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# 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

Writing Committee Members, Bernard J. Gersh, Barry J. Maron, Robert O. Bonow, Joseph A. Dearani, Michael A. Fifer, Mark S. Link, Srihari S. Naidu, Rick A. Nishimura, Steve R. Ommen, Harry Rakowski, Christine E. Seidman, Jeffrey A. Towbin, James E. Udelson and Clyde W. Yancy

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# 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.[1] 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

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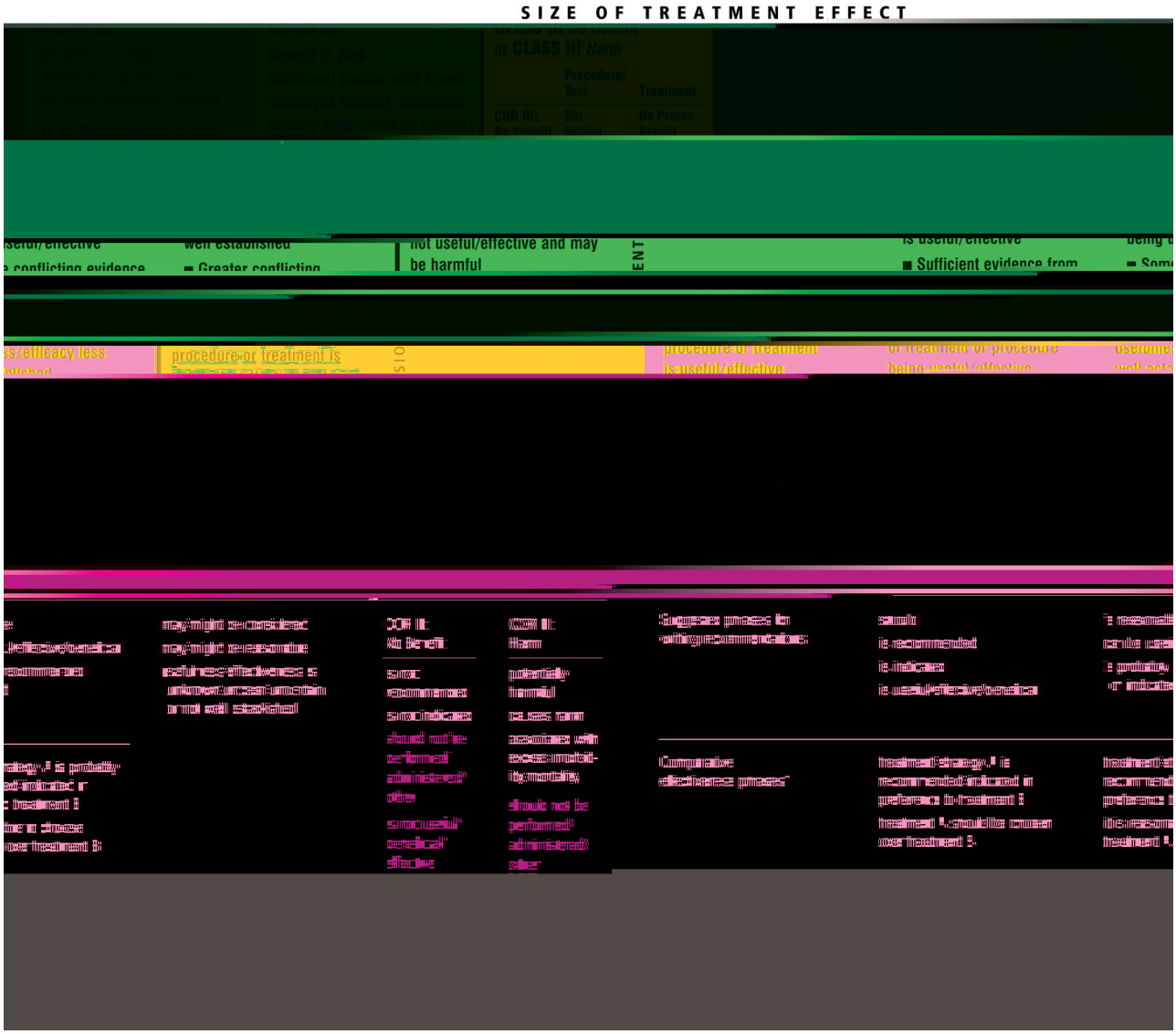
Table 1. Applying Classification of Recommendation and Level of Evidence




A recommenda ion i h Le el of E idence B or C doe no impl ha he recommenda ion i eak. Man impor an clinical q e ion addre ed in he g ideline do no lend hem el e o clinical rial . Al ho gh randomi ed rial are na ailable, here ma be a er clear clinical con en ha a par ic lar e or herap i ef l or effec i e.

