Complete Summary

GUIDELINE TITLE

American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines.

BIBLIOGRAPHIC SOURCE(S)

Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH 3rd, Spirito P, Ten Cate FJ, Wigle ED, Vogel RA, Abrams J, Bates ER, Brodie BR, Danias PG, Gregoratos G, Hlatky MA, Hochman JS, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Eur Heart J 2003 Nov;24(21):1965-91. [273 references] PubMed

COMPLETE SUMMARY CONTENT

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METHODOLOGY - including Rating Scheme and Cost Analysis
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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Hypertrophic cardiomyopathy

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Medical Genetics
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide a perspective on the current state of management of patients with hypertrophic cardiomyopathy
- To clarify and place into perspective those clinical issues relevant to the rapidly evolving management for hypertrophic cardiomyopathy
- To create a document that is not only current and pertinent but also has the potential to remain relevant for many years

TARGET POPULATION

Patients with or at high risk for hypertrophic cardiomyopathy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Beta-adrenergic blocking agents
    - Propranolol; atenolol; metoprolol; nadolol; sotalol
    - Dosage
    - Monotherapy versus combination therapy
2. Calcium antagonist
    - Verapamil; diltiazem
    - Dosage
    - Monotherapy versus combination therapy
3. Type I-A antiarrhythmic agent
    - Disopyramide; procainamide; quinidine
    - Dosage
    - Monotherapy versus combination therapy
4. Diuretics
5. Phosphodiesterase inhibitors
6. Surgical options
    - Heart transplantation
    - Ventricular septal myectomy
    - Myectomy with aortotomy
    - Mitral valve replacement
    - Mitral valvuloplasty (plication)
7. Dual-chamber pacing
8. Percutaneous alcohol septal ablation

MAJOR OUTCOMES CONSIDERED

- Disease progression

- Morbidity and mortality
- Survival rate
- Quality of life
- Risk of death due to heart failure and stroke
- Risk for premature sudden and unexpected death
- Risk for progressive symptoms
- Risk for progression to advanced congestive heart failure (the "end-stage phase") with left ventricular remodeling and systolic dysfunction
- Risk of complications attributable to atrial fibrillation, including embolic stroke.

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

428

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

A. The data were derived from multiple randomized clinical trials
B. The data are based on a limited number of randomized trials, nonrandomized studies, or observational registries
C. The primary basis for the recommendation was expert consensus

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This clinical scientific statement represents the consensus of a panel of experts appointed by the American College of Cardiology (ACC) and the European Society of Cardiology (ESC). The writing group comprises cardiovascular specialists and molecular biologists, each having extensive experience with hypertrophic cardiomyopathy (HCM). The panel focused largely on the management of this complex disease and derived prudent, practical, and contemporary treatment strategies for the many subgroups of patients comprising the broad HCM disease spectrum.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Class of Recommendation

Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence or opinion is in favor of the procedure or treatment

Class IIb: Usefulness/efficacy is less well established by evidence or opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The document was reviewed by 2 official reviewers nominated by the American College of Cardiology Foundation (ACCF), 3 official reviewers nominated by the European Society of Cardiology (ESC), 12 members of the ACCF Clinical Electrophysiology Committee, and 4 additional content reviewers nominated by the Writing Committee. The document was approved for publication by the ACCF Board of Trustees in August 2003 and the Board of ESC in July 2003.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The reader should refer to the original guideline document for discussions of clinical diagnosis, obstruction to left ventricular outflow, genetics and molecular diagnosis, and general considerations for natural history and clinical course.

Symptoms and pharmacological management strategies

A fundamental goal of treatment in hypertrophic cardiomyopathy (HCM) is the alleviation of symptoms related to heart failure. Pharmacological therapy has traditionally been the initial therapeutic approach for relieving disabling symptoms of exertional dyspnea (with or without associated chest pain) and improving exercise capacity for more than 35 years, since the introduction of beta-blockers in the mid-1960s. Also, drugs are often the sole therapeutic option available to the many patients without obstruction to left ventricular (LV) outflow, under resting or provocable conditions, which constitute a substantial proportion of the HCM population. Indeed, it is the convention to empirically initiate pharmacologic therapy when symptoms of exercise intolerance intervene, although there have been few randomized trials to compare the effect of drugs in HCM.

Exertional dyspnea and disability (often associated chest pain), dizziness, presyncope, and syncope usually occur in the presence of preserved systolic function and a nondilated LV. Symptoms appear to be caused in large measure by diastolic dysfunction with impaired filling due to abnormal relaxation and increased chamber stiffness, leading in turn to elevated left atrial and LV end-diastolic pressures (with reduced stroke volume and cardiac output), pulmonary congestion, and impaired exercise performance with reduced oxygen consumption at peak exercise.

The pathophysiology of such symptoms, due to this form of diastolic heart failure, may also be intertwined with other important pathophysiologic mechanisms such as myocardial ischemia, outflow obstruction associated with mitral regurgitation, and atrial fibrillation (AF). Indeed, many patients may experience symptoms largely from diastolic dysfunction or myocardial ischemia in the absence of outflow obstruction (or severe hypertrophy). Other patients (i.e., those with LV outflow obstruction) are more disabled by elevated LV pressures and concomitant mitral regurgitation than by diastolic dysfunction, as is evidenced by the often dramatic symptomatic benefit derived from major therapeutic interventions that reduce or obliterate outflow gradient (most frequently myectomy or alcohol ablation).

Chest pain in the absence of atherosclerotic coronary artery disease (CAD) may be typical of angina pectoris or atypical in character. Most chest discomfort is probably due by bursts of myocardial ischemia, evidenced by the findings of scars at autopsy, fixed or reversible myocardial perfusion defects and the suggestion of scarring by magnetic resonance imaging, net lactate release during atrial pacing, and impaired coronary vasodilator capacity. Myocardial ischemia is probably a consequence of abnormal microvasculature, consisting of intramural coronary arterioles with thickened walls (from medial hypertrophy) and narrowed lumen, and/or a mismatch between the greatly increased LV mass and coronary flow.

Because typical anginal chest pain may be part of the HCM symptom-complex, associated atherosclerotic CAD (which may complicate clinical course) is often overlooked in these patients. Therefore, coronary arteriography is indicated in patients with HCM and persistent angina who are over 40 years of age or who have risk factors for CAD, or when CAD is judged possible prior to any invasive treatment for HCM such as septal myectomy (or alcohol septal ablation).

Beta-adrenergic blocking agents

Beta-blockers are negative inotropic drugs that have traditionally been administered to HCM patients with or without obstruction, usually relying on the patient's own subjective and historical perception of benefit. However, judgments regarding treatment strategies in HCM with beta-blockers are often difficult, taking into account the frequent day-to-day variability in magnitude of symptoms. Treadmill or bicycle exercise—with or without measurement of peak oxygen consumption—have proved helpful in targeting patients for therapy or determining when changes in dosage or drugs are appropriate. If limiting symptoms progress, drug dosage may be increased within the accepted therapeutic range. Patient responses to drugs are highly variable in terms of magnitude and duration of benefit, and the selection of medications has not achieved widespread standardization and has been dependent, in part, on the experiences of individual practitioners, investigators, and centers.

Propranolol was the first drug used in the medical management of HCM, and long-acting preparations of propranolol or more cardioselective agents such as atenolol, metoprolol, or nadolol have been employed more recently. There are many reports of subjective symptomatic improvement and enhanced exercise capacity in a dose range of up to 480 mg per day for propranolol (2 mg/kg in children), both in patients with and without outflow obstruction. Although some investigators have administered massive doses of propranolol (up to 1,000 mg per day), claiming symptomatic benefit and long-term survival without major side effects, this is not generally accepted practice. However, even moderate doses of beta-blockers may affect growth in young children or impair school performance, or trigger depression in children and adolescents, and should be closely monitored in such patients.

Substantial experience suggests that standard dosages of these drugs can mitigate disabling symptoms and limit the latent outflow gradient provoked during exercise when sympathetic tone is high and heart failure symptoms occur. However, there is little evidence that beta-blocking agents consistently reduce outflow obstruction under resting conditions. Consequently, beta-blockers are a preferred drug treatment strategy for symptomatic patients with outflow gradients present only with exertion.

The beneficial effects of beta-blockers on symptoms of exertional dyspnea and exercise intolerance appear to be attributable largely to a decrease in the heart rate with a consequent prolongation of diastole and relaxation and an increase in passive ventricular filling. These agents lessen LV contractility and myocardial oxygen demand and possibly reduce microvascular myocardial ischemia. Potential side effects include fatigue, impotence, sleep disturbances, and chronotropic incompetence.

