

## 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

### A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

*Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons*

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## Preamble

It is essential that the medical profession play a central role in critically evaluating the evidence related to drugs, devices, and procedures for the detection, management, or prevention

of disease. Properly applied, rigorous, expert analysis of the available data documenting absolute and relative benefits and risks of these therapies and procedures can improve the effectiveness of care, optimize patient outcomes, and favorably affect the cost of care by focusing resources on the most effective strategies. One important use of such data is the production of clinical practice guidelines that, in turn, can provide a foundation for a variety of other applications such as performance measures, appropriateness use criteria, clinical decision support tools, and quality improvement tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force) is charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, and the Task Force directs and oversees this effort. Writing committees are charged with assessing the evidence as an independent group of authors to develop, update, or revise recommendations for clinical practice.

Experts in the subject under consideration have been selected from both organizations to examine subject-specific data and write guidelines in partnership with representatives from other medical practitioner and specialty groups. Writing committees are specifically charged to perform a formal literature review, weigh the strength of evidence for or against particular tests, treatments, or procedures, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and clinical outcomes constitute the primary basis for recommendations in these guidelines.

In analyzing the data and developing the recommendations and supporting text, the writing committee used evidence-based methodologies developed by the Task Force, which are described elsewhere.<sup>1</sup> The committee reviewed and ranked evidence supporting current recommendations with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials (RCTs) or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single RCT or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, prospective, or randomized when appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, for which there are no RCTs and treatment is based on clinical experience. When recommendations at Level C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues where sparse data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations and no references are cited. The

Table 1. Applying Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT				
	CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/ administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> <i>Additional studies with focused objectives needed</i> <b>IT IS REASONABLE</b> to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>	
				Procedure/ Test	Treatment
				COR III: No benefit	No Proven Benefit
				COR III: Harm	Excess Cost w/o Benefit or Harmful
<b>LEVEL A</b> Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from multiple randomized trials or meta-analyses</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Sufficient evidence from multiple randomized trials or meta-analyses</li> </ul>	
<b>LEVEL B</b> Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Some conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Greater conflicting evidence from single randomized trial or nonrandomized studies</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Evidence from single randomized trial or nonrandomized studies</li> </ul>	
<b>LEVEL C</b> Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is useful/effective</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation in favor of treatment or procedure being useful/effective</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation's usefulness/efficacy less well established</li> <li>Only diverging expert opinion, case studies, or standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Recommendation that procedure or treatment is not useful/effective and may be harmful</li> <li>Only expert opinion, case studies, or standard of care</li> </ul>	
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective	COR III: Harm potentially harmful causes harm associated with excess morbid- ity/mortality should not 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	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

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

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

schema for Classification of Recommendations and Level of Evidence is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size and the certainty of the treatment effect. A new addition to the ACCF/AHA methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of “no benefit” or associated with “harm” to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment/strategy with respect to another for Class of Recommendation I and IIa, Level of Evidence A or B only have been added.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, are required to disclose all relevant relationships and those 12 months prior to initiation of the writing effort. The policies and procedures for RWI for this guideline were those in effect at the initial meeting of this committee (March 28, 2009), which included 50% of the writing committee with no relevant RWI. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the members voting. Members



who were recused from voting are indicated on the title page of this document with detailed information included in Appendix 1. Members must recuse themselves from voting on any recommendations where their RWI apply. If a writing committee member develops a new RWI during his/her tenure, he/she is required to notify guideline staff in writing. These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing committee and are updated as changes occur. For detailed information regarding guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual.<sup>1</sup> RWI pertinent to this guideline for authors and peer reviewers are disclosed in Appendixes 1 and 2, respectively. Comprehensive disclosure information for the Task Force is also available online at <http://www.cardiosource.org/ACCF/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx>. The work of the writing committee was supported exclusively by the ACCF and AHA without commercial support. Writing committee members volunteered their time for this effort.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are currently unavailable in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of subjects outside of North America, each writing group reviews the potential impact of different practice patterns and patient populations on the treatment effect and on the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. These practice guidelines represent a consensus of expert opinion after a thorough review of the available current scientific evidence and are intended to improve patient care. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are situations in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise for which additional data are needed to better inform patient care; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles.

The guideline will be reviewed annually by the Task Force and considered current unless it is updated, revised, or withdrawn from distribution.

Guidelines are official policy of both the ACCF and AHA.  
*Alice K. Jacobs, MD, FACC, FAHA*  
*Chair, ACCF/AHA Task Force on Practice Guidelines*

## 1. Introduction

### 1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted through January 2011. Searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. Key search words included, but were not limited to, *hypertrophic cardiomyopathy (HCM), surgical myectomy, ablation, exercise, sudden cardiac death (SCD), athletes, dual-chamber pacing, left ventricular outflow tract (LVOT) obstruction, alcohol septal ablation, automobile driving and implantable cardioverter-defibrillators (ICDs), catheter ablation, defibrillators, genetics, genotype, medical management, magnetic resonance imaging, pacing, permanent pacing, phenotype, pregnancy, risk stratification, sudden death in athletes, surgical septal myectomy, and septal reduction*. Additionally, the committee reviewed documents related to the subject matter previously published by the ACCF and AHA. References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm are provided in the guideline, along with confidence intervals and data related to the relative treatment effects, such as odds ratio, relative risk, hazard ratio, or incidence rate ratio.

### 1.2. Organization of the Writing Committee

The committee was composed of physicians and cardiac surgeons with expertise in HCM, invasive cardiology, non-invasive testing and imaging, pediatric cardiology, electrophysiology, and genetics. The committee included representatives from the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons.

### 1.3. Document Review and Approval

This document was reviewed by 2 outside reviewers nominated by both the ACCF and AHA, as well as 2 reviewers each from the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. Other content reviewers included members from the ACCF Adult Congenital and Pediatric Cardiology Council, ACCF Surgeons' Scientific Council, and ACCF Interventional Scientific Council. All information on reviewers' RWI 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 ACCF and the AHA and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.

## 1.4. Scope of the Guideline

Although there are reports of this disease dating back to the 1800s, the first modern pathologic description was provided over 50 years ago by Teare<sup>2</sup> and the most important early clinical report by Braunwald et al in 1964.<sup>3</sup> Since then, there has been a growing understanding of the complexity and diversity of the underlying genetic substrate, the clinical phenotype, natural history, and approaches to treatment.

The impetus for the guideline is based on an appreciation of the frequency of this clinical entity and a realization that many aspects of clinical management, including the use of diagnostic modalities and genetic testing, lack consensus. Moreover, the emergence of 2 different approaches to septal reduction therapy (septal myectomy and alcohol septal ablation) in addition to the ICD has created considerable controversy. The discussion and recommendations about the various diagnostic modalities apply to patients with established HCM and to a variable extent to patients with a high index of suspicion of the disease.

Although the Task Force was aware of the lack of high levels of evidence regarding HCM provided by clinical trials, it was believed that a guideline document based on expert consensus that outlines the most important diagnostic and management strategies would be helpful.

To facilitate ease of use, it was decided that recommendations in the pediatric and adolescent age groups would not appear as a separate section but instead would be integrated into the overall content of the guideline where relevant.

## 2. Prevalence/Nomenclature/Differential Diagnosis

### 2.1. Prevalence

HCM is a common genetic cardiovascular disease. In addition, HCM is a global disease,<sup>4</sup> with epidemiological studies from several parts of the world<sup>5</sup> reporting a similar prevalence of left ventricular (LV) hypertrophy, the quintessential phenotype of HCM, to be about 0.2% (ie, 1:500) in the general population, which is equivalent to at least 600 000 people affected in the United States.<sup>6</sup> This estimated frequency in the general population appears to exceed the relatively uncommon occurrence of HCM in cardiology practices, implying that most affected individuals remain unidentified, probably in most cases without symptoms or shortened life expectancy.

### 2.2. Nomenclature

#### 2.2.1. Historical Context

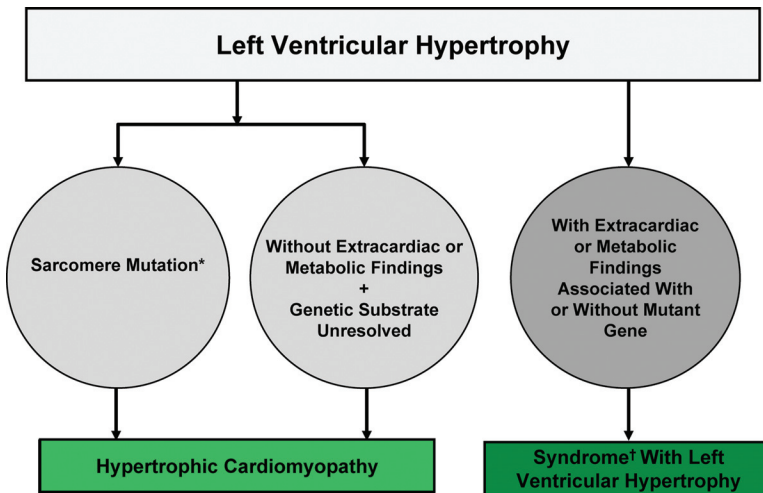
Although HCM is the preferred nomenclature to describe this disease,<sup>7</sup> confusion over the names used to characterize the entity of HCM has arisen over the years. At last count, >80

individual names, terms, and acronyms have been used (most by early investigators) to describe HCM.<sup>7</sup> Furthermore, nomenclature that was popular in the 1960s and 1970s, such as IHSS (idiopathic hypertrophic subaortic stenosis) or HOCM (hypertrophic obstructive cardiomyopathy), is potentially confusing by virtue of the inference that LVOT is an invariable and obligatory component of the disease. In fact, fully one third of patients have no obstruction either at rest or with physiologic provocation.<sup>8</sup> Although terms such as IHSS and HOCM persist occasionally in informal usage, they now rarely appear in the literature, whereas HCM, initially used in 1979, allows for both the obstructive and nonobstructive hemodynamic forms and has become the predominant formal term used to designate this disease.<sup>7</sup>

#### 2.2.2. Clinical Definition and Differential Diagnosis

The generally accepted definition of HCM, the clinical entity that is the subject of this guideline, is a disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient,<sup>6,7,9–12</sup> with the caveat that patients who are genotype positive may be phenotypically negative without overt hypertrophy.<sup>13,14</sup> Clinically, HCM is usually recognized by maximal LV wall thickness  $\geq 15$  mm, with wall thickness of 13 to 14 mm considered borderline, particularly in the presence of other compelling information (eg, family history of HCM), based on echocardiography. In terms of LV wall-thickness measurements, the literature at this time has been largely focused on echocardiography, although cardiovascular magnetic resonance (CMR) is now used with increasing frequency in HCM,<sup>15</sup> and we presume that data with this latter modality will increasingly emerge. In the case of children, increased LV wall thickness is defined as wall thickness  $\geq 2$  standard deviations above the mean ( $z$  score  $\geq 2$ ) for age, sex, or body size. However, it should be underscored that in principle, any degree of wall thickness is compatible with the presence of the HCM genetic substrate and that an emerging subgroup within the broad clinical spectrum is composed of family members with disease-causing sarcomere mutations but without evidence of the disease phenotype (ie, LV hypertrophy).<sup>16–19</sup> These individuals are usually referred to as being “genotype positive/phenotype negative” or as having “subclinical HCM.” Furthermore, although a myriad of patterns and distribution of LV hypertrophy (including diffuse and marked) have been reported in HCM,<sup>15,20,21</sup> about one third of patients have largely segmental wall thickening involving only a small portion of the left ventricle, and indeed such patients with HCM usually have normal calculated LV mass.<sup>15</sup> The clinical diagnosis of HCM may also be buttressed by other typical features, such as family history of the disease, cardiac symptoms, tachyarrhythmias, or electrocardiographic abnormalities.<sup>9,10</sup>

Differential diagnosis of HCM and other cardiac conditions (with LV hypertrophy) may arise, most commonly with hypertensive heart disease and the physiologic remodeling associated with athletic training (“athlete’s heart”).<sup>22–26</sup> These are not uncommon clinical scenarios, and confusion between



**Figure 1.** Summary of the nomenclature that distinguishes HCM from other genetic diseases associated with LV hypertrophy. \*At this time the overwhelming evidence links the clinical diagnosis of HCM with a variety of genes encoding protein components of the cardiac sarcomere. However, it is possible that in the future other nonsarcomeric (but also nonmetabolic) genes may prove to cause HCM. †An example is Noonan syndrome with cardiomyopathy. Modified with permission from Maron et al.<sup>12</sup>

mild morphologic expressions of HCM and other conditions with LV hypertrophy usually arises when maximum wall thickness is in the modest range of 13 to 15 mm. In older patients with LV hypertrophy and a history of systemic hypertension, coexistence of HCM is often a consideration. The likelihood of HCM can be determined by identification of a diagnostic sarcomere mutation or inferred by marked LV thickness >25 mm and/or LVOT obstruction with systolic anterior motion (SAM) and mitral-septal contact.

The important distinction between pathologic LV hypertrophy (ie, HCM) and physiologic LV hypertrophy (ie, athlete's heart) is impacted by the recognition that athletic conditioning can produce LV, right ventricular, and left atrial (LA) chamber enlargement, ventricular septal thickening, and even aortic enlargement<sup>26</sup> but is often resolved by noninvasive markers, including sarcomeric mutations or family history of HCM, LV cavity dimension (if enlarged, favoring athlete's heart), diastolic function, pattern of LV hypertrophy (if unusual location or noncontiguous, favoring HCM), or short deconditioning periods in which a decrease in wall thickness would favor athlete's heart.<sup>22–26</sup>

Notably, it is evident that metabolic or infiltrative storage disorders with LV hypertrophy in babies, older children, and young adults can mimic clinically diagnosed HCM (attributable to sarcomeric protein mutations), for example, conditions such as mitochondrial disease,<sup>27,28</sup> Fabry disease,<sup>29</sup> or storage diseases caused by mutations in the genes encoding the  $\gamma$ -2-regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase (PRKAG2) or the X-linked lysosome-associated membrane protein gene (*LAMP2*; Danon disease).<sup>30–33</sup> Use of the term HCM is not appropriate to describe these and other patients with LV hypertrophy that occurs in the context of a multisystem disorder such as Noonan syndrome (with craniofacial and congenital heart malformations, as well as LV hypertrophy from mutations in genes of the RAS [Rat Sarcoma] pathway<sup>14,15</sup>), or distinct cardiomyopathies such as Pompe disease (also a glycogen storage disease II, with skeletal muscle weakness and cardiomyopathy because of deficiency of  $\alpha$ 1,4 glycosidase [acid maltase])<sup>34–38</sup> (Figure 1). In addition, differential diagnosis of HCM may require distinction from systemic hypertension or

physiologic athlete's heart<sup>23</sup> or from dilated cardiomyopathy when HCM presents in the end stage.<sup>39</sup>

### 2.2.3. Impact of Genetics

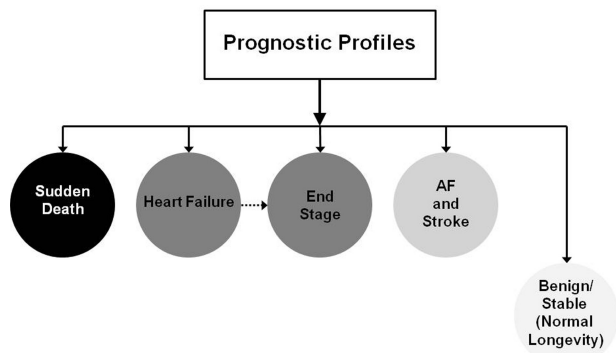
On the basis of the genotype-phenotype data available at this time, HCM is regarded here as a disease entity caused by autosomal dominant mutations in genes encoding protein components of the sarcomere and its constituent myofilament elements.<sup>30,40–42</sup> Intergenetic diversity is compounded by considerable intragenic heterogeneity, with >1400 mutations identified among at least 8 genes. The current weight of evidence supports the view that the vast majority of genes and mutations responsible for clinically diagnosed HCM encode proteins within and associated with the sarcomere, accounting in large measure for those patients described in the voluminous amount of HCM literature published over 50 years.<sup>30,40–42</sup>

In conclusion, the writing committee believes that the most prudent recommendation for nomenclature is that *hypertrophic cardiomyopathy* and the acronym *HCM* remain a clinical diagnosis limited to those patients in whom (1) overt disease expression (with LV hypertrophy) appears to be confined to the heart and (2) the definitive mutation is either one of a gene encoding proteins of the cardiac sarcomere or alternatively when the genotype is unresolved using current genetic testing. Therefore, nomenclature that describes patients as “Noonan hypertrophic cardiomyopathy” is discouraged, whereas “Noonan syndrome with LV hypertrophy” or “Noonan syndrome with cardiomyopathy” is preferred.

### 2.2.4. Hypertrophic Cardiomyopathy Centers

The writing committee considers it important to emphasize that HCM is a complex disease entity with a broad (and increasing) clinical and genetic spectrum.<sup>9</sup> Although HCM is one of the most common forms of genetic heart disease and relatively common in the general population,<sup>6</sup> this disease entity is infrequent in general clinical practice, with most cardiologists responsible for the care of only a few patients with HCM.<sup>43</sup> This principle has led to an impetus for establishing clinical programs of excellence—usually within established centers—in which cardiovascular care is focused on the management of HCM (ie, “HCM centers”).<sup>43,44</sup> Such programs are staffed by cardiologists and cardiac surgeons





**Figure 2.** Prognosis profiles for HCM and targets for therapy. AF indicates atrial fibrillation. Modified with permission from Maron et al.<sup>10</sup>

familiar with the contemporary management of HCM and offer all diagnostic and treatment options, including genetic testing and counseling, comprehensive transthoracic echocardiogram (TTE), CMR imaging, both surgical septal myectomy and alcohol ablation, and the management of atrial fibrillation (AF)/atrial flutter, and ICDs. Another advantage is the potential to perform outcomes research on large groups of patients. Although the writing committee does not necessarily recommend that all patients with HCM should be evaluated in such centers, nevertheless, it is the strong view that patients with this disease may well benefit from a clinical environment with specific expertise in HCM. The selection of patients for referral to an HCM center should be based largely on the judgment of the managing cardiologist and the degree to which he or she is comfortable advising and evaluating patients with HCM with a particular clinical profile.

### 3. Clinical Course and Natural History, Including Absence of Complications

HCM is a heterogeneous cardiac disease with a diverse clinical presentation and course, presenting in all age groups from infancy to the very elderly.<sup>9,10,39,45</sup> Most affected individuals probably achieve a normal life expectancy without disability or the necessity for major therapeutic interventions.<sup>46–49</sup> On the other hand, in some patients, HCM is associated with disease complications that may be profound, with the potential to result in disease progression or premature death.<sup>9,10,39,45,50,51</sup> When the disease does result in significant complications, there are 3 relatively discrete but not mutually exclusive pathways of clinical progression (Figure 2):

1. SCD due to unpredictable ventricular tachyarrhythmias, most commonly in young asymptomatic patients <35 years of age<sup>50–59</sup> (including competitive athletes).<sup>58,59</sup>
2. Heart failure characterized by exertional dyspnea (with or without chest pain) that may be progressive despite preserved systolic function and sinus rhythm, or in a small proportion of patients, heart failure may progress to the end stage with LV remodeling and systolic dysfunction caused by extensive myocardial scarring.<sup>39</sup>
3. AF, either paroxysmal or chronic, also associated with various degrees of heart failure<sup>60</sup> and an increased risk of systemic thromboembolism and both fatal and non-fatal stroke.

**Table 2.** Definitions of Dynamic Left Ventricular Outflow Tract Obstruction

Hemodynamic State	Conditions	Outflow Gradient*
Basal obstruction	Rest	$\geq 30$ mm Hg†
Nonobstructive	Rest	$<30$ mm Hg
	Physiologically provoked	$<30$ mm Hg
Labile obstruction	Rest	$<30$ mm Hg†
	Physiologically provoked	$\geq 30$ mm Hg†

\*Either the peak instantaneous continuous wave Doppler gradient or the peak-to-peak cardiac catheterization gradient, which are equivalent in hypertrophic cardiomyopathy.<sup>73,74</sup>

†Gradients  $\geq 50$  mm Hg either at rest or with provocation are considered the threshold for septal reduction therapy in severely symptomatic patients.

The natural history of HCM can be altered by a number of therapeutic interventions: ICDs for secondary or primary prevention of sudden death in patients with risk factors<sup>54–56</sup>; drugs appropriate to control heart failure symptoms (principally those of exertional dyspnea and chest discomfort),<sup>9,10</sup> surgical septal myectomy<sup>61</sup> or alcohol septal ablation<sup>62</sup> for progressive and drug-refractory heart failure caused by LVOT obstruction; heart transplantation for systolic (or less frequently intractable diastolic) dysfunction associated with severe unrelenting symptoms<sup>39</sup>; and drug therapy or possibly radiofrequency ablation or surgical maze procedure for AF.<sup>63–65</sup>

## 4. Pathophysiology

The pathophysiology of HCM is complex and consists of multiple interrelated abnormalities, including LVOT obstruction, diastolic dysfunction, mitral regurgitation, myocardial ischemia, and arrhythmias.<sup>9,66,67</sup> It is clinically important to distinguish between the obstructive and nonobstructive forms of HCM because management strategies are largely dependent on the presence or absence of symptoms caused by obstruction.

### 4.1. LVOT Obstruction

The original observations by Brock<sup>68</sup> and Braunwald et al<sup>3</sup> emphasized the functional subvalvular LVOT gradient, which was highly influenced by alterations in the load and contractility of the left ventricle. The clinical significance of the outflow tract gradient has periodically been controversial,<sup>69–72</sup> but careful studies have shown definitively that true mechanical obstruction to outflow does occur.<sup>66,67</sup> For HCM, it is the peak instantaneous LV outflow gradient rather than the mean gradient that influences treatment decisions. Throughout the remainder of this document the term *gradient* will be used to denote peak instantaneous gradient. Up to one third of patients with HCM will have obstruction under basal (resting) conditions (defined as gradients  $\geq 30$  mm Hg). Another one third or more of patients will have labile, physiologically provoked gradients ( $<30$  mm Hg at rest and  $\geq 30$  mm Hg with physiologic provocation).<sup>8</sup> The final one third of patients will have the nonobstructive form of HCM (gradients  $<30$  mm Hg at rest and with provocation) (Table 2). Marked gradients  $\geq 50$  mm Hg, either at rest or with provocation, represent the conventional threshold for surgical



or percutaneous intervention if symptoms cannot be controlled with medications.

Obstruction causes an increase in LV systolic pressure, which leads to a complex interplay of abnormalities including prolongation of ventricular relaxation, elevation of LV diastolic pressure, mitral regurgitation, myocardial ischemia, and a decrease in forward cardiac output.<sup>9,66,67</sup> Outflow obstruction usually occurs in HCM by virtue of mitral valve SAM and mitral-septal contact. Although the mechanism of the outflow tract gradient in HCM was initially thought to be caused by systolic contraction of the hypertrophied basal ventricular septum encroaching on the LVOT, most recent studies emphasize that during ventricular systole, flow against the abnormally positioned mitral valve apparatus results in drag force on a portion of the mitral valve leaflets, which pushes the leaflets into the outflow tract.<sup>66,67,75–78</sup> Muscular obstruction can also be present in the midcavitary region, occasionally because of hypertrophied papillary muscles abutting the septum<sup>79</sup> or anomalous papillary muscle insertion into the anterior mitral leaflet.<sup>80</sup>

Obstruction to LV outflow is dynamic, varying with loading conditions and contractility of the ventricle.<sup>3</sup> Increased myocardial contractility, decreased ventricular volume, or decreased afterload increases the degree of subaortic obstruction. Patients may have little or no obstruction of the LVOT at rest but can generate large LVOT gradients under conditions such as exercise, the strain phase of the Valsalva maneuver, or during pharmacologic provocation.<sup>66,67</sup> There is often large spontaneous variation in the severity of the gradient during day-to-day activities or even with food or alcohol intake<sup>81</sup>; exacerbation of symptoms during the postprandial period is common. Importantly, it has been well established that LVOT obstruction contributes to the debilitating heart failure–related symptoms that may occur in HCM<sup>66,67</sup> and is also a major determinant of outcome.<sup>45</sup>

The presence and magnitude of outflow obstruction are usually assessed with 2-dimensional echocardiography and continuous wave Doppler. It is a late-peaking systolic velocity that reflects the occurrence of subaortic obstruction late in systole, and the peak instantaneous gradient derived from the peak velocity should be reported. If the resting outflow gradient is <50 mm Hg, provocative measures may be used to ascertain if higher gradients can be elicited, preferably with physiologic exercise (stress echocardiography) but alternatively with the Valsalva maneuver or selectively with amyl nitrite.<sup>3,10</sup> Provocation with dobutamine infusion during Doppler echocardiography is no longer recommended as a strategy to induce outflow gradients in HCM. However in equivocal cases, cardiac catheterization with isoproterenol infusion may further aid in eliciting a provokable gradient.<sup>82</sup> Otherwise, routine invasive cardiac catheterization to document outflow gradients is necessary only when there are discordant data from Doppler echocardiography and the physical examination.<sup>10</sup> The peak-to-peak gradient obtained with catheterization most closely approximates the peak instantaneous gradient by continuous wave Doppler echocardiography.<sup>73,74</sup>

## 4.2. Diastolic Dysfunction

Diastolic dysfunction arising from multiple factors is a major pathophysiologic abnormality in HCM that ultimately affects both ventricular relaxation and chamber stiffness.<sup>66,67,83</sup> Impairment of ventricular relaxation results from the systolic contraction load caused by outflow tract obstruction, nonuniformity of ventricular contraction and relaxation, and delayed inactivation caused by abnormal intracellular calcium reuptake. Severe hypertrophy of the myocardium results in an increase in chamber stiffness. Diffuse myocardial ischemia may further affect both relaxation and chamber stiffness. A compensatory increase in the contribution of late diastolic filling during atrial systole is associated with these alterations.<sup>84</sup> With exercise or any other type of catecholamine stimulation, the decrease in diastolic filling period as well as myocardial ischemia will further lead to severe abnormalities of diastolic filling of the heart, with chest pain and/or an increase in pulmonary venous pressure causing dyspnea.

