

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

### 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 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

**Table 1. Applying Classification of Recommendation and Level of Evidence**

		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 perform 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 or CLASS III Harm</i>
				Procedure/Test	Treatment
				COR III: No benefit	No Proven Benefit
				COR III: Harm	Excess Cost w/o Benefit or Harmful to Patients or Harmful
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A 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>
	LEVEL 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>
	LEVEL C 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 be recommended	is reasonable	may/might be considered	COR III: No Benefit
Comparative effectiveness phrases†		treatment/strategy A is recommended/indicated in preference to treatment B	can be useful/effective/beneficial	may/might be reasonable	COR III: Harm
		treatment A should be chosen over treatment B	is probably recommended or indicated	usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended
					is not indicated
					should not be performed/administered/other
					is not useful/beneficial/effective
					potentially harmful
					causes harm
					associated with excess morbidity/mortality
					should not be performed/administered/other

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.

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/ACC/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 deter-

mine 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. The full-text version<sup>1a</sup> of the guideline is e-published in the *Journal of the American College of Cardiology and Circulation* and is posted on the ACC ([www.cardiosource.org](http://www.cardiosource.org)) and AHA ([my.americanheart.org](http://my.americanheart.org)) World Wide Web sites. 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*. References selected and

published in this document are representative and not all-inclusive.

### 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>

The impetus for the guidelines 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. Recommendations for HCM

### 2.1. 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>4–9</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>10–14</sup> (*Level of Evidence: B*)
3. Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM.<sup>4–7,9,15,16</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>17–19</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>5,8,15</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>20,21</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>4–9,22</sup> (*Level of Evidence: B*)
2. Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM.<sup>22–25</sup> (*Level of Evidence: B*)

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

#### 2.1.1. 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), transthoracic echocardiogram (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>26–29</sup> (*Level of Evidence: B*)

## 2.2. 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>30–33</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>30–32</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>33</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, atrial fibrillation [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*)

## 2.3. Echocardiography—Recommendations

### Class I

1. A TTE is recommended in the initial evaluation of all patients with suspected HCM.<sup>34–41</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>42–45</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>45,46</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>47–53</sup> (*Level of Evidence: B*)
5. A transesophageal echocardiogram (TEE) is recommended for the intraoperative guidance of surgical myectomy.<sup>54–56</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>57–60</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>60–66</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>35,37,41</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>48,51,53,67,68</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>54–56</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 cardiovascular magnetic resonance (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>43–46</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 ob-

struction or intrinsic mitral valve pathology. (*Level of Evidence: C*)

### 2.4. 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>69–71</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>67,70–72</sup> (*Level of Evidence: B*)

### 2.5. Cardiac Magnetic Resonance—Recommendations

#### Class I

1. CMR imaging is indicated in patients with suspected HCM when echocardiography is inconclusive for diagnosis.<sup>73,74</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>73–77</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>73,75</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 2.13), CMR imaging with assessment of late gadolinium enhancement (LGE) may be considered in resolving clinical decision making.<sup>78–82</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>83–85</sup> (*Level of Evidence: C*)

### 2.6. 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 coronary artery disease (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 tomography (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*)

## 2.7. 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>86</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>32,87</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>32</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>32,38</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>3,38</sup> (*Level of Evidence: C*)

## 2.8. 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>3,32,36,38,88–96</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>3,32,36,89–96</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>32,36,88,97–101</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>36,102–104</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>32,36,88,105–108</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>41,88</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>32,36,88</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>3,32,36,109–111</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>32,40,88,112–117</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>3,102–104,118–121</sup> (*Level of Evidence: B*)

## 2.9. 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>†122</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 9.3.3).

†Eligible patients are defined by all of the following:

- a. Clinical: Severe dyspnea or chest pain (usually New York Heart Association [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 systolic anterior motion (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>60,64,65,123–125</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>126</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>60,62,127–131</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>62,123,128,130,131</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*)

- 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 Data Supplement 2 for additional data regarding invasive therapies.

## 2.10. Pacing—Recommendations

### Class IIa

- 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>132–135</sup> (*Level of Evidence: B*)

### Class IIb

- Permanent pacing may be considered in medically refractory symptomatic patients with obstructive HCM who are suboptimal candidates for septal reduction therapy.<sup>132–136</sup> (*Level of Evidence: B*)

### Class III: No Benefit

- 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>136–138</sup> (*Level of Evidence: C*)
- 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>136–138</sup> (*Level of Evidence: B*)

See Data Supplement 3 for additional data regarding pacing.

## 2.11. Patients With LV Systolic Dysfunction—Recommendations

### Class I

- Patients with nonobstructive HCM who develop systolic dysfunction with an ejection fraction (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>49,139</sup> (*Level of Evidence: B*)
- 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

- 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>49</sup> (*Level of Evidence: C*)
- 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*)

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

### Class I

- Patients with advanced heart failure (end-stage\*) and nonobstructive HCM not otherwise amenable to other treatment interventions, with EF less than 50% (or occasionally with preserved EF), should be considered for heart transplantation.<sup>49,140</sup> (*Level of Evidence: B*)
- 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>141,142</sup> (*Level of Evidence: C*)

