# Hypertrophic Cardiomyopathy A Systematic Review

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YPERTROPHIC CARDIOMYOPathy (HCM) is a complex and relatively common genetic cardiac disease that has been the subject of intense scrutiny and investigation for more than 40 years.1-10 Hypertrophic cardiomyopathy is an important cause of disability and death in patients of all ages, although sudden and unexpected death in young people is perhaps the most devastating component of its natural history. Because of marked heterogeneity in clinical expression, natural history, and prognosis, 11-20 HCM often represents a dilemma to primary care clinicians and cardiovascular specialists, even to those for whom this disease is a focus of their investigative careers. Controversy abounds with regard to diagnostic criteria, clinical course, and management for which difficult questions often arise, particularly among practitioners infrequently engaged in the evaluation of HCM patients. Consequently, it is timely to place in perspective and clarify many of these relevant clinical issues and profile the rapidly evolving concepts regarding HCM.

## METHODS

A systematic search of the medical literature involving 968 articles primarily related to English-language HCM publications (1966-2000) from a varied and extensive number of authors and centers was conducted through MEDLINE or bibliographies of published articles. These studies and others before 1966 were analyzed to create a balanced appraisal of HCM.

Published accounts of HCM have come disproportionately from a rela-

**Context** Throughout the past 40 years, a vast and sometimes contradictory literature has accumulated regarding hypertrophic cardiomyopathy (HCM), a genetic cardiac disease caused by a variety of mutations in genes encoding sarcomeric proteins and characterized by a broad and expanding clinical spectrum.

**Objectives** To clarify and summarize the relevant clinical issues and to profile rapidly evolving concepts regarding HCM.

**Data Sources** Systematic analysis of the relevant HCM literature, accessed through MEDLINE (1966-2000), bibliographies, and interactions with investigators.

**Study Selection and Data Extraction** Diverse information was assimilated into a rigorous and objective contemporary description of HCM, affording greatest weight to prospective, controlled, and evidence-based studies.

Data Synthesis Hypertrophic cardiomyopathy is a relatively common genetic cardiac disease (1:500 in the general population) that is heterogeneous with respect to diseasecausing mutations, presentation, prognosis, and treatment strategies. Visibility attached to HCM relates largely to its recognition as the most common cause of sudden death in the young (including competitive athletes). Clinical diagnosis is by 2-dimensional echocardiographic identification of otherwise unexplained left ventricular wall thickening in the presence of a nondilated cavity. Overall, HCM confers an annual mortality rate of about 1% and in most patients is compatible with little or no disability and normal life expectancy. Subsets with higher mortality or morbidity are linked to the complications of sudden death, progressive heart failure, and atrial fibrillation with embolic stroke. Treatment strategies depend on appropriate patient selection, including drug treatment for exertional dyspnea (B-blockers, verapamil, disopyramide) and the septal myotomymyectomy operation, which is the standard of care for severe refractory symptoms associated with marked outflow obstruction; alcohol septal ablation and pacing are alternatives to surgery for selected patients. High-risk patients may be treated effectively for sudden death prevention with the implantable cardioverter-defibrillator.

**Conclusions** Substantial understanding has evolved regarding the epidemiology and clinical course of HCM, as well as novel treatment strategies that may alter its natural history. An appreciation that HCM, although an important cause of death and disability at all ages, does not invariably convey ominous prognosis and is compatible with normal longevity should dictate a large measure of reassurance for many patients. *JAMA*, 2002;287:1308-1320 www.jama.com

tively small group of highly selected centers in the United States, Canada, and Europe. In addition, perceptions emanating from the author's more than 25 years of extensive experience with HCM interfaced with the literature analysis. Many clinical HCM studies are observational and retrospective in design because of difficulty in organizing large prospective and randomized clinical trials for a disease with heterogeneous expression, selective referral patterns, and diverse mechanisms for morbidity and mortality. Therefore, in HCM, the level of evidence governing management

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decisions is derived primarily from nonrandomized studies. I placed the greatest reliance on evidence-based investigational designs and large, statistically powered and controlled studies, when available.

## RESULTS Prevalence

Epidemiological investigations with diverse study designs have shown similar estimates for prevalence of phenotypically expressed HCM in the adult general population at about 0.2% (1: 500).<sup>20</sup> Therefore, HCM is not rare and is the most common genetic cardiovascular disease, with reports from many countries. Nevertheless, a substantial proportion of individuals harboring a mutant gene for HCM are probably undetected clinically. Hypertrophic cardiomyopathy is, however, uncommon in routine cardiologic practice, affecting no more than 1% of outpatients.21 This limited exposure of clinicians to HCM understandably accounts for the uncertainty that prevails regarding this disease and its management.