## 4.3. Myocardial Ischemia

Severe myocardial ischemia and even infarction may occur in HCM.<sup>85,86</sup> The myocardial ischemia is frequently unrelated to the atherosclerotic epicardial coronary artery disease (CAD) but is caused by supply–demand mismatch. Patients with HCM of any age have increased oxygen demand caused by the hypertrophy and adverse loading conditions. They also have compromised coronary blood flow to the LV myocardium because of intramural arterioles with thickened walls attributable to medial hypertrophy associated with luminal narrowing.<sup>87</sup>

## 4.4. Autonomic Dysfunction

During exercise, approximately 25% of patients with HCM have an abnormal blood pressure response defined by either a failure of systolic blood pressure to rise >20 mm Hg or a fall in systolic blood pressure.<sup>88,89</sup> The presence of this finding is associated with a poorer prognosis.<sup>89,90</sup> This inability to augment and sustain systolic blood pressure during exercise is caused by either the dynamic LVOT obstruction or systemic vasodilatation during exercise. It is speculated that autonomic dysregulation<sup>88</sup> is present in patients with HCM and that the fall in blood pressure associated with bradycardia may be an abnormal reflex response to obstruction.

## 4.5. Mitral Regurgitation

Mitral regurgitation is common in patients with LVOT obstruction and may play a primary role in producing symptoms of dyspnea. The temporal sequence of events of eject-obstruct-leak supports the concept that the mitral regurgitation in most patients is a secondary phenomenon.<sup>66,67,91</sup> The mitral regurgitation is usually caused by the distortion of the mitral valve apparatus from the SAM secondary to the LVOT obstruction. The jet of mitral regurgitation is directed laterally and posteriorly and predominates during mid and late systole. An anteriorly directed jet should suggest an intrinsic abnormality of the mitral valve. If the mitral regurgitation is caused by distortion of leaflet motion by SAM of the mitral valve, the severity of the mitral regurgitation may be proportional to the LVOT obstruction in some patients.

Changes in ventricular load and contractility that affect the severity of outflow tract obstruction similarly affect the degree of mitral regurgitation. It is important to identify patients with additional intrinsic disease of the mitral valve apparatus (prolapse or flail), because this finding influences subsequent treatment options.<sup>92</sup>

## 5. Diagnosis

The clinical diagnosis of HCM is conventionally made with cardiac imaging, at present most commonly with 2-dimensional echocardiography and increasingly with CMR. Morphologic diagnosis is based on the presence of a hypertrophied and nondilated left ventricle in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident in a patient (usually  $\geq 15$  mm in adults or the equivalent relative to body surface area in children). Genetic testing, which is now commercially available, is a powerful strategy for definitive diagnosis of affected genetic status and is currently used most effectively in the identification of affected relatives in families known to have HCM.

### 5.1. Genetic Testing Strategies/Family Screening—Recommendations

#### Class I

1. Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM.<sup>17,31,93–96</sup> (*Level of Evidence: B*)
2. Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient.<sup>97–101</sup> (*Level of Evidence: B*)
3. Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM.<sup>17,31,93,94,96,102,103</sup> (*Level of Evidence: B*)
4. Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause.<sup>104–106</sup> (*Level of Evidence: B*)

#### Class IIa

1. Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM.<sup>17,95,102</sup> (*Level of Evidence: B*)

#### Class IIb

1. The usefulness of genetic testing in the assessment of risk of SCD in HCM is uncertain.<sup>107,108</sup> (*Level of Evidence: B*)

#### Class III: No Benefit

1. Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation.<sup>17,31,93–96,109</sup> (*Level of Evidence: B*)

### 2. Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM.<sup>109–112</sup> (*Level of Evidence: B*)

*See Online Data Supplement 1 for additional data regarding genetic testing strategies/family screening.*

HCM is caused by an autosomal dominant mutation in genes that encode sarcomere proteins or sarcomere-associated proteins. The most vigorous evidence indicates that 8 genes are known to definitively cause HCM: beta myosin heavy chain, myosin binding protein C, troponin T, troponin I, alpha tropomyosin, actin, regulatory light chain, and essential light chain.<sup>11,12,30,40–42</sup> In addition, actinin and myozenin are associated with less definitive evidence for causing HCM. At this time there is inconclusive evidence to support other genes causing HCM,<sup>94,96,113,114</sup> but research is ongoing and other genetic causes may be identified.<sup>93,115</sup> A single mutation in 1 of the 2 alleles (or copies) of a gene is sufficient to cause HCM; however, 5% of patients with HCM have  $\geq 2$  mutations in the same gene or different genes.<sup>110,116</sup>

Genetic and/or clinical screening of all first-degree family members of patients with HCM is important to identify those with unrecognized disease. On the basis of family history, clinical screening, and pedigree analyses, the pattern of inheritance is ascertained to identify and counsel relatives at risk.<sup>101</sup> Because familial HCM is a dominant disorder, the risk that an affected patient will transmit disease to each offspring is 50%. When a pathogenic mutation is identified in an index patient, the genetic status of each family member can be readily ascertained. Because HCM mutations are highly penetrant, a mutation conveys substantial (>95%) risk over a lifetime for developing clinical and/or phenotypic evidence of HCM.<sup>94,96,113,114</sup>

Genetic counseling before genetic testing will increase understanding of the medical and familial implications of test results, enabling informed decision making about potential risks and benefits.<sup>98,99</sup> Genetic counseling can also reduce potential psychologic responses to learning one's mutation status.<sup>4,101</sup> Even when genetic testing is not undertaken, genetic counseling about the potential for familial transmission of HCM is medically important.

The occurrence of HCM can be isolated or sporadic, but the frequency of sporadic HCM is unresolved. Sporadic HCM can reflect an inaccurate family history, incomplete penetrance (absence of clinical expression despite the presence of a mutation) in family members, or a de novo (new) mutation that can initiate new familial disease.<sup>93,115</sup>

Because unrelated patients with HCM will have different mutations, a comprehensive sequence-based analysis of all HCM genes is necessary to define the pathogenic (eg, disease-causing) mutation in an index patient. Experienced clinical laboratories identify the pathogenic HCM mutation in approximately 60% to 70% of patients with a positive family history and approximately 10% to 50% of patients without a family history.<sup>93,102</sup> Genetic testing may identify a pathogenic mutation (eg, analysis defines a sequence variant known to cause HCM) or a “likely pathogenic” mutation, a DNA variant that was previously *unknown* as a cause of HCM but has molecular characteristics that are similar to recognized HCM mutations.

Genetic testing may also identify “variants of uncertain significance.” This term indicates that the nucleotide change is not commonly recognized to be variable (or polymorphic) in the general population and that some molecular characteristics of the variant suggest deleterious consequences (similar to all pathogenic mutations). Genetic analyses of family members can help establish or refute the causality of “likely pathogenic” and “variants of uncertain significance.” When a variant occurs in multiple clinically affected family members but is absent from clinically *unaffected* adult family members, the likelihood for pathogenicity increases. In contrast, when a variant occurs in multiple clinically *unaffected* adult family members, the likelihood for pathogenicity is low.

Adult patients with HCM and an established pathogenic mutation have increased risk for the combined endpoints of cardiovascular death, nonfatal stroke, or progression to New York Heart Association (NYHA) functional class III or IV compared with patients with HCM in whom no mutation is identified.<sup>103</sup> Studies suggest that the presence of >1 HCM-associated sarcomere mutation is associated with greater severity of disease.<sup>110,111,117,118</sup>

When genetic testing reveals a mutation in the index patient, ascertainment of genetic status in first-degree relatives can be predictive of risk for developing HCM.<sup>105</sup> Genetic counseling should precede genetic testing of family members.<sup>101</sup> Relatives with overt HCM will have the same pathogenic HCM mutation as the index patient. Pathogenic mutations may also be identified in other relatives with unknown clinical status. These mutation carriers should be evaluated by physical examination, electrocardiography, and 2-dimensional echocardiography, and if HCM is identified, these individuals should undergo risk stratification (Section 6.3.1). Mutation carriers without evidence of HCM (genotype positive/phenotype negative) are at considerable risk for future development of HCM, and guidelines to evaluate these individuals are discussed below.<sup>13,14</sup> Mutation-negative family members and their descendants have no risk for developing HCM and do not need further evaluation. Information from genotyping may help define clinical manifestations and outcomes in specific families with HCM.<sup>94–96,105,107–109,119</sup>

When genetic testing is not performed or a mutation is not identified in the index patient, clinical screening of all first-degree family members is important to identify those with unrecognized HCM. Offspring of unaffected individuals do not warrant clinical screening unless prompted by unexpected signs or symptoms. For more information on screening intervals, see Section 5.3.1.

#### 5.1.1. Genotype-Positive/Phenotype-Negative Patients—Recommendation

##### Class I

1. In individuals with pathogenic mutations who do not express the HCM phenotype, it is recommended to perform serial electrocardiogram (ECG), TTE, and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 years in adults), based on the patient's age and change in clinical status.<sup>16,120–122</sup> (*Level of Evidence: B*)

**Table 3. Proposed Clinical Screening Strategies With Echocardiography (and 12-Lead ECG) for Detection of Hypertrophic Cardiomyopathy With Left Ventricular Hypertrophy in Families\***

Age <12 y	
Optional unless	
Malignant family history of premature death from HCM or other adverse complications	
Patient is a competitive athlete in an intense training program	
Onset of symptoms	
Other clinical suspicion of early LV hypertrophy	
Age 12 to 18–21 y†	
Every 12–18 mo	
Age >18–21 y	
At onset of symptoms or at least every 5 y. More frequent intervals are appropriate in families with a malignant clinical course or late-onset HCM.	

\*When pathologic mutations are not identified or genetic testing is either ambiguous or not performed.

†Age range takes into consideration individual variability in achieving physical maturity and in some patients may justify screening at an earlier age. Initial evaluation should occur no later than early pubescence.<sup>125</sup>

ECG indicates electrocardiogram; HCM, hypertrophic cardiomyopathy; and LV, left ventricular.

Adapted with permission from Maron et al.<sup>126</sup>

Genetic screening of first-degree relatives of an index patient with HCM can reveal typically young family members with a mutation (genotype positive) but without cardiac hypertrophy (phenotype negative) (Table 3).<sup>13,14,17,105,123,124</sup> As the clinical expression of HCM usually increases with age, clinical screening (by physical examination, electrocardiography, and 2-dimensional echocardiography or CMR) of genotype-positive/phenotype-negative individuals is also recommended at the intervals indicated below. Electrocardiographic abnormalities, increased ejection fraction (EF), and delayed myocardial relaxation can precede the onset of hypertrophy.<sup>17,124</sup> When abnormal, these parameters can indicate early emergence of clinical disease. Information about risk of SCD is limited.<sup>13,14,121,122</sup>

When family history indicates a high risk for SCD, periodic assessment of arrhythmias (by exercise stress testing or Holter monitoring) in genotype-positive/phenotype-negative individuals may be appropriate. Decisions about participation in competitive athletics must be resolved on a case-by-case basis with the patient and family fully informed about the potential risks<sup>13</sup> (Section 6.3.3).

#### 5.2. Electrocardiography—Recommendations

##### Class I

1. A 12-lead ECG is recommended in the initial evaluation of patients with HCM. (*Level of Evidence: C*)
2. Twenty-four-hour ambulatory (Holter) electrocardiographic monitoring is recommended in the initial evaluation of patients with HCM to detect ventricular tachycardia (VT) and identify patients who may be candidates for ICD therapy.<sup>10,127–129</sup> (*Level of Evidence: B*)



3. Twenty-four-hour ambulatory (Holter) electrocardiographic monitoring or event recording is recommended in patients with HCM who develop palpitations or lightheadedness.<sup>10,127,128</sup> (*Level of Evidence: B*)
4. A repeat ECG is recommended for patients with HCM when there is worsening of symptoms. (*Level of Evidence: C*)
5. A 12-lead ECG is recommended every 12 to 18 months as a component of the screening algorithm for adolescent first-degree relatives of patients with HCM who have no evidence of hypertrophy on echocardiography. (*Level of Evidence: C*)
6. A 12-lead ECG is recommended as a component of the screening algorithm for first-degree relatives of patients with HCM. (*Level of Evidence: C*)

#### Class IIa

1. Twenty-four-hour ambulatory (Holter) electrocardiographic monitoring, repeated every 1 to 2 years, is reasonable in patients with HCM who have no previous evidence of VT to identify patients who may be candidates for ICD therapy.<sup>129</sup> (*Level of Evidence: C*)
2. Annual 12-lead ECGs are reasonable in patients with known HCM who are clinically stable to evaluate for asymptomatic changes in conduction or rhythm (ie, AF). (*Level of Evidence: C*)

#### Class IIb

1. Twenty-four-hour ambulatory (Holter) electrocardiographic monitoring might be considered in adults with HCM to assess for asymptomatic paroxysmal AF/atrial flutter. (*Level of Evidence: C*)

The 12-lead ECG is useful largely for raising the suspicion of HCM in family members without LV hypertrophy and in identifying patterns such as Wolff-Parkinson-White syndrome, which may suggest certain phenocopies of HCM.<sup>9,130–132</sup> In addition, patterns mimicking myocardial infarction may provide evidence of the diagnosis and may be present in young individuals before there is manifest evidence of wall thickening on echocardiography.<sup>10,132,133</sup> The 12-lead ECG is abnormal in 75% to 95% of patients with HCM.<sup>9,131,132</sup> These abnormalities do not correlate with severity or pattern of hypertrophy as determined by echocardiography.

Ambulatory electrocardiographic monitoring for detection of ventricular tachyarrhythmias plays an important role in risk stratification of asymptomatic or symptomatic patients with HCM because episodes of nonsustained ventricular tachycardia (NSVT) identify patients at significantly higher risk of subsequent SCD.<sup>9,10,132–134</sup> It is reasonable to perform serial ambulatory electrocardiographic monitoring on an annual basis or every 2 years in patients who are stable and do not manifest arrhythmias on baseline 12-lead ECG and Holter monitoring and who do not have ICDs.

The yield of ambulatory electrocardiographic monitoring for detection of AF or atrial flutter in patients who were previously asymptomatic without arrhythmias is unknown.

### 5.3. Imaging

#### 5.3.1. Echocardiography—Recommendations

##### Class I

1. A TTE is recommended in the initial evaluation of all patients with suspected HCM.<sup>9,20,66,67,135–138</sup> (*Level of Evidence: B*)
2. A TTE is recommended as a component of the screening algorithm for family members of patients with HCM unless the family member is genotype negative in a family with known definitive mutations.<sup>41,126,139,140</sup> (*Level of Evidence: B*)
3. Periodic (12 to 18 months) TTE screening is recommended for children of patients with HCM, starting by age 12 years or earlier if a growth spurt or signs of puberty are evident and/or when there are plans for engaging in intense competitive sports or there is a family history of SCD.<sup>126,141</sup> (*Level of Evidence: C*)
4. Repeat TTE is recommended for the evaluation of patients with HCM with a change in clinical status or new cardiovascular event.<sup>39,45,57,142–145</sup> (*Level of Evidence: B*)
5. A transesophageal echocardiogram (TEE) is recommended for the intraoperative guidance of surgical myectomy.<sup>146–148</sup> (*Level of Evidence: B*)
6. TTE or TEE with intracoronary contrast injection of the candidate's septal perforator(s) is recommended for the intraprocedural guidance of alcohol septal ablation.<sup>62,149–151</sup> (*Level of Evidence: B*)
7. TTE should be used to evaluate the effects of surgical myectomy or alcohol septal ablation for obstructive HCM.<sup>61,62,152–156</sup> (*Level of Evidence: C*)

##### Class IIa

1. TTE studies performed every 1 to 2 years can be useful in the serial evaluation of symptomatically stable patients with HCM to assess the degree of myocardial hypertrophy, dynamic obstruction, and myocardial function.<sup>20,67,136</sup> (*Level of Evidence: C*)
2. Exercise TTE can be useful in the detection and quantification of dynamic LVOT obstruction in the absence of resting outflow tract obstruction in patients with HCM.<sup>8,45,143,145,157</sup> (*Level of Evidence: B*)
3. TEE can be useful if TTE is inconclusive for clinical decision making about medical therapy and in situations such as planning for myectomy, exclusion of subaortic membrane or mitral regurgitation secondary to structural abnormalities of the mitral valve apparatus, or in assessment for the feasibility of alcohol septal ablation.<sup>146–148</sup> (*Level of Evidence: C*)
4. TTE combined with the injection of an intravenous contrast agent is reasonable if the diagnosis of apical HCM or apical infarction or severity of hypertrophy is in doubt, particularly when other imaging modalities such as CMR are not readily available, not diagnostic, or are contraindicated. (*Level of Evidence: C*)
5. Serial TTE studies are reasonable for clinically unaffected patients who have a first-degree relative with HCM when genetic status is unknown. Such follow-up may be considered every 12 to 18 months for children or adolescents from high-risk families

and every 5 years for adult family members.<sup>41,126,140,141</sup> (Level of Evidence: C)

### Class III: No Benefit

1. TTE studies should not be performed more frequently than every 12 months in patients with HCM when it is unlikely that any changes have occurred that would have an impact on clinical decision making. (Level of Evidence: C)
2. Routine TEE and/or contrast echocardiography is not recommended when TTE images are diagnostic of HCM and/or there is no suspicion of fixed obstruction or intrinsic mitral valve pathology. (Level of Evidence: C)

Comprehensive TTE and Doppler studies should be performed in the initial evaluation of all patients with suspected HCM, as well as during follow-up, particularly when there is a change in cardiovascular symptoms or an event. Echocardiographic studies are essential for establishing the diagnosis and the nature and extent of hypertrophy, defining prognosis, and guiding management.<sup>9,20,66,67,135–138</sup> Although septal thickness  $\geq 15$  mm is commonly used to identify HCM, one must be aware of the potential confusion with secondary hypertrophy attributable to aortic valve or discrete subaortic stenosis, systemic hypertension, amyloidosis, and other genetic phenocopies such as Fabry disease.<sup>158</sup> In affected family members with HCM, the degree of hypertrophy may be below the usual diagnostic threshold of  $\geq 15$  mm LV wall thickness, and indeed, some patients carry an HCM-definitive mutation without hypertrophy.

It has been suggested that identification of morphologic subtypes of LV hypertrophy, namely apical hypertrophy<sup>159</sup> or septal hypertrophy with reverse or neutral curvature, or sigmoid shape,<sup>160</sup> has implications for the likelihood of detection of myofilament mutations and prognosis.<sup>139</sup> However, there is no recognized relationship between the pattern or distribution of LV hypertrophy and clinical course or outcome. Nevertheless, documentation of the extent of hypertrophy is important because there is a relatively linear association between maximal wall thickness and sudden death, with highest risk in patients with wall thickness  $\geq 30$  mm.<sup>161</sup>

The presence of dynamic LVOT obstruction is related to symptomatic status, as well as development of AF, embolic complications, and death.<sup>45,57,142–145</sup> Continuous wave Doppler studies can accurately quantitate the LVOT gradient and determine the response to pharmacologic<sup>157</sup> and interventional therapy. Amyl nitrite can be used to provoke echocardiographically documented gradients when available and in laboratories with expertise and has the advantage of being capable of being integrated into a single examination. The correlation between pharmacologic and physiologic exercise provocation of outflow gradients is unresolved. Care must be taken to correctly identify the site of obstruction, distinguish the Doppler spectral profile from cavity obliteration, and avoid contamination of the signal by mitral regurgitation. Although many patients have dynamic LVOT obstruction at rest, a significant number will have new or higher gradients

after the Valsalva maneuver, inhalation of amyl nitrite, or during provocative exercise.<sup>8</sup> In HCM, it is the peak instantaneous LVOT velocity, usually caused by SAM, that should be used to determine the maximum gradient, using the modified Bernoulli formula (Table 2).

Systolic function, as assessed by wall motion and EF, is usually normal in patients with HCM; however, the development of systolic dysfunction heralds the risk of progressive and irreversible heart failure, which may result in heart transplantation or death.<sup>39</sup> The importance of diastolic dysfunction in HCM has led to an extensive search for noninvasive methods to quantify its severity. With the complex interplay of factors causing diastolic dysfunction in HCM, no single noninvasive measure has been demonstrated as superior.<sup>162,163</sup> LA volume may provide a long-term indication of the effects of chronically elevated filling pressures in patients with HCM.<sup>164–166</sup> Patients with HCM and a maximal LA volume index  $\geq 34$  mL/m<sup>2</sup> have a higher incidence of abnormal diastolic filling, a higher mitral inflow/annular velocity (E/e') ratio, a higher calculated LA pressure, and less favorable outcome.<sup>164,166</sup> Moreover, LA volumetric remodeling predicts exercise capacity in nonobstructive HCM and thus may reflect chronic LV diastolic burden independent of LVOT obstruction. The more recent use of myocardial deformation measurements to quantify strain parameters, torsion, and dyssynchrony has detected abnormalities in systolic performance, especially longitudinal strain and twist.<sup>167–171</sup> These methods have also shown promise in better quantifying abnormalities in early relaxation and elevation of filling pressures.<sup>172</sup> They may also be useful in distinguishing HCM from other forms of hypertrophy,<sup>173</sup> as well as detecting preclinical disease.<sup>17,19,174</sup>

Echocardiographic studies are useful in patients with LVOT obstruction who fail to respond to medical therapy and who undergo invasive intervention.<sup>61,146–148,155,175,176</sup> TEE studies, performed before arrival in the operating suite for surgical septal myectomy (and intraoperative TEE), can determine the length and extent of myectomy required, evaluate the presence and severity of mitral regurgitation independent of obstruction, and identify the presence of abnormal papillary muscle architecture.<sup>146–148,155,176</sup> Following myectomy, postbypass intraoperative TEE studies can confirm the adequacy of myectomy and quantitate residual gradients, severity of mitral and aortic regurgitation, ventricular function, and development of a ventricular septal defect.<sup>146–148,155,176</sup> When the myectomy is inadequate based on TEE study, surgical revision can be considered.

Intraprocedural echocardiographic studies should be routinely performed during alcohol septal ablation procedures.<sup>62,149–152,156,177</sup> Contrast-enhanced echocardiographic studies with intracoronary injection of the candidate coronary septal perforator(s) are important in determining the perfusion bed supplied by the septal perforator so that only an appropriate site and degree of myocardium is infarcted and complications avoided.<sup>149–151</sup> After alcohol septal ablation there may be an early recurrence in the LVOT gradient a few days after the procedure, with subsequent reduction over 6 to 12 months.<sup>152,156</sup>

It should be recognized that in some patients TTE studies may be limited by image quality, and other investigations, including CMR, should be performed. In addition, TEE may detect the presence of subaortic membrane causing fixed obstruction with or without coexisting dynamic obstruction. In patients with the apical variant of HCM, the diagnosis is missed by echocardiographic studies in about 10% of patients,<sup>159</sup> and the use of peripheral injection of an echocardiographic contrast agent, as well as CMR, may be useful in establishing the diagnosis. Similarly, a subset of patients with HCM may have an apical LV aneurysm associated with normal epicardial coronary arteries,<sup>159</sup> which is usually best visualized with CMR. TEE studies may be helpful in some patients, particularly when the cause and severity of mitral regurgitation are uncertain.<sup>147,148</sup>

### 5.3.2. Stress Testing—Recommendations

#### Class IIa

1. Treadmill exercise testing is reasonable to determine functional capacity and response to therapy in patients with HCM. (*Level of Evidence: C*)
2. Treadmill testing with monitoring of an ECG and blood pressure is reasonable for SCD risk stratification in patients with HCM.<sup>89,90,178</sup> (*Level of Evidence: B*)
3. In patients with HCM who do not have a resting peak instantaneous gradient of greater than or equal to 50 mm Hg, exercise echocardiography is reasonable for the detection and quantification of exercise-induced dynamic LVOT obstruction.<sup>8,88–90</sup> (*Level of Evidence: B*)

Exercise testing with monitoring of ECG and cuff blood pressure is helpful in risk assessment of patients with HCM, because abnormal blood pressure responses to exercise (defined as either a failure to increase by at least 20 mm Hg or a drop of at least 20 mm Hg during effort) has been demonstrated to be 1 factor associated with risk of SCD.<sup>9,10,89,90,134,178</sup> A hypotensive blood pressure response was defined as either an initial increase in systolic blood pressure with a subsequent fall by peak exercise of >20 mm Hg compared with peak blood pressure value<sup>8,90</sup> or a continuous decrease in systolic blood pressure of >20 mm Hg throughout the exercise test when compared with baseline. A flat response was defined by a change in systolic blood pressure during the whole exercise period of <20 mm Hg compared with the resting systolic blood pressure. Most published studies examining exercise blood pressure response use symptom-limited treadmill exercise testing with a Bruce protocol,<sup>89,178</sup> whereas others use symptom-limited bicycle ergometry, with 25-W increments in 3-minute stages.<sup>90</sup>

Combining exercise testing with Doppler echocardiography is also useful for determining the presence of physiologically provokable LVOT obstruction and is particularly helpful in patients with symptoms during routine physical activities who do not manifest outflow obstruction at rest.<sup>8</sup> Stress testing modalities include either bicycle, treadmill using the Bruce protocol, or cardiopulmonary (metabolic) testing, with measurement of gradient either during or immediately after exercise.<sup>8</sup> In symptomatic patients with a peak

resting gradient of <50 mm Hg, it is helpful to perform exercise echocardiography to determine if a significant exercise-induced gradient (or increase in mitral regurgitation) or augmentation thereof is present.