### Class III: Harm

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

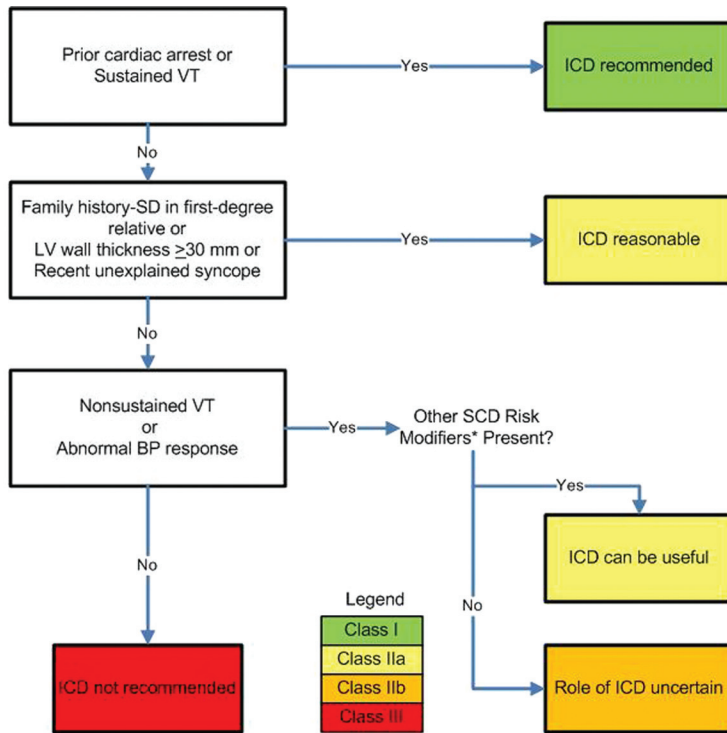
## 2.13. SCD Risk Stratification—Recommendations

### Class I

- All patients with HCM should undergo comprehensive SCD risk stratification at initial evaluation to determine the presence of the following:<sup>30,31,143–152</sup> (*Level of Evidence: B*)
  - A personal history for ventricular fibrillation, sustained VT, or SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias.†
  - A family history for SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias.†
  - Unexplained syncope.
  - Documented nonsustained ventricular tachycardia (NSVT) defined as 3 or more beats at greater than or equal to 120 bpm on ambulatory (Holter) ECG.
  - Maximal LV wall thickness greater than or equal to 30 mm.

\*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.



**Figure 1.** Indications for ICDs in HCM. \*SCD risk modifiers include established risk factors and emerging risk modifiers (Section 9.4.2). 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.

### Class IIa

1. It is reasonable to assess blood pressure response during exercise as part of SCD risk stratification in patients with HCM.<sup>30,71,149</sup> (Level of Evidence: B)
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>78,82</sup> (Level of Evidence: C)
  - b. Double and compound mutations (ie, >1). (Level of Evidence: C)
  - c. Marked LVOT obstruction.<sup>30,48,51,149</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 Data Supplement 4 for additional data regarding SCD risk stratification.

## 2.14. 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 1).<sup>144,150,153,154</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>145,146,148,150</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>155</sup> (Level of Evidence: C)
  - b. A maximum LV wall thickness greater than or equal to 30 mm.<sup>147,156–158</sup> (Level of Evidence: C)
  - c. One or more recent, unexplained syncopal episodes.<sup>152</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>‡33,144</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>‡70,71,149</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>‡144</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>70,71,149</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*)

## 2.15. 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>159–162</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>159</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>136–138,159</sup> (*Level of Evidence: B*)

## 2.16. 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>163,164</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 2.<sup>87</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>163–169</sup> (*Level of Evidence: C*)

## 2.17. 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>170–172</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>173</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>170,172</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>170,174</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>175–179</sup> (*Level of Evidence: B*)
3. Maze procedure with closure of left atrial 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*)

§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>173</sup>

‡SCD risk modifiers are discussed in Section 9.4.2.

**Table 2. 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>87</sup>

## 2.18. 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>43,44,180,181</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 provokable 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*)

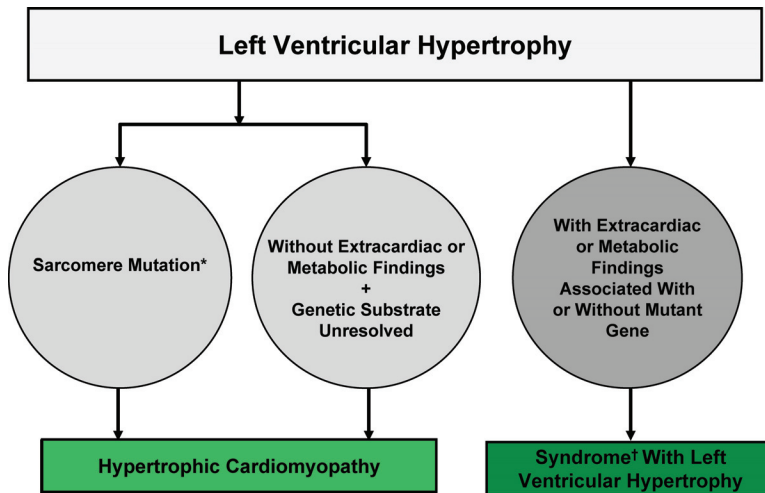
## 3. Prevalence/Nomenclature/ Differential Diagnosis

### 3.1. Prevalence

HCM is a common genetic cardiovascular disease. In addition, HCM is a global disease,<sup>182</sup> with epidemiological studies from several parts of the world<sup>183</sup> reporting a similar prevalence of 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>184</sup>

#### 3.1.1. Clinical Definition and Differential Diagnosis

HCM is the preferred nomenclature to describe this disease,<sup>185</sup> although confusion over the names used to characterize this entity has arisen over the years in part because one third of patients have no obstruction either at rest or with physiologic provocation.<sup>67</sup> The generally accepted definition of HCM 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>32,38,184–187</sup> with the caveat that patients who are genotype positive may be phenotypically negative without overt hypertrophy.<sup>188,189</sup> Clinically, HCM is



**Figure 2.** 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 non-sarcomeric (but also nonmetabolic) genes may prove to cause HCM. †An example is Noonan syndrome with cardiomyopathy. Modified with permission from Maron et al.<sup>187</sup>

usually recognized by a maximal LV wall thickness  $\geq 15$  mm. 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. Furthermore, although a myriad of patterns and distribution of LV hypertrophy (including diffuse and marked) have been reported in HCM,<sup>37,76,190</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>76</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>191–195</sup> usually when maximum wall thickness is in the modest range of 13 to 15 mm.