#### Nomenclature

Since the first modern description in 1958,1 HCM has been known by a confusing array of names, reflecting its clinical heterogeneity and the skewed experience of early investigators. Hypertrophic cardiomyopathy<sup>22</sup> is the preferred name because it describes the overall disease spectrum without introducing misleading inferences that left ventricular (LV) outflow tract obstruction is an invariable feature (hypertrophic obstructive cardiomyopathy [HOCM] or idiopathic hypertrophic subaortic stenosis [IHSS]). Indeed, HCM is predominantly a nonobstructive disease; 75% of patients do not have a sizable resting outflow tract gradient.3,4,7

### Genetics

Hypertrophic cardiomyopathy is inherited as a mendelian autosomal dominant trait and caused by mutations in any 1 of 10 genes, each encoding proteins of the cardiac sarcomere (components of thick or thin filaments with contractile, structural, or regulatory functions).<sup>9,11-13,23-27</sup> The physical similarity of these proteins makes it possible to regard the diverse HCM spectrum as a single disease entity and primary sarcomere disorder. The mechanisms by which disease-causing mutations cause LV hypertrophy (LVH) and the HCM disease state are unresolved, although several hypotheses have been suggested.<sup>28</sup>

Three of the HCM-causing mutant genes predominate, namely, B-myosin heavy chain (the first identified), cardiac troponin T, and myosin-binding protein C. The other genes each account for a minority of HCM cases, namely, cardiac troponin I, regulatory and essential myosin light chains, titin,  $\alpha$ -tropomyosin,  $\alpha$ -actin, and  $\alpha$ -myosin heavy chain. This diversity is compounded by intragenic heterogeneity, with more than 150 mutations identified, most of which are missense with a single amino acid residue substituted with another.9,11-13,26,27 Molecular defects responsible for HCM are usually different in unrelated individuals, and many other genes and mutations, each accounting for a small proportion of familial HCM, remain to be identified.

Contemporary molecular genetic studies throughout the past decade have provided important insights into the considerable clinical heterogeneity of HCM, including the preclinical diagnosis of affected individuals without phenotypic evidence of disease (ie, LVH by echocardiography or electrocardiography [ECG]).25,29 Although DNA analysis for mutant genes is the definitive method for establishing the diagnosis of HCM, it is not yet a routine clinical strategy.9 Because of complex, timeconsuming, and expensive techniques, genotyping is confined to researchoriented investigations of highly selected pedigrees. Development of rapid automated screening for genetic abnormalities will permit more widespread access to the power of molecular biology for resolving diagnostic ambiguities.

Recently, missense mutations in the gene that encodes the  $\gamma$ -2 regulatory subunit of the adenosine monophosphate– activated protein kinase (*PRKAG2*) have been reported to cause familial Wolff-Parkinson-White syndrome associated with conduction abnormalities and LVH<sup>30,31</sup> (because of glycogen accumulation in myocytes).<sup>31</sup> This syndrome is most appropriately regarded as a metabolic storage disease distinct from HCM, which is caused by mutations in genes encoding sarcomeric proteins. Therefore, management and risk assessment of patients with Wolff-Parkinson-White syndrome and cardiac hypertrophy should not be predicated on data derived from patients with HCM.

Of potential importance for understanding HCM pathophysiology are genetic animal models (ie, transgenic mice and rabbits)<sup>32-35</sup> and spontaneously occurring animal diseases.<sup>36</sup> In particular, domestic cats with heart failure commonly show a disease with clinical and morphologic features remarkably similar to HCM in humans.<sup>36</sup>

#### Diagnosis

Clinical diagnosis of HCM is established most easily and reliably with 2-dimensional echocardiography\* by imaging the hypertrophied but nondilated LV chamber, in the absence of another cardiac or systemic disease (eg, hypertension or aortic stenosis) capable of producing the magnitude of hypertrophy evident (FIGURE 1and FIGURE 2A).<sup>19,22</sup> Hypertrophic cardiomyopathy may be initially suspected because of a heart murmur (occasionally during preparticipation sports examinations),43 positive family history, new symptoms, or abnormal ECG pattern.2,44,45 Across the broad disease spectrum of HCM, the physical examination may not be a reliable method for clinical identification, given that most patients do not have LV outflow tract obstruction and most of the well-documented physical findings (eg, loud systolic heart murmur and bifid arterial pulse) are limited to patients with outflow gradients.

With regard to pedigree assessment, it is obligatory for the proband to be informed of the familial nature and auto-

<sup>\*</sup>References 6, 9, 10, 14-16, 19-21, 25, 37-42.

