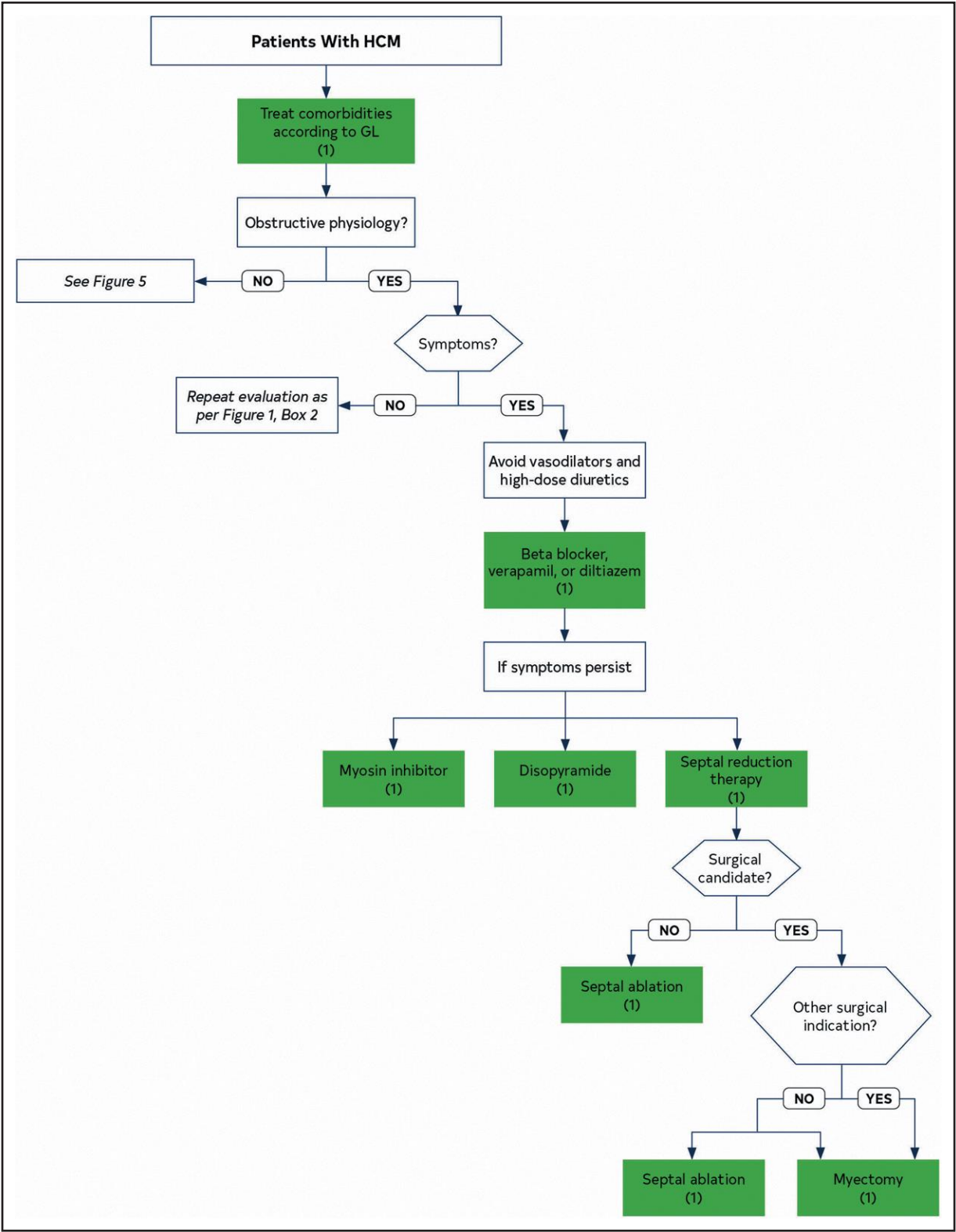
An approach to the management of HF symptoms is shown in Figures 4 and 5. EF often overestimates myocardial systolic function in patients with HCM. An EF <50% is associated with worse outcomes and therefore is considered to represent significantly reduced systolic function.<sup>2,20,26–29</sup> Although uncommon in patients with HCM, an EF <35% confers a particularly high risk of death, the need for advanced HF therapies, and malignant ventricular arrhythmias.<sup>28</sup> As such, in patients with HCM, GDMT for HF with reduced EF is initiated for EF <50% and otherwise is generally based on the AHA/ACC/HFSA HF guideline.<sup>1</sup> An ICD for the primary prevention of SCD, or CRT in patients with EF <50% and NYHA functional class III to class IV symptoms who meet other criteria for CRT, is also reasonable. Regardless of LVEF, if patients experience recurrent ventricular arrhythmias or severe (NYHA functional class III to class IV) symptoms despite optimization of medical therapy and SRT is not an option, heart transplant evaluation is warranted,<sup>10,30</sup> and CPET has a role in risk stratification.<sup>6,7</sup> For patients with NYHA functional class III to class IV symptoms, an LVAD is sometimes used.<sup>17,18</sup>

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 losartan<sup>31</sup> nor spironolactone<sup>32</sup> 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,<sup>2,20,26–29</sup> might be worse than that of patients with dilated cardiomyopathy,<sup>33</sup> and does not vary based on the presence or absence of LV dilation.<sup>34</sup> Further, myocardial transcriptomic profiling has identified substantial overlap in gene network activation between dilated cardiomyopathy and HCM.<sup>35,36</sup> Thus, although HCM has typically been excluded from RCTs in HF, no compelling reason exists to indicate that HCM with reduced EF differs sufficiently to disqualify many highly effective, evidence-based GDMTs for HF with reduced EF as tolerated in the presence of restrictive physiology.<sup>1</sup>

