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AHA/ACC CLINICAL PRACTICE GUIDELINE

2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

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ACC/AHA Joint Committee Members, see page e608

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TABLE OF CONTENTS

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

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

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

4. Optimal care for patients with HCM requires cardiac imaging to confirm the diagnosis, characterize the pathophysiology for the individual, and identify risk markers that may inform decisions regarding interventions for left ventricular outflow tract obstruction and sudden cardiac death (SCD) prevention. Echocardiography continues to be the foundational imaging modality for patients with HCM. Cardiovascular magnetic resonance imaging will also be helpful in many patients, especially those in whom there is diagnostic uncertainty, poor echocardiographic imaging windows, or where uncertainty persists regarding decisions around implantable cardioverter-defibrillator (ICD) placement.
5. Assessment of an individual patient's risk for SCD continues to evolve as new markers emerge (eg, apical aneurysm, decreased left ventricular systolic function, and extensive gadolinium enhancement). In addition to a full accounting of an individual's risk markers, communication with patients regarding not just the presence of risk markers but also the magnitude of their individualized risk is key. This enables the informed patient to fully participate in the decision-making regarding ICD placement, which incorporates their own level of risk tolerance and treatment goals.
6. The risk factors for SCD in children with HCM carry different weights than those observed in adult patients; they vary with age and must account for different body sizes. Coupled with the complexity of placing ICDs in young patients with anticipated growth and a higher risk of device complications, the threshold for ICD implantation in children often differs from adults. These differences are best addressed at primary or comprehensive HCM centers with expertise in children with HCM.
7. Septal reduction therapies (surgical septal myectomy and alcohol septal ablation), when performed by experienced HCM teams at dedicated centers, continue to improve in safety and efficacy such that earlier intervention may be possible in select patients with drug-refractory or severe outflow tract obstruction causing signs of cardiac decompensation. Given the data on the significantly improved outcomes at comprehensive HCM centers, these decisions represent an optimal referral opportunity.
8. Patients with HCM and persistent or paroxysmal atrial fibrillation have a sufficiently increased risk of stroke such that oral anticoagulation with direct oral anticoagulants (or alternatively warfarin) should be considered the default treatment option independent of the CHA_2DS_2VASc score. As rapid atrial fibrillation is often poorly tolerated in patients with HCM, maintenance of sinus rhythm and rate control are key pursuits in successful treatment.
9. Heart failure symptoms in patients with HCM, in the absence of left ventricular outflow tract obstruction, should be treated similarly to other patients with heart failure symptoms, including consideration of advanced treatment options (eg, cardiac resynchronization therapy, left ventricular assist device, transplantation). In patients with HCM, an ejection fraction <50% connotes significantly impaired systolic function and identifies individuals with poor prognosis and who are at increased risk for SCD.
10. Increasingly, data affirm that the beneficial effects of exercise on general health can be extended to patients with HCM. Healthy recreational exercise (moderate intensity) has not been associated with increased risk of ventricular arrhythmia events in recent studies. Whether an individual patient with HCM wishes to pursue more rigorous exercise/training is dependent on a comprehensive shared discussion between that patient and their expert HCM care team regarding the potential risks of that level of training/participation but with the understanding that exercise-related risk cannot be individualized for a given patient.

PREAMBLE

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

INTENDED USE

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

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

CLINICAL IMPLEMENTATION

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

METHODOLOGY AND MODERNIZATION

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

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

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

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of "full revision" and "focused update" will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual[4] and other methodology articles.[5–7]

SELECTION OF WRITING COMMITTEE MEMBERS

The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and professional societies with related interests and expertise are invited to participate as partners or collaborators.

RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES

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

EVIDENCE REVIEW AND EVIDENCE REVIEW COMMITTEES

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

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

GUIDELINE-DIRECTED MANAGEMENT AND THERAPY

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

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

1.2. Organization of the Writing Committee

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

Table 1. Associated Guidelines

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

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

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

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

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

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

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

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

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

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

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

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC and AHA, 1 reviewer each from the American Association for Thoracic Surgery, American Society of Echocardiography, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance, and 26 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

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

1.4. Scope of the Guideline

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

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

1.5. Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 2).[1]

Abbreviation	Meaning/Phrase
AF	atrial fibrillation
CAD	coronary artery disease
CMR	cardiovascular magnetic resonance
CPET	cardiopulmonary exercise test
CRT	cardiac resynchronization therapy
DOAC	direct-acting oral anticoagulants
EF	ejection fraction
GDMT	guideline-directed management and therapy
HCM	hypertrophic cardiomyopathy
HF	heart failure
ICD	implantable cardioverter-defibrillator
LAMP2	lysosome-associated membrane protein-2
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 AF
SCD	sudden cardiac death
SRT	septal reduction therapy
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
VF	ventricular fibrillation
VT	ventricular tachycardia

1.6. Abbreviations

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

2.1. Prevalence

HCM is a common genetic heart disease reported in populations globally. Inherited in an autosomal dominant pattern, the distribution of HCM is equal by sex, although women are diagnosed less commonly than men. The prevalence of HCM depends on whether subclinical or clinically evident cases are being considered, is age dependent, and may have racial/ethnic differences.[1] The prevalence of unexplained asymptomatic hypertrophy in young adults in the United States has been reported to range from 1:200 to 1:500.[2] Symptomatic hypertrophy based on medical claims data has been estimated at <1:3000 adults in the United States; however, the true burden is much higher when unrecognized disease in the general population is considered.[3] Clinical evaluation for HCM may be triggered by occurrence of symptoms, a cardiac event, detection of a heart murmur, an abnormal 12-lead ECG identified on routine examination, or through cardiac imaging during family screening studies.

2.2. Nomenclature/Differential Diagnosis

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

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

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

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

2.3. Definition, Clinical Diagnosis, and Phenotype

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

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

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

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

2.4. Etiology

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

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

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

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

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

2.5. Natural History/Clinical Course

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

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

3. PATHOPHYSIOLOGY

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

3.1. LVOT Obstruction

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

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

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

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

3.2. Diastolic Dysfunction

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

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

3.3. Mitral Regurgitation

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

3.4. Myocardial Ischemia

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