These important distinctions are often resolved by noninvasive markers, including sarcomeric mutations or family history of HCM, LV cavity dimension, diastolic function, pattern of LV hypertrophy, or short deconditioning periods.<sup>191–195</sup>

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>196,197</sup> Fabry disease,<sup>198</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>4,199–201</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<sup>202–206</sup> (Figure 2). In addition, differential diagnosis of HCM may require distinction from dilated cardiomyopathy when HCM presents in the end stage.<sup>49</sup>

### 3.1.2. 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

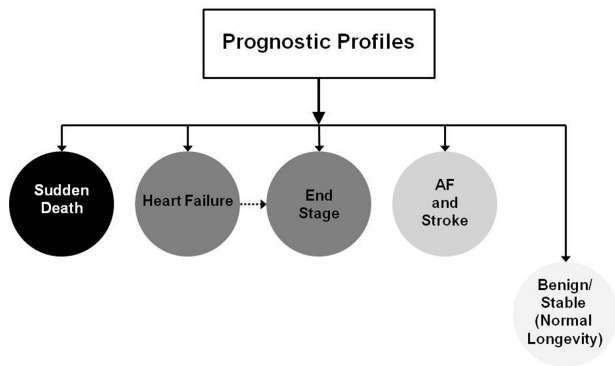
autosomal dominant mutations in genes encoding protein components of the sarcomere and its constituent myofilament elements.<sup>43,199,207,208</sup> Intergenic diversity is compounded by considerable intragenic heterogeneity, with  $>1400$  mutations identified among at least 8 genes. The current weight 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>43,199,207,208</sup>

### 3.1.3. HCM 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>38</sup> Although HCM is one of the most common forms of genetic heart disease and relatively common in the general population,<sup>184</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>209</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>209,210</sup>

## 4. 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>32,38,49,51</sup> Most affected individuals probably achieve a normal life expectancy without disability or the necessity for major therapeutic interventions.<sup>211–214</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>32,38,49,51,147,156</sup> When the disease does result in significant complications, there are 3 relatively discrete but not mutually exclusive pathways of clinical progression (Figure 3):



**Figure 3.** Prognosis profiles for HCM and targets for therapy. AF indicates atrial fibrillation. Modified with permission from Maron et al.<sup>32</sup>

1. SCD due to unpredictable ventricular tachyarrhythmias, most commonly in asymptomatic patients <35 years of age<sup>50,144,147,150,153,154,156,166,168,215</sup> (including competitive athletes).<sup>166,168</sup>
2. Heart failure characterized by exertional dyspnea (with or without chest pain) that may be progressive.<sup>49</sup>
3. AF, also associated with various degrees of heart failure<sup>172</sup> and an increased risk of systemic thromboembolism and stroke.

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>150,153,154</sup>; drugs appropriate to control heart failure symptoms (principally those of exertional dyspnea and chest discomfort),<sup>32,38</sup> surgical septal myectomy<sup>64</sup> or alcohol septal ablation<sup>60</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 unremitting symptoms<sup>49</sup>; and drug therapy or possibly radiofrequency ablation or surgical maze procedure for AF.<sup>175,178,179</sup>

## 5. 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>38,40,41</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.

### 5.1. LVOT Obstruction

The original observations by Brock<sup>216</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>217–220</sup> but careful studies have shown definitively that true mechanical obstruction to outflow does occur.<sup>40,41</sup> For HCM, it is the peak instantaneous LV outflow gradient rather than the mean gradient that influences treatment decisions (Table 3).

Outflow obstruction usually occurs in HCM by virtue of mitral valve SAM and mitral-septal contact. Muscular ob-

**Table 3.** Definitions of Dynamic Left Ventricular Outflow Tract Obstruction

Hemodynamic State	Conditions	Outflow Gradient*
Basal obstruction	Rest	≥30 mm Hg†
Nonobstructive	Rest	<30 mm Hg
	Physiologically provoked	<30 mm Hg
Labile obstruction	Rest	<30 mm Hg†
	Physiologically provoked	≥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>221,222</sup>

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

struction can also be present in the midcavitary region, occasionally because of hypertrophied papillary muscles abutting the septum<sup>223</sup> or anomalous papillary muscle insertion into the anterior mitral leaflet.<sup>224</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>40,41</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>225</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>40,41</sup> and is also a major determinant of outcome.<sup>51</sup>

The presence and magnitude of outflow obstruction are usually assessed with 2-dimensional echocardiography and continuous wave Doppler. Combining exercise testing with Doppler echocardiography is useful in identifying 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>67</sup> Provocation with dobutamine infusion during Doppler echocardiography is no longer recommended as a strategy to induce outflow gradients in HCM.

## 6. 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 ≥15 mm in an adult 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.