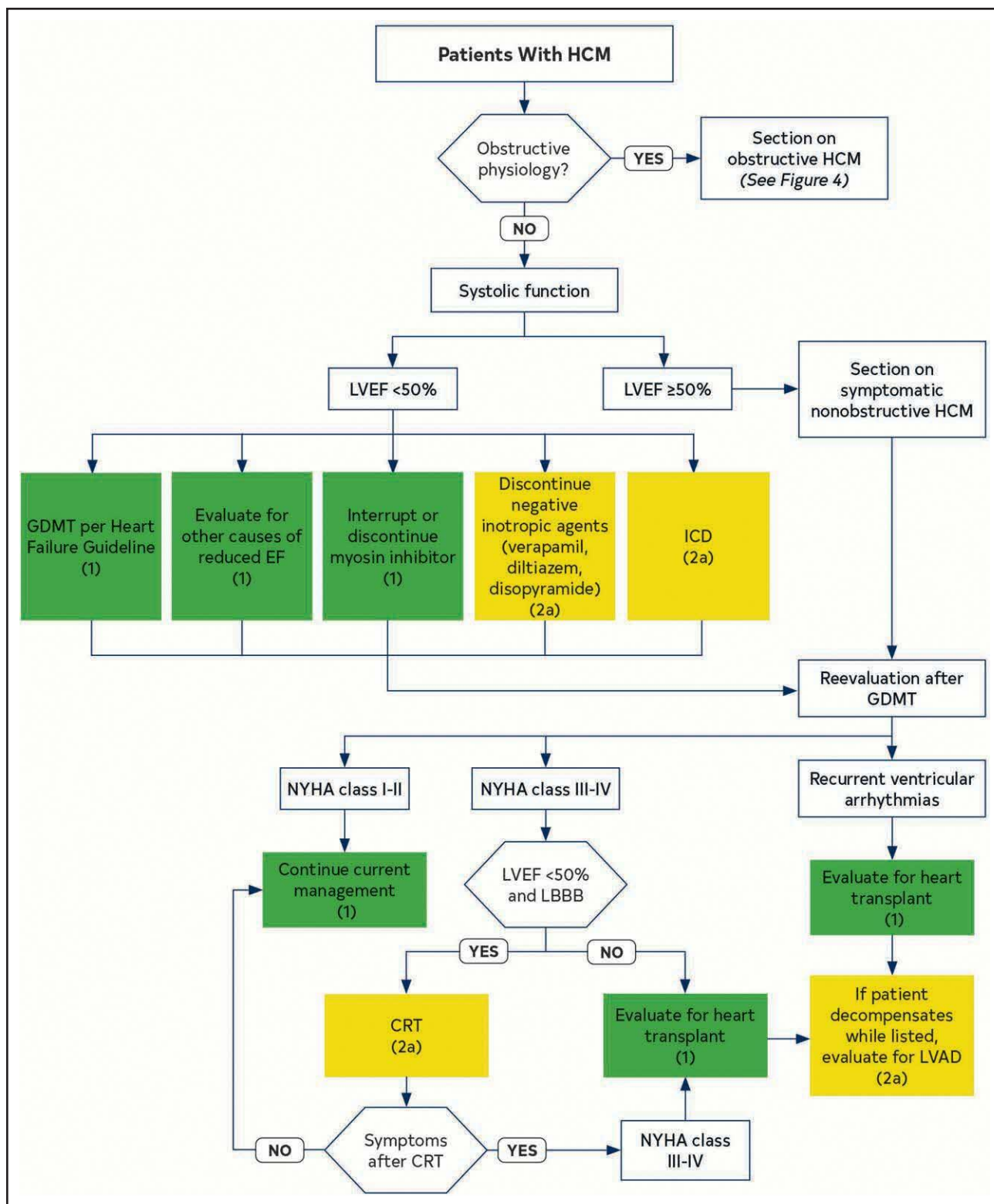
2. Identification of reduced EF in the setting of HCM is uncommon (approximately 5%) and should prompt an appropriate search for other potential contributing causes of LV dysfunction.<sup>2,4,5,28,34</sup> Those causes should include, but are not limited to, HCM phenocopies, CAD, valvular heart disease, and metabolic disorders as outlined in the AHA/ACC/HFSA HF guideline.<sup>1</sup>
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 CO<sub>2</sub> production, and ventilatory anaerobic threshold predict death from HF and need for heart transplantation.<sup>6,7</sup>
4. Patients with HCM, particularly those with LVOTO whose symptoms respond to appropriate therapies, do not warrant evaluation for transplantation. However, advanced HF arises in a subset (3%–8%) of patients with HCM.<sup>2,6,20,28,30</sup> Referral for transplantation should be in accordance with current guidelines.<sup>11</sup> Posttransplant survival in patients with HCM is comparable, and possibly superior, to that of patients with other forms of heart disease.<sup>8,9,12,37,38</sup> Importantly, 20% to 50% of patients with HCM who have advanced HF have preserved EF with restrictive physiology; hence, transplant referral for HCM does not require a reduced EF.<sup>12,30</sup> Patients with HCM and advanced HF are far less likely to receive mechanical circulatory support.<sup>39</sup> This is attributable to smaller LV size and differing hemodynamic profiles, which may increase the risk of adverse outcomes due to prolonged wait time and limited options once listed for transplant. 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. These new listing criteria have significantly increased transplantation rates and reduced wait-list times in patients with HCM.<sup>13</sup> Children with



**Figure 4. Management of Symptoms in Patients With HCM.**  
Colors correspond to Table 3. GL indicates guideline; and HCM, hypertrophic cardiomyopathy.

HCM also warrant consideration for transplantation if they are not responsive to or appropriate candidates for other therapies.<sup>40</sup>

5. Mavacamten is a first-in-class myosin inhibitor that decreases myocardial contractility. Given this mechanism of action, mavacamten reduces LVEF,



**Figure 5. Heart Failure Algorithm.**

Cardiac myosin inhibitor should be discontinued if LVEF <50% and can be restarted at a lower dose if the LVEF recovers. Colors correspond to Table 3. CRT indicates cardiac resynchronization therapy; EF, ejection fraction; GDMT, guideline-directed management and therapy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.



and an LVEF <50% was a prespecified criterion for temporary study drug discontinuation. Thus, in those who develop LVEF <50%, interruption with resumption at lower dose (if LVEF improves) or discontinuation (if LVEF does not improve to >50%) of cardiac myosin inhibitors is required regardless of associated signs and symptoms.<sup>41</sup>

6. 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 systolic dysfunction and worsening HF symptoms. However, these agents may be continued if needed for rate or rhythm control of AF on a case-by-case basis.
7. Patients with HCM have traditionally been ineligible for LVAD support because of small LV cavities and relatively preserved EF. However, several case series have demonstrated that support with continuous flow LVADs results in acceptable outcomes in highly selected patients with HCM.<sup>15–19</sup> Post-LVAD survival is superior in patients with HCM and larger LV cavities (>46–50 mm).<sup>17,18</sup> Only a small number of patients with HCM have received an LVAD as destination therapy, perhaps due to the younger age of this population relative to those with dilated cardiomyopathy (mean, 52 versus 57 years).<sup>18</sup> Limited data are available on the role of temporary or biventricular mechanical circulatory support 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 patients with HCM, showed poor survival, with only 50% either successfully weaned or bridged to transplantation.<sup>42</sup>
8. Patients with HCM were not included in the primary prevention ICD trials for patients with HF. A retrospective study of 706 patients with nonobstructive HCM demonstrated a 68% lower mortality rate over 5 years in patients with ICDs; however, only 11% had an ICD, 8% had EF ≤50%, and specific causes of death were not provided, precluding a causal association.<sup>3</sup> Among patients with HCM whose EF was 35% to 50% and who had an ICD, 9% to 17% received appropriate ICD therapies, and sudden death event rates were approximately 2.5% per year.<sup>2,20,28</sup> Therefore, prophylactic ICD implantation is the generally accepted clinical practice for patients with HCM and systolic dysfunction (EF ≤50%).<sup>1</sup> SHaRe (Sarcomeric Human Cardiomyopathy Registry) further demonstrated a graded spectrum of risk with a very high burden of malignant arrhythmias in those with EF <35%.<sup>28</sup> 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.