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somal dominant transmission of HCM. Screening of first-degree relatives, including history taking and physical examinations, and 2-dimensional echocardiography and ECG should be encouraged, particularly if adverse HCM-related events have occurred in the family. In clinically diagnosed patients, increased LV wall thicknesses range widely from mild  $(13-15 \text{ mm})^{3,7,46}$  to massive  $(\geq 30 \text{ mm} [\text{normal}, \leq 12 \text{ mm}]),^{39,41,42,47}$ including the most substantial in any cardiac disease, namely, up to 60 mm (Figure 1).<sup>40</sup> In trained athletes, mod-





Echocardiographic parasternal long-axis stop-frame images obtained in diastole showing A, massive asymmetric hypertrophy of ventricular septum (VS) with wall thickness >50 mm; B, pattern of septal hypertrophy in which the distal portion is considerably thicker than the proximal region at mitral valve level; C, hypertrophy sharply confined to basal (proximal) septum just below aortic valve (arrows); D, hypertrophy confined to LV apex (asterisk), consistent with the designation of apical hypertrophic cardiomyopathy (HCM); E, relatively mild hypertrophy in a concentric (symmetric) pattern with each segment of ventricular septum and LV free wall showing similar or identical thicknesses (paired arrows); F, inverted pattern of hypertrophy in which anterior VS is less substantially thickened than the posterior free wall (PW), which is markedly hypertrophied (ie, 40 mm). Calibration marks are 1 cm apart. Ao indicates aorta; AML, anterior mitral leaflet; and LA, left atrium. Reproduced from Klues et al<sup>19</sup> with the permission of Elsevier Science, Inc.

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est segmental wall thickening (ie, 13-15 mm) raises the differential diagnosis between extreme physiologic LVH (ie, athlete's heart) and mild morphologic expressions of HCM,<sup>48</sup> which can usually be resolved with noninvasive testing.<sup>49</sup> Magnetic resonance imaging may be of diagnostic value when echocardiographic studies are technically inadequate or in identifying segmental LVH undetectable by echocardiography.

The 12-lead ECG pattern is abnormal in 75% to 95% of HCM patients and typically demonstrates a wide variety of patterns.<sup>25,44,50</sup> Normal ECGs are most commonly encountered in family members identified as part of pedigree screening or when associated with mild localized LVH.<sup>25,44,50</sup> Only a modest relation between ECG voltages and the magnitude of LVH assessed by echocardiography is evident. Nevertheless, ECGs have diagnostic value in raising a suspicion of HCM in family members without LVH on echocardiogram and in targeting athletes for diagnostic echocardiography as part of preparticipation screening.

However, not all individuals harboring a genetic defect will express the clinical features of HCM, such as LVH by echocardiography, abnormal ECG results, or cardiac symptoms.3,9,13,25,29,51-53 Molecular genetic studies have, in fact, demonstrated that there is no minimum wall thickness required for HCM at a given time in life, and it is not unusual for children younger than 13 years to carry a mutant HCM gene without LVH, underscoring the lack of productivity in preadolescent echocardiographic screening.† Substantial LV remodeling with spontaneous appearance of hypertrophy typically occurs with accelerated body growth during adolescence, and morphologic expression is usually completed at physical maturity (about 17-18 years of age).<sup>52,57,58</sup> Abnormalities on 12lead ECG and non-preload-dependent measures of diastolic dysfunction with tissue Doppler ultrasonography may precede the appearance of hypertrophy, providing clues to impending LVH. 25,29,51,54,56,58,59

tReferences 7, 9, 11-13, 23-25, 29, 51, 53-56.

Novel diagnostic criteria for HCM have recently emerged and are based on genotype-phenotype studies showing incomplete disease expression with absence of LVH in adult individuals, most commonly due to cardiac myosinbinding protein C or troponin T mutations.13,23-25,60 In both cross-sectional and serial echocardiographic studies, mutations in the myosin-binding protein C gene may demonstrate age-related penetrance of the HCM phenotype in which delayed de novo onset of LVH may occur in midlife and later.13,25,53,54 Such adult morphologic conversions dictate that it is no longer possible to use a normal echocardiogram to offer definitive reassurance at maturity (or even in middle age) that asymptomatic family members are free of a disease-causing mutant HCM gene13,25,60,61; this observation probably necessitates a strategy of postadolescent echocardiographic examinations every 5 years.

Paradoxically, a small distinctive subset of HCM patients (ie, about 5%-10%) evolve into the end stage (or "burned-out" phase) characterized by LV wall thinning, cavity enlargement, and systolic dysfunction often resembling dilated cardiomyopathy and producing relentlessly progressive and irreversible heart failure.<sup>3,4,7,58,62</sup> It is also possible that other adults experience subtle regression in wall thickness with aging (not linked with clinical deterioration), reflecting gradual, widespread remodeling. 58,63 Therefore, the HCM phenotype is not a static disease manifestation; LVH can appear at virtually any age and increase or decrease dynamically throughout life.

