Dan L. Longo, M.D., *Editor*

Clinical Course and Management of Hypertrophic Cardiomyopathy

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HYPERTROPHIC CARDIOMYOPATHY (HCM), THE MOST COMMON MONO-genic cardiovascular disorder, is diverse in presentation and natural history, frequently misunderstood, and often underrecognized in clinical practice.[1-3] A comprehensive clinical description of the disease was first made 55 years ago by the Braunwald group at the National Institutes of Health; at that time it was called idiopathic hypertrophic subaortic stenosis.[4] An understanding of diagnostic features, genetic factors, clinical course, and management of the broad spectrum of HCM has evolved measurably, particularly in the past 15 years.[1-3,5-10] A vast literature (more than 18,000 reports) has emerged, and in many respects, contemporary HCM differs markedly from the disease of previous eras.

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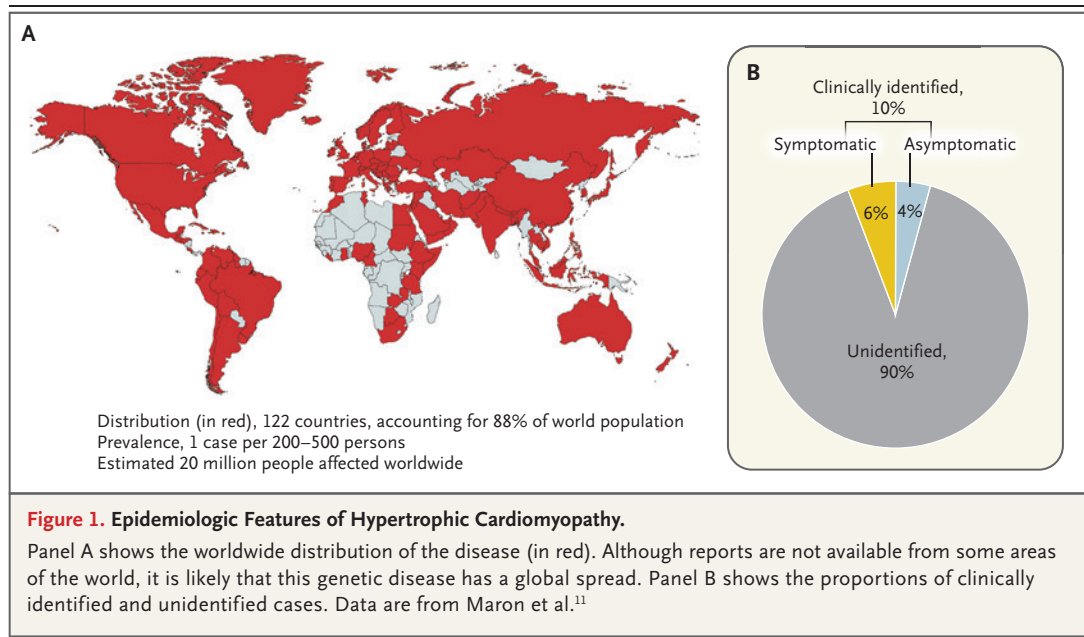
EPIDEMIOLOGIC FEATURES

DIAGNOSIS AND PREVALENCE

Clinical diagnosis of HCM is based on a hypertrophied, nondilated left ventricle — which is identified by means of echocardiography or magnetic resonance imaging (MRI) — in the absence of another cardiac, systemic, metabolic, or syndromic disease.[2,3,6-8] Echocardiography-based epidemiologic studies have shown a disease prevalence of 1 case per 500 persons in the general population[3,6] but a higher prevalence (1 case per 200) when both clinical and genetic diagnoses, including those in family members, are taken into account[9] (Fig. 1). An estimated 750,000 persons in the United States may be affected by HCM. However, the disease has been diagnosed in only a fraction of them (about 100,000), usually by means of noninvasive imaging, which suggests that most persons do not receive a diagnosis during their lifetime (Fig. 1).[10] Underrecognition of HCM has disproportionately affected women and also underserved minorities, with evidence of underrecognition among blacks including deaths on the athletic field of black men with undiagnosed disease and potential underreferral of affected black patients for specialized HCM-related treatments.[12]

GLOBAL BURDEN

HCM has been identified in 122 countries (representing approximately 90% of the world population), with spontaneous (de novo) mutations probably accounting for this disease burden[11] (Fig. 1). It is likely that HCM affects approximately 20 million people globally, well beyond the population that was initially thought to be affected.