9. 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.<sup>1</sup> Whether the same benefits apply to patients with HCM is unclear. Patients with HCM were specifically excluded from some RCTs of CRT in HF,<sup>43,44</sup> and, in others, the proportion of patients with HCM was not clearly defined.<sup>45,46</sup> Furthermore, case series offer conflicting results on the effect of CRT on symptoms, EF, and survival.<sup>21–25</sup> 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.

8.4. Management of Patients With HCM and AF

Recommendations for Management of Patients With HCM and AF Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. In patients with HCM and clinical AF, anticoagulation is recommended with direct-acting oral anticoagulants (DOACs) as first-line option and vitamin K antagonists as second-line option, independent of CHA <sub>2</sub> DS <sub>2</sub> -VASC score. <sup>1–5</sup>
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 DOACs as first-line option and vitamin K antagonists as second-line option, independent of CHA <sub>2</sub> DS <sub>2</sub> -VASC score. <sup>1,6–8</sup>
1	C-LD	3. In patients with AF in whom rate control strategy is planned, beta blockers, verapamil, or diltiazem are recommended, with the choice of agents according to patient preferences and comorbid conditions. <sup>9,10</sup>
2a	C-LD	4. In patients with HCM and subclinical AF detected by internal or external device or monitor, of >5 minutes' duration but <24 hours' duration for a given episode, anticoagulation with DOACs 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. <sup>1,6–8,11</sup>
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. <sup>9,12–24</sup>
2a	B-NR	6. In patients with HCM and symptomatic AF, as part of an AF rhythm-control strategy, catheter ablation for AF can be effective when drug therapy is ineffective, contraindicated, or not the patient's preference. <sup>12,25,26</sup>
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. <sup>13,27–29</sup>

## 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.<sup>1–5</sup> Asymptomatic AF detected by cardiac devices or monitors also increases risk of stroke, so the decision to anticoagulate should take into consideration the duration of episodes as well as underlying risk factors. When a rhythm-control strategy is needed, several 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 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 is a potential rhythm management option in patients undergoing surgical myectomy. 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 no RCTs have been published, 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 10 patients.<sup>1</sup> The stroke risk is independent of CHA<sub>2</sub>DS<sub>2</sub>-VASc score,<sup>30</sup> with a significant number of strokes observed in patients with a score of 0. Several studies have shown that anticoagulation, particularly warfarin with target international normalized ratio 2 to 3, reduces the stroke risk in this population,<sup>2,30</sup> whereas other 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.<sup>3–5</sup> 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.<sup>14</sup>
2. Similar to patients without HCM, asymptomatic or subclinical 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.<sup>7</sup> Device-detected AF was identified in 29 of 114 patients with HCM (25%), resulting in an annualized incidence of 4% per year.<sup>6</sup> In patients without HCM, SCAF has been associated with an increased risk of thromboembolism, albeit lower than the risk described for clinical AF.<sup>8</sup> 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. One study suggested only episodes >24 hours were associated with increased risk.<sup>15</sup> Also influencing risk are the total AF burden<sup>11</sup> and the presence of traditional risk factors, whereas very short episodes lasting a few seconds do not appear to increase risk.<sup>16,17</sup> When making the diagnosis of device-detected AF, review of stored intracardiac ECGs 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 data support improved outcomes with a rhythm-control strategy compared with historical controls.<sup>9,10</sup> For those patients for whom a rate-control strategy is chosen (eg, because of patient choice, antiarrhythmic drug failure, or intolerance), a nondihydropyridine calcium channel blocker, a beta blocker, or a combination of the 2 is preferable. A theoretical concern exists 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. Medication choice should be individually determined according to age, underlying substrate, comorbidities, and severity of symptoms. Dose adjustments are based on the balance between adequate rate control versus adverse 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.
4. SCAF is often observed in patients with HCM and implanted cardiac devices<sup>6,7</sup> and has been associated with an increased risk of thromboembolism.<sup>8</sup> Yet, the minimum duration of SCAF that confers increased risk has not been precisely defined, because a gradient of risk appears to be evident depending on underlying substrate. Although ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the

Atrial Fibrillation Reduction Atrial Pacing Trial) data suggested only episodes >24 hours increased stroke risk,<sup>15</sup> other evidence suggests that shorter duration episodes may pose a risk in patients with traditional risks factors.<sup>16</sup> In ASSERT, the absolute stroke risk increased with increasing CHADS<sub>2</sub> score, reaching a rate of 3.78 per year in those with score >2.<sup>18</sup> Another group stratified risk according to AF duration and CHADS<sub>2</sub> score, with a CHADS<sub>2</sub> score of 1 increasing the risk only if AF duration was >24 hours, whereas for CHADS<sub>2</sub> scores ≥2, episodes >5 minutes increased risk.<sup>19</sup> 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.<sup>30</sup> When very short AF duration is observed, continued surveillance should be maintained as the burden of AF is likely to progress.

5. 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.<sup>9,10</sup> 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 patients with HCM (Table 9). Amiodarone has been used over many years and is generally deemed a favored option.<sup>10,20</sup> Disopyramide has been safely prescribed for reduction of LVOTO, but its efficacy in AF is not well established.<sup>2122</sup> Data on NYHA functional class IC antiarrhythmic agents are limited because of concerns regarding their use in patients with structural heart disease. When used, therapy with NYHA functional class IC agents is safest in the presence of an ICD.<sup>10</sup> NYHA functional class III

agents have been used as well; a report in 25 patients with HCM showed dofetilide to be well tolerated and facilitated AF management.<sup>13</sup> Sotalol has also been shown to be safe and is commonly used in pediatric patients as well, either in oral or intravenous forms.<sup>2324,31,32</sup> 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 in HCM. Although no RCTs exist in this area, several 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.<sup>12,25</sup> 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.<sup>25</sup> 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. 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.<sup>26</sup>
7. AF in patients with HCM is often poorly tolerated; therefore, aggressive rhythm-control strategies