Verapamil

In 1979, the calcium antagonist verapamil was introduced as another negative inotropic agent for the treatment of HCM, and it has been widely used empirically in both the nonobstructive and obstructive forms, with a reported benefit for many patients, including those with a component of chest pain. Verapamil in doses up to 480 mg per day (usually in a sustained-release preparation) has favorable effects on symptoms, probably by virtue of improving ventricular relaxation and filling as well as relieving myocardial ischemia and decreasing LV contractility. However, aside from the mild side effects of constipation and hair loss, verapamil may also occasionally harbor a potential for clinically important adverse consequences and has been reported to cause death in a few HCM patients with severe disabling symptoms (orthopnea and paroxysmal nocturnal dyspnea) and markedly elevated pulmonary arterial pressure in combination with marked outflow obstruction. Adverse hemodynamic effects of verapamil are presumably the result of the vasodilating properties predominating over negative inotropic effects, resulting in augmented outflow obstruction, pulmonary edema, and cardiogenic shock. Because of these concerns, caution should be exercised in administering verapamil to patients with resting outflow obstruction and severe limiting symptoms. Some investigators discourage the use of calcium antagonists in the management of obstructive HCM and instead favor disopyramide (often with a beta-blocker) for such patients with severe symptoms. Verapamil is not indicated in infants due to the risk for sudden death that has been reported with intravenous administration. Dosages of oral verapamil have not been established for infants and preadolescent children.

Most clinicians favor using beta-blockers over verapamil for the initial medical treatment of exertional dyspnea, although it does not appear to be of crucial importance which drug is administered first. It has been common practice, however, to administer verapamil to those patients who do not experience a benefit from beta-blockers or who have a history of asthma. Improvement with verapamil may be due to the primary actions of the drug, and in some instances, partially attributable to withdrawal of beta-blockers and the abolition of side effects that evolved insidiously over time. At present, there is no evidence that combined medical therapy with administration of beta-blockers and verapamil is more advantageous than the use of either drug alone.

Disopyramide

The negative inotropic and Type I-A antiarrhythmic agent disopyramide was introduced into the treatment regimen for patients with obstructive HCM in 1982. There are reports of disopyramide producing symptomatic benefit (at 300 mg to 600 mg per day with a dose-response effect) in severely limited patients with resting obstruction, because of a decrease in systolic anterior motion (SAM), outflow obstruction, and mitral regurgitant volume. Anticholinergic side effects such as dry mouth and eyes, constipation, indigestion, and difficulty in micturition may be reduced by long-acting preparations through which cardioactive benefits are more sustained. Because disopyramide may cause accelerated atrioventricular (A-V) nodal conduction and thus increase ventricular rate during AF, supplemental therapy with beta-blockers in low doses to achieve normal resting heart rate has been advised.

Although disopyramide incorporates antiarrhythmic properties, there is little evidence that proarrhythmic effects have intervened in HCM patients. Nevertheless, this issue remains of some concern in a disease associated with an arrhythmogenic LV substrate; prolongation of the QT interval should be monitored while administering the drug. Furthermore, disopyramide administration may be deleterious in nonobstructive HCM by decreasing cardiac output, causing most investigators to limit its use to patients with outflow obstruction who have not responded to beta-blockers or verapamil.

At present, the information regarding drugs such as sotalol and other calcium antagonists (such as diltiazem) is insufficient to recommend their use in HCM. Diuretic agents may be added to the cardioactive drug regimen prudently—preferably in the absence of marked outflow obstruction. Because many patients have diastolic dysfunction and require relatively high filling pressures to achieve adequate ventricular filling, it may be advisable to administer diuretics cautiously. Nifedipine, because of its particularly potent vasodilating properties, may be deleterious, particularly for patients with outflow obstruction. Combined therapy with disopyramide and amiodarone (or disopyramide and sotalol), or quinidine and verapamil (or quinidine and procainamide), should also be avoided due to concern over proarrhythmia; also, administration of nitroglycerine, angiotensin-converting enzyme (ACE) inhibitors or digitalis are generally contraindicated or discouraged in the presence of resting or provocable outflow obstruction. In patients with severe heart failure refractory to other medications, caution is advised in administrating amiodarone in a high dosage (greater than or equal to 400 mg per day). In patients with erectile dysfunction, phosphodiesterase (PDE) inhibitors should be used with the awareness that a mild afterload-reducing effect may be deleterious in patients with resting or provocable obstruction.

Drugs in end-stage phase

A small but important subgroup of patients with nonobstructive HCM develops systolic ventricular dysfunction and severe heart failure, usually associated with LV remodeling demonstrable as wall thinning and chamber enlargement. This particular evolution of HCM occurs in only about 5% of patients and has been variously known as the "end-stage," "burnt-out," or "dilated" phase. Drug treatment strategies in such patients with systolic failure differ substantially from strategies in HCM patients with typical left ventricular hypertrophy (LVH), nondilated chambers, and preserved systolic function (i.e., involving conversion to after load-reducing agents such as ACE inhibitors or angiotensin II-receptor blockers or diuretics, digitalis, beta-blockers or spironolactone). There is no evidence, however, that beta-blockers prevent or convey a benefit to congestive heart failure and ventricular systolic dysfunction of the "end-of-stage" (by contrast with the experience in dilated cardiomyopathy and CAD). Ultimately, patients with end-stage heart failure may become candidates for heart transplantation, and they represent the primary subgroup within the broad disease spectrum of HCM for when this treatment option is considered.

Asymptomatic patients

Data from largely unselected cohorts and genotyping studies in families suggest that most HCM patients, including many who are not even aware of their disease, probably have no symptoms or only mild symptoms. While most of the

asymptomatic patients do not require treatment, some represent therapeutic dilemmas because of their youthful age and the consideration for prophylactic therapy to prevent sudden cardiac death (SCD) or disease progression.

Prophylactic drug therapy in asymptomatic (or mildly symptomatic) patients to prevent or delay development of symptoms and improve prognosis has been the subject of debate for many years, but it remains on an entirely empiric basis without controlled data to either support or contradict its potential efficacy. This issue is unresolved due to the relatively small patient populations previously available for study, as well as the infrequency with which adverse end-points occur prematurely in this disease. Additionally, there is a growing awareness that an important proportion of HCM patients achieve normal life expectancy. In general, treatments to delay or prevent progression of the disease due to heart failure-related symptoms are most appropriately directed toward relieving LV outflow tract obstruction and controlling or abolishing AF through pharmacologic or intervention-based strategies. Indeed, treatments targeted at aborting the disease progression are now confined to those patients judged to be at high-risk for SCD (as discussed under Risk Stratification and SCD). The efficacy of empiric, prophylactic drug treatment with beta-blockers, verapamil, or disopyramide for delaying the onset of symptoms and favorably altering the clinical course or outcome in asymptomatic young patients with particularly marked LV outflow tract gradients (about 75 mm Hg to 100 mm Hg or more) is unresolved.

Infective endocarditis prophylaxis

In HCM there is a small risk for bacterial endocarditis, which appears largely confined to those patients with LV outflow tract obstruction under resting conditions or with intrinsic mitral valve disease. The site of the valvular vegetation is usually the thickened anterior mitral leaflet, although cases have been reported with lesions on the outflow tract endocardial contact plaque (at the point of mitral-septal contact) or on the aortic valve. Therefore, the American Heart Association (AHA) recommendation should be applied to HCM patients with evidence of outflow obstruction under resting or exercise conditions at the time of dental or selected surgical procedures that create a risk for blood-borne bacteremia.

Pregnancy

There is no evidence that patients with HCM are generally at increased risk during pregnancy and delivery. Absolute maternal mortality is very low (although possibly higher in patients with HCM than in the general population) and appears to be confined principally to women with high-risk clinical profiles. Such patients should be afforded highly specialized preventive obstetrical care during pregnancy. Otherwise, most pregnant HCM patients undergo normal vaginal delivery without the necessity for cesarean section.

Treatment options for drug-refractory patients

In some patients, medical therapy ultimately proves insufficient to control symptoms, and the quality of life becomes unacceptable to the patient. At this point in the clinical course, after a trial administration of maximum drug treatment, the subsequent therapeutic strategies are dictated largely by whether LV outflow obstruction is present.