## HCM Phenotype and Morphologic Features

Left Ventricular Hypertrophy. Structural heterogeneity in HCM is considerable, with no single pattern of LVH regarded as typical (Figure 1).<sup>3,6,15,19,23,41,47</sup> Although many patients show diffusely distributed LVH, almost one third have mild wall thickening localized to a single segment,<sup>15,19,46</sup> including the apical form<sup>37-</sup> <sup>39,61,64</sup> that appears most commonly in Japanese people (Figure 1D).<sup>64</sup> Left ven**Figure 2.** Morphologic Features of the Myocardial Substrate for Sudden Death in Hypertrophic Cardiomyopathy (HCM)



A, Gross heart specimen from a 13-year-old male competitive athlete showing disproportionate thickening of the ventricular septum (VS) with respect to the left ventricular (LV) free wall (RV indicates right ventricular wall); B, marked disarray of cardiac muscle cells in the disproportionately thickened VS with adjacent hypertrophied cells arranged in a chaotic pattern at oblique and perpendicular angles, forming the typical disorganized architecture of HCM; C, LV myocardium showing several abnormal intramural coronary arteries with markedly thickened walls and narrowed lumen, dispersed within replacement fibrosis (hematoxylin and eosin stain in B and C; original magnifications  $\times$ 50). Adapted from Maron BJ. Hypertrophic cardiomyopathy. *Current Probl Cardiol*. 1993;18:637-704 with permission of Mosby Inc.

tricular hypertrophy is characteristically asymmetric, with the anterior septum usually predominant (Figure 1A-D, F; Figure 2A), although a few patients show a symmetric (concentric) pattern (Figure 1E).<sup>15,16,19</sup> Distribution of LV wall thickening shows no direct linkage to outcome, although distal hypertrophy is associated with the absence of obstruction.15,19 Young children may present with LVH resembling HCM as part of other disease states (eg, Noonan syndrome, mitochondrial myopathies, and metabolic disorders) unrelated to HCMcausing sarcomere protein mutations. Other markers of HCM that are not obligatory prerequisites for diagnosis include a hypercontractile LV and dynamic subaortic obstruction typically produced by mitral valve systolic anterior motion and septal contact6,8,65-70 (caused by drag effect69 or possibly the Venturi phenomenon<sup>6,8,67,68,70</sup>), which is responsible for a loud systolic murmur.

Cellular Components. Cardiomyopathic substrate in HCM is defined anatomically by several histological features based on autopsy observations. Left ventricular myocardial architecture is disorganized, composed of hypertrophied cardiac muscle cells (myocytes) with bizarre shapes and multiple intercellular connections often arranged in chaotic alignment at oblique and perpendicular angles (Figure 2B).1,71-75 Cellular disarray may be widely distributed, occupying substantial portions of LV wall (average, 33%), and is more extensive in young patients who die of their disease.72,74,75

Abnormal intramural coronary arteries, characterized by thickened walls with increased intimal and medial collagen and narrowed lumen, may be regarded as a form of small vessel disease (Figure 2).<sup>76,77</sup> Such architectural alterations of the microvasculature, as well as the mismatch between myocardial mass and coronary circulation, are likely responsible for impaired coronary vasodilator reserve<sup>78,79</sup> and bursts of myocardial ischemia<sup>78-90</sup> leading to myocyte death and repair in the form of patchy or transmural replacement scarring (Fig-

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ure 2).<sup>73,76,83-85,90</sup> Such myocardial scarring supports clinical evidence that ischemia frequently occurs within the natural history of HCM<sup>2-8,78,82,86-89,91-93</sup> and may serve as the substrate for premature heart failure–related death.<sup>74</sup> It is also evident that the cardiomyopathic process in HCM is not confined to areas of gross wall thickening and that nonhypertrophied regions also contribute to ischemia or impaired diastolic function.<sup>86,88,89,91,94-96</sup>

Disorganized cellular architecture, 1,71-73,75 myocardial scarring,73,76,83-85,90 and expanded interstitial (matrix) collagen<sup>83,97</sup> probably serve as arrhythmogenic substrates predisposing to life-threatening electrical instability. This substrate is likely the source of primary ventricular tachycardia and ventricular fibrillation, which appear to be the predominant mechanisms of sudden death,98-101 either primarily or in association with triggers intrinsic to the disease process, namely, myocardial ischemia, systemic hypotension, supraventricular tachyarrhythmias, or environmental variables (eg, intense physical exertion).