*Da a a ailable from clinical rial or regi rie abo he ef lne /efficac in differen bpop la ion , ch a e , age, hi or of diabe e , hi or of prior m ocardial infarc ion, hi or of hear fail re, and prior a pirin e.

For compara i e effec i ene recommenda ion (Cla I and IIa; Le el of E idence A and B onl ), die ha ppor he e of compara or erb ho ld in ol e direc compari on of he rea men or ra egie being e al a ed.

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. 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-

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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[1a] 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) and AHA (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, noninvasive 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[2] and the most important early clinical report by Braunwald et al in 1964.[3]

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

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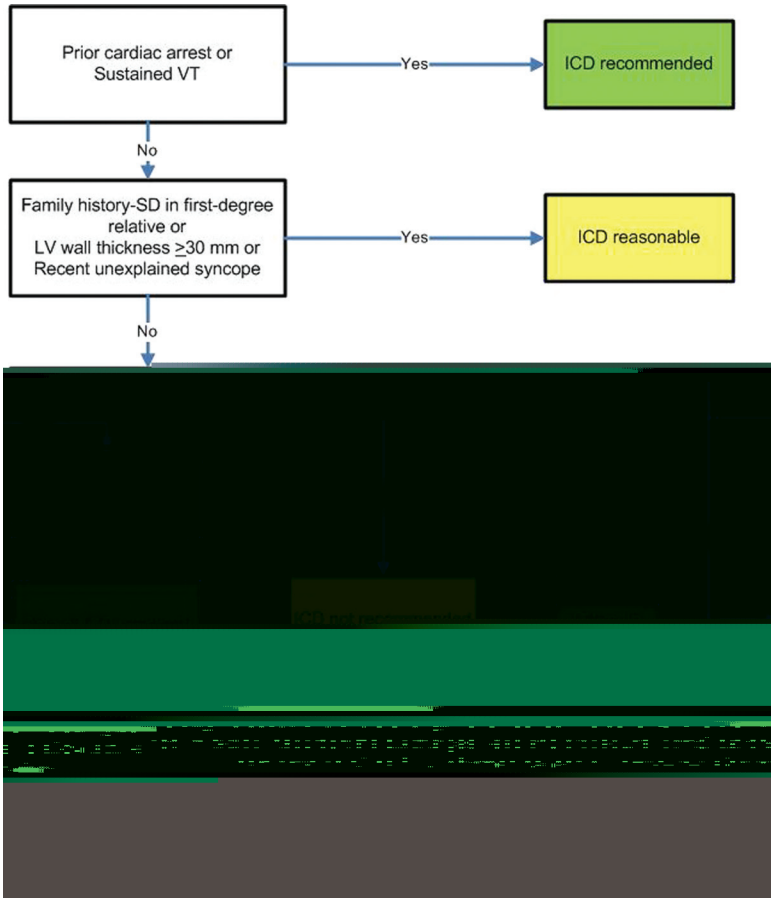


Figure 1. Indications for ICDs in HCM. *SCD risk modi ers include established risk factors and emerging risk modi ers (Section 9.4.2). BP indicates blood pressure; ICD, implantable cardioverter-de brillator; LV, left ventricular; SCD, sudden cardiac death; SD, sudden death; and VT, ventricular tachycardia.