Surgery

Patients in a small but important subgroup comprising only about 5% of all HCM patients in nonreferral settings (but up to 30% in tertiary referral populations), are generally regarded as candidates for surgery. These patients have particularly marked outflow gradients (peak instantaneous usually greater than or equal to 50 mm Hg), as measured with continuous wave Doppler echocardiography either under resting/basal conditions and/or with provocation, preferably utilizing physiologic exercise. In addition, these patients have severe limiting symptoms, usually of exertional dyspnea and chest pain, that are regarded in adults as New York Heart Association (NYHA) functional classes III and IV, refractory to maximum medical therapy. Over the past 40 years, based on the experience of a number of centers throughout the world, the ventricular septal myectomy operation (also known as the Morrow procedure) has become established as a proven approach for amelioration of outflow obstruction and the standard therapeutic option, and the gold standard for both adults and children with obstructive HCM and severe drug-refractory symptoms. The myectomy operation should be confined to centers experienced in this procedure.

Myectomy is performed through an aortotomy and involves the resection of a carefully defined relatively small amount of muscle from the proximal septum (about 5 to 10 g), extending from near the base of the aortic valve to beyond the distal margins of mitral leaflets (about 3 to 4 cm), thereby enlarging the LV outflow tract and, as a consequence in the vast majority of patients, abolishing any significant mechanical impedance to ejection and mitral valve SAM immediately normalizing LV systolic pressures, abolishing mitral regurgitation, and ultimately, reducing LV end-diastolic pressures. Such an abrupt relief of the gradient with surgery (in contrast to slower reduction with alcohol septal ablation in many cases) is particularly advantageous in patients with severe functional limitations.

Some surgeons have utilized a more extensive myectomy procedure for obstructive HCM, with the septal resection widened and extended far more distally than in the classic Morrow procedure (i.e., 7 to 8 cm from the aortic valve to below the level of papillary muscles). In addition, the anterolateral papillary muscle may be dissected partially free from its attachment with the lateral LV free wall to enhance papillary muscle mobility and reduce anterior tethering of the mitral apparatus. Alternatively, mitral valve replacement or repair has been employed in selected patients judged to have severe mitral regurgitation due to intrinsic abnormalities of the valve apparatus (such as myxomatous mitral valve).

Previously, some surgeons found it advantageous in selected patients to perform mitral valve replacement when the basal anterior septum in the area of resection is relatively thin (e.g., less than 18 mm) and muscular resection was judged to present an unacceptable risk of septal perforation or inadequate hemodynamic result. However, currently, some surgical centers experienced with myectomy do not advocate mitral valve replacement (in the absence of intrinsic mitral valve disease), even in the presence of a relatively thin ventricular septum; carefully performed surgical septal reduction is the preferred method.

Mitral valvuloplasty (plication) in combination with myectomy has been proposed for some patients with particularly deformed or elongated mitral leaflets. Muscular

mid-cavity obstruction due to an anomalous papillary muscle requires an extended distal myectomy or, alternatively, mitral valve replacement. Occasionally, patients, usually children, may demonstrate an obstruction to right ventricular outflow due to excessive muscular hypertrophy of trabeculae or crista supraventricularis muscle; resection of the right ventricular outflow tract muscle, with or without an outflow tract patch, has abolished the gradient.

Published reports of over 2,000 patients from North American and European centers show remarkably consistent results with the ventricular septal myectomy operation. Isolated myectomy (without concomitant cardiac procedures such as valve replacement or coronary artery bypass grafting) is now performed with low operative mortality in patients of all ages, including children, at those centers having the most experience with this procedure (reported as 1 to 3%, and even less in the most recent cases). Surgical risk may be higher among very elderly patients (particularly those with severe disabling symptoms associated with pulmonary hypertension), patients with prior myectomy, or those undergoing additional cardiac surgical procedures. Complications such as complete heart block (requiring permanent pacemaker) and iatrogenic ventricular septal perforation have become uncommon (equal to or less than 1 to 2%), while partial or complete left bundle branch block is an inevitable consequence of the muscular resection and is not associated with adverse sequelae. Intraoperative guidance with echocardiography (transesophageal or with the transducer applied directly to the right ventricular surface) is standard at centers performing surgery for HCM and is useful in assessing the site and extent of the proposed myectomy, structural features of the mitral valve, and the effect of muscular resection on SAM and mitral regurgitation.

Septal myectomy is associated with persistent, long-lasting improvement in disabling symptoms and exercise capacity (i.e., increase by one or more NYHA classes and demonstrable increase in peak oxygen consumption with exercise) and decreased frequency of syncope five or more years after surgery. Symptomatic benefit following myectomy appears to be largely the consequence of abolishing or substantially reducing the basal outflow gradient and mitral regurgitation and restoring normal LV systolic and end-diastolic pressures (in more than 90% of patients), which may also favorably influence LV diastolic filling and myocardial ischemia. Because myectomy may result in a decrease in left atrial size, the likelihood of AF occurring after surgery may be mitigated (and sinus rhythm restored with greater ease), especially in patients younger than 45 years.

Selected patients in whom severe refractory symptoms are indisputably linked to marked outflow gradients elicited by exercise (when resting obstruction is absent or mild) usually also benefit from myectomy. Reacquisition of SAM and a large resting LV outflow gradient is exceedingly uncommon after successful myectomy in either adults or children, and the need for reoperation to reduce recurrent outflow gradient is extremely uncommon at centers having the most experience with the septal myectomy operation.

By convention, surgery has not been recommended or performed in asymptomatic or mildly symptomatic patients with obstructive HCM for a number of reasons: 1) the effect of surgery per se on longevity is unresolved, although several surgical series have reported improved late survival after myectomy compared with the

clinical course of nonoperated medically treated patients with severe symptoms; 2) operative mortality is now very low, but in some patients the risk of surgery may exceed the ultimate risks from the disease; 3) outflow obstruction is often compatible with normal longevity; 4) there is little or no evidence that surgical relief of outflow obstruction abolishes the risk for progression to the end-stage phase, which is an independent disease consequence.

Although definitive evidence is lacking, there is some suggestion in retrospective nonrandomized studies that surgical relief of outflow obstruction in severely symptomatic patients may reduce long-term mortality and possibly SCD. It should be emphasized that surgery is not regarded as curative but is performed to achieve an improved quality of life and functional (exercise) capacity. One possible exception to this tenet may be young asymptomatic or mildly symptomatic patients with particularly marked outflow obstruction (e.g., 75 mm to 100 mm Hg or more at rest). There is a paucity of data in this subset, but it is not unreasonable to at least consider surgical intervention for young patients, even if they are not severely symptomatic, in the presence of particularly marked obstruction to LV outflow.

Additional approaches to relieve outflow obstruction and symptoms

Ventricular septal myectomy has generally been confined to selected major centers having substantial experience with this procedure. However, some patients may not have ready access to such specialized surgical care because of geographical factors; or they may not be favorable operative candidates, because of concomitant medical conditions—particularly advanced age, prior cardiac surgery, or insufficient personal motivation. Two techniques can be considered as potential alternatives to surgery for selected patients who otherwise meet the same clinical criteria as candidates for surgery.

Dual-chamber pacing

Several groups had investigated the effects of permanent dual-chamber pacing on severe outflow obstruction and refractory symptoms within observational and uncontrolled study designs. Data in these studies were necessarily based on the subjective perception of symptom level by patients over relatively short periods of time. Such investigations reported dual-chamber pacing to be associated with a substantial decrease in outflow gradient, as well as amelioration of symptoms in most patients. These observations inferred that a reduction of gradient with pacing in turn consistently relieved symptoms. However, other catheterization laboratory studies showed that a decrease in the outflow gradient produced by temporary A-V sequential pacing could be associated with detrimental effects on ventricular filling and cardiac output.

Subsequently, dual-chamber pacing in HCM was subjected to scrutiny in three randomized, cross-over studies (double-blind in two) in which patients received 2 to 3 months each of pacing and also back-up AAI mode (no pacing) as a control, by activating and deactivating the pacemaker accordingly. Two randomized, cross-over, double-blind studies (one multi-center and one from the Mayo Clinic) reported the effects of pacing in HCM patients to be less favorable than the observational data had suggested. For example, the average decrease in outflow gradient with pacing, while statistically significant, was nevertheless much more

modest (about 25 to 40%) than in the uncontrolled studies and varied substantially among individual patients. In one study, the average subaortic gradient, even after nine months of pacing, remained in the preoperative range (e.g., average 48 mm Hg).