**Table 9. Antiarrhythmic Drug Therapy Options for Patients With HCM and AF**

Antiarrhythmic Drug	Efficacy for AF	Adverse Effects	Toxicities	Use in HCM
Disopyramide	Modest	Anticholinergic HF	Prolonged QTc TdP	Particularly with early onset AF Generally used in conjunction with atrioventricular nodal blocking agents
Flecainide and propafenone	...	Prolonged QRS	Proarrhythmia Typical atrial flutter	Not generally recommended in the absence of an ICD
Sotalol	Modest	Fatigue Bradycardia	Prolonged QTc TdP	Reasonable
Dofetilide	Modest	Headache	Prolonged QTc TdP	Reasonable
Dronedarone	Low	HF	Prolonged QTc	...
Amiodarone	Modest-high	Bradycardia	Liver, lung, thyroid, skin, neurologic Prolonged QTc	Reasonable

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

are sometimes required. Because of the lower success rate of catheter ablation in patients with 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.<sup>27,29</sup> In a 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) ( $P<0.001$ ).<sup>10</sup> In this study, with concomitant surgical ablation, freedom from AF at 3 years was 70%, with left atrial size being a predictor of recurrence.<sup>10</sup>

8.5. 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 the Online Data Supplement.		
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. <sup>1,2</sup>
1	B-NR*	2. In adults with HCM and symptomatic ventricular arrhythmias or recurrent ICD shocks despite beta-blocker use, antiarrhythmic drug therapy (eg, amiodarone,† dofetilide,† mexiletine,† or sotalol†) is recommended, with the choice of agent guided by age, underlying comorbidities, severity of disease, patient preferences, and balance between efficacy and safety. <sup>3-6</sup>
	C-LD†	
1	C-LD	3. In children with HCM and recurrent ventricular arrhythmias despite beta-blocker use, antiarrhythmic drug therapy (eg, amiodarone, <sup>3,4</sup> mexiletine, <sup>6</sup> sotalol <sup>3,4</sup> ) 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. <sup>7,8</sup>
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. <sup>9-11</sup>

\*Indicates the LOE for amiodarone. †Indicates the LOE for dofetilide, mexiletine, or sotalol.

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.<sup>12</sup> 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 limited. The choice of pharmacological therapy should be individualized according to individual substrate, but amiodarone is generally considered superior, albeit at the expense of increased adverse 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.<sup>13</sup> 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.<sup>1,2</sup>
2. Most patients with HCM and VT are likely already receiving beta blockers, generally the first treatment option. Because no study has investigated pharmacological 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.<sup>3</sup> Thus, amiodarone was most effective but at the expense of increased adverse effects.<sup>3</sup> In an observational study that included 30 patients, dofetilide was found to decrease the number of ICD therapies even after other agents were ineffective.<sup>5</sup> Proof of efficacy for mexiletine is limited but is often adjunctive to amiodarone.<sup>6</sup> 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.<sup>4</sup> The safety and efficacy of propafenone and flecainide is uncertain, in addition to safety concerns when used in patients with ischemic heart disease.<sup>14</sup>
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), additional antiarrhythmic agents may be used either to address symptoms, suppress recurrent life-threatening events, or to prevent unnecessary ICD shocks. Drugs with risk for proarrhythmia are often initiated in the hospital. ICD shocks, even when appropriate, have been linked to psychological 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.<sup>15–17</sup>

4. ICD therapy has been shown to prevent SCD and improve survival in patients with HCM.<sup>18</sup> 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.<sup>7</sup> 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 pharmacological 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%.<sup>9</sup> Freedom from VT 12 months postablation was found in 11 of 14 patients with VT and apical aneurysms, which is a common source of sustained monomorphic VT in this population,<sup>10</sup> and 78% VT-free survival was reported after combined epicardial and endocardial ablation in 9 patients with sustained monomorphic VT.<sup>11</sup> 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. A recent meta-analysis that included 6 studies confirmed the findings.<sup>19</sup> In 1 case series, surgical aneurysmectomy proved effective in 3 patients with apical aneurysms and incessant ventricular arrhythmias as an alternative to ablation.<sup>20</sup> 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.<sup>15</sup>

## 9. LIFESTYLE CONSIDERATIONS FOR PATIENTS WITH HCM

### 9.1. Recreational Physical Activity and Competitive Sports

Recommendations for Recreational Physical Activity and Competitive Sports Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-R	1. For patients with HCM, mild- to moderate-intensity* recreational† exercise is beneficial to improve cardiorespiratory fitness, physical functioning, and quality of life, and for overall health in keeping with physical activity guidelines for the general population. <sup>1–3</sup>
1	C-EO	2. For athletes with HCM, a comprehensive evaluation and shared decision-making about sports participation with an expert professional is recommended. <sup>4</sup>
2a	B-NR	3. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive sports of any intensity is reasonable. <sup>5,6</sup>
2a	B-NR	4. For patients with HCM, participation in vigorous* recreational activities is reasonable after an annual comprehensive evaluation and shared decision-making with an expert professional who balances potential benefits and risks, with this process being repeated annually. <sup>4,5,7,8</sup>
2b	B-NR	5. For patients with HCM who are capable of a high level of physical performance, participation in competitive sports† may be considered after review by an expert provider with experience managing athletes with HCM who conducts an annual comprehensive evaluation and shared decision-making that balances potential benefits and risks. <sup>5,9–14</sup>
3: No benefit	B-NR	6. For most patients with HCM, universal restriction from vigorous physical activity or competitive sports is not indicated. <sup>5,11–13</sup>
3: Harm	C-EO	7. In patients with HCM, ICD placement for the sole purpose of participation in competitive sports should not be performed. <sup>10</sup>

\*Exercise intensity can be gauged by metabolic equivalents (METs): light <3 METs, moderate 3–6 METs, and vigorous >6 METs;<sup>15</sup> by percentage of maximum heart rate achieved (light 40%–50%, moderate 50%–70%, vigorous >70%), or by level of perceived exertion on the Borg scale (light 7–12, moderate 13–14, vigorous ≥15).<sup>16</sup>

†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. Competitive sports involve systematic training for the primary purpose of competition against others, at multiple levels, including high school, collegiate, master’s level, semiprofessional, or professional sporting activities.