### Class IIa

1. **It is reasonable to assess blood pressure response during exercise as part of SCD risk stratification in patients with HCM.[30,71,149] *(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.[78,82] *(Level of Evidence: C)***
   b. **Double and compound mutations (ie, >1). *(Level of Evidence: C)***
   c. **Marked LVOT obstruction.[30,48,51,149] *(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).[144,150,153,154] *(Level of Evidence: C)***
2. **ICD placement is recommended for patients with HCM with prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant VT.[145,146,148,150] *(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.[155] *(Level of Evidence: C)***
   b. **A maximum LV wall thickness greater than or equal to 30 mm.[147,156–158] *(Level of Evidence: C)***
   c. **One or more recent, unexplained syncopal episodes.[152] *(Level of Evidence: C)***

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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.‡[33,144] *(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.‡[70,71,149] *(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.‡[144] *(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,‡ particularly in the presence of significant outflow obstruction.[70,71,149] *(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.[159–162] *(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.[159] *(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).[136–138,159] *(Level of Evidence: B)***

‡SCD risk modi ers are discussed in Section 9.4.2.

## 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).[163,164] *(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.[87] *(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.[163–169] *(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.[170–172] (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.[173]) *(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.[170,172] *(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.[170,174] *(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.[175–179] *(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 signi cant valve disease, advanced liver failure, or severe renal failure (creatinine clearance 15 mL/min).[173]

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Table 2. Recommendations for the Acceptability of Recreational (Noncompetitive) Sports Activities and Exercise in Patients With HCM*

| In en i Le el | Eligibili Scale for HCM |
|---|---|
| High | |
| Ba ke ball (f ll co r ) | 0 |
| Ba ke ball (half co r ) | 0 |
| Bod b ilding | 1 |
| G mna ic | 2 |
| Ice hocke | 0 |
| Racq e ball/ q a h | 0 |
| Rock climbing | 1 |
| R nning ( prin ing) | 0 |
| Skiing (do nhill) | 2 |
| Skiing (cro -co n r ) | 2 |
| Soccer | 0 |
| Tenni ( ingle ) | 0 |
| To ch (flag) foo ball | 1 |
| Wind rfing | 1 |
| Modera e | |
| Ba eball/ of ball | 2 |
| Biking | 4 |
| Hiking | 3 |
| Mode hiking | 4 |
| Mo orc cling | 3 |
| Jogging | 3 |
| Sailing | 3 |
| S rfing | 2 |
| S imming (lap ) | 5 |
| Tenni (do ble ) | 4 |
| Treadmill/ a ionar bic cle | 5 |
| Weigh lif ing (free eigh ) | 1 |
| Lo | |
| Bo ling | 5 |
| Bri k alking | 5 |
| Golf | 5 |
| Hor eback riding | 3 |
| Sc ba di ing | 0 |
| Ska ing | 5 |
| Snorkeling | 5 |
| Weigh (nonfree eigh ) | 4 |

*Recrea ional por are ca egori ed according o high, modera e, and lo le el of e erci e and graded on a rela i e cale (from 0 o 5) for eligibili , i h 0 o 1 indica ing generall no ad i ed or rongl di co raged; 4 o 5, probabl permi ed; and 2 o 3, in ermedia e and o be a e ed clinicall on an indi id al ba i . The de igna ion of high, modera e, and lo le el of e erci e are eq i alen o an e ima ed 6, 4 o 6, and 4 me abolic eq i alen , re pec i el .

A me ab ence of labora or DNA geno ping da a; herefore, limi ed o clinical diagno i .

The e por in ol e he po en ial for ra ma ic inj r , hich ho ld be aken in o con idera ion for indi id al i h a ri k for impaired con cio ne .

The po ibili of impaired con cio ne occ rring d ring a er-rela ed ac i i ie ho ld be aken in o acco n i h re pec o he indi id al pa ien' clinical profile.

Recommenda ion generall differ from ho e for eigh - raining machine (nonfree eigh ), ba ed largel on he po en ial ri k of ra ma ic inj r a ocia ed i h epi ode of impaired con cio ne d ring bench-pre mane er ; o her i e, he ph iologic effec of all eigh - raining ac i i ie are regarded a imilar i h re pec o he pre en recommenda ion .

Indi id al por ing ac i i no a ocia ed i h he eam por of ice hocke .