In these controlled studies, subjective symptomatic improvement assessed by quality-of-life score was reported with similar frequency by patients both after periods of pacing and after the same time period without pacing (AAI-backup). Objective measures of exercise capacity (e.g., treadmill exercise time and maximal oxygen consumption) did not differ significantly during pacing and without pacing. These observations demonstrate that subjectively reported symptomatic benefit during pacing frequently occurs without objective evidence of improved exercise capacity and can be regarded in part as a placebo effect. Furthermore, no correlation has been demonstrated for gradient reduction between short- and long-term pacing, suggesting that testing the gradient response to short-term pacing in the catheterization laboratory has limited practical clinical value in judging long-term efficacy. However, the failure to achieve gradient reduction with temporary pacing suggests that permanent pacing is probably not indicated.

As part of its design, the randomized, cross-over, single-blind European multi-center HCM pacing trial, Pacing in Cardiomyopathy (PIC), excluded from chronic pacing those patients without significant gradient reduction during temporary pacing. With data very similar to the other two randomized studies, (but also with a large proportion of patients who elected to continue pacing based on their own subjective assessment of treatment), the PIC investigators concluded that pacemaker therapy was an option for most severely symptomatic patients with obstructive HCM refractory to drug treatment. Nevertheless, taken together the available data do not support dual-chamber pacing as a primary treatment for most severely symptomatic patients with obstructive HCM. In a nonrandomized study comparing pacing and the myectomy operation, hemodynamic and symptomatic outcome proved to be superior with surgery.

Although it is not a primary treatment for the disease, there is nevertheless evidence to support utilizing a trial of dual-chamber pacing in selected patient subgroups that may benefit in terms of gradient relief and improvement in symptoms and exercise tolerance. For example, there may be both subjective and objective symptomatic benefit with pacing in some patients of advanced age (over 65 years), for whom alternatives to surgery are often desirable. Otherwise, there are few predictive data upon which to specifically target those patients who are most likely to potentially benefit from pacing therapy; for example, there is little relationship between the magnitude of gradient reduction with chronic pacing and the symptomatic benefit ultimately achieved. Pacing-induced LV remodeling with thinning of the wall was claimed in one uncontrolled study but could not be confirmed in a randomized investigation. Furthermore, there is no evidence that pacing reduces the risk of SCD in HCM, alters or aborts underlying progression of the disease state, or conveys favorable hemodynamic or symptomatic benefit for patients with the nonobstructive form.

Of potential advantage, pacing therapy permits more aggressive drug treatment by obviating the concern for drug-induced bradycardia. Some patients receiving an implantable cardioverter defibrillator (ICD) for high-risk status, in which

obstruction to LV outflow is also present, may benefit from use of the dual-chamber pacing component of the ICD to effect a reduction in outflow gradient. The American College of Cardiology (ACC)/American Heart Association (AHA)/North American Society of Pacing and Electrophysiology (NASPE) 2002 guidelines have designated pacing for severely symptomatic and medically refractory HCM patients with LV outflow obstruction as a class IIB indication.

However, it should be underscored that maintenance of pacing therapy (directed toward alleviating obstruction and symptoms) may be substantially more complex in HCM than in other cardiac conditions; therefore, for optimal results this procedure should be performed in centers highly experienced in both pacemaker therapy and HCM. Producing and maintaining a reduction in gradient (and presumably in symptoms) requires that pre-excitation of the right ventricular apex and distal septum be established and that complete ventricular capture—both at rest and during exercise—without compromising ventricular filling and cardiac output. Hence, ascertaining the optimal A-V interval for dual-chamber pacing is a crucial element of pacing management in HCM. Programming of the pacemaker A-V interval to ensure complete ventricular capture may require slowing of intrinsic A-V nodal conduction with a beta-blocker or verapamil, or possibly ablation of the A-V node in selected cases (thereby rendering the patient pacemaker-dependent), has been suggested. It is also understood that no other treatment modality in HCM (including surgery and alcohol septal ablation) has undergone such rigorous randomized testing in order to validate its efficacy. At present, there are no data concerning the role of biventricular pacing in HCM patients with severe heart disease.

Percutaneous alcohol septal ablation

A second option to surgery is the more recently developed alcohol septal ablation technique. First reported in 1995, this catheter interventional treatment involves the introduction of absolute alcohol into a target septal perforator branch of the left anterior descending coronary artery for the purpose of producing a myocardial infarction within the proximal ventricular septum. Septal ablation mimics the hemodynamic consequences of myectomy by reducing the basal septal thickness and excursion (producing akinetic or hypokinetic septal motion), enlarging the LV outflow tract, and thereby lessening the SAM of the mitral valve and mitral regurgitation.

This technique utilizes conventional methods and technology currently available for atherosclerotic CAD. After standard coronary arteriograms are performed, a coronary balloon is placed into a proximal major septal perforator artery with the aid of flexible coronary guide wires. A temporary pacing catheter is positioned in the right ventricular apex in the event that high-grade A-V block occurs. After the balloon is inflated, an arteriogram is performed through the lumen to verify that the balloon is located in the desired anatomic position and to ensure that leakage of alcohol into the left anterior descending coronary artery or coronary venous system does not occur.

Myocardial contrast echocardiography guidance (with injection of echo contrast or radio-opaque medium) is important in selecting the appropriate septal perforator branch. This technique is useful for determining the precise area of septum targeted for alcohol and infarction and whether the selected septal perforator also

perfuses other distant and unwanted areas of left or right ventricular myocardium or papillary muscles. Some groups prefer a pressure-angiographic and fluoroscopy guided technique. The targeted septal perforator and area for infarction are identified by an immediate fall in outflow gradient following balloon occlusion and/or contrast injection.

The amount of ethanol to be injected is estimated by the angiographic visualization of septal anatomy and whether contrast wash-out is slow or rapid. Usually, about 1 to 3 cc (average 1.5 to 2 cc) of desiccated ethanol (of at least 95% concentration) is slowly infused into the septal perforator and septum via the balloon catheter, inducing a myocardial infarction demonstrable by 400 to 2,500 units of creatinine phosphokinase release, equivalent to an area of necrosis estimated to be 3 to 10% of the LV mass (20% of the septum). However, centers performing a large number of alcohol septal ablation procedures today are using smaller amounts of ethanol, leading to less creatinine phosphokinase release and smaller septal infarcts, and also reducing the incidence of complete heart block.

Successful alcohol septal ablation may trigger a rapid reduction in resting outflow gradient evident in the catheterization laboratory. More frequently, a progressive decrease in the gradient occurs after 6 to 12 months, usually achieving levels in a range equivalent to that with myectomy, and resulting from remodeling of the septum without significant impairment in global LV ejection. This has been reported for patients with large resting gradients at baseline as well as those with outflow obstruction present only under provocable conditions. Often a biphasic response of the gradient is observed with alcohol septal ablation in which an acute response with striking reduction (probably due to stunning of the myocardium) is followed by a rise to about 50% of its pre-procedure level the next day, but within several months may reach greatly reduced levels. Results of myectomy and alcohol ablation compared at two institutions showed similar gradient reductions with the two techniques. Another comparative analysis from a single institution showed both surgery and ablation to substantially reduce resting and provocable gradients, but to a significantly greater degree with surgery.

A number of other favorable structural and functional effects following ablation have been reported, representing the expected consequences of reduced outflow gradient, normalization of LV pressures, and reduced systolic overload. Echocardiographic analyses from two groups have reported ablation to be associated with widespread regression of LVH beyond the alcohol target area, but the extent to which remodeling occurs with time secondary to this procedure is unpredictable and not fully understood. Also, there is concern that extensive wall thinning could lead to arrhythmogenic susceptibility or even the end-stage phase.

A large proportion of ablation patients from several centers have been reported to demonstrate subjective improvement in limiting symptoms and in quality of life in observational studies over relatively short-term follow-up periods of 2 to 5 years. As with surgery, the decrease in symptoms associated with ablation is often dramatic. In addition, improved exercise performance has been shown objectively in terms of total treadmill exercise time and peak oxygen consumption in some studies. However, alcohol septal ablation has yet to be subjected to the scrutiny of randomized or controlled studies or long-term follow-up. A recent study found that both septal myectomy and ablation led to improved exercise testing parameters, but surgery was superior in this regard.