### Synopsis

Regular physical activity promotes longevity and reduces overall cardiovascular disease risk. Most patients with HCM can benefit from at least mild- to moderate-intensity exercise. Some patients with HCM who have no or minimal symptomatic limitation are capable of vigorous activities or competitive sports and place a high personal value on physical fitness, performance, or both. Recommendations for recreational exercise and competitive

sports for patients with HCM are evolving with emergence of data and emphasis on promoting patient autonomy and shared decision-making.<sup>4,17,18</sup> Although previous observational studies identify HCM as a common cause of SCD among competitive athletes,<sup>19</sup> in prospective registries, HCM is the cause of SCD in <10% of young individuals, including athletes.<sup>20–31</sup> Although uncertainty around the risk of SCD associated with exercise exists, a disproportionate risk of SCD has not been demonstrated in athletes in contemporary registries.<sup>5,11–13,30</sup> Although these data provide some reassurance, the nuances and unique individual considerations regarding vigorous exercise or competitive sports warrant annual evaluation by an expert professional, including a shared balanced discussion of potential benefits and risks and an individual emergency preparedness plan.<sup>4,17,18,32,33</sup>

### Recommendation-Specific Supportive Text

1. Inactivity is prevalent among patients with HCM.<sup>34,35</sup> “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.<sup>36</sup> In a randomized trial of exercise training, adult patients with HCM who followed prescriptions of moderate-intensity exercise for 4 months, compared with those doing their usual activity, showed significant improvements in peak oxygen consumption and subjective improvements in physical functioning.<sup>1</sup> No major adverse events and no increase in nonlethal arrhythmias with exercise training were observed. Exercise intensity can be gauged by METs: light <3 METs, moderate 3 to 6 METs, and vigorous >6 METs,<sup>15</sup> by percentage of maximum heart rate achieved (light 40%-50%, moderate 50%-70%, vigorous >70%), or by level of perceived exertion on the Borg scale (light 7-12, moderate 13-14, vigorous ≥15).<sup>16</sup> An initial period of supervised exercise may be warranted in some patients. Children with HCM can typically participate in physical education at school, with an option not to grade, time, or score for performance.
2. Expert professionals will be familiar with the evidence and ongoing studies relevant to discussions about vigorous exercise and sports participation and will be in the best position to provide guidance in the context of shared decision-making.<sup>4</sup> Advice to avoid dehydration or exposures to extreme environmental conditions (eg, heat, humidity) is important, particularly for patients with obstructive physiology. This discussion also provides an opportunity to devise plans for emergency preparedness.
3. Sudden death in genotype-positive, phenotype-negative individuals is rare.<sup>6</sup> Currently, no accurate risk prediction models for SCD in genotype-positive, phenotype-negative individuals are available. In a recent prospective registry, no arrhythmic events were observed in genotype-positive, phenotype-negative individuals (total of 126), including those exercising vigorously or participating in competitive athletics.<sup>5</sup> 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. This is appropriate every 1 to 2 years to assess safety of ongoing competitive athletics participation.
4. Many patients with HCM with no or minimal symptomatic limitation are capable of vigorous-intensity exercise and place a high personal value on physical fitness. Retrospective data have not shown a higher rate of ventricular arrhythmias in individuals with HCM who exercise vigorously.<sup>7</sup> Additionally, a prospective nationwide population-based cohort study in South Korea showed that among individuals with a diagnosis of HCM (mean age, 59 years), those in the highest tertile of exercise (including those exercising vigorously ≥8 METs) had the lowest cardiovascular mortality (2.7% versus 3.8% in midtertile and 4.7% in lowest tertile;  $P < 0.001$ ).<sup>8</sup> In a recently published prospective observational registry of adult and pediatric patients (8-60 years of age) with HCM who were NYHA functional class I to II, those who engaged in vigorous exercise were not more likely to experience an arrhythmic event compared with those exercising moderately or who were less active.<sup>5</sup> Notably, most patients in this study were managed at experienced HCM centers and receiving close follow-up and surveillance. Therefore, although these data can inform discussion between patients and physicians regarding participation in vigorous exercise, these discussions should occur in the context of an annual comprehensive clinical evaluation and risk assessment using an individualized shared decision-making framework by an expert professional with experience in managing patients with HCM.
5. Some patients with HCM who have no or minimal symptomatic limitation are capable of vigorous-intensity training and place a high personal value on physical performance for the purpose of

competition. Prospective studies over the past decade have demonstrated a similar burden of ventricular arrhythmias in adult patients with HCM who have continued to engage in competitive athletics compared with those who have withdrawn from competition.<sup>11–13</sup> In those athletes with ICDs, shock rates in athletes with HCM are similar to those reported in nonathletic populations, with most shocks occurring outside training or competition, and with no reported shock-related injuries or death.<sup>9,10</sup> A large prospective registry examined the impact of recreational exercise and competitive athletics on arrhythmic events and included 259 individuals engaging in competitive athletics, including 42 high school and collegiate athletes with HCM with >3 years' follow-up. Competitive athletes with HCM did not experience an increased arrhythmic risk compared with individuals exercising moderately or not at all.<sup>5</sup> Although these data provide some reassurance and can inform discussions between patients and physicians regarding participation in competitive athletics, not all types of athletes are well-represented in these studies. Evaluations and shared decision-making with athletes who have HCM regarding sports participation should therefore be individualized, be undertaken by professionals with expertise in managing competitive athletes with HCM, and be repeated on at least an annual basis.<sup>4,32</sup> Final eligibility decisions for organized sports participation may involve third parties (eg, team physicians, consultants, institutional leadership) acting on the behalf of schools or teams.

6. Prospective studies to date have suggested that patients with HCM who engage in competitive athletics are not at increased risk of SCD compared with less active individuals,<sup>5</sup> or athletes who withdraw from competitive sports.<sup>11–13</sup>
7. Sudden death risk stratification and recommendations for ICD placement should be made in accordance with the algorithm put forth in this guideline, independent of decisions regarding sports participation. Inappropriate ICD utilization would expose patients unnecessarily to device-related complications and should be avoided.<sup>37,38</sup>

9.2. Occupation in Patients With HCM

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 using a GDMT plan. <sup>1</sup>

Recommendations for Occupation in Patients With HCM (Continued)		
COR	LOE	Recommendations
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. <sup>2</sup>
2b	C-EO	3. It is reasonable for patients with HCM to 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 GDMT in the context of shared decision-making.

Synopsis

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

Recommendation-Specific Supportive Text

1. The Federal Motor Carrier Safety Administration updated its guidelines in 2015.<sup>1</sup> 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 (**see Section 7, “SCD Risk Assessment and Prevention”**).
2. The Federal Aviation Administration guidelines do not explicitly list HCM as a disqualifying diagnosis for piloting an aircraft. However, a report from an occupational aviation work group states that for patients with HCM who are asymptomatic, they may be considered for multicrew flying duties.<sup>2</sup> No restrictions exist 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, firefighters) 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, these decisions should be approached on an individual basis and in the context of shared decision-making.