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>43,186,187,199,207,208</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>7,9,226,227</sup> but research is ongoing.<sup>6,228</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 or different genes.<sup>23,229</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>14</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 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>6,15</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.” Studies suggest that the presence of  $>1$  HCM-associated sarcomere mutation is associated with greater severity of disease.<sup>23,24,230,231</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>18</sup> Genetic counseling should precede genetic testing of family members.<sup>14</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 2.13). 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>188,189</sup> Mutation-negative family members and their descendants have no risk for developing HCM and do not need further

**Table 4. 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>233</sup>

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

evaluation. Information from genotyping may help define clinical manifestations and outcomes in specific families with HCM (Table 4).<sup>7–9,18,20–22,232</sup>

## 6.1. Cardiovascular Magnetic Resonance

CMR provides superior spatial resolution with sharp contrast between blood and myocardium, as well as tomographic imaging of the entire LV myocardium and therefore the opportunity to more accurately characterize the presence and distribution of LV hypertrophy in HCM.

Two-dimensional echocardiography has 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>32,38,67,76,190,220,234</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>76</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>74,76,77</sup> In addition, hypertrophy confined to the apex (ie, apical HCM) may be difficult to visualize with echocardiography but is evident with CMR.<sup>73,75</sup> Furthermore, CMR can more readily detect the presence of apical aneurysms (particularly when small). The latter has potential implications for management with ICDs and/or anticoagulation. The magnitude of LV wall thickening may be underestimated by echocardiography compared with CMR, particularly when this region involves the anterolateral free wall,<sup>76,77</sup> and therefore CMR may identify high-risk status on the basis of massive hypertrophy. 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>235,236</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 literature.<sup>79–81,237,238</sup> Although patients with the end-stage phenotype almost universally demonstrate such findings,<sup>49</sup> patients with HCM with preserved systolic function may also have areas of LGE.<sup>79–81</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>78,80</sup>

It is plausible that areas of LGE (ie, probably largely replacement myocardial fibrosis) could represent a substrate for the generation of malignant ventricular tachyarrhythmias in HCM. 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>81,239</sup> However, there is insufficient evidence at this time to support a significant association between the extent of LGE and outcome. Nonetheless, the present data would support a potential role of LGE as an arbitrator in decision making for primary prevention ICDs in patients in whom risk status remains uncertain after assessment of conventional risk markers.<sup>79,80</sup>

## 7. Concomitant Coronary Disease

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 or a consequence of microvascular dysfunction.<sup>38</sup> Concomitant presence of CAD in patients with HCM identifies a higher risk for adverse outcomes and potential candidates for revascularization.<sup>240,241</sup>

Myocardial bridging of the left anterior descending coronary artery is a frequent component of phenotypically expressed HCM and more common than in other diseases with or without LV hypertrophy. Although it has been suggested that ischemia secondary to bridging could be a potential mechanism for sudden death in HCM,<sup>242</sup> there is no consistent evidence to support this hypothesis in either adults or children.<sup>243,244</sup>

## 8. Choice of Imaging Modality

### 8.1. Invasive Coronary Arteriography

Invasive coronary arteriography is indicated in patients with HCM when knowledge of these features will importantly influence management strategies. Coronary arteriography should be undertaken before alcohol septal ablation in order to define the anatomy of the septal perforators and exclude obstructive coronary stenoses.

### 8.2. 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. A high negative predictive value to exclude CAD is particularly consistent in the literature.

### 8.3. 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>245,246</sup> Several lines of evidence support that these defects, even in the absence of symptoms, represent true flow abnormalities and possibly “silent” ischemia.<sup>247</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>245</sup> and likely correspond to patients who demonstrate LGE in CMR studies.<sup>49</sup>

### 8.4. 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 normal control subjects, the augmentation of blood flow with vasodilation, for example, dipyridamole, may be significantly blunted.<sup>248–251</sup> 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.