Although the disease occurs in many countries, ethnic groups, and races and affects both sexes equally, its clinical and phenotypic expression and genetic substrate do not appear to vary substantially according to demographic characteristics.[11] Hypertrophic cardiomyopathy has been underrecognized in many parts of the world, but an awareness of the disease is now penetrating the health care

Figure 1. Epidemiologic Features of Hypertrophic Cardiomyopathy.

Panel A shows the worldwide distribution of the disease (in red). Although reports are not available from some areas of the world, it is likely that this genetic disease has a global spread. Panel B shows the proportions of clinically identified and unidentified cases. Data are from Maron et al.[11]

systems in China, India, and other developing countries, defining an emerging frontier for diagnosis and management.[13,14]

GENETIC FACTORS

HCM is inherited in an autosomal dominant pattern, associated with mutations (nucleotide sequence variants) in 11 or more genes encoding proteins of thick and thin myofilament contractile components of the cardiac sarcomere or Z disk, with beta-myosin heavy chain and myosin-binding protein C genes most commonly involved.[5,15-21] Genetic testing panels show vast heterogeneity and diverse molecular pathways, with more than 2000 sarcomere mutations identified. Some of the mutations are considered to be pathogenic, but in others pathogenicity is uncertain, and many are confined to single families[15-17,19] (Fig. 2).

These seminal insights have made it possible to diagnose HCM on the basis of laboratory testing in patients who otherwise would be unaware of their genetically affected status. However, genotype–phenotype correlations have been inconsistent, and single (or multiple) sarcomere variants are unreliable in predicting prognosis, with no specific role in risk stratification.[1-3,6,18-21] Thus, important management decisions in cases of HCM are based solely on clinical criteria.[1-3,6,20]

Genetic testing is confined largely to next-generation (cascade) family screening, which affords the opportunity to identify family members

Figure 2 (facing page). Pathophysiological Substrate of Hypertrophic Cardiomyopathy (HCM).