9.3. Pregnancy in Patients With HCM

Recommendations for Pregnancy in Patients With HCM Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
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. <sup>1,2</sup>

Recommendations for Pregnancy in Patients With HCM (Continued)		
COR	LOE	Recommendations
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. <sup>3,4</sup>
1	C-LD	3. In most pregnant women with HCM, vaginal delivery is recommended as the first-choice delivery option. <sup>3,5</sup>
1	B-NR	4. In affected families with HCM, preconceptional and prenatal reproductive and genetic counseling should be offered. <sup>3-6</sup>
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 GDMT. <sup>7-10</sup>
2a	C-LD	7. In pregnant women with HCM, cardioversion for new or recurrent AF, particularly if symptomatic, is reasonable. <sup>6,11</sup>
2a	C-LD	8. In pregnant women with HCM, general or epidural anesthesia is reasonable, with precautions to avoid hypotension. <sup>9</sup>
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.
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.
3: Harm	C-EO	11. In pregnant women, use of mavacamten is contraindicated due to potential teratogenic effects.

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.<sup>7-10</sup> Symptoms (dyspnea, chest pain, palpitations) and complications (HF and arrhythmias) occur in approximately 25% of pregnant women with HCM for whom most had symptoms preceding their pregnancy. No difference in outcomes was 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.<sup>12-14</sup> Both low-molecular-weight heparin and low-dose warfarin carry acceptable risk during pregnancy<sup>2</sup> and should be administered in accordance with the 2020 ACC/AHA valvular heart disease guideline.<sup>1</sup> Insufficient safety data regarding DOACs in pregnancy are available, and a recent meta-analysis

- suggests that they are associated with a higher rate of fetal complications compared with low-molecular-weight heparin or warfarin.<sup>15</sup>
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.<sup>3,4</sup>
  3. In pregnant women with cardiovascular disease, including cardiomyopathies, adverse outcomes during delivery are low (3%-4%) and similar between vaginal delivery and cesarean section.<sup>5</sup> Valsalva maneuver 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 testing, fetal screening, prenatal testing, 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 about prenatal genetic testing and fetal screening.<sup>3-6</sup>
  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 that conveys that maternal mortality with pregnancy is very low, and cardiac events occur primarily in those with preexisting symptoms and previous cardiac events.<sup>7-10</sup> 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. Some antiarrhythmic agents are contraindicated during pregnancy because of potential teratogenic effects, while others 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.<sup>6</sup> 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.<sup>8</sup>
9. Most complications that arise during pregnancy occur in the third trimester. 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 a history of pediatric disease onset or severe disease manifestations in parents or other family members are present.
11. Myosin inhibitors may cause fetal toxicity when administered to a pregnant woman, based on unpublished findings in animal studies.<sup>16</sup>

9.4. Patients With Comorbidities

Recommendations for Patients With Comorbidities Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	C-EO	1. In patients with HCM, adherence to the ACC/AHA primary prevention guideline is recommended to reduce risk of cardiovascular events. <sup>1</sup>
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 <sup>1</sup> and possibly lowering the risk of developing LVOTO, HF, and AF. <sup>2-4</sup>
1	C-LD	3. In patients with HCM and hypertension, lifestyle modifications and medical therapy for hypertension are recommended, <sup>1</sup> with preference for beta blockers and nondihydropyridine calcium channel blockers in patients with obstructive HCM.
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 is recommended. <sup>5-8</sup>

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 symptomatic and asymptomatic patients.<sup>1</sup>
2. Excess weight is very common in adult patients with HCM, with >70% having a body mass index of >25 kg/m<sup>2</sup> and >30% having a body mass index of >30 kg/m<sup>2</sup>.<sup>2-4</sup> Obesity is also common in pediatric patients with HCM, with almost 30% having a body mass index in the 99th percentile for age and sex.<sup>9</sup> Patients who are obese have an increased burden of LVH and mass,<sup>2,3,9</sup> are more symptomatic, are more likely to have LVOTO, and have reduced exercise capacity.<sup>2-4</sup> 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.<sup>4</sup> Although patients who were obese were less likely to carry a sarcomere gene variant, obesity increased risk in genotype-positive and genotype-negative patients. Obesity is also associated with increased susceptibility for developing HCM in genotype-negative patients.<sup>10</sup> Weight loss interventions in patients who are obese 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 approximately 35% to 50%, and affects sarcomere variant-negative patients disproportionately.<sup>11,12</sup> Intuitively, LV 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,<sup>13</sup> and diastolic hypertension is associated with a 4-fold risk of developing HCM in genotype-negative individuals.<sup>10</sup> Target blood pressure should be in keeping with ACC/AHA primary prevention guideline.<sup>1</sup> In patients with symptomatic obstructive HCM, beta blockers or nondihydropyridine calcium channel blockers are often used as first-line therapy. 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. In younger patients with

nonobstructive HCM due to a pathogenic or likely pathogenic cardiac sarcomere genetic variant, who have concomitant hypertension, valsartan may be a good option because of its potential to slow disease progression.<sup>14</sup>

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.<sup>5,7</sup> Obstructive sleep apnea has also been associated with a greater prevalence of AF and NSVT.<sup>6,8</sup> Diagnosis and treatment of obstructive sleep apnea could reduce symptoms and arrhythmic complications in patients with HCM but has not been systematically tested.

## 10. EVIDENCE GAPS AND FUTURE DIRECTIONS

### 10.1. Refining the Diagnosis of HCM

The diagnosis of HCM is currently based on binary cut-offs for LV wall thickness. However, due to imprecision in measurement and variability based on sex, body size, and comorbidities, relying on this single dichotomous metric will result in overdiagnosis in some groups and underdiagnosis in others.<sup>1</sup> Additionally, the phenotype of HCM extends beyond LVH. Evolving toward a more molecular or pathway-based approach to diagnosis, when possible, will enable greater diagnostic accuracy, improve patient stratification, and facilitate implementation of increasingly targeted therapies.

### 10.2. Developing Therapies to Attenuate or Prevent Disease Progression

Developing safe, effective medical therapy that can forestall disease progression is a major therapeutic goal, either with existing medications (eg, valsartan)<sup>1</sup> or emerging medications (eg, cardiac myosin inhibitors).<sup>2</sup> If the specific genetic etiology is identified, gene-based therapies offer the potential for durably impacting disease with a single intervention, and testing is starting in humans. However, for disease-modifying and preventive therapies to be established, much more robust and granular understanding of disease pathogenesis is needed, including identifying predictors of disease development, predictors of adverse outcomes, and intermediate phenotypes that accurately track disease progression and, in turn, response to therapy.