The role of metabolic stress testing (ie, determination of maximum oxygen consumption) in the routine evaluation of patients with HCM remains to be decided, particularly with regard to clinical outcome, but in individual patients this test may be helpful in providing a more precise assessment of functional capacity.<sup>179</sup>

### 5.3.3. Cardiac Magnetic Resonance—Recommendations

#### Class I

1. CMR imaging is indicated in patients with suspected HCM when echocardiography is inconclusive for diagnosis.<sup>180,181</sup> (*Level of Evidence: B*)
2. CMR imaging is indicated in patients with known HCM when additional information that may have an impact on management or decision making regarding invasive management, such as magnitude and distribution of hypertrophy or anatomy of the mitral valve apparatus or papillary muscles, is not adequately defined with echocardiography.<sup>15,180–183</sup> (*Level of Evidence: B*)

#### Class IIa

1. CMR imaging is reasonable in patients with HCM to define apical hypertrophy and/or aneurysm if echocardiography is inconclusive.<sup>180,182</sup> (*Level of Evidence: B*)

#### Class IIb

1. In selected patients with known HCM, when SCD risk stratification is inconclusive after documentation of the conventional risk factors (Section 6.3.1), CMR imaging with assessment of late gadolinium enhancement (LGE) may be considered in resolving clinical decision making.<sup>184–188</sup> (*Level of Evidence: C*)
2. CMR imaging may be considered in patients with LV hypertrophy and the suspicion of alternative diagnoses to HCM, including cardiac amyloidosis, Fabry disease, and genetic phenocopies such as *LAMP2* cardiomyopathy.<sup>189–191</sup> (*Level of Evidence: C*)

There have been significant advances in CMR in recent years, and most centers now have access to this advanced imaging technique. Compared with other noninvasive cardiac imaging modalities, CMR provides superior spatial resolution with sharp contrast between blood and myocardium, as well as complete tomographic imaging of the entire LV myocardium and therefore the opportunity to more accurately characterize the presence, distribution, and extent of LV hypertrophy in HCM. Because of the technical complexity of CMR imaging, data from the published literature are only generalizable if imaging is performed with high technical quality by experienced operators and interpreted by well-trained and experienced readers.

The primary role for CMR in patients with HCM is clarification of diagnosis and phenotype. Advances in



2-dimensional echocardiography have demonstrated the heterogeneity of the hypertrophic phenotype in patients with HCM, particularly with regard to distribution of LV hypertrophy and mechanisms of outflow obstruction.<sup>8–10,15,21,72,192</sup> However, there remain patients in whom the diagnosis of HCM is suspected but the echocardiogram is inconclusive, mostly because of suboptimal imaging from poor acoustic windows or when hypertrophy is localized to regions of the LV myocardium not well visualized by echocardiography.<sup>15</sup> In 1 study, 6% of patients with suspected HCM were identified with increased LV wall thickness (predominantly in the anterolateral wall) by CMR but not by echocardiography.<sup>15,181,183</sup> In addition, in patients with HCM in whom hypertrophy is predominantly confined to the apex (ie, apical HCM), increased wall thickness in this region of the LV myocardium may be difficult to visualize clearly with echocardiography but can be well seen with CMR.<sup>180,182</sup> Similarly, in the subgroup of patients with HCM who develop apical aneurysms, CMR can more readily detect the presence of an aneurysm (particularly when small) compared with noncontrast echocardiography.<sup>182</sup> Identification of the end-stage phenotype and particularly an apical aneurysm has implications for management in that an ICD may be indicated and anticoagulation could be considered, based on the morphologic appearance of the aneurysm. In addition to diagnosis, the extent of maximal LV wall thickening may be underestimated by echocardiography compared with CMR, particularly when this region involves the anterolateral wall.<sup>15,183</sup> This observation is related to the limitation of 2-dimensional echocardiography in differentiating the epicardial border of the lateral LV free wall from thoracic parenchyma, allowing significant underestimation of wall thickness compared with CMR, which provides more reliable definition of the epicardial border. Accurate characterization of the HCM phenotype by CMR may also be useful in management decisions for invasive therapies (septal myectomy or alcohol septal ablation) by more precisely defining the location and magnitude of hypertrophy, as well as characterizing the mitral and submitral apparatus and papillary muscles.<sup>193,194</sup>

The opportunity for contrast-enhanced CMR with LGE to identify areas of myocardial fibrosis in patients with HCM has been the subject of a growing area of the literature.<sup>185–187,195,196</sup> The extent and transmural distribution of areas of infarction can be quantitatively defined in patients with CAD.<sup>197</sup> Many studies have now documented that approximately half of patients with HCM have LGE suggestive of areas of fibrosis that in some patients may occupy a substantial volume of LV myocardium (ie, on average, 10% of the LV wall).<sup>185,195</sup> Although patients with the end-stage phenotype almost universally demonstrate such findings,<sup>39</sup> patients with HCM with preserved systolic function may also have areas of LGE.<sup>185–187</sup> Importantly, patients with HCM with evidence of LGE on CMR imaging tend to have more markers of risk of SCD, such as NSVT on Holter monitoring, than patients without LGE.<sup>184,186</sup>

It is a plausible and attractive concept that areas of LGE (ie, probably largely replacement myocardial fibrosis) could represent a substrate for the generation of malignant ventricular tachyarrhythmias in HCM and thus a marker for risk of

SCD. Several studies have addressed this issue and have reported either trends in such a direction or significant associations between the presence of LGE (not extent) and cardiac outcome events.<sup>187,198</sup> However, there is insufficient evidence at this time to support a significant association between the extent of LGE and outcome. Larger studies with longer follow-up and more events with greater statistical power are needed to fully characterize whether the finding of LGE can be considered a specific risk marker for SCD to the same degree as currently accepted markers such as family history of SCD or extreme LV wall thickness. Nonetheless, the present cross-sectional and short-term follow-up data would support a potential role of contrast-enhanced CMR (with evidence of LGE) as an arbitrator to consider in clinical decision making for primary prevention ICDs in patients in whom high-risk status for SCD remains uncertain after assessment of conventional risk factors.<sup>185,186</sup>

In some patients with LV hypertrophy, CMR imaging can depict patterns of LGE that may suggest an alternative diagnosis. In patients with Anderson-Fabry disease, it has been reported that approximately half have LGE localized to the mid-myocardial portion of the basal inferolateral wall, sparing the subendocardium,<sup>191</sup> a location and distribution of LGE that may help distinguish this disease from other forms of nonischemic cardiomyopathies such as HCM.<sup>189</sup> Patterns of LGE in HCM are heterogeneous, may occur commonly in either the ventricular septum or LV free wall, and usually involve segments of the chamber that are most hypertrophied and do not conform to particular coronary arterial distributions.<sup>185</sup>

Among patients with LV hypertrophy caused by cardiac amyloidosis, it has been reported that approximately 70% demonstrate a pattern of global subendocardial gadolinium enhancement, a pattern of enhancement not usually seen in patients with HCM.<sup>190</sup> These data suggest that gadolinium-enhanced CMR imaging may be useful in select cases to assist a clinician in the differential diagnosis of a patient with LV hypertrophy.

#### 5.4. Detection of Concomitant Coronary Disease—Recommendations

##### Class I

1. **Coronary arteriography (invasive or computed tomographic imaging) is indicated in patients with HCM with chest discomfort who have an intermediate to high likelihood of CAD when the identification of concomitant CAD will change management strategies. (Level of Evidence: C)**

##### Class IIa

1. **Assessment of coronary anatomy with computed tomographic angiography (CTA) is reasonable for patients with HCM with chest discomfort and a low likelihood of CAD to assess for possible concomitant CAD. (Level of Evidence: C)**
2. **Assessment of ischemia or perfusion abnormalities suggestive of CAD with single photon emission computed tomography (SPECT) or positron emission to-**

**mography (PET) myocardial perfusion imaging (MPI; because of excellent negative predictive value), is reasonable in patients with HCM with chest discomfort and a low likelihood of CAD to rule out possible concomitant CAD. (Level of Evidence: C)**

### **Class III: No Benefit**

- 1. Routine SPECT MPI or stress echocardiography is not indicated for detection of “silent” CAD-related ischemia in patients with HCM who are asymptomatic. (Level of Evidence: C)**
- 2. Assessment for the presence of blunted flow reserve (microvascular ischemia) using quantitative myocardial blood flow measurements by PET is not indicated for the assessment of prognosis in patients with HCM. (Level of Evidence: C)**

Chest discomfort is a common symptom in patients with HCM. A key management issue revolves around whether the discomfort may be caused by concomitant epicardial obstructive CAD with inducible ischemia, a consequence of microvascular dysfunction, or a combination of these factors.<sup>9</sup> The concomitant presence of CAD, particularly if severe, in patients with HCM identifies a higher risk for adverse outcomes and patients who are potential candidates for revascularization.<sup>199,200</sup> Moreover, in considering management options such as alcohol septal ablation or septal myectomy for patients with highly symptomatic HCM, knowledge of coronary anatomy is an important factor informing the decision.

Myocardial bridging (ie, tunneling) is a clinical feature in patients with HCM that may be associated with myocardial ischemia in the absence of epicardial coronary stenosis. In myocardial bridging, a segment of the left anterior descending coronary artery courses within the myocardium. The prevalence of myocardial bridging varies based on the type of investigation. In a recent autopsy-based study in patients with HCM, bridging was evident in 40% of hearts,<sup>201</sup> whereas angiographic prevalence in HCM is reported to be 15%.<sup>202</sup> Myocardial bridges are a frequent component of phenotypically expressed HCM and more common than in other disorders with or without LV hypertrophy. Although it has been suggested that ischemia secondary to bridging could be a potential mechanism for sudden death in patients with HCM,<sup>203</sup> there is no consistent evidence to support this hypothesis in either adults or children.<sup>202,204</sup> However, the possibility that coronary arterial bridges could contribute to increased risk in some individual patients cannot be excluded, potentially impacting management decisions on a case-by-case basis.

In patients with HCM who have chest pain and who undergo coronary angiography, the finding of a myocardial bridge raises the question of whether myocardial ischemia associated with the bridge is the cause of symptoms. There are no data assessing stress MPI in patients with HCM with myocardial bridges; however, reports of patients with myocardial bridges who do not have HCM suggest that stress perfusion abnormalities may be commonly detected in the vascular territory distal to the bridge.<sup>205</sup> Although it has been

suggested that systolic compression of a bridged coronary artery may not be responsible for ischemia because most coronary blood flow takes place in diastole, angiographic studies have demonstrated arterial compression in diastole as well.<sup>206,207</sup>

If chest pain symptoms in a patient with HCM are suspected to be related to abnormal coronary blood flow (as a result of bridging), beta blockers may be effective in controlling the symptoms. Intravenous beta blockade in patients with myocardial bridges and non-HCM disease has been shown to have favorable effects on coronary dimensions and myocardial blood flow and diminished ischemia induced by pacing tachycardia.<sup>207</sup> If medical therapy is ineffective, consideration can be given to surgery with supra-arterial myotomy (“unroofing”),<sup>206,208</sup> which may be technically challenging depending on the depth of the tunneled segment. CTA can define the course and depth of a bridged segment and may be useful in planning surgical strategy.<sup>209</sup>

In patients with HCM who are undergoing surgical myectomy and in whom preoperative angiography has demonstrated a myocardial bridge, there are no data to guide the decision on whether to “unroof” the bridged segment during the surgical myectomy. In patients with chest pain in whom perfusion imaging demonstrates blunted flow reserve distal to the myocardial bridge, supra-arterial myotomy has been suggested to reduce anginal symptoms.

#### **5.4.1. Choice of Imaging Modality**

##### **5.4.1.1. Invasive Coronary Arteriography**

Invasive coronary arteriography is the gold standard for defining the presence, extent, severity, and location of epicardial coronary stenoses. Performance of invasive coronary arteriography is indicated in patients with HCM when knowledge of these features will importantly influence management strategies as discussed above. Invasive coronary arteriography should be a routine accompaniment to an invasive catheterization performed in a patient with HCM for assessment of hemodynamic status and in such cases should generally be performed after documentation of hemodynamics so as not to influence important measurements such as the magnitude of the LVOT gradient. When catheterization is performed, invasive coronary arteriography should be undertaken before alcohol septal ablation in order to define the anatomy of the septal perforators in detail and exclude obstructive coronary stenoses. Furthermore, if alcohol septal ablation is being considered, the decision may be influenced by the location and extent of coronary disease as defined by coronary arteriography.

##### **5.4.1.2. Noninvasive CTA**

Although there are no published data specifically assessing the performance characteristics of CTA for documenting the presence or absence of epicardial CAD in HCM, there is no reason to believe that performance of the test should differ in patients with HCM compared with those with suspected or known CAD. Many studies have reported very good capability of contemporary CTA technology to distinguish the presence from absence of a >50% epicardial stenosis.<sup>210</sup> A high negative predictive value to exclude CAD is particularly

consistent in the literature. In this regard, for patients with HCM with chest discomfort, CTA would be a reasonable strategy to assess for possible concomitant CAD. Anatomical demonstration of an epicardial stenosis does not necessarily indicate that the symptoms of chest discomfort are attributable to ischemia but are suggestive and outlines a potential management strategy, as well as indicates the need for specific preventive strategies.

#### 5.4.1.3. Single Photon Emission Computed Tomography Myocardial Perfusion Imaging

Stress SPECT MPI in patients with HCM will often demonstrate reversible or fixed perfusion defects consistent with ischemia or infarction, respectively, even in the absence of epicardial CAD.<sup>211,212</sup> In 1 study, approximately 50% of young patients with HCM (unlikely to have CAD attributable to age) had reversible perfusion defects on exercise stress SPECT MPI that were prevented when exercise imaging was repeated on verapamil.<sup>213</sup> Several lines of evidence support that these defects, even in the absence of symptoms, represent true flow abnormalities and possibly “silent” ischemia. Studies of autopsy specimens or myectomy specimens in patients with HCM have shown that patients with HCM may have structural abnormalities of the myocardial microvasculature.<sup>87</sup> During pacing-induced tachycardia, patients with HCM with reversible SPECT MPI defects demonstrate production of lactate consistent with ischemia,<sup>214</sup> and following relief of outflow tract obstruction with myectomy, patients with HCM with reversible defects often have normal perfusion.<sup>215</sup>

Fixed defects may also be seen with SPECT MPI, a finding consistent with infarction. These patients will often have the “end-stage” clinical phenotype with reduced EF<sup>211</sup> and likely correspond to patients who demonstrate LGE in CMR studies.<sup>39</sup>

The concept that true abnormalities of perfusion at the tissue level may be demonstrated by SPECT MPI in patients with HCM in the absence of epicardial CAD, however, does make the interpretation of SPECT MPI to detect CAD challenging. Moreover, myocardial ischemia in patients with HCM, in the absence of epicardial coronary artery stenosis, may be attributable to intramural small-vessel abnormalities or massive hypertrophy.<sup>216</sup> Given the above discussion, the positive predictive value of an abnormal SPECT MPI study for epicardial obstructive CAD in a patient with HCM with chest discomfort will be relatively low, but the negative predictive value will be high. The demonstration of a reversible defect, even in the absence of CAD, does suggest that the symptoms of chest discomfort may be caused by ischemia, although not necessarily related to the presence of obstructive CAD. Although the true performance characteristics of SPECT MPI for detection of CAD have not been rigorously studied in patients with HCM, it would be expected that the negative predictive value should be high.

In considering any imaging procedure that involves exposure to radiation such as SPECT or PET imaging (Section 5.4.1.4), CTA (5.4.1.2) or invasive procedures, contemporary recommendations suggest that the potential risks of radiation exposure be taken into account and that the benefits of the information gained sufficiently balance

those risks.<sup>217</sup> This concept may be particularly important in patients with HCM, who in general will be younger compared with other subgroups of patients being evaluated for heart disease.

Interpretation of SPECT perfusion imaging studies in patients with HCM should be mindful that areas with substantial wall thickening may appear inordinately “hot,” making other areas without hypertrophy appear to have a relatively mild reduction in tracer activity. Quantitative analysis programs may falsely interpret this as a perfusion defect. Moreover, gated SPECT analysis of EF with use of contouring programs may underestimate EF, because the assumptions driving the contouring algorithms searching for the endocardial borders may not be reliable in some patients with HCM because of the relative brightness of the hypertrophied wall.

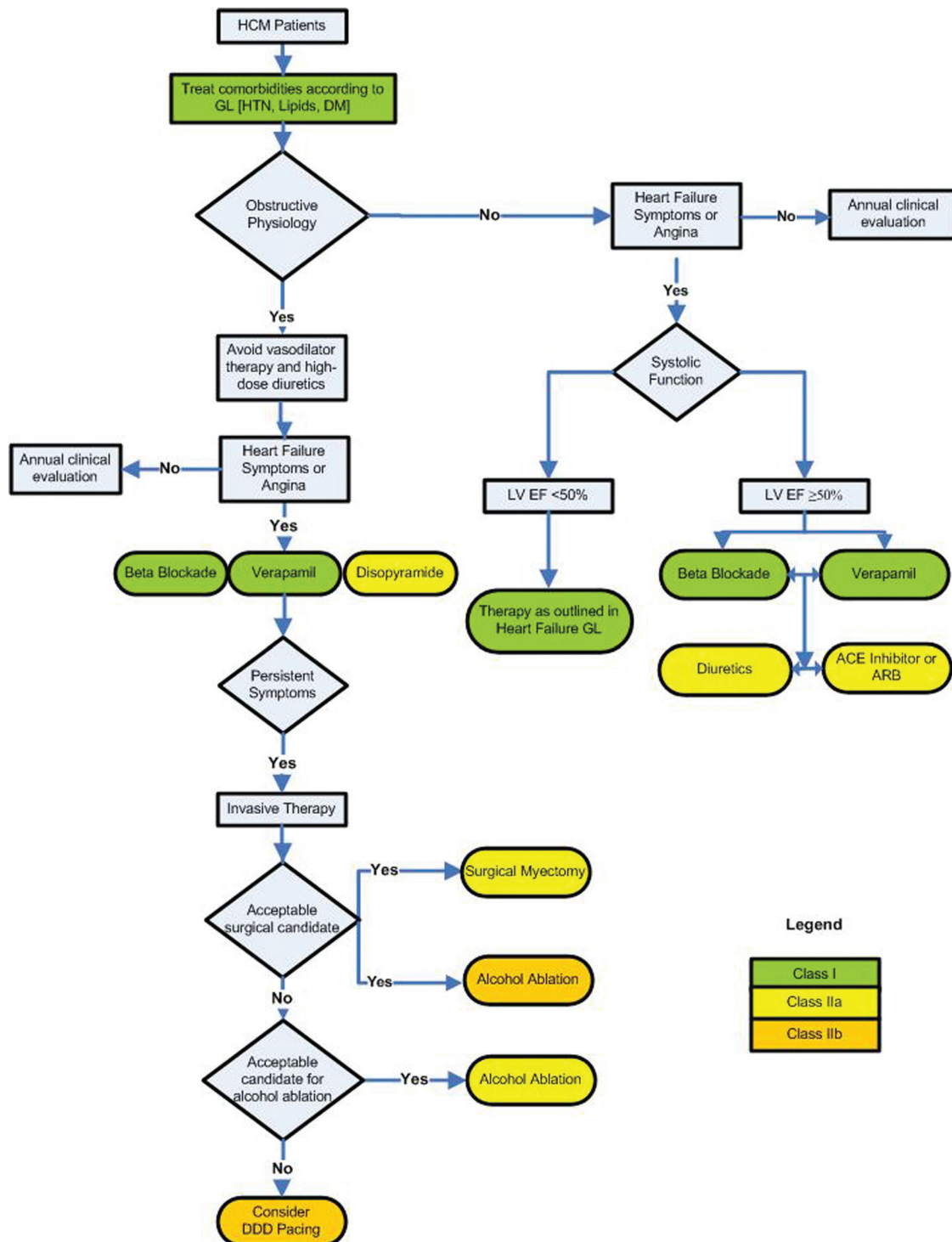
#### 5.4.1.4. Positron Emission Tomography

PET imaging has been used in patients with HCM to study myocardial blood flow as well as myocardial metabolism. In patients with HCM with normal coronary arteries, myocardial perfusion PET studies have shown that although resting myocardial blood flow may be similar to that of normal control subjects, the augmentation of blood flow with vasodilation, for example, dipyridamole, may be significantly blunted.<sup>218–221</sup> In addition, such abnormal myocardial blood flow reserve was shown to be more pronounced in the subendocardial regions, consistent with so-called “apparent” transient ischemic cavity dilatation.<sup>212,218,219</sup> In 1 study using techniques to quantify myocardial blood flow reserve with PET perfusion tracers, patients with HCM who had blunted flow reserve in response to hyperemic stress had more unfavorable event-free survival compared with patients with preserved hyperemic flow reserve.<sup>220</sup> A follow-up study suggested that 1 mechanism for the unfavorable outcomes associated with the flow reserve abnormalities included progression to a remodeled, end-stage phenotype.<sup>221</sup> These findings are consistent with the concept that repetitive episodes of myocardial ischemia may influence long-term outcome of patients with HCM. However, the quantitative PET techniques used in these studies are not part of routine clinical practice, and the management implications of identifying abnormalities in flow reserve are unresolved.

#### 5.4.1.5. Stress Echocardiography

There are no published studies addressing the performance characteristics of stress echocardiography to detect or exclude CAD in patients with HCM. Although performance of this modality has been well studied in patients who do not have HCM and criteria about appropriate use of the test exist,<sup>222</sup> aspects of the HCM phenotype would in theory undermine performance. Patients with HCM have heterogeneous wall-thickness patterns, and wall motion at rest may appear abnormal in regions of hypertrophied myocardium. A wall-motion response to stress therefore would be complex to interpret and may be particularly so in the presence of the enhanced loading that occurs in the setting of outflow tract obstruction, which may be seen in up to 75% of patients during exercise. For these reasons,





**Figure 3.** Treatment algorithm. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DM, diabetes mellitus; EF, ejection fraction; GL, guidelines; HCM, hypertrophic cardiomyopathy; HTN, hypertension; and LV, left ventricular.

stress echocardiography to detect or rule out CAD may be unreliable in HCM but may be useful to document the presence or magnitude of outflow tract obstruction generated by exercise<sup>8</sup> (Section 4.1).

## 6. Management of HCM

Treatment of patients with HCM requires a thorough understanding of the complex, diverse pathophysiology and natural

history and must be individualized to the patient. The general approach of the writing committee is outlined in Figure 3.

### 6.1. Asymptomatic Patients—Recommendations

#### Class I

1. For patients with HCM, it is recommended that comorbidities that may contribute to cardiovascular

disease (eg, hypertension, diabetes, hyperlipidemia, obesity) be treated in compliance with relevant existing guidelines.<sup>223</sup> (*Level of Evidence: C*)

### Class IIa

1. Low-intensity aerobic exercise is reasonable as part of a healthy lifestyle for patients with HCM.<sup>10,224</sup> (*Level of Evidence: C*)

### Class IIb

1. The usefulness of beta blockade and calcium channel blockers to alter clinical outcome is not well established for the management of asymptomatic patients with HCM with or without obstruction.<sup>10</sup> (*Level of Evidence: C*)

### Class III: Harm

1. Septal reduction therapy should not be performed for asymptomatic adult and pediatric patients with HCM with normal effort tolerance regardless of the severity of obstruction.<sup>9,10</sup> (*Level of Evidence: C*)
2. In patients with HCM with resting or provokable outflow tract obstruction, regardless of symptom status, pure vasodilators and high-dose diuretics are potentially harmful.<sup>3,9</sup> (*Level of Evidence: C*)

A large proportion of patients presenting with HCM are asymptomatic, and most will achieve a normal life expectancy.<sup>48,131,225</sup> It is essential to educate these patients and their families about the disease process, including screening of first-degree relatives and avoiding particularly strenuous activity or competitive athletics.<sup>134</sup> Risk stratification for SCD should also be performed in all patients, irrespective of whether symptoms are present.<sup>9,10</sup>

Because concomitant CAD has a significant impact on survival in patients with HCM,<sup>199</sup> it is recommended that other risk factors that may contribute to atherosclerotic cardiovascular disease be treated aggressively in concordance with existing guidelines (Figure 3).<sup>10,223</sup> This includes aggressive modification of risk factors such as hypertension, diabetes, obesity, and hyperlipidemia.<sup>223</sup> A low-intensity aerobic exercise program is also reasonable to achieve cardiovascular fitness.<sup>224</sup>

Hydration and avoidance of environmental situations where vasodilatation may occur are important in the asymptomatic patient with resting or provokable LVOT obstruction. High-dose diuretics and vasodilators (for treatment of other diseases such as hypertension) should be avoided, because these may exacerbate the degree of obstruction.<sup>3,9</sup> However, the lack of symptoms attributable to HCM should not detract from the use of negative inotropic agents such as beta blockers or calcium channel blockers as treatment for relevant comorbidities such as hypertension.<sup>10</sup> Although data support the use of verapamil to relieve symptoms in HCM, other calcium antagonists such as diltiazem, even though widely used, have not been studied systematically.