The mortality and morbidity associated with alcohol ablation in experienced centers have proved to be relatively low, although they are similar in surgical myectomy. Procedure-related mortality has been reported to be from 1 to 4% but is probably reduced in the more recent cases. Reports of permanent pacemaker implantation for induced high-grade A-V block have ranged from 5% to as high as 30%, but this complication appears to be decreasing substantially with the use of smaller amounts of alcohol. In contrast to septal myectomy, which usually produces left bundle branch block, alcohol ablation commonly results in right bundle branch block. It is also possible for coronary artery dissection to occur, as well as backward extravasation of alcohol, producing occlusion or abrupt coronary no-flow and a large anteroseptal myocardial infarction.

Proper selection of patients for alcohol septal ablation remains a crucial issue. Similar to patients recommended for septal myectomy, all candidates for alcohol septal ablation should have severe heart failure symptoms (NYHA classes III or IV) refractory to all medications utilized in HCM, as well as a subaortic gradient of 50 mm Hg or more measured with Doppler echocardiography either under basal conditions and/or with physiologic provocative maneuvers during exercise. Caution should be exercised so that in patients selected for alcohol septal ablation, outflow gradients are documented to be due to SAM and proximal mitral valve septal contact, exclusive of congenital abnormalities of the mitral apparatus such as anomalous papillary muscle insertion into mitral valve, which produces more distal muscular obstruction in the mid-cavity.

Nevertheless, the number of alcohol ablations performed world-wide now approaches an estimated 3,000 over only about a six-year period, exceeding the number of surgical myectomies performed over the 40 years since this operation was introduced. In some instances, the frequency with which myectomy surgery has been performed for obstructive HCM has now been reduced by more than 90% due to the recent accelerated enthusiasm for ablation.

Disproportionality in the frequency with which alcohol septal ablation is performed relative to myectomy (ablations are estimated to be at least 15 to 20 times more common than surgery at present) has raised concerns that there may have an insidious and unjustifiable lowering of the symptom and gradient-level threshold in the selection of patients for ablation, with less symptomatic NYHA class II, less obstructed, and younger patients now undergoing the procedure. This circumstance has evolved in part because of the relative ease with which ablation can be performed (compared to surgery), with substantially less discomfort during a much shorter postoperative hospitalization and recovery period in the absence of a sternotomy. However, this fact does not justify less strict criteria for alcohol septal ablation.

Another factor that has affected patient selection for alcohol septal ablation is the practice of determining eligibility based solely on a subaortic gradient provoked by nonphysiologic interventions such as dobutamine infusion (rather than exercise, for example). Dobutamine is an inotropic and catecholamine-inducing drug that is a powerful stimulant of subaortic gradients in normal hearts or in cardiac diseases other than HCM of questionable physiologic and clinical significance, and occasionally results in adverse consequences to patients with obstruction; dependence on dobutamine to induce gradients can expose some patients to septal ablation in the absence of true impedance to LV outflow. Therefore,

dobutamine is generally not recommended for the purpose of provoking outflow gradients in severely symptomatic HCM patients who are regarded as possible candidates for major interventions.

A predominate concern raised with respect to alcohol septal ablation is the potential long-term risk for arrhythmia-related cardiac events (including SCD) directly attributable to the procedure. Unlike myectomy, alcohol septal ablation potentially creates a permanent arrhythmogenic substrate in the form of a healed intramyocardial septal scar that could increase the risk of lethal reentrant arrhythmias. This is particularly relevant because many patients with HCM already possess an unstable electrophysiologic substrate as part of their underlying disease. However, since HCM patients are at increased risk for SCD over particularly long periods, possibly through much of their lifetimes, it will require many years (and probably decades) to determine the likelihood that risk for arrhythmia-related events and SCD is increased as a consequence of the healed intramyocardial scar produced by alcohol septal ablation. Indeed, this is particularly relevant for young patients in whom even a modest annual increase in the risk of SCD would have the likelihood of shortening life considerably. Reports of the noninducibility of reentrant ventricular tachyarrhythmia in small numbers of patients in the short term after septal ablation do not appear sufficient at this juncture to exclude the possibility of late-onset ventricular tachyarrhythmias and SCD over the long risk period characteristic of HCM.

Therefore, at present, the impact of alcohol ablation on the incidence of SCD is unresolved. Until more is known regarding the natural history of patients undergoing alcohol septal ablation and there is less uncertainty regarding the consequences of the intramyocardial scar, particularly careful selection of patients seems advisable and prudent (by largely confining the procedure to older adults), particularly when the option for surgical myectomy is feasible. There would not appear to be a primary role for alcohol ablation in children, and such procedures are not advised.

Due to morphologic heterogeneity, not all HCM patients with obstruction are ideal candidates for septal ablation. This therapy relies on the fixed anatomic distribution and size of the septal perforator coronary arteries. Therefore, the ablation technique cannot make adjustments for variability in the distribution and size of these arterial vessels in relation to the distribution of septal hypertrophy, or for other complexities of LV outflow tract morphology such as greatly elongated mitral leaflets and anomalous papillary muscle. The direct operative approach provides greater flexibility for relieving obstruction and also allows surgical treatment for associated cardiac abnormalities such as primary valvular disease (e.g., myxomatous mitral valve prolapse or aortic stenosis), atherosclerotic CAD, or segmental myocardial bridging of the left anterior descending coronary artery, as well as anomalies of the mitral valve and apparatus. Also, relief of obstruction with surgery is immediate (but is often delayed with alcohol septal ablation), which may be crucial in some patients with particularly severe symptoms of heart failure.

The "learning curve" for expertise with the alcohol septal ablation technique is steep (due, in part, to the relatively small number of eligible HCM patients), particularly regarding selection of the optimal septal perforator branch; therefore, ablation should not be regarded as a routine technique to be employed by any

expert interventional cardiologist. It is advisable that alcohol ablation (as well as myectomy) be largely confined to centers having substantial and specific experience with HCM and the procedure in order to assure proper patient selection, the lowest possible rates of morbidity and mortality, and the greatest likelihood of achieving benefits.

While alcohol ablation represents an option available to HCM patients and a selective alternative to surgery, it is not at this time regarded as the standard and primary therapeutic strategy for all severely symptomatic patients refractory to maximal medical management with marked obstruction to LV outflow. Septal myectomy remains the gold standard for this HCM patient subset.

Sudden cardiac death

Risk stratification

Since the modern description of HCM by Teare in 1958, sudden and unexpected death (unassociated with severe heart failure) has been recognized as the most devastating and often unpredictable complication and the most frequent mode of premature demise from this disorder. Sudden cardiac death may occur as the initial disease presentation, most frequently in asymptomatic or mildly symptomatic young people. The high-risk HCM patients constitute only a minority of the overall disease population, and historically, a major investigative focus has been the isolation of the small but important subset of patients at high-risk among the overall HCM spectrum. Since SCD can be the initial manifestation of HCM, it often occurs without reliable warning signs or symptoms, and often in the early morning hours after awakening. Although SCD is most frequent in adolescents and young adults less than 30 to 35 years old, such risk also extends through mid-life and beyond; the basis for this particular predilection of SCD for the young is unresolved. Therefore, achieving any particular age does not itself confer an immunity to sudden HCM-related catastrophe. Sudden cardiac death occurs most commonly during mild exertion or sedentary activities (or during sleep), but it is not infrequently triggered by vigorous physical exertion. Indeed, HCM is the most common cause of cardiovascular-related SCD in young people, including competitive athletes (most commonly in basketball and football).

The available data (largely from recorded arrhythmic events that triggered appropriate defibrillator interventions) suggest that complex ventricular tachyarrhythmias emanating from an electrically unstable myocardial substrate are the most common mechanism by which SCD occurs in HCM. Indeed, ventricular arrhythmias are an important clinical feature in adults with HCM. On routine ambulatory (Holter) 24-h electrocardiogram (ECG) monitoring, 90% of adults demonstrate ventricular arrhythmias, which are often frequent or complex, including premature ventricular depolarizations (greater than or equal to 200 in 20% of patients), ventricular couplets (in greater than 40%), or nonsustained bursts of ventricular tachycardia (in 20 to 30%). Alternatively, it is possible that in some patients supraventricular tachyarrhythmias could trigger ventricular tachyarrhythmias or that bradyarrhythmias occur and require back-up pacing.

It has been suggested that life-threatening tachyarrhythmias could be provoked in HCM by a number of variables either secondary to environmental factors (e.g., intense physical exertion) or, alternatively, intrinsic to the disease process. The

latter may involve a vicious cycle of increasing myocardial ischemia and diastolic (or systolic) dysfunction, possibly impacted by outflow obstruction, systemic arterial hypotension, or supraventricular tachyarrhythmias that lead to decreased stroke volume and coronary perfusion.