### 10.3. Improving Care for Nonobstructive HCM

Managing patients with symptomatic nonobstructive HCM remains a major clinical challenge. In contrast to obstructive HCM, where obstructive physiology can be

effectively targeted and treated with medical and surgical approaches,<sup>1–5</sup> determining the driving pathophysiology of nonobstructive HCM remains somewhat elusive. Diastolic abnormalities, including restrictive physiology and myocardial energetics, are thought to be important but are currently not well addressed. The role of cardiac myosin inhibitors in nonobstructive HCM is being investigated in clinical trials.<sup>4</sup> With clinical benefit shown with sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists in patients with HF with preserved EF, investigating whether patients with nonobstructive HCM may also benefit will be important. 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.

### 10.4. Improving and Expanding Risk Stratification

Despite several large, prospective studies<sup>1–3</sup> examining risk predictors of SCD, risk stratification algorithms still have low positive-predictive values such that many ICDs are placed unnecessarily. Conversely, sudden cardiac arrest or SCD occurs in patients with no established risk factors, albeit rarely. 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. Artificial intelligence could prove useful in screening, risk stratification, and/or disease progression monitoring. The presence, pattern, or progression of LGE or abnormal 3D strain on CMR,<sup>4–6</sup> alone or in concert with other biomarkers such as troponin levels, may become useful predictors but must be consistent with existing tools and show value against other risk metrics before clinical adoption. 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 underrepresented racial and ethnic group patients with HCM are particularly needed.

### 10.5. Arrhythmia Management

AF affects a large proportion of adult patients with HCM, is often poorly tolerated, and may be more refractory to pharmacological and catheter-based interventions than in patients without HCM.<sup>1–5</sup> Further work is needed to identify more robust predictors of developing AF, refine risk scores, and better stratify for thromboembolic complications.<sup>6</sup> Technical advances in ablative therapy for AF may increase the success rate in patients with HCM.<sup>7</sup>

## 10.6. Expanding Understanding of the Genetic Architecture of HCM

Genetic evaluation and counseling are not widely available outside of experienced HCM centers. Greater access to genetic counseling and testing, including expert interpretation of results in the clinical context, is needed for all patients with HCM to advance individual care, to improve family management, and to advance the knowledge base. Improved algorithms for the interpretation of variants that are currently classified as variants of uncertain significance are also evolving, including ongoing efforts in expert variant curation by the Clinical Genome Resource (ClinGen), a resource of the National Institutes of Health (<https://clinicalgenome.org/>).<sup>1</sup>

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 result from a combination of polygenic variants and environmental factors.<sup>2,3</sup> Additionally, better understanding of the complex genetics underlying HCM and developing polygenic risk scores will further advance patient stratification and family management, including refining longitudinal screening to be more limited in situations where the risk of heritable disease can be predicted to be low. Investigation into the correlations between genotype and phenotype and clinical outcomes continues to be an important endeavor as the field moves toward more precise and tailored therapies—including gene-specific therapeutics.

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## ARTICLE INFORMATION

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Appendix 1. Author Relationships With Industry and Other Entities–2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Steve R. Ommen, Chair	Mayo Clinic—Director, Hypertrophic Cardiomyopathy Clinic	None	None	None	None	None	None
Carolyn Y. Ho, Vice Chair	Brigham & Women's Hospital—Director, Cardiovascular Genetics Center	RELEVANT • Bristol Myers Squibb • Cytokinetics  NOT RELEVANT • Rocket Pharmaceuticals • Viz.ai	None	None	RELEVANT • Cytokinetics, PI* • Pfizer, PI*	NOT RELEVANT • Biomarin* • Novartis†  RELEVANT • Bristol Myers Squibb*	None
Irfan M. Asif	University of Alabama at Birmingham—Associate Dean, Primary Care and Rural Health; Professor and Chair, Department of Family and Community	None	None	None	None	NOT RELEVANT • CMS* • HRSA*	None
Seshadri Balaji	Oregon Health & Science University—Professor of Pediatrics, Division of Cardiology, School of Medicine; Director, Pediatric Electrophysiology	RELEVANT • Janssen Pharmaceuticals • Milestone Pharmaceuticals	None	None	RELEVANT • Medtronic†	None	NOT RELEVANT • Defendant, Sudden death evaluation, 2022
Michael A. Burke	Emory University School of Medicine—Associate Professor of Medicine	None	None	None	None	NOT RELEVANT • Pfizer†	None
Sharlene M. Day	University of Pennsylvania—Director, Translational Research, Division of Cardiovascular Medicine and Cardiovascular Institute	None	None	None	RELEVANT • Bristol Myers Squibb* • Lexicon Pharmaceuticals*  NOT RELEVANT • Cytokinetics (DSMB)	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
Joseph A. Dearani	Mayo Clinic—Director of Pediatric and Adult Congenital Heart Surgery; Professor of Surgery	None	None	None	None	None	None
Kelly C. Epps	Inova—Interventional Cardiologist	None	None	None	None	None	None
Lauren Evanovich	Patient Representative	None	None	None	None	None	None
Victor A. Ferrari	University of Pennsylvania—Chair, Penn Cardiovascular Imaging Council, Depts. of Medicine, Radiology and Penn Cardiovascular Institute; Professor Cardiovascular Medicine; Professor, Radiology	None	None	None	NOT RELEVANT • NHLBI/NIH (DSMB) <sup>†</sup> • JCMR <sup>†</sup>	None	None
José A. Joglar	UT Southwestern—Program Director, Clinical Cardiac Electrophysiology Fellowship Program	None	None	None	None	None	None
Sadiya S. Khan	Northwestern University—Assistant Professor of Medicine	None	None	None	None	None	None
Jeffrey J. Kim	Baylor College of Medicine—Director, Electrophysiology & Pacing; Professor, Pediatric Cardiology	None	None	None	None	None	None
Michelle M. Kittleson	Cedars-Sinai—Director of Education in Heart Failure and Transplantation; Director of Heart Failure Research; Professor of Medicine	None	NOT RELEVANT • Encore Medical Education • <i>Journal of Heart and Lung Transplantation</i>	None	None	NOT RELEVANT • Actelion <sup>‡</sup> • Eidos <sup>‡</sup> • Gilead (One Legacy/Baylor) <sup>‡</sup> • NIH <sup>‡</sup> • Sanofi (Genzyme) <sup>‡</sup> • United Therapeutics <sup>‡</sup>	None
Chayakrit Krittanawong	Baylor College of Medicine—Staff Physician	None	None	None	None	None	None
Matthew W. Martinez	Atlantic Health System/Morristown Medical Center—Director, Sports Cardiology; Director, Hypertrophic Cardiomyopathy Program	RELEVANT • Bristol Myers Squibb  NOT RELEVANT • Major League Soccer	None	None	None	RELEVANT • Cytokinetics <sup>‡</sup>	None
Seema Mital	Hospital for Sick Children—Head, Cardiovascular Research; Staff Cardiologist, Heart Function and Transplant Program	RELEVANT • Bristol Myers Squibb • Tenaya Therapeutics	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
Srihari S. Naidu	New York Medical College—Professor of Medicine; Westchester Medical Center—Director, HCM Center and Cardiac Cath Labs	RELEVANT <ul style="list-style-type: none"><li>Bristol Myers Squibb</li><li>Cytokinetics</li></ul>	None	None	None	None	None
Sara Saberi	University of Michigan Health Systems—Assistant Professor, Division of Cardiovascular Medicine	RELEVANT <ul style="list-style-type: none"><li>Bristol Myers Squibb*</li><li>Cytokinetics</li></ul>	None	None	RELEVANT <ul style="list-style-type: none"><li>Bristol Myers Squibb†</li><li>Cytokinetics†</li><li>Novartis†</li></ul>	NOT RELEVANT <ul style="list-style-type: none"><li>HCMS†</li></ul>	None
Christopher Semsarian	The University of Sydney—Professor of Medicine; Centenary Institute—Head, Molecular Cardiology Program; Royal Prince Alfred Hospital, Central Clinical School—Cardiologist	None	None	None	None	None	None
Sabrina Times§	AHA/ACC—Science and Health Advisor, Guidelines	None	None	None	None	None	None
Cynthia Burstein Waldman	HCMBeat—Founder and Editor; MGM, Vice President, Library Rights Management	None	None	None	None	None	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. 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 ≥5% of the voting stock or share of the business entity, or ownership of ≥\$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.