Preliminary data in the animal model suggest that inhibitors of the renin-angiotensin pathway or statins or the calcium

channel inhibitor diltiazem<sup>226</sup> may prevent progression of hypertrophy in animal models of HCM.<sup>227,228</sup> However, there is no completed RCT to indicate that these drugs are effective in reducing hypertrophy in humans with HCM. Thus, these drugs should not be given with the intent of altering HCM-related clinical outcome but only for the control of heart failure-related symptoms. Finally, the indication for septal reduction therapy is to improve symptoms that are not relieved by medical therapy and that impair the patient's quality of life, usually consistent with NYHA functional classes III or IV.<sup>9,10</sup> Thus, septal reduction therapy with either septal myectomy or alcohol septal ablation should not be performed in the asymptomatic patient, regardless of the severity of obstruction.<sup>9,10</sup>

## 6.2. Symptomatic Patients

### 6.2.1. Pharmacologic Management—Recommendations

#### Class I

1. Beta-blocking drugs are recommended for the treatment of symptoms (angina or dyspnea) in adult patients with obstructive or nonobstructive HCM but should be used with caution in patients with sinus bradycardia or severe conduction disease.<sup>3,9,10,134,137,229–236</sup> (*Level of Evidence: B*)
2. If low doses of beta-blocking drugs are ineffective for controlling symptoms (angina or dyspnea) in patients with HCM, it is useful to titrate the dose to a resting heart rate of less than 60 to 65 bpm (up to generally accepted and recommended maximum doses of these drugs).<sup>3,10,137,229–236</sup> (*Level of Evidence: B*)
3. Verapamil therapy (starting in low doses and titrating up to 480 mg/d) is recommended for the treatment of symptoms (angina or dyspnea) in patients with obstructive or nonobstructive HCM who do not respond to beta-blocking drugs or who have side effects or contraindications to beta-blocking drugs. However, verapamil should be used with caution in patients with high gradients, advanced heart failure, or sinus bradycardia.<sup>10,134,137,237–241</sup> (*Level of Evidence: B*)
4. Intravenous phenylephrine (or another pure vasoconstricting agent) is recommended for the treatment of acute hypotension in patients with obstructive HCM who do not respond to fluid administration.<sup>137,242–244</sup> (*Level of Evidence: B*)

#### Class IIa

1. It is reasonable to combine disopyramide with a beta-blocking drug or verapamil in the treatment of symptoms (angina or dyspnea) in patients with obstructive HCM who do not respond to beta-blocking drugs or verapamil alone.<sup>10,134,137,245–248</sup> (*Level of Evidence: B*)
2. It is reasonable to add oral diuretics in patients with nonobstructive HCM when dyspnea persists despite the use of beta blockers or verapamil or their combination.<sup>67,134</sup> (*Level of Evidence: C*)

#### Class IIb

1. Beta-blocking drugs might be useful in the treatment of symptoms (angina or dyspnea) in children or

adolescents with HCM, but patients treated with these drugs should be monitored for side effects, including depression, fatigue, or impaired scholastic performance. (Level of Evidence: C)

2. It may be reasonable to add oral diuretics with caution to patients with obstructive HCM when congestive symptoms persist despite the use of beta blockers or verapamil or their combination.<sup>10,134,137</sup> (Level of Evidence: C)
3. The usefulness of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the treatment of symptoms (angina or dyspnea) in patients with HCM with preserved systolic function is not well established, and these drugs should be used cautiously (if at all) in patients with resting or provokable LVOT obstruction. (Level of Evidence: C)
4. In patients with HCM who do not tolerate verapamil or in whom verapamil is contraindicated, diltiazem may be considered. (Level of Evidence: C)

### Class III: Harm

1. Nifedipine or other dihydropyridine calcium channel-blocking drugs are potentially harmful for treatment of symptoms (angina or dyspnea) in patients with HCM who have resting or provokable LVOT obstruction. (Level of Evidence: C)
2. Verapamil is potentially harmful in patients with obstructive HCM in the setting of systemic hypotension or severe dyspnea at rest. (Level of Evidence: C)
3. Digitalis is potentially harmful in the treatment of dyspnea in patients with HCM and in the absence of AF.<sup>3,10,137,249–251</sup> (Level of Evidence: B)
4. The use of disopyramide alone without beta blockers or verapamil is potentially harmful in the treatment of symptoms (angina or dyspnea) in patients with HCM with AF because disopyramide may enhance atrioventricular conduction and increase the ventricular rate during episodes of AF.<sup>10,66,134,252–257</sup> (Level of Evidence: B)
5. Dopamine, dobutamine, norepinephrine, and other intravenous positive inotropic drugs are potentially harmful for the treatment of acute hypotension in patients with obstructive HCM.<sup>3,82,242–244,258–260</sup> (Level of Evidence: B)

The major goal of pharmacologic therapy in symptomatic patients with HCM is to alleviate symptoms of exertional dyspnea, palpitations, and chest discomfort, which may reflect pathophysiologic mechanisms such as LVOT obstruction, reduced supply of myocardial oxygen, mitral regurgitation, and impaired LV diastolic relaxation and compliance.<sup>9,10,134</sup>

Beta blockers are the mainstay of pharmacologic therapy and the first-line agents because of their negative inotropic effects<sup>261</sup> and their ability to attenuate adrenergic-induced tachycardia (Figure 3). These effects improve myocardial oxygen supply-demand relationships and hence reduce myocardial ischemia. The reduction in heart rate also prolongs the diastolic filling period, which may allow for more efficient inactivation of myocardial contractile proteins, thereby improving diastolic filling.<sup>262,263</sup>

In those patients unable to tolerate beta blockers or those with symptoms unresponsive to beta blockers, calcium channel blockers may provide effective symptomatic relief. Verapamil has been the most intensively studied such agent (Figure 3).<sup>239,264</sup> Possible mechanisms for symptomatic improvement include negative inotropic and rate-lowering effects similar to those of beta blockers. However, the effect of verapamil on diastolic dysfunction is controversial.<sup>84,265–268</sup> Whether improvement in indices of diastolic performance is a direct effect of verapamil or the result of reduction in ischemia is uncertain.<sup>213</sup> Diltiazem has also been shown to improve measures of diastolic performance<sup>269</sup> and to prevent or diminish myocardial ischemia.<sup>270</sup> Both verapamil and diltiazem should be used cautiously in patients with severe outflow tract obstruction, elevated pulmonary artery wedge pressure, and low systemic blood pressure, because a decrease in blood pressure with treatment may trigger an increase in outflow obstruction and precipitate pulmonary edema. Administration of beta-blocking drugs with either verapamil or diltiazem should also be performed with caution because of the potential for high-grade atrioventricular block. In addition, because of the bradycardic effects when both classes of agents are used concomitantly, the addition of verapamil or diltiazem to a beta blocker may prevent titration of the beta blocker to optimal dosage. Dihydropyridine class calcium channel blockers (eg, nifedipine) should not be used in patients with obstructive physiology because their vasodilatory effects may aggravate outflow obstruction.

In patients with obstructive HCM who remain symptomatic despite the use of beta blockers and calcium channel blockers, alone or in combination, disopyramide may be effective in ameliorating symptoms in many patients (Figure 3).<sup>157,271</sup> Anticholinergic side effects may occur and can be managed if necessary by dose reduction. Symptomatic benefit with disopyramide appears to represent a pure negative inotropic effect. The initiation of disopyramide should be performed in-hospital with cardiac monitoring for potential arrhythmias and lengthening of the QT. Diuretics may be effective for symptomatic relief in patients with pulmonary congestion but should be used judiciously in those with outflow tract obstruction.

### 6.2.2. Invasive Therapies—Recommendations

#### Class I

1. Septal reduction therapy should be performed only by experienced operators\* in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction.<sup>†272</sup> (Level of Evidence: C)

\* Experienced operators are defined as an individual operator with a cumulative case volume of at least 20 procedures or an individual operator who is working in a dedicated HCM program with a cumulative total of at least 50 procedures (Section 6.2.2.3).

† Eligible patients are defined by all of the following:

- a. Clinical: Severe dyspnea or chest pain (usually NYHA functional classes III or IV) or occasionally other exertional symptoms (such as syncope or near syncope) that interfere with everyday



activity or quality of life despite optimal medical therapy.

- b. Hemodynamic: Dynamic LVOT gradient at rest or with physiologic provocation  $\geq 50$  mm Hg associated with septal hypertrophy and SAM of the mitral valve.
- c. Anatomic: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

## Class IIa

1. Consultation with centers experienced in performing both surgical septal myectomy and alcohol septal ablation is reasonable when discussing treatment options for eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. (*Level of Evidence: C*)
2. Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction.<sup>61,62,155,273–275</sup> (*Level of Evidence: B*)
3. Surgical septal myectomy, when performed at experienced centers, can be beneficial in symptomatic children with HCM and severe resting obstruction ( $>50$  mm Hg) for whom standard medical therapy has failed.<sup>276</sup> (*Level of Evidence: C*)
4. When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms (usually NYHA functional classes III or IV).<sup>62,153,277–281</sup> (*Level of Evidence: B*)

## Class IIb

1. Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation.<sup>153,273,278,280,281</sup> (*Level of Evidence: B*)
2. The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked (ie,  $>30$  mm) septal hypertrophy, and therefore the procedure is generally discouraged in such patients. (*Level of Evidence: C*)

## Class III: Harm

1. Septal reduction therapy should not be done for adult patients with HCM who are asymptomatic with normal exercise tolerance or whose symptoms are controlled or minimized on optimal medical therapy. (*Level of Evidence: C*)
2. Septal reduction therapy should not be done unless performed as part of a program dedicated to the longitudinal and multidisciplinary care of patients with HCM. (*Level of Evidence: C*)

3. Mitral valve replacement for relief of LVOT obstruction should not be performed in patients with HCM in whom septal reduction therapy is an option. (*Level of Evidence: C*)
4. Alcohol septal ablation should not be done in patients with HCM with concomitant disease that independently warrants surgical correction (eg, coronary artery bypass grafting for CAD, mitral valve repair for ruptured chordae) in whom surgical myectomy can be performed as part of the operation. (*Level of Evidence: C*)
5. Alcohol septal ablation should not be done in patients with HCM who are less than 21 years of age and is discouraged in adults less than 40 years of age if myectomy is a viable option. (*Level of Evidence: C*)

See Online Data Supplement 2 for additional data regarding invasive therapies.

Although the writing committee recognizes that surgical myectomy and ablation are methodologically very different approaches and interventions, in this section they are discussed together because they are the 2 generally accepted methods for relief of symptoms in patients with LVOT obstruction. Most patients with HCM lead active lifestyles with minimal or no symptoms, but some patients incur significant symptoms that interfere with everyday activity or quality of life.<sup>48</sup> For symptoms that are attributable to LVOT obstruction, invasive therapies can be used to improve quality of life (Figure 3). Surgical approaches have been used for 5 decades<sup>72,144</sup> so that relief of outflow tract obstruction and symptoms can be achieved with minimal perioperative morbidity or mortality in experienced centers.<sup>61,155</sup> However, some patients are not optimal surgical candidates (eg, because of comorbidities or advanced age) or have such a strong desire to avoid surgery that alternative therapeutic interventions have been implemented. Alcohol septal ablation, which has been in use for the past 17 years, has become the leading strategy in these circumstances.<sup>282</sup> This procedure causes a regional infarction of the basal septum, thereby initially decreasing contractility and eventually causing thinning (because of scarring) of the basal septum and consequent widening of the outflow tract.

Dual-chamber pacing has also been used and studied for the relief of outflow tract obstruction. The proposed mechanism relates to a change in the activation sequence of the septum and possibly long-term remodeling. RCTs suggested a modest benefit of pacing therapy, primarily in those  $>65$  years of age.<sup>283,284</sup> In the current era, application of dual-chamber pacing for the relief of symptoms attributable to outflow tract obstruction is primarily used in patients with significant comorbidities for whom both surgical septal myectomy and alcohol septal ablation are considered to have unacceptable risk or in patients who already have an implanted dual-chamber pacing device (often implanted for nonhemodynamic indications).

### 6.2.2.1. Selection of Patients

It is well recognized that the appropriate selection of patients for individual procedures is an important predictor of outcome. Because the majority of patients with HCM can

achieve control of their symptoms with optimal pharmacologic therapy, and in light of the complications inherent with invasive therapies, a core set of clinical, anatomic, and hemodynamic criteria are required before patients are considered candidates for invasive therapies. Specifically, patients must have symptoms attributable to LVOT obstruction that are refractory to optimal pharmacologic therapy. Similarly, it must be demonstrated that the obstruction is caused by apposition of the mitral valve with the hypertrophied septum (and not attributable to systolic cavity obliteration).<sup>72,144</sup> It has been generally accepted that maximal instantaneous gradients of at least 50 mm Hg at rest or with physiologic provocation are necessary to produce symptoms amenable to invasive therapies.<sup>10</sup>

Given the duration of experience, documented long-term results, and safety data, surgical septal myectomy is considered the preferred treatment for most patients who meet these criteria (Figure 3). Considerations that would favor surgical intervention include younger age, greater septal thickness, and concomitant cardiac disease independently requiring surgical correction (eg, intrinsic mitral valve disease or coronary artery bypass grafting). Additionally, specific abnormalities of the mitral valve and its support apparatus can contribute significantly to the generation of outflow tract obstruction, suggesting the potential value of additional surgical approaches (eg, plication, valvuloplasty, and papillary muscle relocation) and making myectomy more appropriate than alcohol septal ablation in some patients.<sup>16,80,285–290</sup> Among patients who meet the core selection criteria, factors that influence a decision to proceed with alcohol septal ablation include older or advanced age, significant comorbidity that selectively increases surgical risk, (eg, significant concerns about lung or airway management) and the patient's strong desire to avoid open-heart surgery after a thorough discussion of both options.

#### 6.2.2.2. Results of Invasive Therapy for the Relief of LVOT Obstruction

More detailed discussions specific to each type of procedure follow in subsequent sections of this document. Overall, reports suggest that technical success, variably defined, is achieved in 90% to 95% of patients who undergo surgical myectomy,<sup>291</sup> less in septal ablation, and only in the minority of patients studied in trials of pacemaker therapy.<sup>292–295</sup> Patients undergoing septal ablation may have hemodynamic and symptomatic improvement comparable to septal myectomy if the area of the SAM-septal contact can be accessed by the first septal perforator and ablated. However, compared with septal myectomy in which the hypertrophied muscle is directly visualized and resected, successful septal ablation is dependent on the variable septal artery anatomy, which may not supply the targeted area of the septum in up to 20% to 25% of patients.<sup>62,296</sup>

In a nonrandomized retrospective evaluation of patients with HCM <65 years of age, survival free from recurrent symptoms favored myectomy over ablation (89% versus 71%;  $P=0.01$ ).<sup>62</sup> Procedural success is associated with very low mortality (<1% for myectomy,<sup>61,155,297</sup> ranging from 0% to 4% for ablation),<sup>298–300</sup> and low nonfatal complication

rates (2% to 3% in experienced centers). The exception is high-grade atrioventricular block requiring permanent pacemakers following septal ablation (in 10% to 20% of patients), an inherent aspect of the septal infarction.<sup>301–303</sup> The data from trials of dual-chamber pacing suggest that there was a significant placebo effect and inconsistent symptomatic benefit.<sup>283,284,294</sup>

#### 6.2.2.3. Operator Experience

Operator and institutional experience, including procedural volume, is a key determinant of successful outcomes and lower complication rates for any procedure. For HCM, a disease of substantial heterogeneity that is relatively uncommon in general cardiology practice, this is an important issue. As with the recommendations made in the “2008 Focused Update Incorporated Into the ACCF/AHA Guidelines for the Management of Patients With Valvular Heart Disease” about expected outcomes for surgeons offering mitral valve repair,<sup>304</sup> it would be prudent and appropriate for individual centers, surgeons, and interventional cardiologists to demonstrate sufficient success and safety to justify ongoing use of these procedures. Although it is difficult to define a precise case volume or cumulative experience required to perform these procedures, at least 1 study suggests that the learning curve relative to invasive therapy in HCM may require the performance of at least 40 procedures.<sup>272</sup> As a consensus opinion, the writing committee recommends an operator volume of at least 20 procedures or that the operator work within the context of an HCM program with a cumulative procedural volume of at least 50 procedures. In addition, given the data available from experienced centers, operators and institutions should aim to achieve mortality rates of <1% and major complication rates of <3%, with documented success in both hemodynamic and symptom benefit for their patients. This is best achieved in the context of a systematic program dedicated to the multidisciplinary and longitudinal care of patients with HCM.

#### 6.2.2.4. Surgical Therapy

Transaortic septal myectomy is currently considered the most appropriate treatment for the majority of patients with obstructive HCM and severe symptoms unresponsive to medical therapy (Figure 3).<sup>276,291,305–313</sup> Surgical results, although vastly improved in recent years, are nevertheless limited to relatively few centers with extensive experience and particular interest in the management of HCM.<sup>288,314</sup> Both the traditional myectomy (Morrow procedure) with about a 3-cm long resection<sup>309</sup> or extended myectomy (a resection of about 7 cm) are currently used.<sup>288,314</sup>

The transaortic approach remains the primary method of exposure. Virtual abolition of the LV outflow gradient and mitral regurgitation is usually accomplished by muscular resection resulting in physical enlargement of the outflow tract and by interruption of the mitral valve SAM, which is usually responsible for the outflow gradient.<sup>315</sup> Septal myectomy in the current era is commonly referred to as an “extended myectomy.” This refers to the fact that the muscular resection becomes progressively wider as the resection proceeds into the ventricle (ie, toward the apex), effectively making the trough wider at the mid-ventricular level. As a

result, the myectomy resection is opposite the lateral portion of the anterior leaflet (to avoid conduction tissue), the chordae, and both papillary muscles. In addition, muscular resection is also performed along the left lateral free wall (also part of the LVOT), resulting in a much more extensive myectomy than that originally described by Morrow et al about 50 years ago.<sup>309</sup>

The transaortic approach remains the primary method of exposure. Virtual abolition of the LV outflow gradient and mitral regurgitation is usually accomplished by muscular resection resulting in physical enlargement of the outflow tract and by interruption of the mitral valve SAM, which is usually responsible for the outflow gradient.<sup>315</sup> In selected circumstances, some surgeons have also used concomitant mitral valve repair, particularly when the anterior leaflet is elongated. This valve repair maneuver usually involves shortening the height of the anterior leaflet. However, residual mitral valve regurgitation after adequate septal myectomy is almost always caused by intrinsic mitral valve abnormalities such as ruptured chordae, myxomatous degeneration with prolapse, or annular dilatation, and can be corrected by direct valve repair. Finally, enlarged or malpositioned papillary muscles can also contribute to residual obstruction. This can be effectively treated by shaving the hypertrophied papillary muscles, incising papillary muscles off the ventricular free wall, and in selected circumstances repositioning one papillary muscle by suture approximation to the adjacent papillary muscle.

The surgical specimen obtained at the time of myectomy should be submitted for pathologic examination, not only to confirm the histopathology of HCM, but also for special stains to rule out storage diseases that can mimic HCM.<sup>31</sup>

**6.2.2.4.1. Selection of Patients.** It is important to underscore that the subjective assessment of operative risk by clinicians frequently results in an overestimate of risk, resulting in the denial of proven therapies for eligible patients in favor of less effective or less proven options.<sup>316</sup> In patients perceived to be at prohibitively high risk because of major comorbidities, including age, the use of objective risk tools in the context of individual institutional experience could lead to a reassessment of operative risk that is lower than initially thought.

#### 6.2.2.4.2. Outcomes

**Early Results.** Based on the experience and data assembled from multiple centers worldwide over the last 4 decades,<sup>276,291,305,307,308,310,311</sup> septal myectomy is established as the most effective and proven approach for reversing the consequences of heart failure by providing amelioration of obstruction (and relief of mitral regurgitation) at rest, with restoration of functional capacity and acceptable quality of life at any age, exceeding that achievable with long-term administration of cardioactive drugs.<sup>10,175</sup> These salutary benefits have been demonstrated subjectively by patient history and objectively by increased treadmill time, maximum workload, peak oxygen consumption, and improved myocardial oxygen demand, metabolism, and coronary flow.<sup>10,273,294</sup>

LV outflow gradient reduction with myectomy results from basal septal thinning with resultant enlargement of the LVOT area (and redirection of forward flow with loss of the drag and Venturi effects on the mitral valve)<sup>317</sup> and consequently abolition of SAM and mitral-septal contact.<sup>314,318,319</sup> Mitral regurgitation is also usually eliminated without the need for additional mitral valve surgery.<sup>148</sup> With myectomy, LA size (and possibly long-term risk for AF) is reduced<sup>155</sup> and LV pressures (and wall stress) are normalized.<sup>10,61,148,317,320</sup> Thus, obstructive HCM is a surgically and mechanically reversible form of heart failure. In experienced centers, operative risk is now particularly low, in the range of <1%.<sup>175</sup>

**Late Results.** Relief of outflow obstruction by septal myectomy may also extend the longevity of patients with HCM.<sup>61</sup> Although RCTs involving myectomy surgery have not been performed, in a nonrandomized study, myectomy resulted in excellent long-term survival similar to that in the general population. After septal myectomy, long-term actuarial survival was 99%, 98%, and 95% at 1, 5, and 10 years, respectively (when considering HCM-related mortality). This survival rate did not differ from that expected in a matched general US population and was superior to that achieved by patients with obstructed HCM who did not undergo surgical myectomy.<sup>61</sup> Similarly, the rate of SCD or appropriate ICD discharge after myectomy is very low (<0.9%).<sup>61,321,322</sup> Nonetheless, surgical myectomy does not eliminate the need to assess each patient's risk for SCD and to consider placement of an ICD in those with a significant risk burden.

**6.2.2.4.3. Complications.** Complications following myectomy are rare when performed in experienced centers.<sup>315</sup> The risk of complete heart block is approximately 2% with myectomy (higher in patients with preexisting right bundle-branch block), but in myectomy patients who have had previous alcohol septal ablation, risk is much higher (50% to 85%).<sup>323</sup> Iatrogenic ventricular septal defect occurs in <1% of patients. Finally, the risk of aortic valve or mitral valve injury is also low (<1%), particularly when myectomy is performed by an experienced operator.

**6.2.2.4.4. Mitral Valve Abnormalities and Other Anatomic Issues.** Abnormalities of the mitral valve and subvalvar apparatus (including anomalous direct anterolateral papillary muscle insertion into anterior mitral leaflet and elongated mitral leaflets)<sup>80,324</sup> can be identified preoperatively with TTE or intraoperative TEE and can be corrected with modified mitral valve repair or extended myectomy techniques without the need for mitral valve replacement. Indeed, the excellent early and late outcomes of extended myectomy for treatment of obstructive HCM have made mitral valve replacement exceedingly rare.<sup>315</sup> Associated degenerative mitral valve disease (ie, prolapse, ruptured chordae) can be treated by concomitant mitral valve repair at the time of myectomy. Mitral valve repair techniques may need to be modified in HCM to avoid subsequent development of SAM.<sup>325</sup>

Mitral valve replacement in patients with obstruction has been performed rarely when septal reduction therapy was judged unsafe or likely to be ineffective. When the basal



septum is only mildly hypertrophied (<16 mm), the risk for either iatrogenic ventricular septal defect from excessive muscular resection or residual postoperative outflow obstruction from inadequate resection increases. Mitral valve replacement may be an option in rare patients.<sup>326,327</sup>

#### 6.2.2.5. Alcohol Septal Ablation

First reported in 1995,<sup>282</sup> alcohol septal ablation uses transcatheter administration of absolute ethanol via a percutaneous approach to induce a localized infarction of the basal septum at the point of contact of the anterior mitral valve leaflet, thereby reducing outflow tract gradient and associated mitral regurgitation and simulating the results of surgical myectomy. Developed as an alternative to surgical septal myectomy, the technique is particularly useful when surgery is contraindicated and in patients who are considered poor surgical candidates.<sup>279</sup> Since its development, alcohol septal ablation has been performed successfully in a large number of patients.<sup>153</sup>

After measurement of resting or provoked outflow tract gradients, a temporary pacemaker is placed in the right ventricle because of the risk of procedural complete heart block.<sup>328–330</sup> With the use of standard angioplasty equipment and anticoagulation, a guidewire and coronary angioplasty balloon are placed in the septal perforator that appears to perfuse the target myocardium. Contrast angiography of the septal perforator through the balloon central lumen with simultaneous echocardiographic guidance<sup>331,332</sup> confirms delivery to only the target myocardium. About 1 to 3 mL of alcohol is infused in controlled fashion.<sup>151,333–335</sup> Incorporation of myocardial contrast echocardiography reduces the number of septal branches into which ethanol is injected and may both improve the success rate and lower cardiac biomarker release and the need for pacing.<sup>331–333,336</sup> It is important that the balloon be inflated and that a contrast injection also show that there is no extravasation of dye into the distal left anterior descending coronary artery. Contrast enhancement of other regions (papillary muscles, free wall) indicates collateral circulation from the septal perforator artery, and alcohol should not be infused. A decrease in resting and provoked gradients usually occurs immediately after the procedure (because of stunning), and remodeling can result in continued or variable gradient reduction over the first 3 months after the procedure. Patients are monitored for arrhythmias and conduction disturbances in the intensive care unit for 24 to 48 hours; implantation of a permanent pacemaker may be necessary for complete or high-grade atrioventricular block and through discharge at 3 to 4 days.

**6.2.2.5.1. Selection of Patients.** Alcohol septal ablation has the potential for greater patient satisfaction because of the absence of a surgical incision and general anesthesia, less overall discomfort, and a much shorter recovery time. The benefit of alcohol septal ablation in patients of advanced age is similar to that in other patients.<sup>277,337</sup> Because the postoperative risks and complications of cardiac surgery increase with age, ablation may offer a selective advantage in older patients, in whom operative risk may be increased because of comorbidities. Alcohol septal ablation is not indicated in children.