Adap ed i h permi ion from Maron e al.[87]

## 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.[43,44,180,181] *(Level of Evidence: C)***
2. **For patients (mother or father) with HCM, genetic counseling is indicated before planned conception. *(Level of Evidence: C)***
3. **In women with HCM and resting or provocable LVOT obstruction greater than or equal to 50 mm Hg and/or cardiac symptoms not controlled by medical therapy alone, pregnancy is associated with increased risk, and these patients should be referred to a high-risk obstetrician. *(Level of Evidence: C)***
4. **The diagnosis of HCM among asymptomatic women is not considered a contraindication for pregnancy, but patients should be carefully evaluated in regard to the risk of pregnancy. *(Level of Evidence: C)***

### Class IIa

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

### Class III: Harm

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

# 3. Prevalence/Nomenclature/ Differential Diagnosis

## 3.1. Prevalence

HCM is a common genetic cardiovascular disease. In addition, HCM is a global disease,[182] with epidemiological studies from several parts of the world[183] 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.[184]

### *3.1.1. Clinical Definition and Differential Diagnosis*

HCM is the preferred nomenclature to describe this disease,[185] 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.[67] 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,[32,38,184–187] with the caveat that patients who are genotype positive may be phenotypically negative without overt hypertrophy.[188,189] Clinically, HCM is

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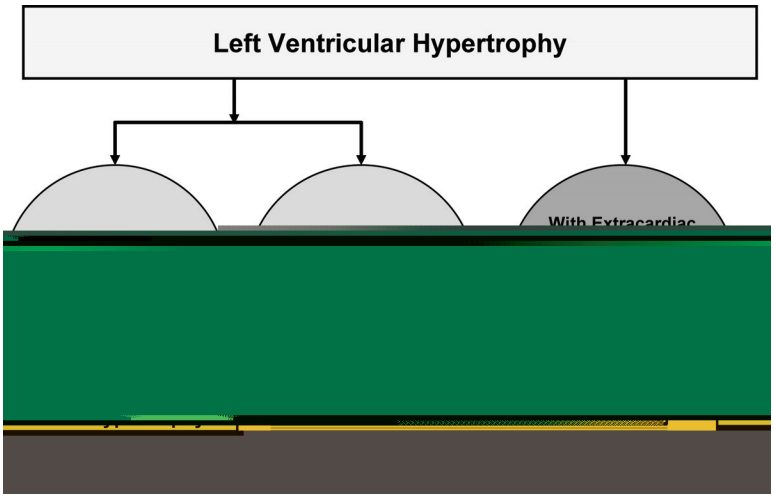


Figure 2. Summary of the nomenclature that distinguishes HCM from other genetic diseases associated with LV hypertrophy. *At this time the overwhelming evidence links the clinical diagnosis of HCM with a variety of genes encoding protein components of the cardiac sarcomere. However, it is possible that in the future other nonsarcomeric (but also nonmetabolic) genes may prove to cause HCM. †An example is Noonan syndrome with cardiomyopathy. Modi ed with permission from Maron et al.[187]

usually recognized by a maximal LV wall thickness ≥15 mm. In the case of children, increased LV wall thickness is defined as wall thickness ≥2 standard deviations above the mean (z score ≥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,[37,76,190] 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.[76]

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"),[191–195] 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.[191–195]

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,[196,197] Fabry disease,[198] or storage diseases caused by mutations in the genes encoding the γ-2-regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase (PRKAG2) or the X-linked lysosome-associated membrane protein gene (*LAMP2*; Danon disease).[199–201] 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[202–206] (Figure 2). In addition, differential diagnosis of HCM may require distinction from dilated cardiomyopathy when HCM presents in the end stage.[68]

### 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.[43,199,207,208] Intergenetic diversity is compounded by considerable intragene 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.[43,199,207,208]

### 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.[38] Although HCM is one of the most common forms of genetic heart disease and relatively common in the general population,[184] this disease entity is infrequent in general clinical practice, with most cardiologists responsible for the care of only a few patients with HCM.[209] 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").[209,210]

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

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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,[8,40] it is recommended that other risk factors that may contribute to atherosclerotic disease be aggressively treated in concordance with existing guidelines (Figure 4).[32,86]