Penetrance and variability of phenotypic expression are undoubtedly influenced by factors other than diseasecausing mutant genes such as modifier genes (eg, angiotensin-converting enzyme genotype),<sup>102,103</sup> coexistent hypertension, or lifestyle. Indeed, several phenotypic manifestations of HCM do not primarily involve sarcomeric proteins, including increased interstitial collagen,<sup>83,97</sup> abnormal intramural arteries,<sup>76,77</sup> and mitral valve malformations such as elongated leaflets<sup>18,104</sup> or direct papillary muscle insertion into the mitral valve.<sup>17</sup>

## **Clinical Course**

Hypertrophic cardiomyopathy is unique among cardiovascular diseases by virtue of its potential for clinical presentation during any phase of life (from infancy to >90 years of age).‡ Although adverse clinical consequences have been recognized for many years, particularly

‡References 1-8, 19, 20, 51, 52, 54, 98, 99, 105-115. sudden cardiac death,<sup>1,2,5-8,116-119</sup> a more balanced perspective regarding prognosis has evolved recently.<sup>111,114,120-127</sup>

Historically, misperceptions regarding the clinical significance of HCM have prevailed because of its relatively low prevalence in cardiac populations,<sup>20,21</sup> extreme heterogeneity,3,6 and skewed patterns of patient referral that created important selection biases.111,121,122 Indeed, much of the data assembled throughout the past 40 years have been disproportionately generated by a few tertiary centers largely composed of patients preferentially referred because of their high-risk status or severe symptoms requiring specialized care such as surgery.<sup>111,121,122</sup> Hence, the older literature was dominated by the most adverse consequences of HCM, while clinically stable, asymptomatic, and elderly patients were underrepresented. 105,112-115,121

Consequently, the risks of HCM would appear to have been overestimated by dependence on frequently cited, ominous mortality rates of 3% to 6% annually.108,119 These figures, based largely on skewed tertiary-center experience, have contributed greatly to the misguided perception that HCM is a generally unfavorable disorder. Recent reports throughout the last 7 years from less selected regional or community-based HCM patient cohorts cite much lower annual mortality rates, about 1%,120-126 not dissimilar to that for the general adult US population.111 Such data provide a more balanced view in which HCM may be associated with important symptoms and premature death but more frequently with no or relatively mild disability and normal life expectancy. 105,111,113,115,123,124

Elderly HCM patients (≥75 years) have been reported to compose as much as 25% of an HCM cohort, with only a minority having severe manifestations of heart failure.<sup>111</sup> Outflow obstruction is commonly evident in patients of advanced age (ie, in about 40%), suggesting that subaortic gradients may be well tolerated for long periods without adverse consequences. Indeed, HCM in elderly patients can be a genetic disorder caused by dominant sarcomere protein mutations most commonly in cardiac myosin-binding protein C and troponin I genes.<sup>128</sup>

## Profiles of Prognosis and Treatment Strategies

The clinical course for individual HCM patients is most appropriately viewed in terms of specific subgroups rather than only from perceptions of the overall disease spectrum (FIGURE 3). Some patients progress along certain relatively discrete, adverse pathways: (1) high risk for sudden death§; (2) congestive symptoms of heart failure with exertional dyspnea and functional disability often associated with chest pain and usually in the presence of preserved LV systolic function<sup>111,119,120</sup>; and (3)

SReferences 1-8, 11, 12, 24, 41-43, 47, 98, 99, 101, 108, 114, 116-118, 127.

consequences of atrial fibrillation (AF),<sup>129-131</sup> including embolic stroke.

Sudden Death. *Risk Stratification*. Sudden death is the most common mode of demise and the most devastating and unpredictable complication of HCM.<sup>1-4,7,8,98-100,114</sup> Therefore, within the broad HCM disease spectrum, for which overall annual mortality rate is about 1%, exist small subsets at a much higher risk (perhaps at least 5% annually).



Hypertrophic cardiomyopathy (HCM) clinical subgroups are not necessarily mutually exclusive; overlap or progression from one subgroup to another may occur (thin solid and dashed arrows). Most patients with HCM who are at high risk of sudden death or who develop atrial fibrillation are initially in the "None or Mild Symptoms" clinical subgroup. Asterisk indicates that patients with a positive genotype and negative phenotype may subsequently show morphologic conversion to the HCM phenotype with left ventricular hypertrophy (usually in adolescence, but also in mid-life or later). Dagger indicates that drug therapy may include β-blockers, calcium channel blockers (particularly verapamil), disopyramide, as well as diuretic agents. Double dagger indicates that for major interventions, obstructive HCM is generally regarded as a left ventricular outflow gradient of approximately 50 mm Hg at rest or with provocative maneuvers; in this context, nonobstructive HCM is regarded as a left ventricular outflow gradient of less than approximately 30 to 50 mm Hg at rest as well as with provocative maneuvers. Width of the arrows from the overall HCM population represent the approximate relative proportion of patients with HCM within each major clinical subgroup. Adapted from Spirito et al<sup>7</sup> with permission of the Massachusetts Medical Society.