On the other hand, longer-term follow-up data are available for septal myectomy than for septal ablation, a consideration relevant to the selection of patients for either septal reduction therapy. The likelihood of implantation of a permanent pacemaker is 4- to 5-fold higher after septal ablation than after septal myectomy. Clinical and hemodynamic benefit is achieved immediately after recovery from septal myectomy but may be delayed for up to 3 months after septal ablation, although many patients achieve a notable symptomatic benefit after the procedure. Furthermore, patients with massive septal thickness approaching or exceeding 30 mm may experience little or no benefit from septal ablation. The surgeon can tailor the myectomy under direct visualization to address specific anatomic abnormalities of the LVOT or mitral valve apparatus, whereas alcohol septal ablation indirectly (and is restricted to) targets the distribution of the septal perforator artery.

Septal myectomy is the preferred treatment option for most severely symptomatic patients with obstructive HCM, especially in younger, healthy adults, whereas septal ablation is preferred in patients for whom surgery is contraindicated or considered high risk (particularly the elderly) (Figure 3). Data comparing alcohol septal ablation with septal myectomy are inadequate to fully inform clinical decision making in certain cases. For such patients, the principle of patient autonomy dictates that it is appropriate for the informed patient to choose between the 2 procedures.

**6.2.2.5.2. Results.** Necrosis of the basal ventricular septum<sup>338</sup> produces an immediate fall in gradient from decreased septal contraction in >90% of patients.<sup>156,300,339–341</sup> This effect is followed by LV remodeling over 6 to 12 months, a process that includes scar retraction and resultant widening of the outflow tract, associated with further reduction in gradient and degree of mitral regurgitation, regression of hypertrophy, and improvement in diastolic function.<sup>154,300,342–344</sup> LA pressure is reduced, which may promote a decreased incidence of AF and amelioration of pulmonary hypertension.<sup>345</sup> Two studies have demonstrated that, as with septal myectomy, the benefit of septal ablation in patients with provokable gradients is similar to that in patients with resting gradients.<sup>346,347</sup> The beneficial results of alcohol septal ablation have been reported to almost 5 years after the procedure with improved functional and angina classes, exercise capacity, and quality of life.<sup>153,300,348–351</sup> However, hemodynamic and symptomatic success is dependent on the ability to cannulate and ablate a septal perforator artery that supplies the area of the SAM-septal contact.

Although RCTs comparing surgical myectomy with alcohol septal ablation have not been conducted and are highly unlikely in the future, meta-analyses have noted similar hemodynamic and functional improvement over 3 to 5 years when examining the cumulative average of outcomes.<sup>352–354</sup> What the meta-analyses do not report are a subset of patients in whom alcohol septal ablation is unreliable because of the inability to ablate the area of the SAM-septal contact.<sup>355</sup> Older patients, especially those considered to be at high surgical risk, may be well served by alcohol septal ablation, whereas younger patients may benefit most from surgical myectomy.<sup>62,279</sup> Despite age differences in treatment allocation,

tion, with septal ablation patients on average approximately 10 years older in clinical practice,<sup>352,353</sup> the 4-year survival rate is similar for the 2 procedures.<sup>62,278</sup> Most studies that have compared surgical myectomy and alcohol septal ablation have involved a large single-center experience in which treatment assignment was not randomized.

**6.2.2.5.3. Complications.** In approximately half of patients undergoing alcohol septal ablation, temporary complete atrioventricular block occurs during the procedure.<sup>328–330</sup> Persistent complete heart block prompting implantation of a permanent pacemaker occurs in 10% to 20% of patients based on the available data.<sup>36</sup> Approximately 5% of patients have sustained ventricular tachyarrhythmias during hospitalization. The in-hospital mortality rate is up to 2%.<sup>62,153,279,353</sup> Because of the potential for creating a ventricular septal defect, septal ablation should not be performed if the target septal thickness is  $\leq 15$  mm.

Alcohol septal ablation is a therapeutic alternative to surgical myectomy for selected patients and produces a transmural infarction of ventricular septum occupying on average 10% of the overall LV wall.<sup>53,296,356</sup> There has been concern that the potential ventricular arrhythmogenicity of the scar created by septal ablation might augment risk in the HCM population. Several studies have documented the occurrence of sustained ventricular arrhythmias<sup>332,349,357–363</sup> and SCD following septal ablation<sup>322</sup> in about 3% to 10% of patients both with or without risk factors for SCD. In a single-center experience (n=91), 21% of patients experienced sudden or other cardiac death, aborted SCD, and/or appropriate ICD discharge resulting in an annualized event rate of 4.4% per year after ablation.<sup>322</sup> In a second single-center experience (n=89), no mortality was attributable to SCD in  $5.0 \pm 2.3$  years of follow-up. However, in a selected subset of 42 patients with an ICD or permanent pacemaker that enabled detection of device-stored electrograms, the annualized event rate (VT, ventricular fibrillation, and/or appropriate ICD discharge, including periprocedural arrhythmias) was 4.9% per year.<sup>362</sup> Data from another center suggest appropriate ICD intervention rates after ablation of 2.8% per year<sup>364</sup>; similarly, the multicenter HCM ICD registry (n=506) demonstrated that the rate of appropriate ICD therapy among ablation patients with primary prevention ICDs was 3 to 4 times more frequent than in other patients in that registry (10.3% per year compared with 2.6% per year).<sup>55</sup> Patients with HCM considered to carry sufficient risk to warrant ICD placement have an annual incidence of appropriate interventions for VT/ventricular fibrillation of 3% to 10%.<sup>55,360,364</sup> It is uncertain how common such events are attributable to the procedure or alternatively to the underlying disease, but the incidence of sustained ventricular arrhythmias after myectomy is extremely low (0.2% to 0.9% per year).<sup>61,321,322</sup>

Meta-analyses have indicated no difference between septal ablation and myectomy in the medium-term incidence of SCD or all-cause mortality.<sup>352,365</sup> Although no definitive evidence is available that the ablation scar as such increases (or does not increase) long-term risk for SCD in absolute terms in this patient population, resolution will require greatly extended follow-up studies in larger patient cohorts.<sup>53,357</sup>

#### 6.2.2.6. Pacing—Recommendations

##### Class IIa

1. In patients with HCM who have had a dual-chamber device implanted for non-HCM indications, it is reasonable to consider a trial of dual-chamber atrial-ventricular pacing (from the right ventricular apex) for the relief of symptoms attributable to LVOT obstruction.<sup>292,294,295,366</sup> (*Level of Evidence: B*)

##### Class IIb

1. Permanent pacing may be considered in medically refractory symptomatic patients with obstructive HCM who are suboptimal candidates for septal reduction therapy.<sup>283,292,294,295,366</sup> (*Level of Evidence: B*)

##### Class III: No Benefit

1. Permanent pacemaker implantation for the purpose of reducing gradient should not be performed in patients with HCM who are asymptomatic or whose symptoms are medically controlled.<sup>283,284,367</sup> (*Level of Evidence: C*)
2. Permanent pacemaker implantation should not be performed as a first-line therapy to relieve symptoms in medically refractory symptomatic patients with HCM and LVOT obstruction who are candidates for septal reduction.<sup>283,284,367</sup> (*Level of Evidence: B*)

See Online Data Supplement 3 for additional data regarding pacing.

Implantation of a dual-chamber pacemaker was proposed as an alternative treatment for patients with severe symptomatic obstructive HCM.<sup>369–371</sup> Pacing the right ventricular apex with maintenance of atrioventricular synchrony results in a decrease in the LVOT gradient and improvement of symptoms in a subset of patients. Although the exact mechanism of improvement with pacing remains unknown, the decrease in gradient may be caused by timing of septal contraction but may also reflect long-term remodeling.<sup>369</sup> Although there was an initial enthusiasm for dual-chamber pacing as a primary treatment for patients with obstructive HCM, subsequent RCTs demonstrated long-lasting beneficial results in only a small minority of patients, whereas most perceived improvement was judged to be a placebo effect.<sup>283,284,367</sup> A trial of dual-chamber pacing may be considered for symptomatic patients with obstruction in whom an ICD has already been implanted for high-risk status.

**6.2.2.6.1. Results of DDD Pacing.** Initial cohort studies of the results of dual-chamber pacing in patients with obstructive HCM and limiting symptoms showed symptomatic improvement in almost 90% of patients, accompanied by an improvement in exercise time and a reduction in gradient.<sup>368–371</sup> However, there have been 3 randomized crossover trials in which patients received 2 to 3 months of continuous DDD pacing but also underwent a back-up AAI mode (no pacing)

as a control arm.<sup>283,284,367</sup> DDD pacing consists of continuously sensing or pacing the atrium and pacing the right ventricular apex. The overall reduction in outflow tract gradient was modest (25% to 40%) with substantial variation among individual patients. Objective measurements of exercise capacity were improved during DDD pacing versus baseline, but there was no significant difference comparing the AAI back-up mode with continuous DDD pacing. Although symptomatic improvement was reported by the majority of patients following continuous DDD pacing, a similar frequency of improvement was reported by patients during the AAI mode (control mode without pacing). These findings suggest a placebo effect as well as a “training effect” contributing to the initial symptomatic improvement of patients undergoing dual-chamber pacing.<sup>283,284,372</sup>

Overall, the percentage of patients with sustained symptomatic improvement from continuous dual-chamber pacing varies from 30% to 80%.<sup>292,294,295,366</sup> A consistent improvement in symptoms with a decrease in gradient and objective improvement in exercise duration is seen in <50% of patients. The overall success rate in terms of symptom relief and gradient reduction is significantly lower than that seen in patients who undergo septal myectomy. The mean residual gradient after septal myectomy is <10 mm Hg compared with a 40 to 50 mm Hg gradient after dual-chamber pacing.<sup>283,284,295,369</sup> There is no reliable predictor of success for dual-chamber pacing, including the results of acute hemodynamic studies or morphologic echocardiographic features.<sup>295,367,373</sup> Patients >65 years of age may be a subgroup who achieve the greatest benefit.<sup>283</sup> There are no data that indicate dual-chamber pacing either reduces the risk of SCD in patients with HCM or alters the underlying progression of disease.<sup>283,369</sup> Dual-chamber pacing has not been shown to be beneficial for patients with nonobstructive HCM.<sup>374</sup>

**6.2.2.6.2. DDD Pacing: Caveats.** A thorough understanding of the complex interplay between pacemaker programming and the hemodynamics of HCM is necessary to achieve possible beneficial results from this therapy. It is necessary to optimize the atrioventricular delay because too short an interval results in hemodynamic deterioration and too long an atrioventricular interval without complete preexcitation of the ventricle results in an inadequate response.<sup>375</sup> The position of the pacemaker lead is important, requiring distal apical capture for optimal hemodynamic results.<sup>376</sup> Programming of rate-adaptive pacing is also necessary so that full preexcitation of the ventricle is obtained during exercise.

**6.2.2.6.3. Pacing and ICDs.** Patients with HCM are at increased risk for ventricular tachyarrhythmias and SCD. Comprehensive SCD risk stratification should be performed in all patients with HCM (Section 6.3.1). However, current SCD risk stratification does not identify all patients at risk for ventricular arrhythmias and SCD.<sup>377</sup> An ICD has been shown to be effective at aborting SCD in patients with HCM.<sup>55</sup> Consideration of an ICD if a pacing device is indicated for either

rhythm or hemodynamic indications is controversial in contrast to the situation in patients with established risk factors for SCD.

### 6.2.3. Patients With LV Systolic Dysfunction—Recommendations

#### Class I

1. Patients with nonobstructive HCM who develop systolic dysfunction with an EF less than or equal to 50% should be treated according to evidence-based medical therapy for adults with other forms of heart failure with reduced EF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and other indicated drugs.<sup>39,378</sup> (*Level of Evidence: B*)
2. Other concomitant causes of systolic dysfunction (such as CAD) should be considered as potential contributors to systolic dysfunction in patients with HCM. (*Level of Evidence: C*)

#### Class IIb

1. ICD therapy may be considered in adult patients with advanced (as defined by NYHA functional class III or IV heart failure) nonobstructive HCM, on maximal medical therapy, and EF less than or equal to 50%, who do not otherwise have an indication for an ICD.<sup>39</sup> (*Level of Evidence: C*)
2. For patients with HCM who develop systolic dysfunction, it may be reasonable to reassess the use of negative inotropic agents previously indicated, for example, verapamil, diltiazem, or disopyramide, and to consider discontinuing those therapies. (*Level of Evidence: C*)

Although HCM has typically been excluded from RCTs in heart failure, there is no compelling reason to believe that the etiology of reduced EF heart failure differs sufficiently to disqualify many highly effective, evidence-based, guideline-directed therapies for heart failure with reduced EF.<sup>379</sup> Standard heart failure therapies should be implemented in patients with HCM when the EF is  $\leq 50\%$  for patients with CAD.<sup>39</sup>

The discovery of reduced EF in the setting of HCM is not inconsistent with the known natural history of HCM but is uncommon (approximately 3%) and should prompt an appropriate search for other potential contributing causes of LV dysfunction.<sup>39</sup> Those causes should include, but are not limited to, CAD, valvular heart disease, and metabolic disorders.

Patients with HCM were not included in the primary prevention ICD trials for patients with heart failure due to CAD or dilated cardiomyopathy (and reduced EF). Prophylactic ICD implantation is nevertheless the generally accepted clinical practice for HCM patients with systolic dysfunction. Furthermore, despite the absence of clinical trials or observational data, the use of negative inotropic drugs that would otherwise be discouraged in the setting of conventional heart failure with reduced EF can be considered in patients with HCM.



#### 6.2.4. Selection of Patients for Heart Transplantation—Recommendations

##### Class I

1. Patients with advanced heart failure (end stage\*) and nonobstructive HCM not otherwise amenable to other treatment interventions, with EF less than or equal to 50% (or occasionally with preserved EF), should be considered for heart transplantation.<sup>39,381</sup> (Level of Evidence: B)
2. Symptomatic children with HCM with restrictive physiology who are not responsive to or appropriate candidates for other therapeutic interventions should be considered for heart transplantation.<sup>382,383</sup> (Level of Evidence: C)

##### Class III: Harm

1. Heart transplantation should not be performed in mildly symptomatic patients of any age with HCM. (Level of Evidence: C)

In general, the indications for heart transplantation include advanced heart disease, typically with NYHA functional class III or IV symptoms that are refractory to all other reasonable interventions. Transplant referral for refractory symptoms does not absolutely require reduced EF, although this treatment strategy is rarely recommended and performed in the presence of preserved EF. For patients with HCM, outcome after heart transplantation is not different from that of patients with other heart diseases.<sup>39,384,385</sup>

### 6.3. Prevention of SCD

#### 6.3.1. SCD Risk Stratification—Recommendations

##### Class I

1. All patients with HCM should undergo comprehensive SCD risk stratification at initial evaluation to determine the presence of the following:<sup>50,53,55,127,128,386–392</sup> (Level of Evidence: B)
  - a. A personal history for ventricular fibrillation, sustained VT, or SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias.<sup>†</sup>
  - b. A family history for SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias.<sup>†</sup>
  - c. Unexplained syncope.
  - d. Documented NSVT defined as 3 or more beats at greater than or equal to 120 bpm on ambulatory (Holter) ECG.
  - e. Maximal LV wall thickness greater than or equal to 30 mm.

##### Class IIa

1. It is reasonable to assess blood pressure response during exercise as part of SCD risk stratification in patients with HCM.<sup>89,127,390</sup> (Level of Evidence: B)

\*Characterized by systolic dysfunction (EF ≤50%), often associated with LV remodeling, including cavity enlargement and wall thinning, and because of diffuse myocardial scarring.

†Appropriate ICD discharge is defined as ICD therapy triggered by VT or ventricular fibrillation, documented by stored intracardiac electrogram or cycle-length data, in conjunction with the patient's symptoms immediately before and after device discharge.

2. SCD risk stratification is reasonable on a periodic basis (every 12 to 24 months) for patients with HCM who have not undergone ICD implantation but would otherwise be eligible in the event that risk factors are identified (12 to 24 months). (Level of Evidence: C)

##### Class IIb

1. The usefulness of the following potential SCD risk modifiers is unclear but might be considered in selected patients with HCM for whom risk remains borderline after documentation of conventional risk factors:
  - a. CMR imaging with LGE.<sup>184,188</sup> (Level of Evidence: C)
  - b. Double and compound mutations (ie, >1). (Level of Evidence: C)
  - c. Marked LVOT obstruction.<sup>45,127,143,390</sup> (Level of Evidence: B)

##### Class III: Harm

1. Invasive electrophysiologic testing as routine SCD risk stratification for patients with HCM should not be performed. (Level of Evidence: C)

See Online Data Supplement 4 for additional data regarding SCD risk stratification.

A minority of clinically recognized patients with HCM are judged to be at increased risk for SCD, with a rate of about 1% per year.<sup>53,55,386–389</sup> ICDs offer the only effective means of preventing SCD and prolonging life in patients with HCM.<sup>55</sup> Selection of patients who are appropriate for implantation for primary as opposed to secondary prevention can be a difficult clinical decision, owing to the individuality of each patient and family, variable definitions for risk markers, sparse clinical data, the relative infrequency of both HCM and SCD in most clinical practices, and the cumulative morbidity of living with an ICD.

#### 6.3.1.1. Established Risk Markers

**6.3.1.1.1. Prior Personal History of Ventricular Fibrillation, SCD, or Sustained VT.** As expected, patients with HCM who have experienced SCD or sustained VT represent the highest risk for subsequent arrhythmogenic events. The annualized rate of subsequent events is approximately 10% per year, although it has been shown that individuals may have no recurrent events or may have decades-long arrhythmia-free intervals between episodes.<sup>55,387–389,393</sup>

**6.3.1.1.2. Family History of SCD.** It has been recognized that SCD events can cluster in families. Notably, some studies have not demonstrated an independent link between family history of SCD and risk for individual patients on multivariate analysis,<sup>50,390,394</sup> whereas others have suggested that family history is an independent predictor.<sup>394</sup> These differences may be explained in part by the relative infrequency of events but also likely reflect variability in the definition of a family history of SCD. Some studies have used a definition of SCD in ≥2 first-degree relatives,<sup>50</sup> whereas others have counted a single event.<sup>127,390</sup> None of these studies have

rigorously accounted for the total number of clinically apparent patients with HCM in each family, nor have they included SCD in more remote relations (eg, cousins, uncles, aunts, grandparents).

**6.3.1.1.3. Syncope.** Syncope represents a complex symptom with a multifactorial etiology that requires a careful clinical history before it can be considered a potential marker for SCD.<sup>50,392</sup> In one analysis, syncope that was unexplained or thought to be consistent with arrhythmia (ie, not neurally mediated) showed a significant independent association with SCD only when the events occurred in the recent past (<6 months) but not if the syncopal episodes occurred >5 years before the clinical visit.<sup>392</sup> One other large study reports a similar independent association between recent unexplained syncope and SCD.<sup>127</sup> Another study showed that it was the interaction between syncope and family history that was an important prognostic marker.<sup>50</sup>

**6.3.1.1.4. Nonsustained Ventricular Tachycardia.** Although sustained ventricular arrhythmia is clearly associated with SCD, the data for NSVT are less robust. Only 1 of 5 studies showed a univariate association between NSVT on 24-hour ambulatory monitors and SCD,<sup>50,128,389,395–397</sup> whereas 1 contemporary and larger study showed that NSVT is independently associated with SCD on multivariate analysis<sup>127</sup> and is more important in younger patients (<30 years of age).<sup>129</sup> Furthermore, exercise-induced NSVT has been found to have independent association with SCD.<sup>398</sup> NSVT probably should not be considered in a simply binary manner (ie, as either positive or negative), and there may be some value in long-term ambulatory monitoring when NSVT is discovered on the screening 24-hour assessment. Intuitively, it would seem appropriate to place more weight on frequent, longer, and/or faster episodes of NSVT; however, there have been no systematic investigations of whether number of episodes and duration or ventricular rate of episodes of NSVT definitely have an impact on SCD risk.

**6.3.1.1.5. Maximum LV Wall Thickness.** The relationship between severity of LV hypertrophy and SCD has been investigated in several studies predicated on the concept that the more severe the disease expression, the more likely the individual patient is to experience adverse events. Most, but not all,<sup>51,399</sup> studies have shown at least a univariate association between maximum wall thickness and SCD,<sup>389,396,399</sup> whereas other large studies have shown that when magnitude of hypertrophy is  $\geq 30$  mm, there is an independent association with SCD.<sup>50,161,392</sup> Notably, 3 reports derive from overlapping samples of patients<sup>50,127,391</sup> have shown different strengths in the relationship between wall thickness and SCD that may reflect a slight variance in exclusion criteria, definition of other risk markers, and the number of risk markers included in multivariate analysis. It is crucial to recognize that the risk estimate does not abruptly increase for patients with  $\geq 30$  mm wall thickness but rather increases in a linear fashion<sup>161</sup> and appears to carry more prognostic significance in younger patients.<sup>400</sup> With this in mind, a young adult with hypertrophy that approaches 30 mm may have similar or greater SCD risk than older patients with maximum wall thickness  $\geq 30$  mm.

**6.3.1.1.6. Abnormal Blood Pressure Response During Exercise.** For up to a third of patients with HCM, there is an inappropriate systemic systolic blood pressure response during exercise testing (defined as either a failure to increase by

at least 20 mm Hg or a drop of at least 20 mm Hg during effort).<sup>89,90</sup> It has been postulated that this finding is a risk factor for SCD. Two studies have shown a univariate association between this finding and subsequent SCD.<sup>50,89,127,390</sup> It is also unclear how this finding is related to the well-recognized increase in dynamic LVOT obstruction that occurs with effort, a hemodynamic condition that is readily modifiable with medication or mechanical procedures. It would be appropriate to reassess this particular SCD risk marker following invasive therapies to relieve outflow tract obstruction, although there are no data in such patients.

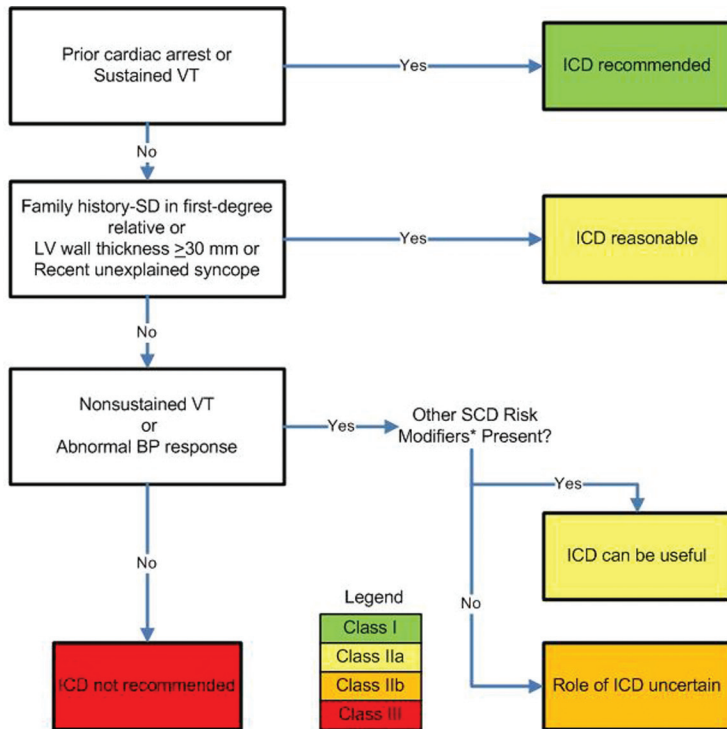
### 6.3.1.2. Other Potential SCD Risk Modifiers

**6.3.1.2.1. LVOT Obstruction.** Although some studies have not found a significant association between LVOT obstruction and SCD,<sup>45,47,161</sup> other studies have found higher rates of SCD among patients with resting gradients  $\geq 30$  mm Hg<sup>127,390</sup> and that the risk is positively correlated with severity of LVOT obstruction.<sup>127</sup> Conversely, relief of outflow tract obstruction through surgical myectomy is associated with very low rates of SCD.<sup>61,321</sup> A limitation to using LVOT obstruction as an independent risk marker is that the obstruction in HCM is dynamic and highly variable from hour to hour to the extent that no gradient may be detectable during one evaluation, whereas the next day (or even a short time later during the same day), a moderate to severe gradient may be apparent.<sup>81,401</sup> This variability makes it not only difficult to assess risk in the individual patient, but it also likely explains the difficulty in demonstrating statistical significance in smaller studies. Whether exercise-induced augmentation of the gradient is one of the mechanisms that results in syncope and/or abnormal blood pressure response during exercise has not been completely addressed.

**6.3.1.2.2. LGE on CMR Imaging.** There has been considerable interest in promoting LGE on CMR imaging as a potential SCD risk marker in HCM. Because LGE is believed to represent myocardial fibrosis or scarring, it has been hypothesized that LGE may represent myocardium prone to ventricular tachyarrhythmia.<sup>188</sup> Indeed, LGE has been associated with NSVT and ventricular ectopy but has not been associated with clinical SCD events or ICD discharge in published studies.<sup>184,185,188</sup> More recent studies have shown a relationship between LGE and SCD and heart failure but with low positive predictive accuracy.<sup>186,187</sup> LGE is a common feature observed in patients with HCM, and there is no consensus on the appropriate imaging protocols or threshold for detection of LGE. Both of these features currently limit the role of LGE as an independent risk marker.

**6.3.1.2.3. LV Apical Aneurysm.** A subset of patients with HCM (prevalence about 2%) develop a thin-walled LV apical aneurysm associated with regional scarring<sup>182</sup> and more adverse clinical events during follow-up, including progressive heart failure and evolution into the end-stage phase as well as SCD. Although data on LV aneurysms in HCM are limited, this abnormality may warrant consideration in SCD risk-assessment strategies.