Panel A (hematoxylin and eosin) shows the histopathological features of HCM: disorganized architecture of the left ventricular (LV) myocardium with adjacent myocytes arranged at perpendicular and oblique angles (left), an abnormal intramural coronary arteriole with a thickened wall (media) and narrowed lumen (center), and a myocardial scar (right). Panel B shows hypertrophy confined to the anterolateral free wall (asterisk), a pattern most reliably visualized on MRI. RV denotes right ventricle, and VS ventricular septum. Panel C shows a thin-walled apical aneurysm (arrowheads), a finding associated with an increased risk of sudden death at any age in association with VS hypertrophy. D denotes distal cavity, LA left atrium, and P proximal cavity. The diagram of a cardiac sarcomere in Panel D shows 11 HCM sarcomere genes. Panel E shows an HCM family pedigree with a myosin-binding protein C (MBPC3) mutation. The father and two of his children had HCM, another child was unaffected and was excluded from further clinical testing, and one child had a pathogenic mutation without LV hypertrophy. Black symbols denote affected family members, white symbols unaffected family members, squares male family members, and circles female family members; the arrow indicates the proband. The numbers under the symbols indicate age (in years) at the time of testing. The echocardiograms in Panels F and G are from the same patient. Panel F shows LV outflow obstruction due to mitral-valve systolic anterior motion and septal contact (arrow), and Panel G shows waveforms from a continuous-wave Doppler study, with a subaortic gradient estimated to be about 100 mm Hg. Panel H shows areas of late enhancement (white) after the administration of gadolinium, a finding that is consistent with fibrosis in the VS (arrow). RA denotes right atrium.
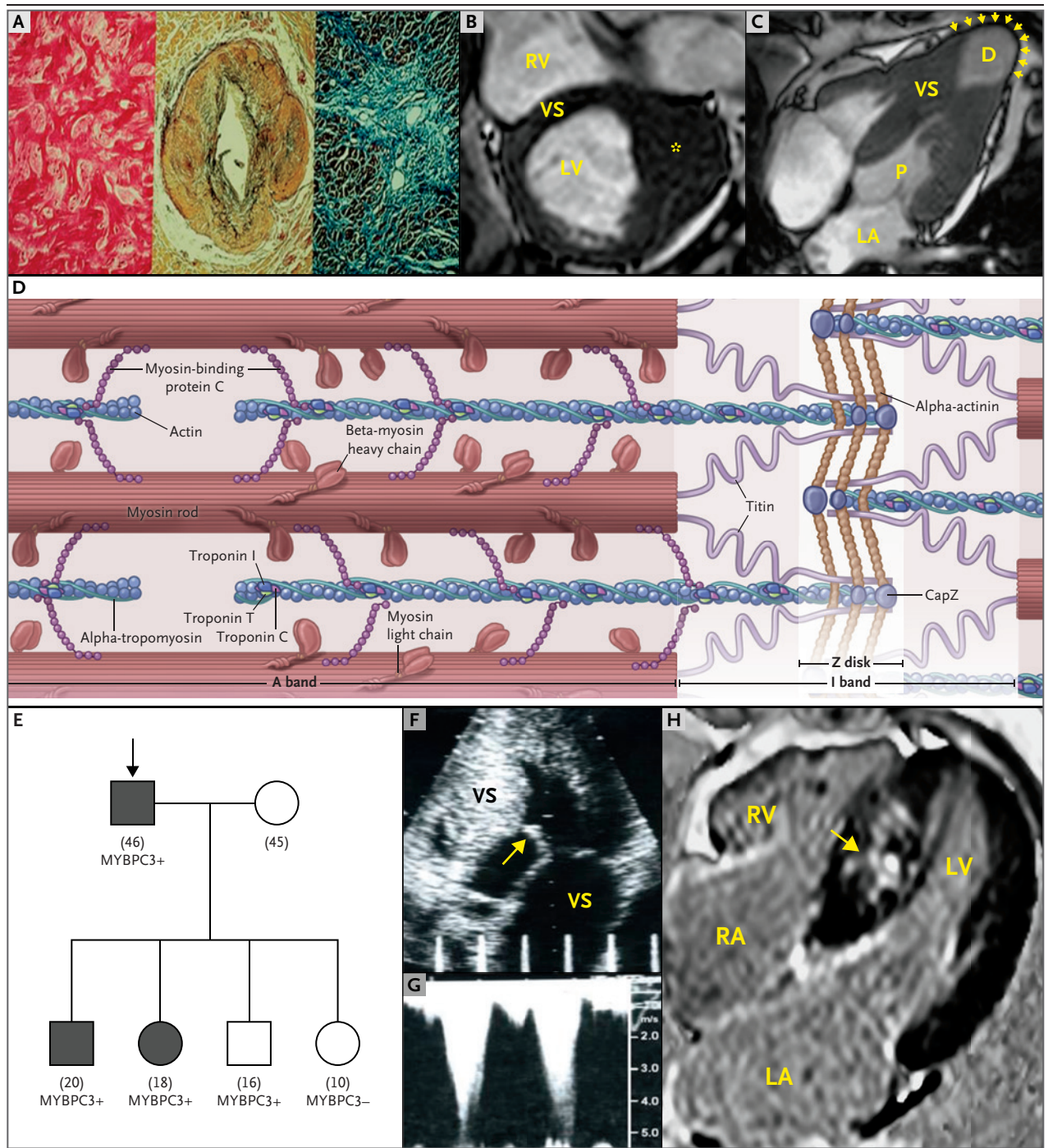
who are unlikely to inherit HCM, as well as affected family members without left ventricular hypertrophy[2,3,5,6,19] (Fig. 2). Such gene carriers characteristically have no cardiac events or symptoms, and many carriers will never have HCM but can nevertheless transmit disease-causing mutations to subsequent generations.[8,22,23] Genetic testing can also identify metabolic and storage phenocopies (e.g., lysosome-associated membrane protein 2 [LAMP2] cardiomyopathy, Fabry's disease, PRKAG2, and amyloidosis) that mimic HCM.[2,5,6,19]