### 8.5. Stress Echocardiography

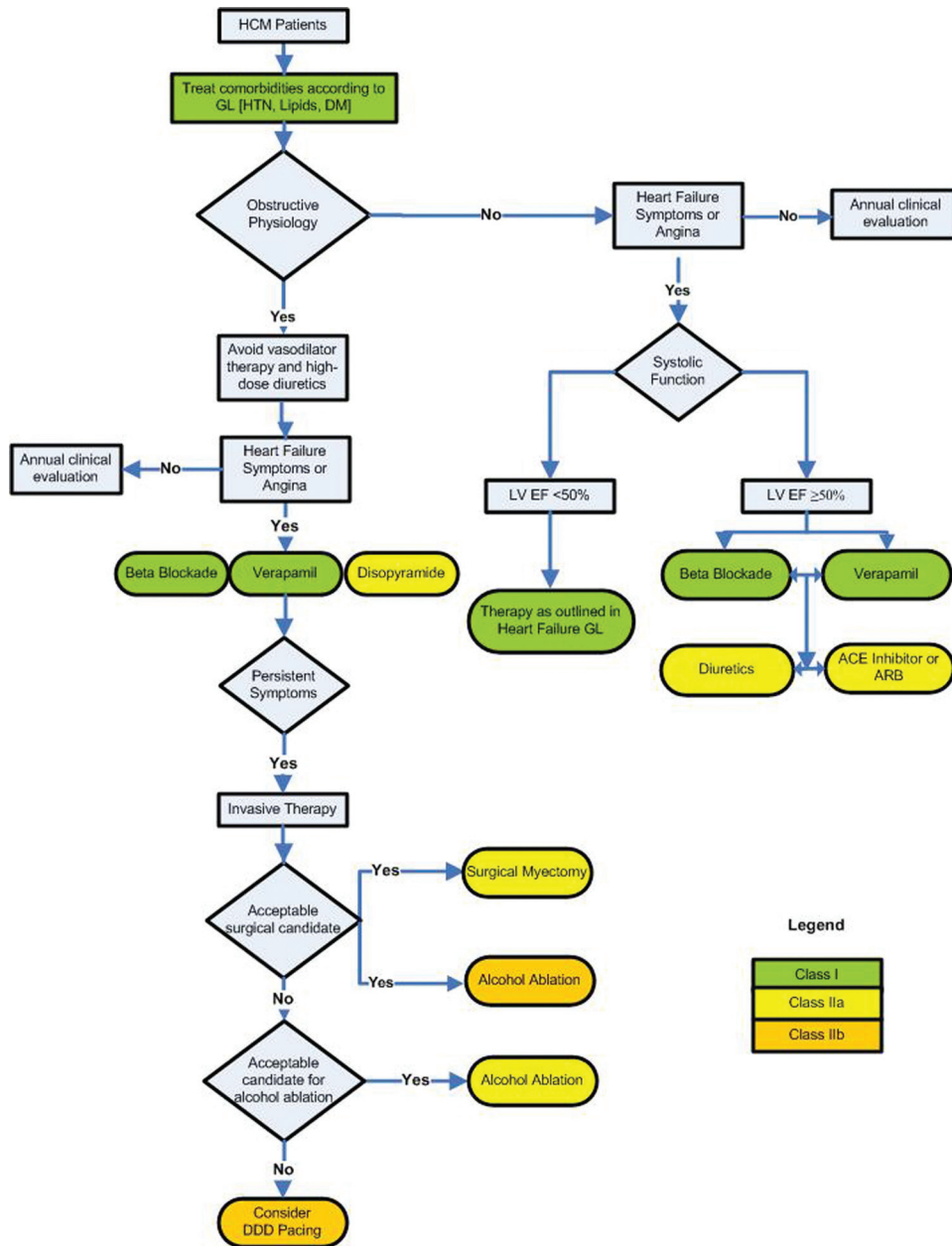
There are no published studies addressing the performance characteristics of stress echocardiography to detect or exclude CAD in patients with HCM. Patients with HCM have heterogeneous wall-thickness patterns, and wall motion at rest may appear abnormal in regions of hypertrophied myocardium. Therefore, 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>67</sup> (Section 5.1).

## 9. 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, but the general approach of the writing committee is outlined in Figure 4.

### 9.1. Asymptomatic Patients

A large proportion of patients presenting with HCM are asymptomatic, and most will achieve a normal life expectancy.<sup>213,252,253</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>88</sup> Risk stratification for SCD should also be performed in all patients, irrespective of whether symptoms are present.<sup>32,38</sup>



**Figure 4.** 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.

Because concomitant CAD has a significant impact on survival in patients with HCM,<sup>240</sup> it is recommended that other risk factors that may contribute to atherosclerotic disease be aggressively treated in concordance with existing guidelines (Figure 4).<sup>32,86</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>3,38</sup>

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>32,38</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>32,38</sup>

**9.2. Symptomatic Patients**

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>32,38,88</sup>

Beta blockers are the mainstay of pharmacologic therapy and the first-line agents because of their negative inotropic effects<sup>260</sup> and their ability to attenuate adrenergic-induced tachycardia (Figure 4). 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>255,256</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 4).<sup>99,257</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>258–262</sup> Diltiazem has also been shown to improve measures of diastolic performance<sup>263</sup> and to prevent or diminish myocardial ischemia.<sup>264</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 used with caution because of the potential for high-grade atrioventricular block. 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 (Figure 4).<sup>68,265</sup> Diuretics may be effective for symptomatic relief in patients with pulmonary congestion but should be used judiciously in those with outflow tract obstruction at rest or with provocation.

### 9.3. Invasive Therapies

For severe refractory symptoms that are attributable to LVOT obstruction, invasive therapies can be used to improve quality of life (Figure 4). Surgical approaches have been used for 5 decades<sup>52,220</sup> so that relief of outflow tract obstruction and symptoms can be achieved with minimal perioperative morbidity or mortality in experienced centers.<sup>64,65</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 used for the past 17 years, has become the leading strategy in these circumstances.<sup>266</sup>

#### 9.3.1. 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.<sup>52,220</sup> 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>32</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 4). Considerations that 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>26,224,267–272</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.

#### 9.3.2. 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>273</sup> less in septal ablation, and only in the minority of patients studied in trials of pacemaker therapy.<sup>132,134,135,274</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>60,275</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>60</sup> Procedural success is associated with very low mortality (<1% for myectomy,<sup>64,65,276</sup> ranging from 0% to 4% for ablation),<sup>277–279</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>279a–c</sup>

#### 9.3.3. 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 and relatively uncommon

in general cardiology practice, this is an important issue. 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.

#### 9.3.4. 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 4).<sup>126,273,280–288</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>270,289</sup> Both the traditional myectomy (Morrow procedure) with about a 3-cm long resection<sup>284</sup> or extended myectomy (a resection of about 7 cm) are currently used.<sup>270,289</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>297</sup>

In selected circumstances, some surgeons have also used concomitant mitral valve repair, particularly when the anterior leaflet is elongated. 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.