Hydration and avoidance of environmental situations where vasodilatation may occur are important in the asymptomatic patient with resting or provocable 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.[31,38]

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.[32,38] 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.[32,38]

## 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.[32,38,88]

Beta blockers are the mainstay of pharmacologic therapy and the first-line agents because of their negative inotropic effects[260] and their ability to attenuate adrenergic-induced tachycardia (Figure 4). The reduction in heart rate also

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prolongs the diastolic filling period, which may allow for more efficient inactivation of myocardial contractile proteins, thereby improving diastolic filling.[255,256]

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).[99,257] 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.[258–262] Diltiazem has also been shown to improve measures of diastolic performance[263] and to prevent or diminish myocardial ischemia.[264] 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).[64,265] 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[52,220] so that relief of outflow tract obstruction and symptoms can be achieved with minimal perioperative morbidity or mortality in experienced centers.[64,65] 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.[266]

### *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.[52,220] Maximal instantaneous gradients of at least 50 mm Hg at rest or with physiologic provocation are necessary to produce symptoms amenable to invasive therapies.[32]

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.[224,267–272] 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,[273] less in septal ablation, and only in the minority of patients studied in trials of pacemaker therapy.[133,134,135,274] 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.[60,275]

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).[60] Procedural success is associated with very low mortality ( 1% for myectomy,[64,65,276] ranging from 0% to 4% for ablation),[277–279] 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.[279a–c]

### *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

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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).[126,273,280–288] 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.[270,289] Both the traditional myectomy (Morrow procedure) with about a 3-cm long resection[284] or extended myectomy (a resection of about 7 cm) are currently used.[270,289]

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.[287]

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,[126,273,280,282,283,285,286] 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.[62,290]

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)[291] and consequently abolition of SAM and mitral-septal contact.[288,292,293] Mitral regurgitation is also usually eliminated without the need for additional mitral valve surgery.[56] With myectomy, left atrial size (and possibly long-term risk for AF) is reduced[65] and LV pressures (and wall stress) are normalized.[32,56,64,291,294] Thus, obstructive HCM is a surgically and mechanically reversible form of heart failure. In experienced centers, operative risk is now particularly low, in the range of 1%.[290]

*Late Results.* Relief of outflow obstruction by septal myectomy may also extend the longevity of patients with HCM.[64] 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.[64] Similarly the rate of SCD or appropriate ICD discharge after myectomy is very low ( 0.9%).[64,295,296] 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.[287] 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%).[297,298] 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)[224,299] 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,[56,66] alcohol septal ablation uses transcoronary 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.[129] Since its development, alcohol septal ablation has been performed successfully in a large number of patients.[62]

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

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|---|---|---|---|---|---|---|---|
| Dual-chamber pacing for HCM: A randomized, double-blind, crossover trial<br><br>Nishimura, R, et al. (35) | To determine the intermediate term outcome of DDD pacing in pts with HCM | Randomized double-blind crossover study. Pts randomized for 3 mo each of DDD pacing and back-up AAI pacing. | 21 pts (Mean age 58; 35-74 y). | Single center trial of selected pts with obstructive HCM and severe symptoms refractory to drug therapy | Symptoms, NYHA class, LVOT gradient, quality of life, treadmill time, peak $VO_2$. | 6 mo of follow-up, LVOT gradient had decreased from 76 +/- 61 to 55 +/- 38 mmHg after DDD pacing and 83 +/- 59 mmHg after AAI pacing. Quality of life and exercise duration were significantly improved from the baseline state compared to the DDR, but not significantly different between the DDD arm and the back-up arm. 63% of pts had symptomatic improvement during the DDD arm, but 42% had symptomatic improvement during the AAI arm. Peak oxygen consumption did not differ significantly. Symptoms did not change in 31% and 5% experienced deterioration of symptoms. | This trial showed that dual-chamber pacing may relieve symptoms and decrease gradient in pts with HCM, but there are some pts in whose symptoms do not change and become even worse. Symptomatic improvement may occur without hemodynamic benefit suggesting the role of a placebo effect. |