With technological advances (whole-genome sequencing), variants of uncertain significance have become more numerous,[15-19] making interpretation of pathogenicity increasingly complex[15-19,24]

and potentially leading to misinterpretation of benign variants as pathogenic in diverse racial, ethnic, and ancestry populations.[18,24] Indeed, at present, only one third of probands with HCM have pathogenic (or probably pathogenic) mutations suitable for family screening.[3,19,24] Sporadic (nonfamilial) HCM (i.e., sarcomere mutations in a patient without a family history of HCM) may be more common than currently thought.[25]

MORPHOLOGIC FEATURES ON IMAGING STUDIES

LEFT VENTRICULAR HYPERTROPHY

Characterization of the HCM phenotype has been based on almost 50 years of echocardiographic imaging.[8] High-resolution tomographic MRI can provide a more reliable assessment of left ventricular hypertrophy in some patients,[7] as well as enhanced risk stratification through in vivo identification of myocardial fibrosis[7,26,27] (Fig. 2).

In most clinically diagnosed cases, left ventricular wall thickness is 15 mm or more (average, 21 mm), but there is massive thickness (30 to 50 mm) in some cases.[2,3,6,8,28] Borderline thickness (13 to 14 mm) often requires differential diagnosis from systemic hypertension or physiologic athlete's heart (Fig. 2).[2,3,7,8] However, any left ventricular wall thickness is consistent with the clinical spectrum of HCM, including normal dimensions in gene carriers.[5,7,8,19,23] Greater left ventricular thickness is associated with an increased risk of sudden death[28] but not necessarily of progression to heart failure.[3,6]

Phenotype expression includes a myriad of asymmetric patterns of hypertrophy that are highly variable even among first-degree relatives. These patterns can be diffuse, segmental (including apical), focal, or noncontiguous or could involve extension into the right ventricle, as well as elongated mitral leaflets or blood-filled crypts.[3,5-8,23,29]

The preferred option for initial family screening is diagnostic imaging every 12 to 18 months from the ages of 12 to 21 years, given that left ventricular hypertrophy commonly develops during adolescence and periods of accelerated growth, although adverse events punctuating the clinical course are rare (Fig. 2).[6-8] The possibility of delayed penetrance of the phenotype into midlife can justify extended imaging surveillance at 5-year intervals.[7,22]

Echocardiographic assessment with pulsed and tissue Doppler, strain rate imaging, and digital speckle tracking has provided mechanistic and functional insights into diastolic dysfunction, global and regional myocardial mechanics, and determinants of systolic ejection. However, these initiatives have not yet substantially affected disease prognosis or management.

OUTFLOW OBSTRUCTION

HCM is predominantly an obstructive disease, with 70% of patients having mechanical impedance to left ventricular outflow (gradients ≥30 mm Hg) at rest or with physiological provocation (i.e., exercise)[30] (Fig. 2). Subaortic gradients are characteristically dynamic and subject to change with physiological loading conditions (e.g., increased with reduced ventricular volume due to dehydration, alcohol or food consumption, or a change from a sitting to a standing position), and these changes are often responsible for daily fluctuations in symptoms.

Outflow obstruction is usually produced by mitral-valve systolic anterior motion and septal contact due to flow drag, also resulting in mitral regurgitation[2,3,7,8,30,31] (Fig. 2). Congenital, anomalous insertion of the papillary muscle directly into the mitral valve (without interposition of chordae) is occasionally responsible for midventricular muscular obstruction and is relevant to the planning of invasive treatment strategies.[7,8,31]