Although the available data on the stratification of SCD risk are substantial and a large measure of understanding has been achieved, it is important to underscore that precise identification of all individual high-risk patients by clinical risk markers is not completely resolved. This issue remains a challenge due largely to the heterogeneity of HCM disease presentation and expression, its relatively low prevalence in cardiologic practice, and the complexity of potential pathophysiologic mechanisms. Nevertheless, it is possible to identify most high-risk patients by noninvasive clinical markers, and only a small minority of those HCM patients who die suddenly (about 3%) are without any of the currently acknowledged risk markers. The highest risk for SCD has been associated with the following: 1) prior cardiac arrest or spontaneously occurring and sustained ventricular tachycardia (VT); 2) family history of a premature HCM-related SCD particularly if sudden, in a close relative, or if multiple in occurrence; 3) identification of a high-risk mutant gene; 4) unexplained syncope, particularly in young patients or when exertional or recurrent; 5) nonsustained VT (of 3 beats or more and of at least 120 beats/min) evident on ambulatory (Holter) ECG recordings; 6) abnormal blood pressure response during upright exercise which is attenuated or hypotensive, indicative of hemodynamic instability, and of greater predictive value in patients less than 50 years old or if hypotensive; and 7) extreme LVH with maximum wall thickness of 30 mm or more, particularly in adolescents and young adults.

HCM patients (particularly those less than 60 years old) should undergo comprehensive clinical assessments on an annual basis for risk stratification and evolution of symptoms, including careful personal and family history, noninvasive testing with two-dimensional echocardiography (primarily for assessment of magnitude of LVH and outflow obstruction), 24- or 48-h ambulatory (Holter) ECG recording for VT, and blood pressure response during maximal upright exercise (treadmill or bicycle). Subsequent risk analysis should be performed periodically and when there is a perceived change in clinical status.

Recent attention has focused on the magnitude of LVH (as assessed by conventional two-dimensional echocardiography) as an indicator of risk. Two independent groups have reported a direct association between magnitude of LV wall thickness and risk of SCD in large HCM populations. In one study, extreme LVH (maximum thickness of 30 mm or more), present in approximately 10% of HCM patients, conveyed substantial long-term risk. Sudden cardiac death was most common in asymptomatic or mildly symptomatic adolescents or young adults and was estimated at 20% over 10 years and 40% over 20 years (i.e., annual mortality about 2%). There is supporting circumstantial evidence from retrospective cross-sectional analyses that extreme hypertrophy represents a risk factor for premature SCD because it is observed less commonly in older than in younger patients; this finding could reflect either preferential SCD at a young age, structural remodeling with wall thinning, or both. This relationship of extreme hypertrophy to age is accentuated with wall thicknesses of 35 mm or more, which appear in less than 1% of patients older than 50 years. Another group, however, has maintained that extreme hypertrophy is a predictor of SCD only when

associated with other risk factors such as unexplained syncope, family history of premature SCDs, nonsustained VT on Holter, or an abnormal blood pressure response during exercise. At present, although it is not unequivocally resolved as to whether extreme hypertrophy as a sole risk factor is sufficient to justify a recommendation for prevention of SCD with an ICD, serious consideration for such an intervention should be given to young patients.

The concept that risk of SCD is related to the magnitude of hypertrophy does not, however, infer that the risk is necessarily low when LV wall thickness is less than 30 mm, because other risk markers may be present in a given patient; indeed, the majority of patients who die suddenly do, in fact, have wall thicknesses of less than 30 mm. Furthermore, a small number of high-risk pedigrees with troponin T and I mutations have been reported in whom SCD was associated with particularly mild forms of LVH, including a few individuals with normal LV wall thickness and mass. However, such events appear to be uncommon within the overall HCM patient spectrum. Although prognosis is generally not tightly linked to the pattern and distribution of LVH, the preponderance of evidence suggests that segmental wall thickening at the low end of the morphologic spectrum (i.e., less than 20 mm thickness, regardless of its precise location), generally confers a favorable prognosis in the absence of other major risk factors. Such localized hypertrophy includes the nonobstructive form of HCM confined to the most distal portion of LV ("apical HCM").

Disorganized cardiac muscle cell arrangement, myocardial replacement scarring as a repair process following cell death (possibly resulting from ischemia due to abnormal microvasculature consisting of intramural small vessel disease or muscle mass-to-coronary flow mismatch) and the expanded interstitial (matrix) collagen compartment probably serve as the primary arrhythmogenic substrate predisposing some susceptible patients to reentrant, life-threatening ventricular tachyarrhythmias. That extreme degrees of LVH can be linked to sudden events is perhaps not unexpected, considering the potential impact of such wall thickening on myocardial architecture, oxygen demand, coronary vascular resistance, and capillary density, all of which thereby create an electrophysiologically unstable substrate. The degree of hypertrophy does not appear to be directly associated with the severity of diastolic dysfunction and limiting symptoms. Paradoxically, most patients with massive degrees of LVH do not experience marked symptomatic disability, LV outflow obstruction, or left atrial enlargement.

It is a clinical perception that the premonitory symptom most associated with the likelihood of SCD in HCM is impaired consciousness (i.e., syncope or near syncope). However, the sensitivity and specificity of syncope as a predictor of SCD is low, possibly because most such events in this disease are probably not in fact secondary to arrhythmias or related to outflow obstruction. Indeed, there are many potential causes of syncope, some of which are unrelated to the basic disease state and are often neurocardiogenic (i.e., vagal, neurally-mediated syndromes) in origin. Even when an underlying cause for impaired consciousness cannot be identified, this symptom-complex can be compelling in some HCM patients, particularly when it is exertional or recurrent, when it occurs in the young, or in the context of a single recent syncopal episode judged to be disease-related. Therefore, syncope may represent the basis of a defibrillator implant to ensure preservation of life should a life-threatening arrhythmia intervene.

Available data suggest that LV outflow obstruction (gradient 30 mm Hg or more) can only be regarded as a minor risk factor for SCD in HCM. The impact of gradient on SCD risk is not sufficiently strong (positive predictive value of only 7%) for obstruction to merit a role as the sole (or predominant) deciding clinical parameter and the primary basis for decisions to intervene prophylactically with an ICD.

Identification of HCM in young children is exceedingly uncommon and often creates a specific clinical dilemma because such an initial diagnosis occurring so early in life (frequently fortuitously) raises uncertainty regarding future risk over particularly long time periods. One report suggests that short tunneled (bridged) intramyocardial segments of left anterior descending coronary artery independently convey increased risk for cardiac arrest, probably mediated by myocardial ischemia. However, potential biases in patient selection, the frequency of coronary arterial bridging in surviving adults and those who have died of noncardiac causes, and the need for routine invasive coronary arteriography in order to identify this abnormality prospectively seem to mitigate the potential power of coronary bridging as a risk factor for SCD.

It has been proposed, based on genotype-phenotype correlations, that the genetic defects responsible for HCM could represent the primary determinant and stratifying marker of prognosis and for SCD and heart failure risk, with specific mutations conveying either favorable or adverse prognosis (i.e., high- and low-risk mutations). For example, it has been suggested that some cardiac beta-myosin heavy chain mutations (such as Arg403Gln and Arg719Gln) and some troponin-T mutations are associated with higher incidence of premature death, decreased life expectancy, and early onset disease manifestations, while other HCM genes, such as cardiac myosin-binding protein C (particularly InsG791) or alpha-tropomyosin (Asp175Asn), convey a more favorable prognosis. However, routine clinical testing for specific mutations believed to be high (or low) risk has been shown to have low yield. Therefore, it is premature to draw definitive conclusions regarding gene-specific clinical outcomes based solely on the presence of a particular mutation, by virtue of extrapolation from available epidemiologic-genetic data which are formulated from relatively small numbers of genotyped families largely skewed toward high-risk status. Consequently, it is becoming increasingly evident that the presence or absence of a particular mutation does not by itself represent sufficient data to convey clear prognostic implications and that HCM mutations may not possess distinctive clinical signatures.

The particular prognosis attached to adult carriers with a mutant HCM gene but without LVH and clinical expression of HCM, or those individuals who develop hypertrophy de novo in adulthood, is uncertain; however, at this early juncture, this subgroup would not appear to be associated with an adverse prognosis. An exception to this tenet may be the small number of SCDs in young people with little or no LVH reported in a very few families with troponin-T mutations.