Significant improvement

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic pts with obstructive HCM. A randomized, double-blind, crossover study (M-PATHY)<br><br>Maron, B, et al. (37) | To determine the intermediate term outcome of DDD pacing in pts with HCM. | Randomized double-blind crossover study. DDD pacing implants in all pts, randomized then to a DDD mode and pacing back-up AAI mode in a double-blind crossover study design, followed by an uncontrolled 6-mo pacing trial. | 48 pts (age 53 +/- 17, 22-83 y). | Pts with obstructive HCM and severe symptoms refractory to drug therapy | Symptoms, NYHA class, LVOT gradient, quality of life, treadmill time, peak $VO_2$. | DDD versus AAI mode comparison at 6 mo indicated no significant change in exercise capacity, quality of life, or NYHA class. During a 12-mo follow-up of 6 further mo of continuous pacing, there was a significant increase in functional class and quality of life, but no change in peak oxygen consumption. The gradient was reduced from 82 +/- 32 mmHg to 48 +/- 32 mmHg. There was no change in gradient in 43%. Only 12% had a clinical response (improvement in NYHA class, quality of life, treadmill time), and these were all pts age >65 y. | This trial showed perceived symptomatic improvement was most consistent with a substantial placebo effect during the randomization process. Longer uncontrolled pacing periods had subjective benefit, but did not have objective improvement in cardiovascular performance and there was only modest reduction in outflow tract gradient. |
| Dual chamber pacing for pts with hypertrophic obstructive cardiomyopathy: A clinical perspective in 2000.<br><br>Erwin, J, et al. (38) | To determine the long-term outcome of pts with HCM. | Cohort trial (single center) DDD pacemakers implanted in all pts | 28 pts (56 +/- 16 y) | Pts with obstructive HCM and severe symptoms refractory to drug therapy | Symptoms and LVOT gradient. | At a follow-up of 24 +/- 14 mo (max 50 mo), 47% of pts improved but 53% of pts did not improve in terms of symptomatic response. LVOT gradient decreased from 95 +/- 40 to 62 +/- 47 mmHg. | This is a much lower "success" rate with long-term follow-up of pts who underwent dual-chamber pacing, with less than half of the pts having symptomatic improvement. There was no difference in the gradient response between those pts who improved versus those who did not improve. The residual gradient was still >60 mmHg, which is severe obstruction. |
| Long-term follow-up of pts with obstructive HCM treated with dual-chamber pacing.<br><br>Megevand, A, et al. (39) | To determine the long-term outcome of DDD pacing in pts with HCM. | Single center cohort trial. DDD pacemaker implanted in all pts. | 18 pts (mean age 47 y) | Pts with obstructive HCM and severe symptoms refractory to drug therapy. Only pts who had an initial acute hemodynamic benefit | Outflow tract gradient and NYHA class | At the end of a follow-up of 49 +/- 33 mo, the gradient of 82 +/- 35 dropped to 32 +/- 23. There was a beneficial result in NYHA class from 2.4 to 1.8. | This study reports the long-term outcome of a cohort of pts who had a dual-chamber pacemaker implanted who had a beneficial acute hemodynamic study. There was a significant reduction in symptoms as well as sustained decrease in LVOT obstruction at a follow-up of over 4 years. |

HCM indicates hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NYHA, New York Hear Association; $VO_2$, oxygen consumption and patients, pts.

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Prognosis of asymptomatic pts with HCM and NSVT.<br><br>Spirito P, et al. (43) | Assess prognostic significance of NSVT in asymptomatic or mildly symptomatic HCM pts | 3 center retrospective study | 151 pts | HCM Pts. Exclusions: prior syncope, NYHA class >2; any cardioactive medications | SD | Univariate | | | p=0.24 | | | | | |
| | | | | | | Multi-variate | | | | | | | | |
| Prognostic value of NSVT and the potential role of amiodarone treatment in HCM assessment in an unselected non-referral based patient population.<br><br>Cecchi F, et al. (44) | Evaluate antiarrhythmic therapy in HCM pts | Single center registry | 167 pts | HCM Pts. Exclusions: amiodarone use and/or absence of 24 h ambulatory ECG | Cardiac and SD | Univariate | | | NS | | | | | Only 1 SD in entire study population |

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