CLINICAL COURSE AND MANAGEMENT

The clinical course of HCM, defined primarily on the basis of observational data from tertiary referral centers, is characteristically diverse (Figs. 3 and 4). Many patients remain free of clinically significant symptoms and adverse events, do not require major treatment interventions, and have normal or extended longevity.[1-3,6,33] Increasingly, such patients are identified fortuitously, usually with mild disease expression. In other patients, HCM progresses along specific disease pathways, punctuated by clinical events that alter the natural history of the disease and dictate targeted and effective treatment strategies[1,3,33] (Fig. 4).
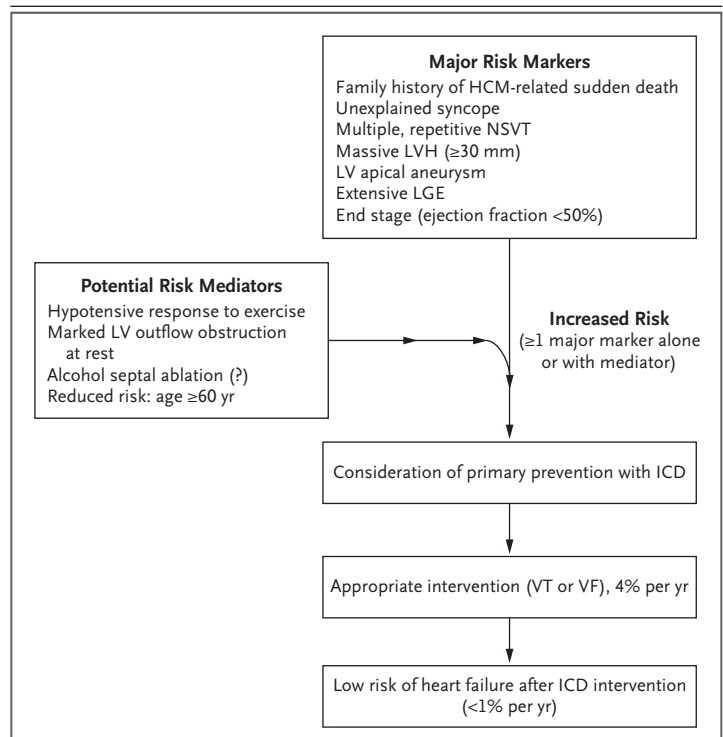
SUDDEN DEATH

HCM was initially described in the context of sudden death, which remains the most visible

complication of the disease in patients with or without obstruction (Fig. 4),[1-3,6,34-44] especially given media coverage of cardiac arrests in competitive athletes.[43] In cases of sudden death due to ventricular tachyarrhythmias, the unpredictable arrhythmogenic substrate is defined by the histopathological hallmarks of disorganized myocardial architecture, interstitial collagen deposition, and replacement scarring after myocyte death as a consequence of coronary microvascular-mediated flow dysfunction and ischemia[3,26,27,45,46] (Fig. 2).

Several clinical markers have been assembled into a risk-stratification algorithm in accordance with consensus management guidelines (U.S. and Canadian) published by the American College of Cardiology and the American Heart Association (ACC–AHA)[6] and more recent data.[26,42] This strategy has been highly effective and sensitive for identifying the vast majority of individual patients at increased risk for sudden death, in whom subsequent device therapy reliably terminates ventricular tachycardia and fibrillation.[33-42] Prophylactic defibrillator placement should be considered for young and middle-aged patients whose clinical profiles include one or more conventional risk factors judged to be major (Fig. 3). On the basis of the history taking, imaging studies, and ambulatory electrocardiographic (ECG) monitoring, the most important established risk markers are unexplained syncope, extreme left ventricular wall thickness, HCM-related sudden death in a first-degree relative, and multiple or prolonged episodes of nonsustained ventricular tachycardia.[33-42] Left ventricular apical aneurysm with regional scarring, as well as extensive myocardial fibrosis seen as late gadolinium enhancement on MRI, has been added to the risk-stratification algorithm for HCM[1,3,26-28,36,42] (Figs. 2 and 3). If the level of risk remains uncertain, other clinical features such as left ventricular outflow obstruction can serve as mediating factors,[3,6,35,36] in association with shared decision making[47] (Fig. 3).