**6.3.1.2.4. Genetic Mutations.** SCD may cluster in certain families with HCM, and the possibility that specific sarcomere mutations may confer SCD risk has been hypothesized. Indeed, several early studies of HCM pedigrees implicated certain mutations as “malignant.”<sup>107,114,402,403</sup> However, subsequent studies of less selected consecutive patients with



**Figure 4.** Indications for ICDs in HCM. \*SCD risk modifiers include established risk factors and emerging risk modifiers (Section 6.3.1.2). BP indicates blood pressure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; SCD, sudden cardiac death; SD, sudden death; and VT, ventricular tachycardia.

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

HCM found that it was problematic to infer likelihood of SCD events on the basis of the proposed mutations, because in some instances the rate of adverse events (and prevalence of associated SCD risk markers) was lower in patients with “malignant” mutations than it was in those with mutations believed to be “benign.”<sup>95,404–406</sup> The data from unselected consecutive outpatients suggest that most mutations are “novel” and limited to particular families (“private” mutations). Therefore, routine mutational screening would appear to be of little prognostic value in HCM.

**6.3.1.3. Utility of SCD Risk Markers in Clinical Practice**  
Other than cardiac arrest, each of the HCM risk factors has low positive predictive value (approximately 10% to 20%) and modestly high negative predictive value (85% to 95%). Multiple risk markers in individual patients would intuitively suggest greater risk for SCD; however, the vast majority of patients with  $\geq 1$  risk marker will not experience SCD, and simple arithmetic summing of risk markers is not precise because of the uncertainty implicit in assigning a relative weight to any individual risk factor.<sup>50,51,407</sup> Notably, in the international HCM-ICD registry,<sup>55</sup> the number of risk factors did not correlate with the rate of subsequent appropriate ICD discharges among presumably high-risk patients selected for ICD placement. These data suggest that the presence of a single risk marker may be sufficient to warrant ICD placement in many patients, but these decisions need to be individualized with regard to age, the strength of the risk factor, and the risk-benefit of lifelong ICD therapy.<sup>55,408</sup>

### 6.3.2. Selection of Patients for ICDs—Recommendations

#### Class I

1. The decision to place an ICD in patients with HCM should include application of individual clinical judgment, as well as a thorough discussion of the strength of evidence, benefits, and risks to allow the informed patient’s active participation in decision making (Figure 4).<sup>53–56</sup> (Level of Evidence: C)
2. ICD placement is recommended for patients with HCM with prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant VT.<sup>55,387–389</sup> (Level of Evidence: B)

#### Class IIa

1. It is reasonable to recommend an ICD for patients with HCM with:
  - a. Sudden death presumably caused by HCM in 1 or more first-degree relatives.<sup>394</sup> (Level of Evidence: C)
  - b. A maximum LV wall thickness greater than or equal to 30 mm.<sup>50,51,161,400</sup> (Level of Evidence: C)
  - c. One or more recent, unexplained syncopal episodes.<sup>392</sup> (Level of Evidence: C)
2. An ICD can be useful in select patients with NSVT (particularly those <30 years of age) in



the presence of other SCD risk factors or modifiers.<sup>‡53,129</sup> (*Level of Evidence: C*)

3. An ICD can be useful in select patients with HCM with an abnormal blood pressure response with exercise in the presence of other SCD risk factors or modifiers.<sup>‡89,90,390</sup> (*Level of Evidence: C*)
4. It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation. (*Level of Evidence: C*)

### Class IIb

1. The usefulness of an ICD is uncertain in patients with HCM with isolated bursts of NSVT when in the absence of any other SCD risk factors or modifiers.<sup>‡53</sup> (*Level of Evidence: C*)
2. The usefulness of an ICD is uncertain in patients with HCM with an abnormal blood pressure response with exercise when in the absence of any other SCD risk factors or modifiers,<sup>‡</sup> particularly in the presence of significant outflow obstruction.<sup>89,90,390</sup> (*Level of Evidence: C*)

### Class III: Harm

1. ICD placement as a routine strategy in patients with HCM without an indication of increased risk is potentially harmful. (*Level of Evidence: C*)
2. ICD placement as a strategy to permit patients with HCM to participate in competitive athletics is potentially harmful. (*Level of Evidence: C*)
3. ICD placement in patients who have an identified HCM genotype in the absence of clinical manifestations of HCM is potentially harmful. (*Level of Evidence: C*)

Although the overall rate of SCD in HCM is approximately 1% per year, clearly there are individuals at higher risk for whom prophylactic therapy may be indicated. Pharmacologic therapy has not been demonstrated to provide protection from SCD. Conversely, the ICD has proved to be effective in terminating life-threatening ventricular tachyarrhythmias in HCM, altering the natural course of the disease and prolonging life.

The decision for placement of primary prevention ICD in HCM often involves a large measure of individual clinical judgment, particularly when the evidence for risk is ambiguous. The potential for SCD needs to be discussed with each fully informed HCM patient and family member in the context of their concerns and anxieties and should be balanced against the risks and benefits of proposed prophylactic ICD strategy. Consideration of the patient's age is warranted, particularly because device complications are more likely in children and young adults over the long period of follow-up.<sup>55,408</sup>

#### 6.3.2.1. Results of ICD Therapy in HCM

There have been 2 reports from an international, multicenter registry of patients with HCM who have undergone ICD placement on the basis of the clinical perception of SCD sufficient to justify device therapy.<sup>54,55</sup> Among patients who received a device as a result of a prior personal history of cardiac arrest or sustained ventricular arrhythmia (secondary prevention ICD), the annualized rate of subsequent appropriate ICD discharge was 10% per year. Patients with primary prevention ICDs placed on the basis of 1 or more of the conventional risk markers experienced appropriate ICD therapy at a rate of approximately 4% per year.<sup>54,55</sup> Among these patients, who were selected for ICD placement based on clinical risk perceptions, the number of risk markers present did not predict subsequent device discharge. Whether this is related to the highly selected population involved or possibly because an appropriate ICD discharge may not necessarily be synonymous with SCD prevention is uncertain. The relative weight of the individual risk markers in predicting device discharge rate has not been reported.<sup>55,408</sup>

#### 6.3.2.2. Complications of ICD Therapy in HCM

It is important to recognize and discuss with patients potential ICD-related complications (both procedural and long term) that occur at a rate of 4% per year in patients with HCM.<sup>408</sup> Potential early problems may include pneumothorax, pericardial effusion, pocket hematoma, acute pocket infection, and/or lead dislodgment. Late complications include upper extremity deep venous thrombosis, lead dislodgment, infection, high defibrillation threshold necessitating lead revision, and inappropriate shocks, that is, shocks triggered by supraventricular arrhythmias, sinus tachycardia, lead fractures or dislodgment, oversensing, double counting, and programming malfunctions.

Reported rates of complications include approximately 25% of patients with HCM who experienced inappropriate ICD discharge; 6% to 13% who experienced lead complications (fracture, dislodgment, oversensing); 4% to 5% who developed device-related infection; and approximately 2% to 3% who experienced bleeding or thrombosis complications.<sup>55,408</sup> The rate of inappropriate shocks and lead fractures appears to be higher in children than in adults, largely because their activity level and body growth places continual strain on the leads, which are the weakest link in the system.<sup>386</sup> This issue is of particular concern, given the long periods that young patients will have prophylactically implanted devices.

Industry-related ICD problems have affected patients with HCM. Prominent recalls have included defective generators leading to several deaths<sup>409</sup> and small-diameter high-voltage leads prone to fracture.<sup>410,411</sup> The implant procedure has been largely free of significant risk, without reported deaths, although selected patients with extreme hypertrophy or who have received amiodarone may require high-energy output generators or epicardial lead systems.<sup>412</sup>

#### 6.3.2.3. Overall Risk Assessment and Selection of Patients for ICD Therapy

The decision to recommend and pursue ICD placement is a complex process that can be oversimplified. The individuality

<sup>‡</sup>SCD risk modifiers are discussed in Section 6.3.1.2.

of each patient and family circumstance, including level of anxiety, life situation, and views on death, and individual assessment of the relative weight of potential benefits compared with potential risks must be processed for each patient. The low positive predictive value of any of the SCD risk factors and the variability in the strength of data also introduce a degree of ambiguity to the SCD risk assessment and dramatically limit the applicability of counting the number of risk factors as the primary risk assessment methodology. Based on the weight of evidence, plausibility, and consensus judgment reflecting clinical experience, it is recognized that patients with massive hypertrophy, a family history of HCM-related SCD, or recent unexplained syncope would probably benefit from ICD placement. Apart from these, it was believed that a combination of conventional risk factors and other risk modifiers provided the optimal identification of the subset of patients with HCM with sufficient risk of SCD to warrant strong consideration of ICD placement (Figure 4).

#### 6.3.2.4. Selection of ICD Device Type—Recommendations

##### Class IIa

1. In patients with HCM who meet indications for ICD implantation, single-chamber devices are reasonable in younger patients without a need for atrial or ventricular pacing.<sup>410,413–415</sup> (*Level of Evidence: B*)
2. In patients with HCM who meet indications for ICD implantation, dual-chamber ICDs are reasonable for patients with sinus bradycardia and/or paroxysmal AF.<sup>413</sup> (*Level of Evidence: C*)
3. In patients with HCM who meet indications for ICD implantation, dual-chamber ICDs are reasonable for patients with elevated resting outflow gradients greater than 50 mm Hg and significant heart failure symptoms who may benefit from right ventricular pacing (most commonly, but not limited to, patients >65 years of age).<sup>283,284,367,413</sup> (*Level of Evidence: B*)

All ICDs incorporate a right ventricular lead that has both pacing and defibrillation capabilities. ICDs are available as single-chamber, dual-chamber, or 3-chamber (ie, cardiac resynchronization therapy) devices. Whether a patient receives a dual-chamber or cardiac resynchronization therapy system depends on other considerations, including the need for atrial pacing, enhanced supraventricular tachycardia (SVT) discrimination, right ventricular pacing, and importantly, consideration of the patient's age and the subsequent longevity of the lead and ICD system.<sup>416</sup> In patients with LVOT obstruction, particularly the elderly, in whom ICDs are indicated, dual-chamber pacing may have the potential to reduce gradient and symptoms in some patients (Section 6.2.2.6).

ICD leads fail at a rate of 0.5% to 1% per year, although there are data showing that failure rates are increased in a younger, healthier population.<sup>410</sup> When a lead fails, a new lead is needed; the old lead can remain in, which over time places the patient at risk for venous obstruction, or the old lead may be removed, which carries a significant risk of morbidity and mortality. In young patients with HCM, an ICD may be needed for up to 70 years. There is no expectation that a single lead will remain functional for that

amount of time. Thus, in general, the younger the patient, the more appropriate it is for single-chamber devices to be used to decrease the amount of hardware in the venous system.

Dual-chamber devices have been advocated to increase the ability of the ICD to differentiate between SVT and ventricular arrhythmias. Data to support this hypothesis are mixed with some studies showing no difference between inappropriate therapy for SVT<sup>417,418</sup> and others showing a benefit.<sup>419,420</sup> Currently, discrimination of SVT is inadequate as a sole justification for a dual-chamber device in patients with HCM.

Whether cardiac resynchronization therapy devices are useful for patients with HCM is unclear. There is a paucity of published data on the use of cardiac resynchronization therapy devices in patients with HCM and end-stage heart failure.<sup>421</sup>

#### 6.3.3. Participation in Competitive or Recreational Sports and Physical Activity—Recommendations

##### Class IIa

1. It is reasonable for patients with HCM to participate in low-intensity competitive sports (eg, golf and bowling).<sup>422,423</sup> (*Level of Evidence: C*)
2. It is reasonable for patients with HCM to participate in a range of recreational sporting activities as outlined in Table 4.<sup>224</sup> (*Level of Evidence: C*)

##### Class III: Harm

1. Patients with HCM should not participate in intense competitive sports regardless of age, sex, race, presence or absence of LVOT obstruction, prior septal reduction therapy, or implantation of a cardioverter-defibrillator for high-risk status.<sup>58,59,422–426</sup> (*Level of Evidence: C*)

A number of large cohort studies from the United States indicate that HCM is the most common cardiovascular cause of SCD in young athletes, accounting for about one third of these events.<sup>58,59,425,427</sup> The American College of Cardiology Bethesda Conference No. 36<sup>422,429</sup> as well as the European Society of Cardiology guidelines<sup>423,429</sup> indicate that risk for SCD is increased during intense competitive sports and also suggest that the removal of these individuals from the athletic arena can diminish their risk. This principle is the basis for disqualification of athletes with HCM from sanctioned high school and college sports.<sup>422,429</sup> It should be underscored that these consensus recommendations for competitive athletes are independent of those for noncompetitive, informal recreational sporting activities.<sup>224</sup>

General recommendations for recreational exercise in patients with HCM should be tailored to the individual's desires and abilities; however, certain guidelines prevail. For example, aerobic exercise as opposed to isometric exercise is preferable. Patients with HCM should avoid recreational sports in which participation is intense and simulates competitive organized athletics. Also, burst exertion, in which an abrupt increase in heart rate is triggered (eg, sprinting in half-court basketball), is less desirable than swimming laps or cycling. Finally, it is prudent for such patients to avoid physical activity in extreme environmental conditions of heat, cold, or high humidity, with

**Table 4. Recommendations for the Acceptability of Recreational (Noncompetitive) Sports Activities and Exercise in Patients With HCM\***

Intensity Level	Eligibility Scale for HCM†
<b>High</b>	
Basketball (full court)	0
Basketball (half court)	0
Body building‡	1
Gymnastics	2
Ice hockey‡	0
Racquetball/squash	0
Rock climbing‡	1
Running (sprinting)	0
Skiing (downhill)‡	2
Skiing (cross-country)	2
Soccer	0
Tennis (singles)	0
Touch (flag) football	1
Windsurfing§	1
<b>Moderate</b>	
Baseball/softball	2
Biking	4
Hiking	3
Modest hiking	4
Motorcycling‡	3
Jogging	3
Sailing§	3
Surfing§	2
Swimming (laps)§	5
Tennis (doubles)	4
Treadmill/stationary bicycle	5
Weightlifting (free weights)‡	1
<b>Low</b>	
Bowling	5
Brisk walking	5
Golf	5
Horseback riding‡	3
Scuba diving§	0
Skating¶	5
Snorkeling§	5
Weights (nonfree weights)	4

\*Recreational sports are categorized according to high, moderate, and low levels of exercise and graded on a relative scale (from 0 to 5) for eligibility, with 0 to 1 indicating generally not advised or strongly discouraged; 4 to 5, probably permitted; and 2 to 3, intermediate and to be assessed clinically on an individual basis. The designations of high, moderate, and low levels of exercise are equivalent to an estimated >6, 4 to 6, and <4 metabolic equivalents, respectively.

†Assumes absence of laboratory DNA genotyping data; therefore, limited to clinical diagnosis.

‡These sports involve the potential for traumatic injury, which should be taken into consideration for individuals with a risk for impaired consciousness.

§The possibility of impaired consciousness occurring during water-related activities should be taken into account with respect to the individual patient's clinical profile.

||Recommendations generally differ from those for weight-training machines (nonfree weights), based largely on the potential risks of traumatic injury associated with episodes of impaired consciousness during bench-press maneuvers; otherwise, the physiologic effects of all weight-training activities are regarded as similar with respect to the present recommendations.

¶Individual sporting activity not associated with the team sport of ice hockey.

Adapted with permission from Maron et al.<sup>224</sup>

attention paid to maintaining volume status. Detailed recommendations for individual sports appear in Table 4.

## 6.4. Management of AF—Recommendations

### Class I

1. Anticoagulation with vitamin K antagonists (ie, warfarin, to an international normalized ratio of 2.0 to 3.0) is indicated in patients with paroxysmal, persistent, or chronic AF and HCM.<sup>60,430,431</sup> (Anticoagulation with direct thrombin inhibitors [ie, dabigatran§] may represent another option to reduce the risk of thromboembolic events, but data for patients with HCM are not available.<sup>432</sup>) (*Level of Evidence: C*)
2. Ventricular rate control in patients with HCM with AF is indicated for rapid ventricular rates and can require high doses of beta antagonists and nondihydropyridine calcium channel blockers.<sup>60,430</sup> (*Level of Evidence: C*)

### Class IIa

1. Disopyramide (with ventricular rate-controlling agents) and amiodarone are reasonable antiarrhythmic agents for AF in patients with HCM.<sup>430,433</sup> (*Level of Evidence: B*)
2. Radiofrequency ablation for AF can be beneficial in patients with HCM who have refractory symptoms or who are unable to take antiarrhythmic drugs.<sup>63–65,434,435</sup> (*Level of Evidence: B*)
3. Maze procedure with closure of LA appendage is reasonable in patients with HCM with a history of AF, either during septal myectomy or as an isolated procedure in selected patients. (*Level of Evidence: C*)

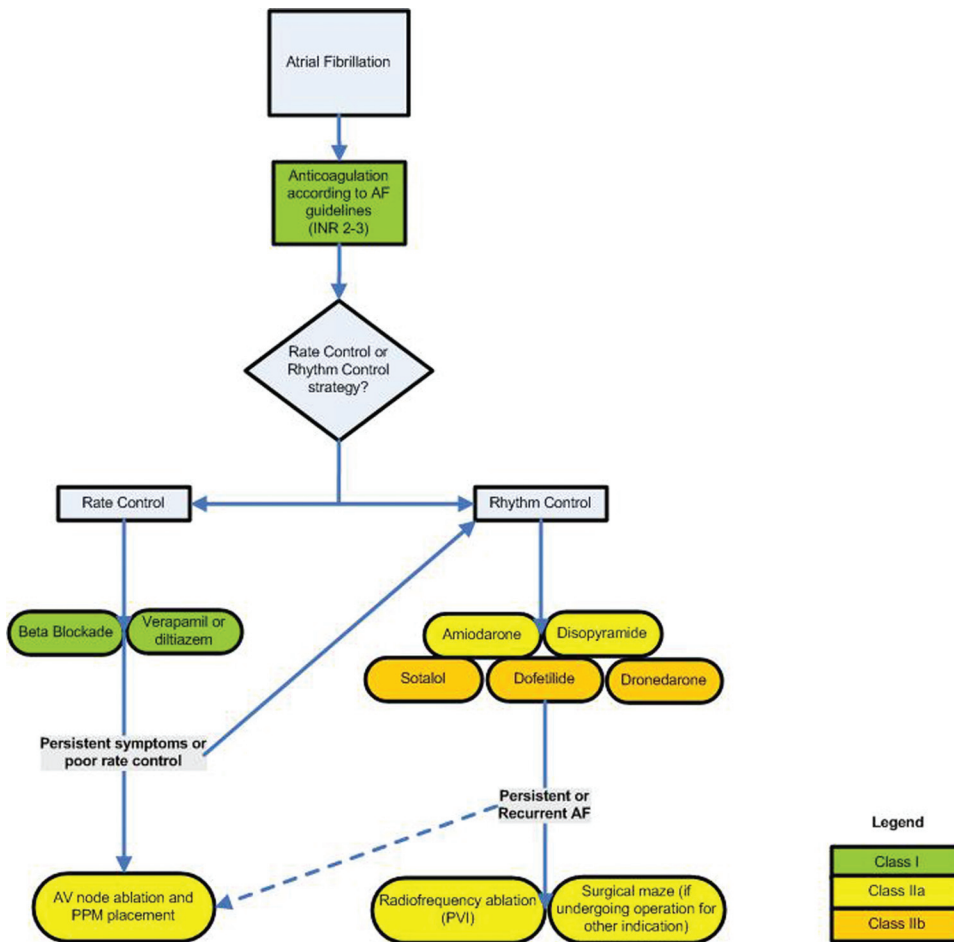
### Class IIb

1. Sotalol, dofetilide, and dronedarone might be considered alternative antiarrhythmic agents in patients with HCM, especially in those with an ICD, but clinical experience is limited. (*Level of Evidence: C*)

AF is an important cause of symptoms, morbidity, and even mortality in patients with HCM.<sup>57,60</sup> Diagnosis may be made by an ECG during an AF episode or occasionally on ambulatory Holter monitoring; use of an event recorder may be helpful in some patients. Patients with HCM are at increased risk of AF compared with age-matched cohorts, but AF is seldom seen in young patients with HCM who are <30 years of age and becomes more prevalent with age. Risk factors for AF in HCM include age, congestive heart failure, and LA function, diameter, and volume.<sup>60,436</sup> A family history of AF is a risk factor in the Framingham Heart Study, but there are no data in patients with HCM. AF occurring in HCM may not be associated with symptoms or hemodynamic compromise in one third of patients but is poorly tolerated in many others. There is evidence that AF is an indicator of unfavorable prognosis, including increased risk of HCM-related heart failure, death, and stroke.<sup>60,437</sup>

§Dabigatran should not be used in patients with prosthetic valves, hemodynamically significant valve disease, advanced liver failure, or severe renal failure (creatinine clearance <15 mL/min).<sup>432</sup>





**Figure 5.** Management of AF in HCM. AF indicates atrial fibrillation; AV, atrioventricular; INR, international normalized ratio; PPM, permanent pacemaker; and PVI, pulmonary vein isolation.

Therapy for AF includes prevention of thromboembolic stroke and controlling symptoms (Figure 5). The risk of systemic embolization is high in patients with HCM with AF but is not related to the severity of symptoms.<sup>57,60</sup> Occurrence of paroxysmal, persistent, or chronic AF is a strong indication for anticoagulation with a vitamin K antagonist.<sup>430</sup> Whether there is a threshold for AF that warrants anticoagulation is unresolved; however, given the high risk of thromboembolism in HCM, even patients with short episodes of AF should be strongly considered for anticoagulation. Even a single episode of AF should be cause to consider anticoagulation because the likelihood of recurrent AF is high. Aspirin should be reserved for those who cannot or will not take warfarin or other oral anticoagulants, but its efficacy in HCM is unestablished. The role of LA occlusion devices in HCM is untested but could possibly be a future option in patients who cannot tolerate anticoagulant therapy.<sup>438</sup>

Symptom control may be attained with adequate rate control, although many patients will require rhythm control. Rate control is best maintained by beta blockers and calcium channel blockers. High doses of these agents may be required. Digoxin may modestly reduce ventricular rate at rest and to a lesser extent with exertion. Because there is a paucity of data on rhythm control in patients with HCM, evidence from other patient populations is extrapolated to HCM. However, whether patients with HCM respond similarly to antiarrhythmic agents is not clear. The “2011 ACCF/AHA/

HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation” state that disopyramide and amiodarone are potential agents for rhythm control.<sup>430</sup> The limited published data on amiodarone suggest that it is safe and effective for patients with HCM.<sup>439–442</sup> Disopyramide has been shown to be safe when prescribed for reduction of LVOT obstruction, but its safety and efficacy in AF are not well established.<sup>157,443</sup> Dronedarone, an antiarrhythmic agent similar to amiodarone but lacking the iodine moiety and much of the long-term toxicity, has been approved for use in the United States. There are no data regarding the efficacy of dronedarone or the use of flecainide and propafenone in patients with HCM. In the CAST (Cardiac Arrhythmia Suppression Trial) trial, Class IC agents were associated with an increased mortality in patients with CAD.<sup>444</sup> Thus, caution is advised when these agents are prescribed for patients with HCM and their use should probably be limited to individuals with an ICD. The management of atrial flutter in HCM is similar to that in other disease states, including the role of radiofrequency ablation.

The long-term benefits of radiofrequency ablation versus antiarrhythmic drugs in patients with HCM remain to be established. It does appear that early success and complication rates are similar between HCM and other forms of heart disease or absence of heart disease.<sup>63–65,445</sup> Thus, radiofrequency ablation may play a role in the management of AF, but further investigation is necessary. The surgical maze procedure for AF has

shown some limited success<sup>446</sup>; however, whether a prophylactic or therapeutic surgical maze procedure is indicated for patients undergoing other open chest surgical procedures (ie, septal myectomy) is unresolved.

## 7. Other Issues

### 7.1. Pregnancy/Delivery—Recommendations

#### Class I

1. In women with HCM who are asymptomatic or whose symptoms are controlled with beta-blocking drugs, the drugs should be continued during pregnancy, but increased surveillance for fetal bradycardia or other complications is warranted.<sup>41,140,447,448</sup> (*Level of Evidence: C*)
2. For patients (mother or father) with HCM, genetic counseling is indicated before planned conception. (*Level of Evidence: C*)
3. In women with HCM and resting or provocable LVOT obstruction greater than or equal to 50 mm Hg and/or cardiac symptoms not controlled by medical therapy alone, pregnancy is associated with increased risk, and these patients should be referred to a high-risk obstetrician. (*Level of Evidence: C*)
4. The diagnosis of HCM among asymptomatic women is not considered a contraindication for pregnancy, but patients should be carefully evaluated in regard to the risk of pregnancy. (*Level of Evidence: C*)

#### Class IIa

1. For women with HCM whose symptoms are controlled (mild to moderate), pregnancy is reasonable, but expert maternal/fetal medical specialist care, including cardiovascular and prenatal monitoring, is advised. (*Level of Evidence: C*)

#### Class III: Harm

1. For women with advanced heart failure symptoms and HCM, pregnancy is associated with excess morbidity/mortality. (*Level of Evidence: C*)

Women with HCM safely experience pregnancy and labor with minimal documented risks. The maternal mortality rate is extraordinarily low and limited to those patients with particularly advanced disease.<sup>449</sup> Nevertheless, careful evaluation of the mother and functional assessment is paramount during and just prior to pregnancy. Usually, special medical precautions are unnecessary, and cesarean delivery is not obligatory. However, women with advanced disease, including progressive heart failure, severe diastolic dysfunction, VT, SVT, or marked LVOT obstruction, will require the care of a high-risk maternal/fetal medical team with close involvement of a cardiologist. For the woman whose disease is well controlled with medical therapy (beta blockers, verapamil, or disopyramide), there should be no interruption of therapy, but careful maternal and fetal monitoring is advised.<sup>157</sup> For any woman of childbearing age with HCM, it is paramount that genetic counseling be advised before conception. Such patients should be counseled prospectively about the risks of pregnancy and discouraged if deemed necessary. Care-

ful monitoring is advisable in the first 24 hours after delivery, when large fluid shifts can lead to acute pulmonary edema in the setting of a noncompliant and hypertrophied left ventricle.