There is no convincing evidence that invasive markers such as those defined with laboratory electrophysiologic testing (i.e., programmed ventricular stimulation) have an important routine role in identifying those HCM patients who have an unstable electrical substrate and are at high-risk for SCD due to life threatening arrhythmias. Similar to the experience in CAD and dilated cardiomyopathy, polymorphic VT and ventricular fibrillation (VF) (which are the most commonly

provoked arrhythmias) are generally regarded as nonspecific electrophysiologic testing responses to multiple ventricular extra-stimuli, and these specialized laboratory studies are highly dependant on the level of aggression of the protocol. For example, stimulation with three ventricular premature depolarizations rarely triggers monomorphic VT in HCM (in contrast to CAD), but frequently induces polymorphic VT or VF, even in some patients at low risk for SCD.

It is now the predominant view that the risk stratification strategies involving laboratory induction of such ventricular arrhythmias are neither desirable in HCM patients on a routine basis nor, per se, justify aggressive intervention. Electrophysiologic studies with or without programmed ventricular stimulation may, however, have some value in selected patients such as those with otherwise unexplained syncope.

Most of the clinical markers of SCD risk in HCM are limited by relatively low positive predictive values due in part to relatively low-event rates. However, the high negative predictive values (at least 90%) of these markers suggest that the absence of risk factors and certain other clinical features can be used to develop a profile of patients having a low likelihood of SCD or other adverse events. Adult patients can probably be considered low risk if they demonstrate: 1) no or only mild symptoms of chest pain or exertional dyspnea (NYHA functional classes I and II); 2) absence of family history of premature death from HCM; 3) absence of syncope judged to be HCM-related; 4) absence of nonsustained ventricular tachycardia during ambulatory (Holter) ECG; 5) outflow tract gradient at rest of less than 30 mm Hg; 6) normal or relatively mild increase in left atrial size (less than 45 mm); 7) normal blood-pressure response to upright exercise; and 8) mild LVH (wall thickness less than 20 mm).

Patients with an apparently favorable prognosis in the absence of risk factors constitute an important proportion of the overall HCM population. Most such patients probably will not require aggressive major medical treatment and generally deserve a large measure of reassurance regarding their prognoses. Little or no restriction is necessary with regard to recreational activities and employment, although exclusion from intense competitive sports is advised.

Prevention

Efforts at the prevention of SCD have historically targeted only the minority of patients with HCM in whom SCD risk was unacceptably high. Historically, treatment strategies to prophylactically reduce the risk for SCD or delay progression of congestive symptoms have been predicated on the administration of drugs such as beta adrenergic-blockers, verapamil, and type I-A antiarrhythmic agents (i.e., quinidine, procainamide) to those patients perceived to be at high risk. However, there is no evidence that this practice of prophylactically administering such drugs empirically to asymptomatic HCM patients to mitigate the risk for SCD is efficacious, and this strategy now seems outdated with the current availability of measures that more effectively prevent SCD, such as the ICD. In addition, low-dose (less than 300 mg) amiodarone has been associated with improved survival in HCM, but this agent requires careful monitoring and may not be tolerated due to its potential toxicity over the long risk periods incurred by young patients.

When risk level for SCD is judged by contemporary criteria to be unacceptably high and deserving of intervention, the ICD is the most effective and reliable treatment option available, harboring the potential for absolute protection and altering the natural history of this disease in some patients. In one multicenter retrospective study, ICDs appropriately sensed and automatically aborted potentially lethal ventricular tachyarrhythmias by restoring sinus rhythm in almost 25% of a high-risk cohort, followed for a relatively brief period of 3 years. Appropriate device interventions occurred at a rate of 11% per year for secondary prevention (the implant following cardiac arrest or spontaneous and sustained ventricular tachycardia) and at 5% per year for primary prevention (implant based solely on noninvasive risk factors), usually in patients with no or only mild prior symptoms. There was only a 4 to 1 excess of ICDs implanted to lives saved. Patients receiving appropriate defibrillation shocks were generally young (mean age 40 years). ICDs often remained dormant for prolonged periods before discharging (up to 9 years), emphasizing the unpredictable timing of SCD events in this disease, the potentially long risk period, and the requirement for extended follow-up duration to assess survival in HCM studies. Therefore, while the decision to implant a defibrillator for primary prevention cannot reasonably be deferred beyond the time when high-risk status is first judged to be present, it may precede considerably the time at which the device ultimately discharges. There is an ongoing multicenter international study of HCM patients with ICDs for the purpose of obtaining data on interventional devices in a much larger population over longer periods of time.

The ICD is strongly warranted for secondary prevention of SCD in those patients with prior cardiac arrest or sustained and spontaneously occurring VT. The presence of multiple clinical risk factors conveys increasing risk for SCD of sufficient magnitude to justify aggressive prophylactic treatment with an ICD for primary prevention of SCD. Strong consideration should be afforded for a prophylactic ICD in the presence of one risk factor regarded as major in that patient (e.g., a family history of SCD in close relatives).

Because the positive predictive value of any single risk factor is low, such management decisions must often be based on individual judgment for the particular patient, by taking into account the overall clinical profile including age, the strength of the risk factor identified, the level of risk acceptable to the patient and family, and the potential complications largely related to the lead systems and to inappropriate device discharges. It is also worth noting that physician and patient attitudes toward ICDs (and the access to such devices within the respective health care system) can vary considerably among countries and cultures and thereby have an important impact on clinical decision-making and the threshold for implant in HCM. The ACC/AHA/NASPE 2002 guidelines have designated the ICD for primary prevention of SCD as a class IIb indication and for secondary prevention (after cardiac arrest) as a class I indication.

There is, at present, an understandable reluctance on the part of pediatric cardiologists to implant such devices chronically in children (particularly for primary prevention) considering the necessary, ongoing commitment required for maintenance and the likelihood that lead or other (ICD-related) complications will occur over very long time periods. However, while adolescence may represent a psychologically difficult age to be encumbered by an ICD, it should also be emphasized that this is coincidently the period of life consistently showing the

greatest predilection for SCD in HCM. One alternative but empiric strategy proposed for some very young high-risk children is the administration of amiodarone as a bridge to later ICD placement after sufficient growth and maturation has occurred. Some investigators also regard the end-stage phase of HCM as a risk factor for SCD, justifying implantation of a cardioverter defibrillator during the waiting period prior to the availability of a heart for transplant.

Athlete recommendations

In accord with the recommendations of the Expert Consensus panel of the 26th Bethesda Conference, young patients with HCM should be restricted from intense competitive sports to reduce the risk for SCD that may be associated with such extreme lifestyle. A linkage has been established between SCD and intense exertion in trained athletes with underlying cardiovascular disease (including HCM) and SCD.

There is indirect and circumstantial evidence that the removal of young athletes from the competitive arena reduces risk for SCD. Not all trained athletes with HCM die suddenly during their competitive phase of life, only some HCM-related SCDs are associated with intense physical activity, and precision in the stratification of risk for athletes with HCM is particularly difficult given the extreme environmental conditions to which they are often exposed (associated with alterations in blood volume hydration and with electrolytes). Nevertheless, the consensus of the general medical community prudently supports avoiding exposure to most competitive sports for young athletes with HCM to reduce SCD risk, and therefore withdrawal from the athletic arena can be regarded as a treatment modality in this disease. However, stringent lifestyle or employment modifications for other HCM patients (who are not participants in organized athletics) do not seem justified or practical, although intense physical activity involving burst exertion (e.g., sprinting) or systematic isometric exercise (e.g., heavy lifting) should be discouraged. Although data are scarce, there is presently no evidence to suggest that genetically affected but phenotypically normal family members are generally at increased risk for SCD. Therefore, there is little basis for subjecting such individuals to the same activity restrictions as many other HCM patients, or excluding them from competitive athletics in the absence of cardiac symptoms, family history of SCD, or a mutant gene regarded as malignant. However, periodic (probably annual) noninvasive clinical evaluation directed toward risk assessment is warranted in this subset of patients.