Paradoxically, patients with HCM who survive into the seventh decade and beyond, even those with risk markers, are largely protected from sudden death (rate, 0.2% per year,[48] which is similar to the rate in the general population) (Fig. 3). Decisions about prophylactic defibrillator placement in such patients are made on a case-by-case basis.[48] It is notable that a small

minority of patients without risk markers can nevertheless have fatal arrhythmic events, which underscores the importance of expanding risk stratification.[49]

HCM is the most important cause of sudden death on the athletic field in the United States.[43] Intense competitive sports represent a primary risk marker that can justify prudent disqualifica-
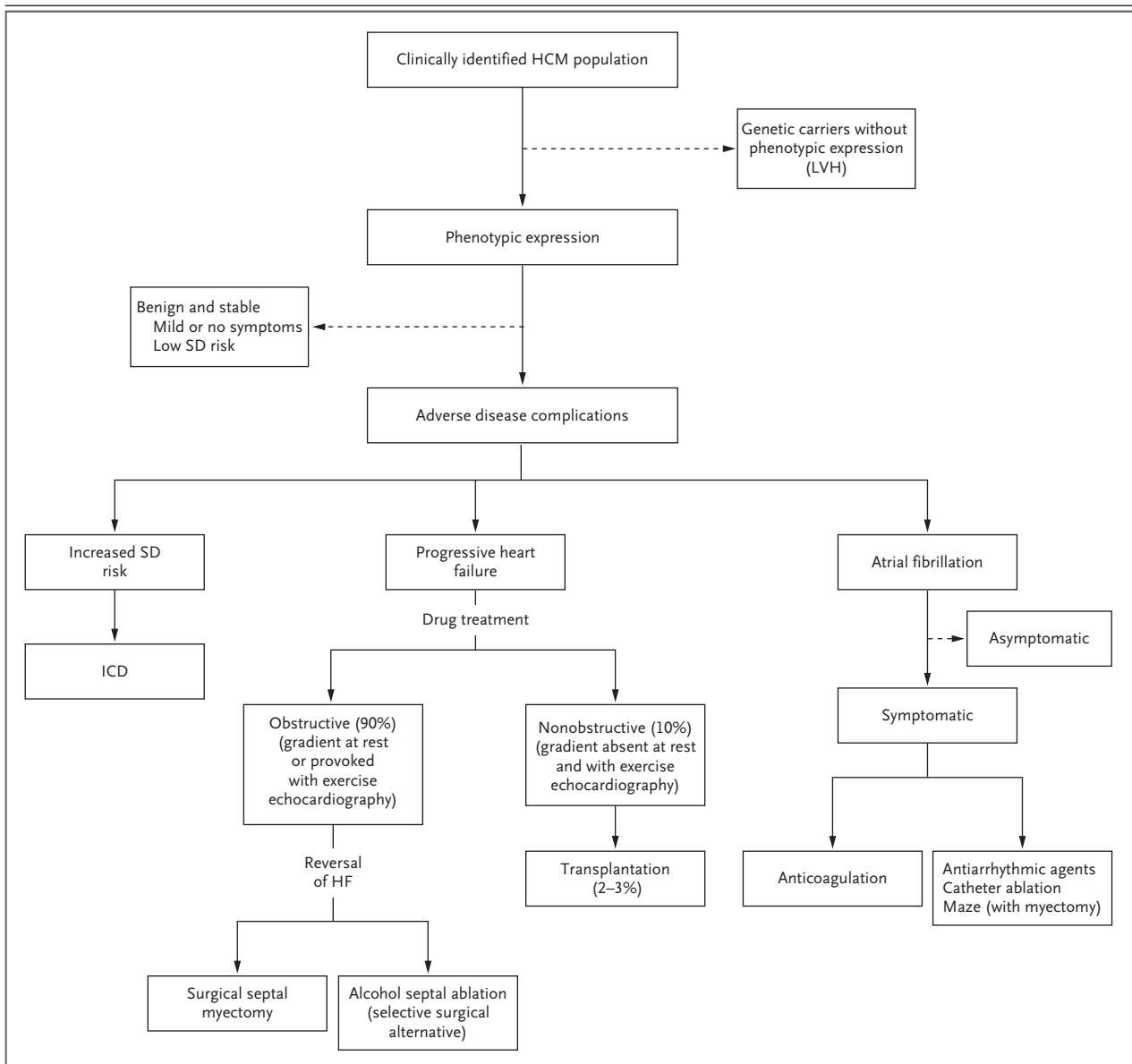
Figure 3. Risk Stratification and Primary Prevention of Sudden Death with Implantable Cardioverter–Defibrillators (ICDs) in Patients with HCM.