##### 9.3.4.1. Outcomes

**Early Results.** Based on the experience and data assembled from multiple centers worldwide over the last 4 decades,<sup>126,273,280,282,283,285,286</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>32,290</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>291</sup> and consequently abolition of SAM and mitral-septal contact.<sup>289,292,293</sup> Mitral regurgitation is also usually eliminated without the need for additional mitral valve surgery.<sup>56</sup> With myectomy, left atrial size (and possibly long-term risk for AF) is reduced<sup>65</sup> and LV pressures (and wall stress) are normalized.<sup>32,56,64,291,294</sup> Thus, obstructive HCM is a surgically and mechanically reversible form of heart failure. In experi-

enced centers, operative risk is now particularly low, in the range of <1%.<sup>290</sup>

**Late Results.** Relief of outflow obstruction by septal myectomy may also extend the longevity of patients with HCM.<sup>64</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>64</sup> Similarly the rate of SCD or appropriate ICD discharge after myectomy is very low (<0.9%).<sup>64,295,296</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.

##### 9.3.4.2. Complications

Complications following myectomy are rare when performed in experienced centers.<sup>297</sup> The risk of complete heart block is approximately 2% with myectomy (higher in myectomy 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>298</sup> Iatrogenic ventricular septal defect occurs in <1% of patients.

##### 9.3.4.3. 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>224,299</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.

#### 9.3.5. Alcohol Septal Ablation

First reported in 1995,<sup>266</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>129</sup> Since its development, alcohol septal ablation has been performed successfully in a large number of patients.<sup>62</sup>

Contrast angiography of the septal perforator through the balloon central lumen with simultaneous echocardiographic guidance<sup>300,301</sup> confirms delivery to only the target myocardium. About 1 to 3 mL of alcohol is infused in controlled fashion.<sup>59,302–304</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 provokable 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.

### 9.3.5.1. 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>127,305</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. 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 4). 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.

### 9.3.5.2. Results

Necrosis of the basal ventricular septum<sup>306</sup> produces an immediate fall in gradient from decreased septal contraction in >90% of patients.<sup>66,279,307–309</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>63,279,310–312</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>62,279,313–316</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>317–319</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>320</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>60,129</sup> Despite age differences in treatment allocation, with septal ablation patients on average approximately 10 years older in clinical practice,<sup>317,318</sup> the 4-year survival rate is similar for the 2 procedures.<sup>60,128</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.

### 9.3.5.3. Complications

In approximately half of patients undergoing alcohol septal ablation, temporary complete atrioventricular block occurs during the procedure.<sup>321–323</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>60,62,129,318</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>144,275,324</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>301,314,325–331</sup> and SCD following septal ablation<sup>296</sup> in about 3% to 10% of patients both with or without risk factors for SCD. 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>150,328,332</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>64,295,296</sup>

Meta-analyses have indicated no difference between septal ablation and myectomy in the medium-term incidence of SCD or all-cause mortality.<sup>317,333</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>144,325</sup>

### 9.3.6. DDD Pacing

Implantation of a dual-chamber pacemaker was proposed as an alternative treatment for patients with severe symptomatic obstructive HCM.<sup>335–337</sup> However, there have been 3 randomized crossover trials showing that 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 responsible for the perceived improvement in symptoms.<sup>136,137,338</sup> However, there is some evidence that patients >65 years of age may be a subgroup who achieve the greatest benefit.<sup>136</sup> There are no data that dual-chamber pacing either reduces the risk of SCD in patients with HCM, alters the underlying progression of disease, or is of benefit to patients with nonobstructive HCM.<sup>136,335,339</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.

### 9.3.7. LV Systolic Dysfunction

Standard heart failure therapies should be implemented in patients with HCM when EF is  $\leq 50\%$ . 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.

## 9.4. Prevention of SCD

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>143–146,148,150</sup> ICDs offer the only effective means of preventing SCD and prolonging life in patients with HCM.<sup>150</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.

### 9.4.1. Established Risk Markers

#### 9.4.1.1. 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>145,146,148,150,340</sup>

#### 9.4.1.2. 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>147,149,155</sup> whereas others have suggested that family history is an independent predictor.<sup>155</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.

#### 9.4.1.3. 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>147,152</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).<sup>152</sup>

#### 9.4.1.4. Nonsustained Ventricular Tachycardia

Although sustained ventricular arrhythmia is clearly associated with SCD, the data for NSVT are less robust. However, 1 contemporary study showed that NSVT is independently associated with SCD on multivariate analysis<sup>30</sup> and is more important in younger patients (<30 years of age).<sup>33</sup> Furthermore, exercise-induced NSVT has been found to have independent association with SCD.<sup>341</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.

#### 9.4.1.5. 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>156,342</sup> studies have shown at least a univariate association between maximum wall thickness and SCD,<sup>148,342,343</sup> whereas other large studies have shown that when magnitude of hypertrophy is  $\geq 30$  mm, there is an independent association with SCD.<sup>147,152,158</sup>

#### 9.4.1.6. 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>70,71</sup> Two studies have shown a univariate association between this finding and subsequent SCD.<sup>30,71,147,149</sup>

### 9.4.2. Other Potential SCD Risk Modifiers

#### 9.4.2.1. LVOT Obstruction

Although some studies have not found a significant association between LVOT obstruction and SCD,<sup>51,158,212</sup> other studies have found higher rates of SCD among patients with resting gradients  $\geq 30$  mm Hg<sup>30,149</sup> and that the risk is positively correlated with severity of LVOT obstruction.<sup>30</sup> Conversely, relief of outflow tract obstruction through surgical myectomy is associated with very low rates of SCD.<sup>64,307</sup> A limitation to using LVOT obstruction as an independent risk marker is that the obstruction in HCM is dynamic and highly variable.<sup>225,344</sup>

#### 9.4.2.2. 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>82</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>78,79,82</sup> More recent studies have shown a relationship between LGE and SCD and heart failure, but with low positive predictive accuracy.<sup>80,81</sup>

#### 9.4.2.3. LV Apical Aneurysm

A subset of patients with HCM (prevalence about 2%) develop a thin-walled LV apical aneurysm associated with regional scarring<sup>75</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.