\*Significant relationship.  
†No financial benefit.  
‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

§Sabrina Times is an AHA/ACC joint staff member and acts as the Guideline Advisor for the "2024 AHA/ACC/AMSSM/HRS/PACES Guideline for the Management of Hypertrophic Cardiomyopathy." No relevant relationships to report. Nonvoting author on measures and not included/counted in the RWI balance for this writing committee.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; AMSSM, American Medical Society for Sports Medicine; CMS, Centers for Medicare & Medicaid Services; DSMB, data and safety monitoring board; HCM, hypertrophic cardiomyopathy; HCMS, Hypertrophic Cardiomyopathy Medical Society; HRS, Heart Rhythm Society; HRSA, Health Resources & Services Administration; JCMR, *Journal of Cardiovascular Magnetic Resonance*; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; PACES, Pediatric & Congenital Electrophysiology Society; PI, principal investigator; RWI, relationships with industry and other entities; and UT, The University of Texas.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)—2024 AHA/ACC/AMSSM/HRS/ PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Mark S. Link, Chair	AHA/ACC HCM Guideline Peer Review Committee	UT Southwestern Medical Center	None	None	None	None	<ul style="list-style-type: none"><li>Journal Watch Cardiology</li><li><i>Circulation</i>, Associate Editor†</li><li>UpToDate†</li></ul>	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
Anandita Agarwala	AHA/ACC HCM Guideline Peer Review Committee	Baylor Scott & White Health—The Heart Hospital Baylor Plano	None	None	None	• NIH*	None	None
Chad Asplund	AHA/ACC HCM Guideline Peer Review Committee, representing AMSSM	Georgetown University	None	None	None	None	None	None
Michael Ayers	AHA/ACC HCM Guideline Peer Review Committee	University of Virginia	• Atheneum • Bristol Myers Squibb† • HFSA	• Bristol Myers Squibb†	None	None	• Cytokinetics‡	• Plaintiff, Chest pain, 2023
C. Anwar Chahal	AHA/ACC HCM Guideline Peer Review Committee	Wellspar Health; Mayo Clinic Barts Heart Centre	None	None	None	None	None	None
Jonathan Chrispin	AHA/ACC HCM Guideline Peer Review Committee	Johns Hopkins University	• Abbott† • Biosense Webster • Boston Scientific*	None	None	None	• Abbott‡ • Biosense Webster‡	None
Aarti Dalal	AHA/ACC HCM Guideline Peer Review Committee	Vanderbilt University	• Medtronic†	None	None	None	None	None
Alejandro E. De Feria Alsina	AHA/ACC HCM Guideline Peer Review Committee	University of Pennsylvania	None	None	None	None	None	None
Jonathan Drezner	AHA/ACC HCM Guideline Peer Review Committee	University of Washington	None	None	None	• AMSSM* • National Center for Catastrophic Sports Injury Research*	None	None
Rajesh Kabra	AHA/ACC HCM Guideline Peer Review Committee	Kansas City Heart Rhythm Institute University of Tennessee Health Science Center	• Volta Medical	None	None	None	• Abbott, Fellowship Grant† • Biosense Webster, Fellowship Grant† • Medtronic, Fellowship Grant† • Iqvia Biotech‡ • Medtronic‡	None
Sabeeda Kadavath	AHA/ACC HCM Guideline Peer Review Committee	St. Bernards Medical Center	None	None	None	None	None	None
Elizabeth S. Kaufman	AHA/ACC HCM Guideline Peer Review Committee Member, representing HRS	The MetroHealth System	None	None	None	None	• CIH‡	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
Sabra Lewsey	AHA/ACC HCM Guideline Peer Review Committee	Johns Hopkins University	None	None	None	None	• Associate of BlackCardiologists, Volunteer position*	None
James P. MacNamara	AHA/ACC HCM Guideline Peer Review Committee	UT Southwestern Medical Center	• Lexicon	None	None	• Boehringer Ingelheim • Bristol Myers Squibb† • Cytokinetics† • Sardacort	None	None
Anjali Owens	AHA/ACC HCM Guideline Peer Review Committee	University of Pennsylvania	• BioMarin Pharmaceuticals • Bristol Myers Squibb† • Cytokinetics† • Edgewise Therapeutics • Lexeo Therapeutics • Lexicon • Myokardia† • Pfizer • Renovacor • Stealth Bio-therapeutics • Tenaya Therapeutics	None	None	• Array Biopharma, PI*	None	None
Hena Patel	AHA/ACC HCM Guideline Peer Review Committee	University of Chicago	None	None	None	None	None	None
Nosheen Reza	AHA/ACC HCM Guideline Peer Review Committee, representing ACC/ AHA JCPM	University of Pennsylvania	• Bristol Myers Squibb* • Roche Diagnostics • Zoll	None	None	• NIH†	• Alleviant Medical, Inc. • AstraZeneca* • Bristol Myers Squibb† • Cytokinetics*‡ • Pfizer‡	None
Aldo L. Schenone	AHA/ACC HCM Guideline Peer Review Committee	Montefiore Medical Center	None	• Bristol Myers Squibb	None	None	None	None
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