An important but complex objective has been the identification of such higher-risk individuals among the vast HCM spectrum. For example, sudden death can be the initial manifestation of HCM, and such patients usually have no or only mild prior symptoms. Although sudden death occurs most commonly in children and young adults, risk extends across a wide age range through midlife and beyond<sup>114</sup>; therefore, achieving a particular age does not confer immunity to sudden catastrophe. Sudden death occurs most commonly during mild exertion or sedentary activities but is not infrequently related to vigorous physical exertion.43,114,118 Indeed, HCM is the most common cause of cardiovascular sudden death in young people, including trained competitive athletes (most commonly in basketball and football and in black athletes).43

The majority of HCM patients (55%) do not demonstrate any of the acknowledged risk factors in this disease, and it is exceedingly uncommon for such patients to die suddenly47; the subset at increased risk appears to comprise about 10% to 20% of the HCM population.47 Highest risk for sudden death in HCM has been associated with any of the following noninvasive clinical markers (Figure 3) : prior cardiac arrest or spontaneous sustained ventricular tachycardia; family history of premature HCMrelated death, particularly if sudden, in close relatives, or multiple; syncope and some cases of near-syncope, particularly when exertional or recurrent, or in young patients when documented as arrhythmia-based or clearly unrelated to neurocardiogenic mechanisms; multiple and repetitive or prolonged bursts of nonsustained ventricular tachycardia on serial ambulatory (Holter) ECG recordings; hypotensive blood pressure response to exercise, particularly in patients younger than 50 years; and extreme LVH with maximum wall thickness ≥30 mm, particularly in adolescents and young adults.

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The latter risk factor emanates from a continuous, direct relationship between maximum LV wall thickness and sudden death, which supports the magnitude of LVH as a determinant of prognosis in HCM.<sup>6,41,42,47</sup> Exceptions to that association are a few highly selected HCM families with multiple sudden deaths and mild LVH caused by troponin T mutations.<sup>23,24,60</sup> Description of the total HCM risk profile is probably incomplete, and no single disease feature or test is capable of stratifying risk in all patients.

There is only a suggested association<sup>41,111,127</sup> but no clinically relevant and independent linkage between sudden death and outflow obstruction,<sup>3,7,41,111,114,120,137</sup> although data on particularly large ( $\geq$ 100 mm Hg) gradients are limited.<sup>111,127</sup> One report suggests that short, tunneled (bridged) segments of left anterior descending coronary artery, mediated by ischemia, independently convey increased risk for cardiac arrest in children with HCM.<sup>138</sup>

Presentation of HCM in young children is exceedingly uncommon and usually creates a clinical dilemma because of diagnosis (often fortuitous) so early in life and the uncertainty regarding risk over such long periods.<sup>89,96-98</sup> Studies of HCM in children report annual mortality rates of 2% (communitybased populations)<sup>101</sup> to 6% (tertiary referral cohorts).<sup>98,107-109</sup>

It has been proposed, based on genotype-phenotype correlations, that the genetic defects responsible for HCM<sup>3,7,9,11-13,23-27,139</sup> could represent the primary determinant and stratifying marker for sudden death risk, with specific mutations conveying either favorable or adverse prognosis.140 For example, some *β*-myosin heavy chain mutations (eg, Arg403Gln and Arg719Gln) and some troponin T mutations may be associated with a higher frequency of premature death compared with other mutations, such as those of myosin-binding protein C (InsG791) or a-tropomyosin (Asp175Asn).<sup>3,7,9,11-13,23,24,26,27</sup> However, caution is warranted before strong conclusions are drawn regarding prognosis based solely on the available epidemiologic genetic data, which are relatively limited and skewed by virtue of selection bias toward high-risk families.<sup>9,139</sup> Access to the molecular biology of HCM does not yet represent a clinically relevant strategy that routinely affects disease management.

Prognosis attached to adult gene carriers without LVH appears to be mostly benign.<sup>13,25,53,54</sup> There is no available evidence to justify routinely precluding genotype positive–phenotype negative individuals of any age from most activities or employment opportunities.<sup>9</sup>

The role of invasive strategies such as electrophysiologic testing with programmed ventricular stimulation and the significance of induced arrhythmias in detecting the substrate for ventricular fibrillation in individual HCM patients are unresolved.<sup>141,142</sup> Limitations include the infrequency with which monomorphic ventricular fibrillation is provoked and the nonspecificity of rapid polymorphic ventricular tachycardia and ventricular fibrillation.<sup>142</sup>

Although attention has understandably focused on high-risk HCM patients, the absence of risk factors and certain clinical features can be used to develop a profile of HCM patients at low likelihood for sudden death caused by life-threatening rhythm disturbances, as well as other adverse events (eg, at a rate of <1% annually).7 Adult patients most likely at lowest risk are those with no or only mild congestive symptoms in the absence of the following: family history of HCM-related premature death; syncope (or near-syncope) judged unlikely to be neurocardiogenic in origin; nonsustained ventricular tachycardia during ambulatory Holter ECGs; marked LV outflow gradient of at least 50 mm Hg; substantial LVH (wall thickness  $\geq$  20 mm); left atrial enlargement (>45 mm); and hypotensive blood pressure response to exercise.¶ Such patients with favorable prognosis constitute an important proportion of the overall HCM population and generally

¶References 3, 4, 6-13, 23, 24, 26, 27, 41, 42, 47, 134-136, 139-141.