### 7.2. Occupational Considerations

In 2002, the US Department of Transportation Federal Motor Carrier Safety Administration published its "Cardiovascular Advisory Panel Guidelines for the Medical Examination of Commercial Motor Vehicle Drivers." The guidelines state that "irrespective of symptoms, a person should not be certified as a [commercial motor vehicle] driver if a firm diagnosis of [HCM] is made..."<sup>450(p83)</sup> Although consideration has subsequently been given to liberalizing this restriction, the guidelines have not yet been revised.

The criteria for the disqualification of aircraft pilots with cardiovascular disease are set by the Federal Aviation Administration. Currently, HCM is regarded as generally incompatible with the highest grade aviation license for commercial pilots, based on the unpredictable risk for impairment in the cockpit attributable to HCM.<sup>452</sup>

## 8. Future Research Needs

Despite progress in the understanding of the etiology and pathophysiology of HCM and in certain aspects of management, more substantial insights into the fundamental and clinical components of HCM provide considerable opportunities to improve patient outcomes. The research priorities in HCM were detailed in 2010 by a National Heart, Lung, and Blood Institute working group.<sup>453</sup>

### 8.1. Establishing the Cause of HCM

Over the past 20 years there have been major advances in identification of genetic mutations that cause HCM. Contemporary data sets include >1400 mutations that primarily occur in at least 8 genes that encode protein components of the sarcomere. Nonetheless, the genetic cause remains unknown for a substantial proportion of patients with clinical manifestations of HCM. Mutation-negative patients may have LV hypertrophy attributable to another genetic (or nongenetic) cause, with morphologic features that mimic HCM but with distinctive pathophysiology and clinical outcomes. Definition of the cause(s) of HCM morphology in mutation-negative patients is important for the basic understanding of mechanisms that remodel the heart and for determining whether or not the clinical practice guidelines established for HCM are relevant in these patients. The ability to pool data from multiple registries is encouraged.

### 8.2. Defining the Link Between Genotype and Phenotype

The emergence of newer sequencing methodologies provides unparalleled opportunities for defining the precise mutation

[The Federal Motor Carrier Safety Administration defines *commercial motor vehicle* as a motor vehicle or combination of motor vehicles used in commerce to transport passengers or property if the motor vehicle:

- (a) has a gross combination weight rating of  $\geq 11\,794$  kg ( $\geq 26\,001$  lb) inclusive of a towed unit(s) with a gross vehicle weight rating of  $\geq 4536$  kg (10 000 lb); or
- (b) has a gross vehicle weight rating of  $\geq 11\,794$  kg ( $\geq 26\,001$  lb); or
- (c) is designed to transport  $\geq 16$  passengers, including the driver; or
- (d) is of any size and is used in the transportation of hazardous materials as defined [by the Federal Motor Carrier Safety Administration].<sup>451</sup>

in most patients with HCM. Such information can expand our understanding of the relationship between genotype and phenotype in HCM, a link that remains incompletely understood. Directing future efforts to identify genetic modifiers (ie, genes that influence clinical expression) and environmental influences may expand understanding of the signaling pathways that are responsible for phenotypic expression of HCM and related disease states. These strategies also hold the potential to define novel therapeutic targets that may attenuate the consequences of sarcomere gene mutations, so that disease expression may be delayed or conceivably prevented.

### 8.3. Management and Evaluation of HCM Genotype-Positive/Phenotype-Negative Relatives

Gene-based diagnosis of HCM families has increased the identification of genotype-positive/phenotype-negative individuals. There are many unanswered questions about the natural history of these patients, including the identity of factors that influence duration of the preclinical phase, the likelihood of clinical identification by screening with echocardiography (or CMR), the risk of SCD, and decisions about the periodicity of clinical screening, the use of ICDs for primary prevention, and participation in competitive sports. Longitudinal data are needed to develop appropriate management recommendations for this growing subset of patients. In addition, as more information is accrued regarding the signaling pathways that account for clinical manifestation associated with sarcomere protein gene mutations, the study of therapeutic interventions aimed at preventing the emergence of disease in preclinical patients can be expected.

### 8.4. Clinical Significance of Myocardial Fibrosis

Myocardial fibrosis of the heart is increased in HCM because of an expansion of the interstitial matrix and also myocardial replacement scarring (caused by microvascular ischemia and other factors). Consistent with histopathologic findings, serum biomarkers of collagen turnover are elevated in patients with clinically overt HCM. Recent studies in HCM models indicate that extracellular matrix remodeling predates the emergence of hypertrophy and may contribute to diastolic dysfunction.<sup>18</sup> Studies are needed to ascertain whether prevention of interstitial (matrix) expansion or replacement scarring can improve HCM pathophysiology and reduce late outcomes such as progressive heart failure.

Replacement fibrosis and scarring can be visualized (in vivo) by CMR gadolinium contrast enhancement. Clearer understanding of the relationship between LGE, fibrosis, and clinical outcomes (including ventricular tachyarrhythmias and SCD) is needed.

### 8.5. Therapies to Directly Modify the HCM Pathophysiology

The most widely used medical therapies for patients with HCM (beta-adrenergic blockers, calcium channel blockers, disopyramide) nonspecifically address aspects of the hemodynamic abnormalities in patients with HCM, such as reducing contractility to diminish the magnitude of outflow tract obstruction. As noted above, a more sophisticated understanding of the links between the molecular pathophysiology and outcome is neces-

sary in HCM to promote the development of more relevant and targeted treatment strategies.<sup>453</sup> For example, characterization of the fundamental biophysical defects produced by different mutations in sarcomere proteins, assessment of energy requirements of the heart in HCM, and assessment of the role of myocardial ischemia may lead to interventions that alter the natural history of disease expression.

### 8.6. Refining Risk Stratification for SCD

As noted in this document, identifiable clinical markers are being used successfully in risk stratification for SCD in HCM, assisting in recommendations about prophylactic ICDs. Nonetheless, much ambiguity is often encountered in using the current SCD risk stratification algorithm in individual patients, and there is a need to identify additional and more sensitive/specific risk factors. Moreover, SCD may occasionally occur in “low-risk” patients without conventional risk factors. The assembly of larger cohorts from multiple centers with detailed clinical, genetic, and lifestyle information may improve SCD risk stratification and enable more efficient use of ICDs.

### 8.7. Comparative Assessment of Septal Reduction Strategies

The opportunity for percutaneous strategies to reduce outflow tract obstruction in HCM was realized through the development of alcohol septal ablation. The potential of this approach to provide clinical benefit in reducing symptoms with lower patient morbidity and reduced healthcare expenditures has been somewhat undermined by a concern for increased ventricular arrhythmias following the procedure. Robust information about the types and frequency of adverse outcomes following alcohol septal ablation are needed in addition to rigorous assessment of whether these events are intrinsic to the procedure or related to underlying hypertrophic substrate, concomitant coronary or other comorbid disease, or the advanced age at which patients receive this therapy versus myectomy. In addition, observational registries might be useful to compare rates of HCM-related death. Such comparisons of short- and long-term outcomes of patients treated with alcohol septal ablation or myectomy surgery would foster appropriate use of these strategies and improve patient symptoms and outcomes.

### 8.8. Therapies to Treat and Prevent AF and Its Associated Risks

AF is a common cause of morbidity and mortality in patients with HCM. Anticoagulation is well established in other causes of AF and almost certainly extends to the HCM patient with paroxysmal, chronic, or persistent AF. However, whether anticoagulation should extend to those patients with HCM who are at high risk of development of AF is unclear. In addition, the relative roles of antiarrhythmic agents, radiofrequency ablation, and surgical maze procedure need improved definition.

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KEY WORDS: AHA Scientific Statements ■ ablation ■ cardiomyopathy, hypertrophic ■ defibrillators, implantable ■ hypertrophy ■ myocardial disease ■ surgical procedures, operative

**Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy**

Committee Member	Employer/Title	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section Number*
Bernard J. Gersh, Co-Chair	Mayo Clinic—Professor of Medicine	<ul style="list-style-type: none"> <li>Abbott Laboratories†</li> <li>AstraZeneca</li> <li>Boston Scientific</li> <li>Bristol-Myers Squibb</li> </ul>	None	None	<ul style="list-style-type: none"> <li>Amorcyte (DSMB)</li> </ul>	<ul style="list-style-type: none"> <li>CV Therapeutics</li> </ul>	None	6.2.2.6 6.2.3 6.3.2 6.3.2.4
Barry J. Maron, Co-Chair	Minneapolis Heart Institute Foundation—Director, Hypertrophic Cardiomyopathy Center	<ul style="list-style-type: none"> <li>GeneDx‡</li> </ul>	None	None	<ul style="list-style-type: none"> <li>Medtronic‡</li> </ul>	None	None	5.1 6.3.2 6.3.2.4
Robert O. Bonow	Northwestern University Feinberg School of Medicine—Goldberg Distinguished Professor of Medicine; Chief, Division of Cardiology	None	None	None	None	None	None	None
Joseph A. Dearani	Mayo Clinic—Professor of Surgery	None	None	None	None	None	None	None
Michael A. Fifer	Massachusetts General Hospital—Director, Hypertrophic Cardiomyopathy Program	None	None	None	<ul style="list-style-type: none"> <li>Merck‡</li> </ul>	None	None	6.2.1
Mark S. Link	Tufts Medical Center—Professor of Medicine	None	<ul style="list-style-type: none"> <li>Medtronic</li> <li>Guidant</li> </ul>	None	<ul style="list-style-type: none"> <li>Guidant</li> </ul>	None	<ul style="list-style-type: none"> <li>Plaintiff, wrongful death secondary electrocution, 2007–2009</li> <li>Defendant, postoperative valve replacement management, 2007–2010</li> </ul>	6.2.2.6 6.3.2 6.3.2.4
Srihari S. Naidu	Winthrop University Hospital—Director, Cardiac Catheterization Laboratory; Director, Hypertrophic Cardiomyopathy Center	None	<ul style="list-style-type: none"> <li>Abbott Vascular</li> <li>Cordis</li> <li>Medtronic</li> </ul>	None	None	None	None	6.2.2.6 6.3.2 6.3.2.4
Rick A. Nishimura	Mayo Clinic—Consultant in Cardiology	None	None	None	None	None	None	None
Steve R. Ommen	Mayo Clinic—Professor of Medicine	None	None	None	None	None	None	None
Harry Rakowski	Toronto General Hospital, University Health Network—Director, Hypertrophic Cardiomyopathy Center; Wigle Chair for HCM Research; Professor of Medicine, University of Toronto	None	None	None	<ul style="list-style-type: none"> <li>Medtronic Valve Device (DSMB)</li> </ul>	None	None	None
Christine E. Seidman	Howard Hughes Medical Institute; Harvard Medical School/Brigham and Women's Hospital—Investigator; T.W. Smith Professor of Medicine and Genetics	None	None	None	None	None	None	None
Jeffrey A. Towbin	Cincinnati Children's Hospital—Executive Co-Director, The Heart Institute; Professor and Chief, Pediatric Cardiology	None	None	None	None	None	None	None
James E. Udelson	Tufts Medical Center—Chief, Division of Cardiology	None	None	None	None	None	None	None
Clyde W. Yancy	Baylor University Medical Center—Medical Director	None	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$10\,000$  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.

\*Writing committee members are required to recuse themselves from voting on sections where their specific relationships with industry may apply.

†No financial benefit.

‡Significant relationship.

DSMB indicates data safety monitoring board.

## Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
David R. Holmes, Jr	Official Reviewer—ACCF Board of Governors/ACCF Interventional Scientific Council	None	None	None	None	None	None
William J. McKenna	Official Reviewer—AHA	None	None	None	None	None	None
William G. Stevenson	Official Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Carole A. Warnes	Official Reviewer—ACCF Board of Trustees	None	None	None	None	None	None
Michael Argenziano	Organizational Reviewer—AATS	None	None	None	None	None	None
Drew E. Baldwin	Organizational Reviewer—SCAI	None	None	None	<ul style="list-style-type: none"> <li>● Atrium†</li> <li>● GlaxoSmithWellcome†</li> <li>● Harvard Clinical Research Institute†</li> </ul>	<ul style="list-style-type: none"> <li>● Greater New Orleans Health Services Corps*</li> </ul>	None
Hugh Calkins	Organizational Reviewer—HRS	<ul style="list-style-type: none"> <li>● Medtronic</li> </ul>	<ul style="list-style-type: none"> <li>● Boston Scientific</li> </ul>	None	<ul style="list-style-type: none"> <li>● Boston Scientific*</li> <li>● Medtronic*</li> <li>● St. Jude Medical*</li> </ul>	None	None
Milind Y. Desai	Organizational Reviewer—ASNC	None	None	None	None	None	None
Vasken Dilsizian	Organizational Reviewer—ASNC	None	None	None	None	None	None
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(Continued)



## Appendix 2. Continued

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**Appendix 3. Abbreviation List**

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AF	Atrial fibrillation
CAD	Coronary artery disease
CMR	Cardiovascular magnetic resonance
CTA	Computed tomographic angiography
ECG	Electrocardiogram
EF	Ejection fraction
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter-defibrillator
LA	Left atrial
LGE	Late gadolinium enhancement
LV	Left ventricular
LVOT	Left ventricular outflow tract
NSVT	Nonsustained ventricular tachycardia
NYHA	New York Heart Association
PET	Positron emission tomography
RCT	Randomized controlled trial
SAM	Systolic anterior motion
SCD	Sudden cardiac death
SPECT MPI	Single photon emission computed tomography myocardial perfusion imaging
SVT	Supraventricular tachycardia
TEE	Transesophageal echocardiogram
TTE	Transthoracic echocardiogram
VT	Ventricular tachycardia

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2011 HCM Guideline Data Supplements

Data Supplement 1. Genetics Table

Study Name/Author (Citation)	Aim of Study	Study Design	Study Size	Patient Population	Endpoints	Results	Comments
Quality of life and psychological distress in HCM mutation carriers: a cross-sectional cohort study  Christiaans, et al. (1)	To determine the quality of life and psychological distress in HCM mutation carriers.	Cross sectional cohort study	228 pts who underwent genetic testing for HCM mutation	Carriers of HCM mutations. 49.1% men, 88.7% with children. Study group divided between those with known HCM and those with unknown clinical status, in whom genotype would be predictive (n=123). Among those with predictive genotype: 43% were men and 57% were women, with 76.4% had children.	Quality of life and psychological distress assessed. Mutation carrier responses were compared to the general population.	Overall scores of quality of life were not different from the general population. Among those with overt HCM, quality of life and distress were worst than general population. Predictive genetic testing did not cause worse psychological test scores than those in the general population. Among those whose DNA testing indicated they did not carry a HCM mutation, quality of life scores were better than general population.	This was the first study to show that there was no psychologic harm caused by predictive genetic testing in HCM.
Characteristics and prognostic implications of myosin missense mutations in familial HCM  Watkins H, et al. (2)	To assess the role of <i>MYH7</i> mutations in unrelated families with HCM	Genetic analyses of <i>MYH7</i>	25 unrelated HCM probands and ~250 family members	Familial HCM of European descent.	Identification of pathogenic mutations.	Dominant missense mutations in <i>MYH7</i> accounted for HCM in 12/25 families, indicating this gene accounts for ~50% of familial HCM. Mutations allowed identification of individuals at risk for developing HCM. Different mutations did not appreciably alter the clinical manifestations of familial HCM.	Different missense mutations in the $\beta$ cardiac myosin heavy-chain gene can be identified in ~50% of families with HCM. The study authors suggest the precise definition of the disease-causing mutation can provide important prognostic information about affected members.
Comprehensive analysis of the beta-myosin heavy chain gene in 389 unrelated pts with HCM  Van Driest SL, et al. (3)	Assessment of the prevalence of <i>MYH7</i> mutations in an unselected HCM cohort	DNA sequence analyses	389 HCM pts	Unrelated HCM pts with familial or sporadic disease referred to a tertiary center.	Identification of pathogenic mutations.	58 pts (15%) had 40 different mutations in <i>MYH7</i> . HCM pts with <i>MYH7</i> compared to HCM pts without <i>MYH7</i> mutations, were younger at diagnosis (32.9 vs. 42.7 years, respectively, p=0.0002), had more hypertrophy (LV wall thickness of 24.2 vs. 21.1 mm, respectively, p=.0009), and more frequently underwent myectomy (60% vs. 38%, respectively, p=0.002). HCM pts with <i>MYH7</i> mutations compared to HCM pts without <i>MYH7</i> mutations more often had a family history of HCM	Mutations were identified using indirect methods that are less sensitive than contemporary approaches, such as DNA sequencing. This is likely to account for the lower prevalence of <i>MYH7</i> mutations than is currently found by contemporary clinical and research mutation tests.



						(43% vs. 29%, respectively, p=.006).	
Mutations in the genes for cardiac troponin T and alpha-tropomyosin in HCM  Watkins H, et al. (4)	To determine the role of troponin T and alpha-tropomyosin mutations in HCM	DNA sequence analyses	127 unrelated HCM probands	Probands with familial HCM included 14 from Europe, 10 from North America and 1 each from South America, Africa and India. 100 HCM probands without family histories had diverse racial and ethnic origins.	Identification of pathogenic mutations and clinical status of mutation carriers.	Dominant mutations in cardiac troponin T account for ~15% of familial HCM; dominant mutations in alpha-tropomyosin account for ~3% of HCM.	The high detection rate of troponin T mutations may be due to the referral-center population studied. Subsequent analyses indicate troponin T mutations account for somewhat less (10%) of HCM.
Mutations in the gene for cardiac myosin-binding protein C and late-onset familial HCM  Niimura H, et al. (5)	To determine the spectrum of myosin binding protein C mutations and associated clinical features	DNA Sequence analyses	Unrelated HCM probands and 574 family members	Single center analyses of familial HCM.	Identification of pathogenic mutations and clinical status of mutation carriers.	Dominant missense and truncation mutations in cardiac myosin binding protein C account for ~50% of familial HCM. Only 58% of adults age <50 y with a cardiac myosin-binding protein C mutation had clinical manifestations of HCM. Disease penetrance remained incomplete through the age of 60 y.	This was the first study to show myosin binding protein C mutations can delay clinical expression of HCM. This study was significant in that clinical evaluations of family members at risk for HCM must continue throughout life, unless genetic status is ascertained.
Sporadic HCM due to de novo myosin mutations  Watkins H, et al. (6)	To determine if isolated cases of HCM, like familial HCM are due to gene mutations.	Single center cohort genetic study	7 pts	Unrelated pts with sporadic HCM.	Identification of pathogenic mutations.	Mutations in the beta cardiac MHC gene were identified in 2 probands with sporadic disease. In each case, the parents were neither clinically nor genetically affected; indicating mutations arose de novo. Transmission of the mutation and disease to an offspring occurred in 1 pedigree, predicting these are germline mutations.	This study demonstrated de novo mutations account for some instances of sporadic HCM and these mutations can be transmitted to children, indicating genetic testing is warranted in pts with sporadic disease.
Shared genetic causes of cardiac hypertrophy in children and adults  Morita H, et al. (7)	To determine if idiopathic cardiac hypertrophy in childhood that occurs without a family history of cardiomyopathy has a shared genetic etiology with HCM.	Genetic study of children with idiopathic hypertrophy	84 pts	63 boys/ 21 girls diagnosed before age 15 y (mean [±SD], 6.99±/−6.12 y).	Identification of pathogenic mutations and assessment of mutation in family members.	Pathogenic mutations were identified 25 of 51 affected children without family histories of cardiomyopathy and in 21 of 33 affected children with familial HCM. Among 11 of the 25 children with presumed sporadic disease, 4 cases had new mutations and 7 cases had unrecognized inherited mutations.	This study showed mutations in HCM genes account for ~50% of cases of pediatric onset of idiopathic hypertrophy, despite substantially different clinical presentation. In 1/3 of cases, de novo mutations were found. Genetic testing of childhood-onset hypertrophy can help define cause and aid in family evaluations.

<p>Glycogen storage diseases presenting as HCM</p> <p>Arad M, et al. (8)</p>	<p>To determine the genetic causes of HCM with atypical features.</p>	<p>Cohort genetic study of pts with atypical HCM</p>	<p>55 pts</p>	<p>Unrelated HCM pts with massive hypertrophy, early presentation, absent family history, or concurrent electrophysiologic abnormalities.</p>	<p>Identification of pathogenic mutations and assessment of clinical features associated with different genotypes.</p>	<p>Mutations in <i>LAMP2</i> and <i>PRKAG2</i> cause hypertrophy with additional features. Clinical features associated with <i>PRKAG2</i> mutations included electrophysiological abnormalities (pre-excitation and progressive conduction system disease). Clinical manifestations of <i>LAMP2</i> mutations included male sex, severe hypertrophy, early onset (at age 8 to 17 y), ventricular preexcitation, and asymptomatic elevations of 2 serum proteins.</p>	<p>This study showed that <i>LAMP2</i> or <i>PRKAG2</i> mutations resembles HCM but are distinguished by electrophysiological abnormalities, and for <i>LAMP2</i> mutations, extra- cardiac manifestations. The clinical courses associated with these mutations are distinct from HCM. Gene-based diagnosis can distinguish between HCM and these disorders. This information is helpful to counsel pts and to devise appropriate management strategies.</p>
<p>Preclinical diagnosis of familial HCM by genetic analysis of blood lymphocytes</p> <p>Rosenzweig A, et al. (9)</p>	<p>To determine if genetic information identifies mutation carriers and to define preclinical manifestations of HCM.</p>	<p>Single center family study</p>	<p>29 family members of index HCM patient</p>	<p>15 adult family members and 14 offspring (ages 1- 20 y).</p>	<p>Definition of genotype and clinical features of all study subjects.</p>	<p>In 15 adult relatives there was perfect agreement between genotype and the clinical diagnosis (8 affected and 7 not affected). Clinical analysis of the 14 offspring of affected adults identified 1 child with echocardiographic findings diagnostic of HCM. However, genetic analyses showed 6 other children had also inherited the mutation. Some genotype positive children without LVH had EKG abnormalities, indicating that electrophysiologic manifestations precede LVH in HCM.</p>	<p>This study shows that knowledge of the genetic cause for HCM in an index patient allows preclinical diagnosis of mutation carriers, and identification of relatives who have no risk of developing HCM. Genotype information can precisely define individuals who warrant serial clinical evaluations for HCM.</p>
<p>Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical HCM</p> <p>Ho CY, et al. (10)</p>	<p>To determine the preclinical phenotypes in carries of HCM mutations who do not exhibit LVH.</p>	<p>Cohort study</p>	<p>72 pts</p>	<p>36 subjects with HCM mutations; 18 without LVH (genotype+/LVH-) and 18 with LVH (genotype+/LVH+). Controls = 36 age/gender matched individuals without an HCM mutation.</p>	<p>LV function using 2-D echocardiography with Doppler tissue imaging.</p>	<p>LVEF was significantly higher in both genotype (+) groups vs. control subjects. Mean early diastolic myocardial velocities (Ea) were significantly lower in both genotype (+) subgroups, irrespective of LVH.</p>	<p>This study defines the earliest clinical manifestations of HCM. Abnormalities of diastolic function were shown to precede the development of LVH in individuals with HCM mutations. This finding supports the rationale for serial evaluation of genotype + individuals, to enable early detection of the emergence of HCM.</p>

<p>A DNA resequencing array for pathogenic mutation detection in HCM</p> <p>Fokstuen S, et al. (11)</p>	<p>To define gene mutations in familial and sporadic HCM using contemporary sequencing techniques.</p>	<p>Cohort study from a single center</p>	<p>38 pts</p>	<p>17 index pts with familial HCM; 21 with sporadic HCM.</p>	<p>12 genes clearly implicated in HCM were sequenced in all pts. (Genes = <i>MYH7</i>, <i>MYBPC3</i>, <i>TNNT2</i>, <i>TPM1</i>, <i>TNNI3</i>, <i>MYL3</i>, <i>MYL2</i>, <i>CSRP3</i>, <i>PLN</i>, <i>ACTC</i>, <i>TNNC1</i>, and <i>PRKAG2</i>).</p>	<p>Pathogenic mutations were identified in 60% (10/17) of familial HCM and 10% of sporadic cases (2/21).</p>	<p>Contemporary DNA sequencing strategies can detect HCM mutations in ~60% of pts with familial disease and 10% of subjects with sporadic disease.</p>
<p>Diastolic dysfunction without left ventricular hypertrophy is an early finding in children with HCM-causing mutations in the beta-myosin heavy chain, alpha-tropomyosin, and myosin-binding protein C genes</p> <p>Poutanen T, et al. (12)</p>	<p>To compare biomarkers, LVH and diastolic function in children with a HCM mutation (genotype positive) versus healthy control children</p>	<p>Cohort study from a single center</p>	<p>53 children</p>	<p>27 children with a HCM mutation and 28 controls (mutation negative).</p>	<p>Clinical analyses of 27 children with HCM mutations (genotype +) compared to age-matched children without mutations.</p>	<p>Genotype-positive children had thicker septal measurements compared to the control children (p=.004), but only 3 (11%) genotype-positive children fulfilled criteria for body surface area adjusted maximal LV thickness of healthy children. However all genotype-positive children had prolonged isovolumetric relaxation time, increased left atrial volume, or increased levels of <i>NT-proANP</i>.</p>	<p>This study confirms LVH is a late manifestation of HCM. Children with HCM mutations have other clinical abnormalities including diastolic dysfunction.</p>
<p>Myofilament protein gene mutation screening and outcome of pts with HCM</p> <p>Olivotto I, et al. (13)</p>	<p>Assessment of clinical course in pts with a known mutation versus pts in whom no mutation is defined.</p>	<p>Cohort study from a single center</p>	<p>203 HCM pts</p>	<p>87 pts with a mutation and 126 pts without a mutation. 8 myofilament genes were sequenced (<i>MYH7</i>, <i>MYBPC3</i>, <i>TNNT2</i>, <i>TPM1</i>, <i>TNNI3</i>, <i>MYL3</i>, <i>MYL2</i>, <i>ACTC</i>) and clinical course assessed over a mean of 4 y.</p>	<p>Cardiovascular death, nonfatal stroke, or progression to NYHA class III or IV.</p>	<p>Despite similar baseline features, pts with HCM mutations had increased risk of the combined endpoints of cardiovascular death, nonfatal stroke, or progression to NYHA class III or IV compared with the pts without mutations. Mutation positive pts also had greater LV dysfunction (systolic and diastolic abnormalities) in comparison to mutation negative pts</p>	<p>This study showed a direct relationship between a positive genotype and outcomes in HCM. Unlike pts in whom no mutation was identified, those with a sarcomere gene mutation had a significantly poorer prognosis.</p>



Compound and double mutations in pts with HCM: implications for genetic testing and counseling  Ingles J, et al. (14)	To compare the clinical phenotypes in carries of one or multiple HCM mutations.	Cohort genetic and clinical study	80 unrelated HCM index pts and family members	19 index pts with 1 mutation, 4 index pts and 11 family members with >1 mutation.	Clinical manifestations and course (SD, transplant, etc) in single and multiple mutation subjects.	5% of the HCM cohort had >1 mutation. 6 of 14 (43%) of affected individuals with >1 HCM mutation had sudden cardiac death vs. 10 of 55 (18%) in affected individuals with 1 mutation. There was an increased LVH in pts with >1 mutations (mean: 30.7 mm) vs. 24.4 mm in pts with 1 mutation.	Multiple gene mutations cause more severe HCM possible due to a “double dose” effect.
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DNA indicates deoxyribonucleic acid; EKG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; patients; pts; and SD, sudden death.