Atrial fibrillation

Atrial fibrillation is the most common sustained arrhythmia in HCM and usually justifies aggressive therapeutic strategies. Paroxysmal episodes or chronic AF ultimately occur in 20 to 25% of HCM patients, linked to left atrial enlargement and an increasing incidence with age. Furthermore, it is possible that subclinical AF (i.e., identified only by Holter recording) may be even more common. Clinical cohort studies show that AF is reasonably well tolerated by about one-third of patients and is not an independent determinant of sudden unexpected death; however, it is possible that in certain susceptible patients, AF may trigger life-threatening ventricular arrhythmias. Nevertheless, AF is independently associated with heart failure-related death, occurrence of fatal and nonfatal stroke, as well as long-term disease progression with heart failure symptoms; transient episodes

occur in about 30% of patients immediately following septal myectomy, often in patients with a prior history of AF. Risk for complications of AF is enhanced when the arrhythmia becomes chronic, onset is before 50 years of age, and outflow obstruction is present.

Paroxysmal episodes of AF may also be responsible for acute clinical deterioration, with syncope or heart failure resulting from the reduced diastolic filling and cardiac output—as a consequence of increased ventricular rate and with the loss of atrial contraction (and its contribution to ventricular filling) in a hypertrophied LV with preexisting impaired relaxation and compliance. Atrial fibrillation in HCM should be managed generally in accordance with the ACC/AHA guidelines. In particular, electrical or pharmacologic cardioversion are indicated in those patients presenting within 48 h of onset, assuming that the presence of atrial thrombi can be excluded with a reasonable degree of certainty. Although comparative data regarding the efficacy of antiarrhythmic drugs are not available for HCM patients, amiodarone is generally regarded as the most effective antiarrhythmic agent for preventing recurrences of AF, based largely on extrapolation from its use in other heart diseases.

A generally aggressive strategy for maintaining sinus rhythm is warranted in HCM because of the association of AF with progressive heart failure and mortality, as well as stroke. In chronic AF, beta-blockers, verapamil (and digoxin) have proved effective in controlling heart rate, although A-V node ablation and permanent ventricular pacing may occasionally be necessary in selected patients. Anticoagulant therapy (with warfarin) is indicated in patients with either paroxysmal or chronic AF. Because even one or two episodes of paroxysmal AF have been associated with increased risk for systemic thromboembolization in HCM, the threshold for initiation of anticoagulant therapy should be low and can include patients after the initial AF paroxysm. Since warfarin has proved superior to aspirin in other cardiac conditions associated with AF, it is the recommended anticoagulant agent in HCM patients judged to be at risk for thromboembolism. While anticoagulation reduces the risk of thromboembolic events in patients with AF and HCM, it is also recognized that anticoagulation does not completely abolish the risk of stroke. Such clinical decisions should be tailored to the individual patient after considering the risk for hemorrhagic complications, lifestyle modifications, and expectations for compliance.

The most appropriate management for patients with asymptomatic nonsustained supraventricular tachycardia (detected only on ambulatory [Holter] ECG or exercise testing), and associated with left atrial enlargement is presently unresolved. Also, at present, there is little experience specifically in HCM patients with emerging and novel alternative treatment strategies for AF such as pulmonary vein radio-frequency ablation, the surgical MAZE procedure, or implantable atrial defibrillators to warrant definitive recommendations at this time.

CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for the clinical presentation and treatment strategies for patient subgroups within the broad clinical spectrum of hypertrophic cardiomyopathy.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

Because of the relatively low prevalence of hypertrophic cardiomyopathy (HCM) in general cardiologic practice, its diverse presentation, and mechanisms of death and disability and skewed patterns of patient referral, the level of evidence governing management decisions for drugs or devices has often been derived from nonrandomized and retrospective investigations.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of hypertrophic cardiomyopathy using prudent, practical, and contemporary treatment strategies

POTENTIAL HARMS

- Even moderate doses of beta-blockers may affect growth in young children or impair school performance, or trigger depression in children and adolescents, and should be closely monitored in such patients.
- Potential side effects [of beta-blockers] include fatigue, impotence, sleep disturbances, and chronotropic incompetence.
- Aside from the mild side-effects of constipation and hair loss, verapamil may also occasionally harbor a potential for clinically important adverse consequences and has been reported to cause death in a few hypertrophic cardiomyopathy (HCM) patients with severe disabling symptoms (orthopnea and paroxysmal nocturnal dyspnea) and markedly-elevated pulmonary arterial pressure in combination with marked outflow obstruction. Adverse hemodynamic effects of verapamil are presumably the result of the vasodilating properties predominating over negative inotropic effects, resulting in augmented outflow obstruction, pulmonary edema, and cardiogenic shock.
    - Because of these concerns, caution should be exercised in administering verapamil to patients with resting outflow obstruction and severe limiting symptoms.
- Anticholinergic side effects [of disopyramide] such as dry mouth and eyes, constipation, indigestion, and difficulty in micturition may be reduced by long-acting preparations through which cardioactive benefits are more sustained.
- Disopyramide administration may be deleterious in nonobstructive hypertrophic cardiomyopathy by decreasing cardiac output.
- Nifedipine, because of its particularly potent vasodilating properties, may be deleterious, particularly for patients with outflow obstruction.
- Combined therapy with disopyramide and amiodarone (or disopyramide and sotalol), or quinidine and verapamil (or quinidine and procainamide), should also be avoided due to concern over proarrhythmia.

- Verapamil is not indicated in infants due to the risk for sudden death that has been reported with intravenous administration.

CONTRAINDICATIONS

CONTRAINDICATIONS

Administration of nitroglycerine, angiotensin-converting enzyme inhibitors, or digitalis is generally contraindicated or discouraged in the presence of resting provocable outflow obstruction.

QUALIFYING STATEMENTS

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- Because of the relatively low prevalence of hypertrophic cardiomyopathy (HCM) in general cardiologic practice, its diverse presentation, and mechanisms of death and disability and skewed patterns of patient referral, the level of evidence governing management decisions for drugs or devices has often been derived from nonrandomized and retrospective investigations. Large-scale controlled and randomized study designs, such as those that have provided important answers regarding the management of coronary artery disease (CAD) and congestive heart failure, have generally not been available in HCM as a result of these factors. Therefore, treatment strategies have necessarily evolved based on available data that have frequently been observational in design, sometimes obtained in relatively small patient groups, or derived from the accumulated clinical experience of individual investigators, and reasonable inferences drawn from other cardiac diseases. Consequently, the construction of strict clinical algorithms designed to assess prognosis and dictate treatment decisions for all patients has been challenging and has not yet achieved general agreement. In some clinical situations, management decisions and strategies unavoidably must be individualized to the particular patient.
- Understanding of the molecular basis, clinical course, and treatment of HCM has increased substantially in the last decade. In particular, there has been a growing awareness of the clinical and molecular heterogeneity characteristic of this disorder and the many patient subgroups that inevitably influence considerations for treatment. Some of these management strategies are novel and evolving, and this guideline cannot, in all instances, convey definitive assessments of their role in the treatment armamentarium. Also, for some uncommon subsets within the broad disease spectrum, there are little data currently available to definitively guide therapy. With these considerations in mind, the panel has aspired to create a guideline that is not only current and pertinent but also has the potential to remain relevant for many years.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH 3rd, Spirito P, Ten Cate FJ, Wigle ED, Vogel RA, Abrams J, Bates ER, Brodie BR, Danias PG, Gregoratos G, Hlatky MA, Hochman JS, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Eur Heart J 2003 Nov;24(21):1965-91. [273 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

American College of Cardiology Foundation - Medical Specialty Society
European Society of Cardiology - Medical Specialty Society

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GUIDELINE COMMITTEE

American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents; European Society of Cardiology Committee for Practice Guidelines

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Task Force on Clinical Expert Consensus Documents makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest to inform the writing effort. These statements are reviewed by the parent task force, reported orally to all members of the writing panel at the first meeting, and updated as changes occur.

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Swedish Society of Cardiology - Medical Specialty Society
Turkish Society of Cardiology - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the European Society of Cardiology Web site.

Print copies: Available from Elsevier Publishers Ltd. 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44.207.424.4422; Fax: +44 207 424 4515; E-mail: gr.davies@elsevier.com.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, Spirito P, Ten Cage FJ, Wigle ED. Comprehensive bibliography on hypertrophic cardiomyopathy, including relevant, supplementary references to the ACC/ESC Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. American College of Cardiology Foundation and the European Society of Cardiology. 2003.

Electronic copies: Available in Portable Document Format (PDF) from the European Society of Cardiology Web site.

Print copies: Available from Elsevier Publishers Ltd. 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44.207.424.4422; Fax: +44 207 424 4515; E-mail: gr.davies@elsevier.com.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 13, 2004. The information was verified by the guideline developer on July 29, 2004.

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