References 3, 7, 9, 40-42, 47, 98, 101, 111, 116-119, 127, 132-136.

deserve a measure of reassurance regarding their disease.<sup>3,7</sup>

Most HCM patients should undergo a risk stratification assessment (probably with the exception of patients older than 60 years) that requires, in addition to careful history taking and physical examination, noninvasive testing with 2-dimensional echocardiography, 24- or 48-hour ambulatory Holter ECGs, and treadmill (or bicycle) exercise testing. Such evaluation and follow-up should be carried out by (or involve) qualified specialists in cardiovascular medicine.

Prevention. In HCM, treatment strategies to reduce risk for sudden death have been historically predicated on drugs such as *B*-blockers, verapamil, and antiarrhythmic agents (ie, quinidine, procainamide, and amiodarone).4,116,117,143-145 Nevertheless, there is little evidence144 that prophylactic pharmacological strategies and rhythmmodulating drugs effectively reduce risk for sudden death; furthermore, because of its potential toxicity, amiodarone is unlikely to be tolerated throughout the long risk periods characteristic of young HCM patients. Therefore, there would appear to be little justification for prophylactic drug treatment in asymptomatic HCM patients, whether or not they are judged to be at high risk.143

At present, the implantable cardioverter-defibrillator (ICD) appears to be the most effective treatment modality for the high-risk HCM patient, with the potential to alter natural history (Figure 3).98-100 In a large multicenter study, ICDs aborted potentially lethal ventricular tachyarrhythmias and restored sinus rhythm in almost 25% of patients throughout a brief 3-year follow-up.98 Appropriate device interventions occurred at 11% annually for secondary prevention (implant following cardiac arrest) and 5% annually for primary prevention (implant based on risk factors), usually in patients with no or only mild prior symptoms.98 Patients receiving appropriate shocks were young (mean, 40 years), and ICDs often remained dormant for prolonged periods before discharging (up to 9 years),

emphasizing the unpredictability of sudden death events in HCM.

Sudden death prevention with the ICD is most strongly warranted for patients with prior cardiac arrest or sustained spontaneous ventricular tachycardia. Although multiple risk factors convey increasingly greater suddendeath risk,47 a single major risk factor in an individual patient may be sufficient to justify strong consideration for primary prevention with an ICD. Nevertheless, uncertainty persists regarding precisely which HCM patients with only 1 risk factor should be candidates for prophylactic ICD treatment,41,42,98 and therefore individual clinical judgment taking into account the overall clinical profile, including age, apparent strength of the risk factor identified, and the level of risk acceptable to the patient and family, may be necessary to definitively resolve many of these clinical decisions. Also, physician and patient attitudes toward ICDs (and also access to the devices) can vary considerably among countries and cultures and profoundly affect clinical decision making.42,98,146

Intense physical exertion constitutes a sudden-death trigger in susceptible individuals.<sup>43</sup> Therefore, to reduce risk, disqualification of athletes with unequivocal evidence of HCM from most competitive sports has been prudently recommended by a national consensus panel.<sup>147</sup>

Atrial Fibrillation. Atrial fibrillation is the most common sustained arrhythmia in HCM, accounting for unexpected hospital admissions and unscheduled work loss, and therefore usually justifies aggressive therapeutic strategies (Figure 3). Paroxysmal episodes or chronic AF ultimately occur in 20% to 25% of HCM patients, increase in incidence with age, and are linked to left atrial enlargement.111,120,129-131 Atrial fibrillation is reasonably tolerated by about one third of patients and is not an independent determinant of sudden death.130 However, AF is associated with embolic stroke (incidence, about 1% annually; prevalence, 6%), leading to death and disability most frequently in the elderly,131 as well as progressive heart failure, particularly when AF onset occurs before 50 years of age and is associated with basal outflow obstruction.<sup>130</sup>

Paroxysmal AF may be responsible for acute clinical decompensation, requiring electrical or pharmacological cardioversion.47.8 Although data in HCM patients are limited, amiodarone is regarded as effective for reducing AF recurrences. In chronic AF, B-blockers and verapamil effectively control heart rate. although A-V node ablation with permanent ventricular pacing may occasionally be necessary. Because of the potential for clot formation and embolization, anticoagulant therapy with warfarin is indicated in patients with either recurrent or chronic AF. Since 1 or 2 paroxysms of AF have been associated with the risk for systemic thromboembolism in HCM, the threshold for initiation of anticoagulant therapy should be low.130,131 However, such clinical decisions should be tailored to the individual patient after the obligatory lifestyle modifications, risk of hemorrhagic complications, and expectations for compliance have been considered.