Data Supplement 2. Invasive Therapies Table

Study Name/Author (Citation)	Aim of Study	Study Design	Study Size	Patient Population	Endpoints	Results	Comments
Usefulness of clinical, echocardiographic, and procedural characteristics to predict outcome after percutaneous transluminal septal myocardial ablation.  van der Lee C, et al. (15)	To assess outcomes after septal ablation	Multiple center retrospective review of consecutive pts	131 pts	HCM pts treated with septal ablation	Complications (in-hospital; follow-up); unsuccessful therapy	Ablation success in 90%; complications in 15% including death in 3.8%.	Long-term success was related to procedural volume.
Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy. A comparison of clinical, haemodynamic and exercise outcomes.  Firoozi S, et al. (16)	To compare subjective outcomes among HCM pts undergoing surgical myectomy and septal ablation	Single center retrospective review	44 pts	24 HCM pts treated with surgical myectomy; 20 HCM pts treated with septal ablation	Echocardiographic gradient; NYHA class; cardiopulmonary exercise testing;	Gradient and NYHA improvements were similar between the 2 treatment modalities. Objective exercise parameters improved more with surgical myectomy.	
Long-term effects of surgical septal myectomy on survival in pts with obstructive HCM.  Ommen SR, et al. (17)	To determine impact of surgical myectomy on long-term survival	Multiple center retrospective review of concurrent patient cohorts	1337 pts	289 HCM pts treated with surgical myectomy; 228 pts with obstructive HCM treated pharmacologically; 820 nonobstructive HCM pts	Overall and cardiac survival	1, 5, and 10 y survival (98%, 96%, and 83%, respectively) after surgical myectomy is equivalent to healthy age and gender matched population. Overall and cardiac survival superior to that of obstructive pts not offered operation.	30-d mortality = 0.8%. Annualized cardiac mortality rate 0.5% per/y
Hypertrophic obstructive cardiomyopathy: comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score.  Ralph-Edwards A, et al. (18)	Review of early outcomes after surgical myectomy or septal ablation	Single center retrospective review of concurrent patient cohorts	150 pts	90 HCM pts treated with surgical myectomy; 60 HCM pts treated with septal ablation	Survival, NYHA class, echocardiographic gradient	Superior 4 y survival, gradient reduction, and NYHA class improvement were observed in the myectomy pts after adjusting for baseline differences.	

Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy.  Smedira NG, et al. (19)	To assess effectiveness and risks of surgical myectomy	Single center retrospective review of consecutive pts	323 pts	HCM pts treated with surgical myectomy	Echocardiographic gradient; NYHA class; need for reintervention for HCM	Gradient decreased from 68 mmHg to 17 mmHg ; no in-hospital mortality; freedom from reintervention at 8 y was 92%;	
Outcome of alcohol septal ablation for obstructive HCM.  Sorajja P, et al. (20)	Assess outcomes after septal ablation	Single center retrospective review	138 pts	HCM pts treated with septal ablation	Gradient, survival, complications	Relief of LVOT gradient 83% (p<0.001); 1.4% procedural death rate with ablation; 4 y overall survival = 88%; 4 y survival free from NYHA class III to IV symptoms was 76% after ablation.	Posthoc Analysis: among pts age <65 y, survival free of symptoms was better with myectomy.
Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive HCM.  Woo A, et al. (21)	Determine clinical and echocardiographic factors associated with long-term morbidity and mortality after surgical myectomy	Single center retrospective review of consecutive pts	338 pts	HCM pts treated with surgical myectomy	Mortality, predictors of mortality, NYHA class	Early post-op mortality = 1.5%, 10 y survival = 83+/-3%; Improvement to NYHA class I to II observed in 83%	Predictors of major CV events were age, female sex, preoperative AF, concomitant CABG and preoperative left atrial size
Follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy. The Baylor and Medical University of South Carolina experience, 1996 to 2007.  Fernandes VL, et al. (22)	Determine long-term outcome after alcohol septal ablation	Retrospective review of consecutive pts	629 pts	HCM pts treated with alcohol septal ablation	Mortality, complications, repeat invasive therapy for HCM pacemaker requirement, and NYHA class	Early mortality = 1%, 1, 5, 8 y survival (97%, 92%, 89%, respectively), Permanent pacemaker required in 8.2%. Mean NYHA class at 4-5 y decreased from 2.8 +/- 0.6 to 1.2 +/-0.5 (p<0.001) = 1.2	
Transcatheter ablation of septal hypertrophy for hypertrophic obstructive cardiomyopathy: feasibility, clinical benefit, and short term results in elderly pts.  Gietzen FH, et al. (23)	Evaluate symptomatic and hemodynamic results of septal ablation in elderly pts	Single center retrospective review of consecutive pts	157 pts	HCM pts treated with septal ablation. Group I age <60 y, Group II age ≥60 y.	Mortality, gradient, complications, NYHA class	Early mortality similar between groups. Total mortality 3.8% in Group I vs. 9.1% in Group II. Similar improvement in symptoms and exercise time. Pts age ≥60 y more likely to have persistent atrioventricular heart block (5% vs. 17%, p=0.015. NYHA class improved from 2.7 to 1.4 in Group I and 3.0 to 1.7 in Group II.	



Survival after transcatheter ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience.  Kuhn H, et al. (24)	Determine impact of septal ablation on survival	Single center retrospective review of consecutive pts	644 pts	HCM pts treated with septal ablation	Mortality (early and late)	Early mortality = 1.2%, annual mortality = 3.2% per/ y	Early and late mortality improved after converting to low alcohol dosing
Long-Term Outcomes in High-Risk Symptomatic Pts With HCM Undergoing Alcohol Septal Ablation.  Kwon DH, et al. (25)	Assess outcomes after septal ablation in high-risk pts	Single center retrospective review	55 pts	HCM pts at high risk for cardiac surgery treated with septal ablation	Gradient, quality of life, NYHA class, mortality	Gradient and quality of life improved at 3 mo and sustained through 1 y. Reduction in number of pts with NYHA class $\geq 3$ (93% NYHA class $>2$ ). Early mortality = 2%, 1, 5, 10 y survival (96%, 87%, 76%)	
Comparison of ethanol septal reduction therapy with surgical myectomy for the treatment of hypertrophic obstructive cardiomyopathy.  Nagueh SF, et al. (26)	Compare hemodynamic efficacy of surgical myectomy and septal ablation	Multicenter retrospective case-control comparison	82 pts	41 HCM pts treated with septal ablation; 41 age and gradient matched HCM pts treated with surgical myectomy	Gradient, NYHA class, exercise capacity	At 1 y after procedure, improvements in gradient, symptoms and exercise capacity were similar between the 2 groups	
Outcome of pts with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery.  Qin JX, et al. (27)	Evaluate results of surgical myectomy as compared to septal ablation	Single center retrospective review	51 pts	25 HCM pts treated with septal ablation; 26 HCM pts treated with surgical myectomy	Gradient, NYHA class	Gradient reduction more robust with surgery; NYHA improvements similar	Ablation pts in this study were on average 15 y older than myectomy pts
Updated meta-analysis of septal alcohol ablation versus myectomy for HCM.  Agarwal S, et al. (28)	Compare outcomes of HCM pts undergoing surgical myectomy with septal ablation	Meta-analysis	12 published studies	HCM pts treated with either surgical myectomy or septal ablation	Mortality, complications, NYHA class, gradient	No differences in mortality, NYHA class, ventricular arrhythmia, or need for reintervention. Ablation pts had higher residual gradient and rate of advanced conduction abnormalities.	

Meta-analysis of septal reduction therapies for obstructive HCM. Comparative roles of overall mortality and SCD after treatment.  Leonardi RA, et al. (29)	Compare outcomes of HCM pts undergoing surgical myectomy with septal ablation	Meta-analysis	27 published studies	HCM pts treated with either surgical myectomy or septal ablation	Survival and rate of SCD	No differences were observed between the treatment strategies in terms of overall, cardiac or sudden death related survival	
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CABG indicates coronary artery bypass graft; CV, cardiovascular; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; patients; pts; and SCD, sudden cardiac death.

Data Supplement 3. Pacing Table

Study Name/Author (Citation)	Aim of Study	Study Design	Study Size	Patient Population	Endpoints	Results	Comments
Functional assessment of pts treated with permanent dual-chamber pacing as a primary treatment for HCM  McDonald, K, et al. (30)	To determine the improvement in objective exercise capacity in pts with HCM undergoing DDD pacing	Cohort 2 center trial - DDD pacemaker implanted in all pts	11 pts (mean age 50 +/- 12 y)	Eleven selected pts with obstructive HCM and severe symptoms refractory to drug therapy studied at 2 centers who underwent initial implantation of a DDD pacemakers.	Symptoms, NYHA class and exercise time	Within 1 wk, there was an improvement in NYHA class in all pts. The exercise duration increased from 7.7 to 11.5 min. In 5 pts at a follow-up of 3 mo to 1y, there was an increase in exercise time from 6.2 to 8.8 min.	One of the first studies which showed an improvement in exercise time during continuous DDD pacing.
Effects of dual-chamber pacing in HCM  Jeanrenaud, X, et al. (31)	To determine the effects of acute and long-term dual-chamber pacing in pts with HCM.	Cohort series. Acute pacing study and long-term implantation of a dual-chamber pacemaker.	13 pts with acute study and 8 pts with follow-up (age 56 +- 14 y)	Selected pts with obstructive HCM and severe symptoms refractory to drug therapy	NYHA class, outflow tract gradient.	At a follow-up of 14 +/- 11 mo, NYHA class had decreased from III to II in terms of dyspnea. Outflow tract gradient had decreased from 67 +/- 42 to 17 +/- 10 mmHg. When the pacemaker was turned off at follow-up, the gradient was 31 +/- 36 mmHg.	This study showed that synchronized and ventricular pacing in at an optimal atrioventricular interval does reduce intraventricular pressure gradient at the time of acute study. There is a long-term drop in pressure gradient during chronic pacing with improvement in functional tolerance.
Long-term results of dual chamber pacing in obstructive HCM: evidence for progressive symptomatic and hemodynamic improvement and reduction of LVH  Fananapazir, L, et al. (32)	To determine the intermediate term outcome of DDD pacing in pts with HCM.	Cohort single center trial - implant DDD pacemakers in all pts	84 pts (mean age 49 +/-16 y)	Consecutive pts with obstructive HCM and severe symptoms refractory to drug therapy referred to a single center	Symptoms, NYHA class, LVOT gradient, LVH	At a mean follow-up of 2.3 +/- 0.8 y, there was improvement in NYHA class (3.2 +/- 0.5 to 1.6 +/- 0.6, p<.0001). The LVOT gradient decreased from 100 +/- 47 mmHg to 29 +/- 34 mmHg - p<.01. A subset of pts had reversal of LV wall thickness.	The high success rate of DDD pacing in this cohort trial has not been replicated in subsequent randomized pacing trials.



DDD pacing in HCM: A multicentre clinical experience  Slade, A, et al. (33)	To determine the outcome of DDD pacing in pts with HCM.	Cohort multicentre trial. Implant DDD pacemaker in all pts.	56 pts from 4 centers,(mean age 48 +/- 18 y)	Selected pts with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms, NYHA class, LVOT gradient	44 out of 53 pts had an improvement in functional class. At a mean follow-up of 11 +/- 11 mo, there was a reduction in gradient from 78 +/- 31 to 36 +/- 25 mmHg.	There was symptomatic improvement in the majority of pts. However, there was no correlation between the magnitude of the gradient drop and the functional improvement. This is another study that showed the results of acute temporary pacing studies had no correlation with outcome. Thus, there remains a discrepancy between perceived symptomatic benefit and modest objective improvement. Also, optimal outcome was achieved only with continued pharmacologic treatment.
Pacing in hypertrophic obstructive cardiomyopathy: A randomized crossover study  Kappenberger, L, et al. (34)	To determine the intermediate term outcome of DDD pacing in pts with HCM.	Randomized multicenter single blind crossover study. Pts then randomized to 12 wks of activated pacing or inactivated pacing in a single blind crossover study.	83 pts (mean age 53 :25-87 y)	Pts with obstructive HCM and severe symptoms refractory to drug therapy. The pts all had acute hemodynamic response to pacing.	Symptoms, exercise duration, and gradient	NYHA class improved from 2.4 to 1.4 for dyspnea and 1.0 to 0.4 for angina (p<0.007). Quality of life showed improvement. After 12 wks of pacing, the gradient fell from 59 +/- 36 to 30 +/- 25 mmHg with active pacing. Exercise tolerance improved by 21%, but only in those pts who at baseline had a severe limitation of <10 min at Bruce protocol.	This trial showed clinical and hemodynamic benefit for pts with hypertrophic obstructive cardiomyopathy and LVOT obstruction. This multicenter trial included only pts who had an acute hemodynamic response >30% reduction in gradient in the catheterization laboratory. There was no overall change in exercise time when looking at all pts. Although 70% improved, the degree of improvement was not related to acute hemodynamic results.

Dual-chamber pacing for HCM: A randomized, double-blind, crossover trial  Nishimura, R, et al. (35)	To determine the intermediate term outcome of DDD pacing in pts with HCM	Randomized double-blind crossover study. Pts randomized for 3 mo each of DDD pacing and back-up AAI pacing.	21 pts (Mean age 58; 35-74 y).	Single center trial of selected pts with obstructive HCM and severe symptoms refractory to drug therapy	Symptoms, NYHA class, LVOT gradient, quality of life, treadmill time, peak VO <sub>2</sub> .	6 mo of follow-up, LVOT gradient had decreased from 76 +/- 61 to 55 +/- 38 mmHg after DDD pacing and 83 +/- 59 mmHg after AAI pacing. Quality of life and exercise duration were significantly improved from the baseline state compared to the DDR, but not significantly different between the DDD arm and the back-up arm. 63% of pts had symptomatic improvement during the DDD arm, but 42% had symptomatic improvement during the AAI arm. Peak oxygen consumption did not differ significantly. Symptoms did not change in 31% and 5% experienced deterioration of symptoms.	This trial showed that dual-chamber pacing may relieve symptoms and decrease gradient in pts with HCM, but there are some pts in whose symptoms do not change and become even worse. Symptomatic improvement may occur without hemodynamic benefit suggesting the role of a placebo effect.
Significant improvement of quality of life following atrioventricular synchronous pacing in pts with hypertrophic obstructive cardiomyopathy. Data from 1 year of follow-up  Gadler, F, et al. (36)	To determine the outcome of pacing on quality of life during 1 y follow-up.	Cohort trial - implant DDD pacemaker in all pts	83 pts (mean age 53, 32-87 y).	Pts with obstructive HCM and severe symptoms refractory to drug therapy.	NYHA class and Karolinska quality of life.	At the end of 1 y, no patient had hemodynamic deterioration. NYHA class I (36 pts follow-up vs. 0 pts initial); NYHA class II (31 pts follow-up vs. 37 pts initial); NYHA class III (8 pts follow-up vs./ 45 pts initial). 76 of the pts preferred pacing and 4 pts preferred AAI mode.	This study showed that atrioventricular synchronous pacing had a beneficial effect on most domains of quality of life at 1 y follow-up.

<p>Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic pts with obstructive HCM. A randomized, double-blind, crossover study (M-PATHY)</p> <p>Maron, B, et al. (37)</p>	<p>To determine the intermediate term outcome of DDD pacing in pts with HCM.</p>	<p>Randomized double-blind crossover study. DDD pacing implants in all pts, randomized then to a DDD mode and pacing back-up AAI mode in a double-blind crossover study design, followed by an uncontrolled 6-mo pacing trial.</p>	<p>48 pts (age 53 +/- 17, 22-83 y).</p>	<p>Pts with obstructive HCM and severe symptoms refractory to drug therapy</p>	<p>Symptoms, NYHA class, LVOT gradient, quality of life, treadmill time, peak VO<sub>2</sub>.</p>	<p>DDD versus AAI mode comparison at 6 mo indicated no significant change in exercise capacity, quality of life, or NYHA class. During a 12-mo follow-up of 6 further mo of continuous pacing, there was a significant increase in functional class and quality of life, but no change in peak oxygen consumption. The gradient was reduced from 82 +/- 32 mmHg to 48 +/- 32 mmHg. There was no change in gradient in 43%. Only 12% had a clinical response (improvement in NYHA class, quality of life, treadmill time), and these were all pts age &gt;65 y.</p>	<p>This trial showed perceived symptomatic improvement was most consistent with a substantial placebo effect during the randomization process. Longer uncontrolled pacing periods had subjective benefit, but did not have objective improvement in cardiovascular performance and there was only modest reduction in outflow tract gradient.</p>
<p>Dual chamber pacing for pts with hypertrophic obstructive cardiomyopathy: A clinical perspective in 2000.</p> <p>Erwin, J, et al. (38)</p>	<p>To determine the long-term outcome of pts with HCM.</p>	<p>Cohort trial (single center) DDD pacemakers implanted in all pts</p>	<p>28 pts (56 +/- 16 y)</p>	<p>Pts with obstructive HCM and severe symptoms refractory to drug therapy</p>	<p>Symptoms and LVOT gradient.</p>	<p>At a follow-up of 24 +/- 14 mo (max 50 mo), 47% of pts improved but 53% of pts did not improve in terms of symptomatic response. LVOT gradient decreased from 95 +/- 40 to 62 +/- 47 mmHg.</p>	<p>This is a much lower "success" rate with long-term follow-up of pts who underwent dual-chamber pacing, with less than half of the pts having symptomatic improvement. There was no difference in the gradient response between those pts who improved versus those who did not improve. The residual gradient was still &gt;60 mmHg, which is severe obstruction.</p>
<p>Long-term follow-up of pts with obstructive HCM treated with dual-chamber pacing.</p> <p>Megevand, A, et al. (39)</p>	<p>To determine the long-term outcome of DDD pacing in pts with HCM.</p>	<p>Single center cohort trial. DDD pacemaker implanted in all pts.</p>	<p>18 pts (mean age 47 y)</p>	<p>Pts with obstructive HCM and severe symptoms refractory to drug therapy. Only pts who had an initial acute hemodynamic benefit</p>	<p>Outflow tract gradient and NYHA class</p>	<p>At the end of a follow-up of 49 +/- 33 mo, the gradient of 82 +/- 35 dropped to 32 +/- 23. There was a beneficial result in NYHA class from 2.4 to 1.8.</p>	<p>This study reports the long-term outcome of a cohort of pts who had a dual-chamber pacemaker implanted who had a beneficial acute hemodynamic study. There was a significant reduction in symptoms as well as sustained decrease in LVOT obstruction at a follow-up of over 4 years.</p>

HCM indicates hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NYHA, New York Hear Association; VO<sub>2</sub>, oxygen consumption and patients, pts.



Data Supplement 4. Sudden Cardiac Death Risk Factor Table

Study Name/Author (Citation)	Aim Of Study	Study Design	Study Size	Patient Population	End-points	Results								Comments
						FHSCD	MLVWT	NSVT	SYNCOPE	ABPR	LVOTO	Multiple RF		
Prospective prognostic assessment of blood pressure response during exercise in pts with HCM.  Sadoul N, et al. (40)	Assess prognostic significance of blood pressure response to exercise in HCM pts	Single center prospective data collection of consecutive pts	161 pts	HCM pts age ≤40 y	SD	Univariate					OR: 3.0, p<0.005			
						Multi-variate								
SD in HCM: Identification of high-risk pts.  Elliott PM, et al. (41)	Identify HCM pts at high risk for SCD	Single center prospective data collection of consecutive pts	368 pts	HCM pts. Exclusions: prior SCD event, current amiodarone use, incomplete risk assessment age <40 y	SD	Univariate	p=0.15	OR: 4.1, p=0.001	p=0.21	p=0.13	OR: 2.4, p=0.04		2 or more RF: OR: 5.6, p=0.0001	
						Multivariate	Combined with syncope (OR: 5.3, p=0.002)	OR: 2.9, p=0.03	p=0.18	Combined with family history (OR: 5.3, p=0.002)	p=0.22			
Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in pts with HCM: a prospective study.  Maron BJ, et al. (42)	Assess prognostic significance of 24 h ambulatory ECG monitoring in HCM pts	Single center prospective data collection of consecutive pts	84 pts	HCM pts. Exclusions: myectomy pts	SD	Univariate			p=0.02					
						Multi-variate								

Prognosis of asymptomatic pts with HCM and NSVT.  Spirito P, et al. (43)	Assess prognostic significance of NSVT in asymptomatic or mildly symptomatic HCM pts	3 center retrospective study	151 pts	HCM Pts. Exclusions: prior syncope, NYHA class >2; any cardioactive medications	SD	Univariate			p=0.24					
						Multi-variate								
Prognostic value of NSVT and the potential role of amiodarone treatment in HCM assessment in an unselected non-referral based patient population.  Cecchi F, et al. (44)	Evaluate antiarrhythmic therapy in HCM pts	Single center registry	167 pts	HCM Pts. Exclusions: amiodarone use and/or absence of 24 h ambulatory ECG	Cardiac and SD	Univariate			NS					Only 1 SD in entire study population
						Multi-variate								
Predictors of SCD in HCM.  Maki S, et al. (44)	Identify HCM pts at high risk for SCD	Single center data collection.	309 pts	HCM pts, consecutive	SD	Univariate	p=0.03	p=0.33	p=0.41	p=0.07	p=0.0002	p=0.0009		
						Multi-variate								
Magnitude of LVH and risk of SD in HCM  Spirito P, et al.	Assess the relation between LVH and survival in	2 centers retrospective data collection	480 pts	HCM Pts; excluded pts with prior cardiac arrest and/or	SD	Univariate	p=0.23					p=0.0006		

(45)	HCM pts			no follow up		Multi-variate		OR: 1.76 per 5 mm increase, p=0.003				p=0.76		
Relation between severity of LVH and prognosis in pts with HCM.  Elliott PM, et al. (46)	Assess prognostic significance of LVH in relation to other SCD risk factors	Single center data collection.	630 pts	HCM pts, consecutive	SD or ICD discharge	Univariate		OR: 1.31 per 5 mm increase, p=0.03					OR: 2.1, p=0.0001	
						Multi-variate		OR: 1.26 per 5 mm increase, p=0.06					OR: 2.0, p=0.0001	
Maximum left ventricular thickness and risk of SD in pts with HCM.  Olivotto I, et al. (47)	Assess relationship between LVH and outcome in HCM pts	Single center data collection.	237 pts	HCM pts, consecutive	SD or ICD discharge	Univariate		p=0.27						
						Multi-variate								
LVOT and SD risk in pts with HCM.  Elliott PM, et al. (48)	Assess influence of symptoms and LVOTO on risk for SCD in HCM pts	Single center data collection.	917 pts	HCM pts, consecutive	SD or ICD discharge	Univariate							OR: 1.8-2.0, p<0.001	
						Multi-variate	OR: 1.9, p=0.04	p=0.2	OR: 3.8, p<0.0001	OR: 2.3, p=0.01	p=0.3	OR: 1.01 per mmHg, p=0.002		OR: 3.8 if LVOTO >90 mmHg, p=0.005
Syncope and risk of SD in HCM.  Spirito P, et al. (49)	Assess clinical implications of syncope in	Multicenter data collection	1511 pts	HCM pts, consecutive	SD or ICD discharge	Univariate				p=0.08				

	HCM pts					Multi-variate	p=0.12	p=0.06		p=0.29;		p=0.29		For unexplained syncope <6 mo prior to evaluation, OR: 4.9, p=0.006
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ABPR indicates abnormal blood pressure response; ECG, electrocardiogram; FHSCD, family history of sudden cardiac death; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; MLVWT, maximum left ventricular wall thickness; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; OR, odds ratio; patients; pts; RF, risk factor; SCD, sudden cardiac death and SD, sudden death.

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## 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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