#### 9.4.2.4. 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>20,227,345,346</sup> However, subsequent studies of less selected consecutive patients with 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>8,347–349</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.

#### 9.4.3. 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>147,156,350</sup> Notably, in the international HCM-ICD registry,<sup>150</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 respect to age, the strength of the risk factor, and the risk-benefit of lifelong ICD therapy.<sup>150,351</sup>

### 9.5. ICD Therapy in HCM

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 tachyarrhythmia 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>150,351</sup>

There have been 2 reports from an international, multi-center 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>150,153</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 4% per year.<sup>150,153</sup> The number of risk markers present did not predict subsequent device discharge.<sup>150,351</sup>

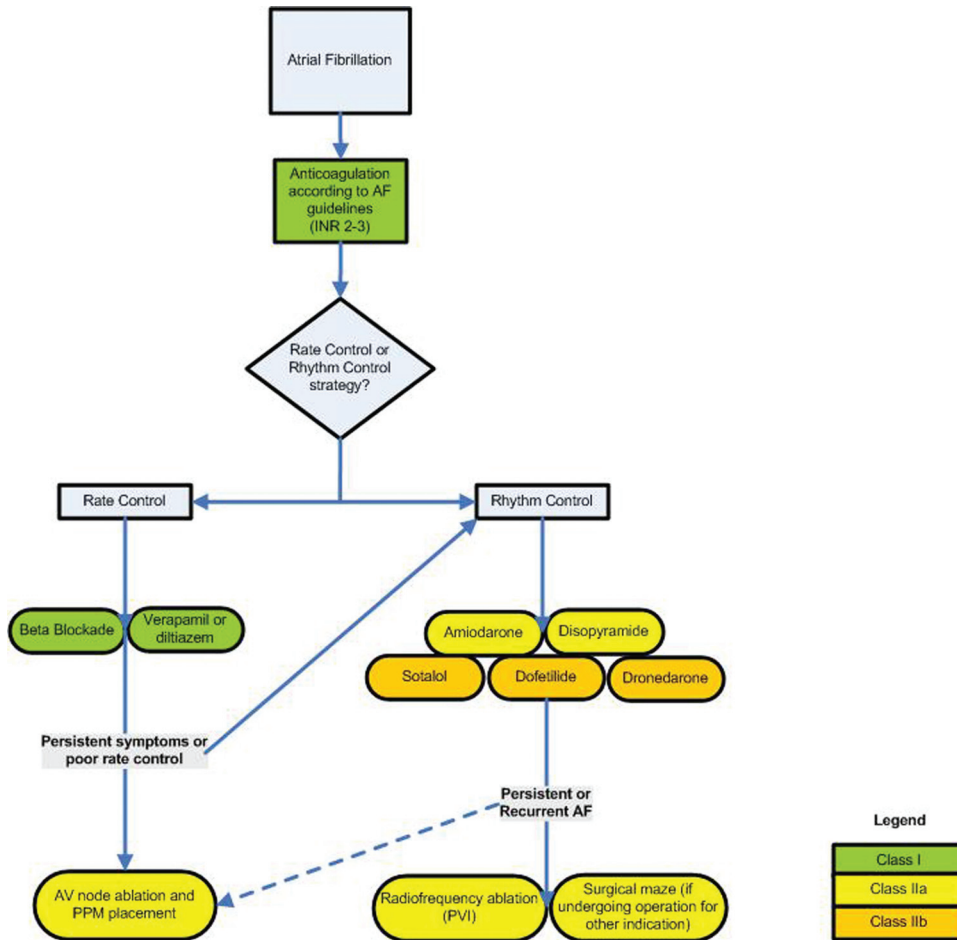
#### 9.5.1. Complications of ICD Therapy in HCM

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>351</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 a device-related infection; and approximately 2% to 3% who experienced bleeding or thrombosis complications.<sup>150,351</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>143</sup> ICD leads fail at a rate of 0.5% to 1% per year, although there are data showing that failure rates are increased in younger populations.<sup>160</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>352</sup> and small-diameter high-voltage leads prone to fracture.<sup>160,353</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>354</sup>

In patients with LVOT obstruction in whom ICDs are indicated, dual-chamber pacing may have the potential to reduce gradient and symptoms (Section 2.10). In general, the younger the patient, the more appropriate it is for single-



**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.

chamber devices to be used to decrease the amount of hardware in the venous system.

**9.6. Participation in Competitive or Recreational Sports and Physical Activity**

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>166–168,355</sup> The American College of Cardiology Bethesda Conference No. 36,<sup>163,339</sup> as well as the European Society of Cardiology guidelines<sup>164,356</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>163,356</sup> It should be underscored that these consensus recommendations for competitive athletes are independent of those for noncompetitive, informal recreational sporting activities.<sup>87</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 com-

petitive 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 attention paid to maintaining volume status. Detailed recommendations for individual sports appear in Table 2.

**9.7. Atrial Fibrillation**

AF is an important cause of symptoms, morbidity, and even mortality in patients with HCM.<sup>50,172</sup> Patients with HCM are at increased risk of AF compared with age-matched cohorts, but AF is seldom seen in patients with HCM who are <30 years of age and becomes more prevalent with age. 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>172,357</sup>

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>50,172</sup> Occurrence of paroxysmal, persistent, or chronic AF is a strong



indication for anticoagulation with a vitamin K antagonist.<sup>170</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. Aspirin should be reserved for those who cannot or will not take warfarin or other oral anticoagulants, but its efficacy in HCM is unestablished.