Heart Failure. Presentation. Symptoms such as exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and fatigue are common, characteristically in the presence of normal or supranormal LV contractility and independent of whether outflow obstruction is present (Figure 3).<sup>2-8,148-154</sup> Such symptoms of HCM-related heart failure are usually deferred until adulthood but may occur at any age.

Marked symptom progression (to New York Heart Association classes III and IV) is relatively infrequent, developing in about 15% to 20% of an unselected population, and such exertional disability may evolve at varying rates; deterioration is often gradual and punctuated with long periods of stability and day-to-day variability (Figure 3).<sup>2,3,7</sup>

Congestive symptoms and exertional limitation in HCM appear to be largely the consequence of diastolic dysfunction in which impaired LV relaxation, increased chamber stiffness, and compromised left atrial systolic function impede filling, leading to elevated left

Alternatives to Surgery. Some operative candidates may not have ready access to major centers experienced with myotomy-myectomy because of geographical factors, or they may not be regarded as favorable operative candidates because of concomitant medical conditions, advanced age, prior cardiac surgery, or insufficient motivation.<sup>7</sup>

Therefore, 2 treatment options have emerged as potential alternatives to surgery for selected patients (Figure 3). First, in uncontrolled and observational studies, chronic dual-chamber pacing was associated with amelioration of symptoms and reduction of outflow gradient in many HCM patients. 192-194 However, several randomized crossover clinical trials reported that subjective symptomatic benefit during pacing frequently occurs with little objective evidence of improved exercise capacity<sup>195-199</sup> and can be largely explained as a placebo effect. 192,195,196,198 Although pacing is not a primary treatment for HCM, 1 study showed that elderly patients (older than 65 years), a subgroup for which alternatives to surgery are often desirable, experienced objective improvement in symptoms with pacing.195 While myotomy-myectomy provides superior results to pacing in most patients, 181 a dual-chamber pacing trial prior to myotomy-myectomy could be of value in selected candidates, given that pacing (1) is implicitly less invasive than surgery or alcohol septal ablation, (2) is a more widely accessible method to the practicing cardiologist, (3) can permit more aggressive drug treatment by obviating concern for drug-induced bradycardia, (4) may be withdrawn, and (5) does not obviate subsequent implementation of invasive procedures. Pacing does not reduce sudden-death risk significantly<sup>193,195</sup> or trigger LV remodeling.195

A second alternative therapy to surgery is the recently developed alcohol septal ablation technique, which is a percutaneous coronary artery intervention using methods and technology available for atherosclerotic coronary artery disease.<sup>200-205</sup> Absolute alcohol (about 1-4 mL) is introduced into the target septal perforator coronary artery branch to produce myocardial infarction, which in turn reduces basal septal thickness and motion, enlarges the LV outflow tract, and decreases mitral valve systolic anterior motion, thereby mimicking the hemodynamic consequences of myotomymyectomy.200-207 Indeed, reductions in outflow gradient associated with alcohol septal ablation have been reported to be similar to those resulting from myotomy-myectomy,205 although a recent comparative analysis showed surgery to be superior to ablation in reducing resting and provocable gradients.207 Also, similar proportions of ablation and surgical patients have been reported to show subjective200-203,205 and objective204 improvements in congestive symptoms and quality of life over relatively short periods, largely in observational studies; in addition, there are unconfirmed claims of diffuse regression of LVH following ablation.204 However, alcohol septal ablation in HCM has not yet been subjected to the scrutiny of randomized or controlled studies. 191,206

Septal ablation is associated with operative morbidity and mortality, similar to that of myotomy-myectomy; complications include permanent pacemaker for high-grade A-V block, coronary dissection, and large anterior infarction.<sup>200-203,205</sup> In contrast to that for surgery, the postprocedural follow-up for alcohol septal ablation is relatively brief (about 3-5 years compared with 40 years for myotomy-myectomy).<sup>191</sup>

Furthermore, ablation alone potentially creates a permanent, electrically unstable substrate for lethal reentrant ventricular tachyarrhythmias by virtue of the healed intramyocardial septal scar in some HCM patients who are already undoubtedly predisposed to arrhythmogenesis; this consideration raises some uncertainty regarding the longterm risks of alcohol septal ablation.<sup>191</sup>

Heart Transplantation. Therapeutic options are considerably limited for patients who have the nonobstructive form of HCM and experience drugrefractory severe symptoms, including those in the end-stage phase.<sup>61</sup> This subset of patients, among the broad HCM spectrum, may become candidates for heart transplantation.<sup>61,62</sup> Funding/Support: This work was supported by grants from the Minneapolis Heart Institute Foundation and Paul G. Allen Foundations.

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