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>170</sup> The limited published data on amiodarone suggest that it is safe and effective for patients with HCM.<sup>358–361</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>68,362</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. 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>175,178,179,363</sup> The surgical maze procedure for AF has shown some limited success<sup>364</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.

## 10. 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>365(p83)</sup> Although consider-

ation 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>367</sup>

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||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>366</sup>

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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 ≥5% of the voting stock or share of the business entity, or ownership of ≥\$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. Section numbers apply to the full-text guideline.

†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 Dilisizian	Organizational Reviewer—ASNC	None	None	None	None	None	None
N.A. Mark Estes III	Organizational Reviewer—HRS	<ul style="list-style-type: none"> <li>● Boston Scientific*</li> </ul>	None	None	None	None	None
Michael Givertz	Organizational Reviewer—HFSA	None	None	None	None	None	None
Stuart Katz	Organizational Reviewer—HFSA	<ul style="list-style-type: none"> <li>● Amgen</li> <li>● Bristol-Myers Squibb</li> <li>● Paracor</li> <li>● Terumo</li> </ul>	<ul style="list-style-type: none"> <li>● Otsuka</li> </ul>	None	None	None	None
John A. Kern	Organizational Reviewer—AATS	None	None	None	None	None	None
Sherif Nagueh	Organizational Reviewer—ASE	None	None	None	None	None	None
Paul Sorajja	Organizational Reviewer—SCAI	None	None	None	None	None	None
Kirk T. Spencer	Organizational Reviewer—ASE	None	None	None	None	None	None
Gus J. Vlahakes	Organizational Reviewer—STS	None	None	None	None	None	None
Herbert B. Ward	Organizational Reviewer—STS	None	None	None	None	None	None
Nancy M. Albert	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Jeffrey L. Anderson	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	<ul style="list-style-type: none"> <li>● AstraZeneca (DSMB)</li> <li>● Toshiba</li> </ul>	None	None
Richard G. Bach	Content Reviewer	None	None	None	None	None	None
Jorge A. Belardi	Content Reviewer—ACCF Interventional Scientific Council	<ul style="list-style-type: none"> <li>● Boston Scientific</li> <li>● Medtronic CardioVascular</li> <li>● Medtronic Vascular</li> </ul>	<ul style="list-style-type: none"> <li>● Abbott</li> <li>● Boston Scientific</li> </ul>	None	None	None	None
Eugene Braunwald	Content Reviewer	None	None	None	None	None	None
John E. Brush, Jr	Content Reviewer	<ul style="list-style-type: none"> <li>● Prometheus Payment†</li> <li>● United Healthcare</li> </ul>	None	None	None	None	None
James A. Burke	Content Reviewer—ACCF Interventional Scientific Council	None	None	None	None	None	None
Jose G. Diez	Content Reviewer—ACCF Interventional Scientific Council	<ul style="list-style-type: none"> <li>● Sanofi-aventis</li> </ul>	<ul style="list-style-type: none"> <li>● Sanofi-aventis</li> </ul>	None	None	None	None
Jon C. George	Content Reviewer—ACCF Interventional Scientific Council	None	None	None	None	None	None
Robert A. Guyton	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Judith S. Hochman	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	<ul style="list-style-type: none"> <li>● GlaxoSmithKline</li> </ul>	None	None	None	None	None

(Continued)

## Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Frederick G. Kushner	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Gilead I. Lancaster	Content Reviewer—ACCF Board of Governors	None	None	● Cardiogal	None	None	None
Bruce W. Lytle	Content Reviewer	None	None	None	None	None	None
Abeel A. Mangi	Content Reviewer	None	None	None	None	None	None
Gerard R. Martin	Content Reviewer—ACCF Adult Congenital and Pediatric Cardiology Council	None	None	None	None	None	None
Debabrata Mukherjee	Content Reviewer—ACCF Interventional Scientific Council	None	None	None	None	None	None
Joseph P. Murgio	Content Reviewer	None	None	None	None	None	None
Patrick T. O'Gara	Content Reviewer	None	None	None	None	None	None
E. Magnus Ohman	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
John F. Robb	Content Reviewer—ACCF Board of Governors	None	None	None	None	None	None
George P. Rodgers	Content Reviewer—ACCF Board of Governors	None	None	None	None	None	None
Chris Semsarian	Content Reviewer	None	None	None	None	None	None
Richard J. Shemin	Content Reviewer—ACCF Surgeons' Scientific Council	● Edwards Lifesciences	None	None	None	None	None
Mark V. Sherrid	Content Reviewer	None	● Boston Scientific ● GeneDx ● Medtronic ● St. Jude Medical	None	● CardioNet	None	None
William H. Spencer	Content Reviewer	None	None	● Medtronic*	None	None	None
Paolo Spirito	Content Reviewer	None	None	None	None	None	None
Edward F. Terrien	Content Reviewer—ACCF Board of Governors	None	None	None	None	None	None
Juan Villafane	Content Reviewer—ACCF Board of Governors	None	None	None	None	None	None
Gary D. Webb	Content Reviewer—ACCF Adult Congenital and Pediatric Cardiology Council	None	None	None	None	None	None
Walter R. Wilson	Content Reviewer	None	None	None	None	None	None

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\*Significant relationship.

†No financial benefit.

AATS indicates American Association for Thoracic Surgery; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; DSMB, data safety monitoring board; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; SCAI, Society for Cardiovascular Angiography and Interventions; and STS, Society of Thoracic Surgeons.