Selection of patients for prophylactic ICD placement is based on major markers of risk, sometimes in association with potential risk mediators. A positive family history is usually defined as a first-degree relative who died suddenly from HCM. Extensive late gadolinium enhancement (LGE) (≥15% of LV mass) on MRI indicates diffuse fibrosis and is a recent addition to the list. An LV apical aneurysm warrants consideration of defibrillator therapy as primary prevention, regardless of the size of the aneurysm or the patient's age, and is not a primary indication for surgery. Risk stratification for the prevention of sudden death in the subgroup of patients who undergo alcohol septal ablation has not been resolved. By convention, patients awaiting heart transplantation receive ICDs. Resuscitation after cardiac arrest is an unequivocal indication for secondary prevention with an implantable defibrillator. Patients with HCM who have had an ICD intervention subsequently have a low risk of heart failure or death (<1% per year); in contrast, the risk of death 1 year after an ICD intervention in patients with ischemic heart disease is 20%, with a 30% risk of heart failure requiring hospitalization.[32] LVH denotes left ventricular hypertrophy, NSVT nonsustained ventricular tachycardia (on ambulatory monitoring), VT ventricular tachycardia, and VF ventricular fibrillation.

Figure 4. Management Algorithm for the Clinical Spectrum of HCM.

In addition to transplantation, treatments for advanced heart failure (HF) in patients with nonobstructive HCM include cardioactive drugs, cardiac-resynchronization therapy, and LV-assist devices. SD denotes sudden death.

tion of young student athletes with HCM from such activities.[43] However, a moderate level of noncompetitive, recreational exercise is acceptable, since there is no evidence that it increases susceptibility to important tachyarrhythmias, and genetically affected persons without left ventricular hypertrophy are not disqualified from competitive sports in the United States.[6,43] A variety of abnormal ECG patterns (present in up to 90% of patients) do not predict the clinical course but

may represent diagnostic markers for the subsequent development of HCM.[6]

A sudden-death risk score, accessible with an online calculator, has been promoted by the European HCM guidelines.[2,50] However, when applied to individual patients with HCM, the risk score has low sensitivity for making clinically relevant decisions about implantable cardioverter–defibrillator (ICD) placement, significantly under-identifying high-risk patients who would remain

unprotected and susceptible to sudden death without ICD therapy.[36,40,42,51,52]

During the past 15 years, transvenous ICDs have taken the place of pharmacologic strategies and have made the prevention of sudden death a reality for both adults and children with HCM, altering the clinical course for many patients[1,32-42] (Fig. 4). This management paradigm is based on consistent data from a number of large multicenter and international high-risk registries.[32-42]

Defibrillator interventions effectively terminate ventricular tachycardia or fibrillation — with these events occurring most often in midlife — at an average rate of 4% per year for primary prevention based on clinical risk markers and at a rate of 10% per year for secondary prevention after cardiac arrest[33-41] (Fig. 3), although many patients receiving ICDs may not ultimately have device therapy. The timing of ICD interventions can be unpredictable, and intervals of 10 to 15 years have been reported between implantation and intervention.[38,53] Unlike ICD interventions in patients with ischemic heart disease, device interventions in patients with HCM are not associated with subsequent clinical deterioration, including death from heart failure and renal dysfunction[32] (Fig. 3). Surveys show that patients with HCM who undergo treatment with defibrillators report acceptably low levels of anxiety and depression.[32]

The decision to implant a defibrillator requires consideration of the rate of device complications (3 to 5% per year) — most frequently, inappropriate shocks due to supraventricular or sinus tachycardia and lead fractures.[2,6,32,37] Subcutaneous defibrillators have potential advantages, particularly protection of the venous system in younger patients and avoidance of long-term lead complications, although the efficacy of such defibrillators in aborting spontaneous ventricular fibrillation in patients with HCM remains unclear.[54]

HEART FAILURE

A large proportion of patients with HCM have mild-to-severe functional impairment, usually expressed as exertional dyspnea and fatigue (with or without chest pain); orthopnea and paroxysmal nocturnal dyspnea are uncommon.[55] Women are underrepresented in clinical cohorts but on presentation tend to be older than men (and with a delayed diagnosis) and have more severe symptoms, with greater impairment in cardiopulmonary exercise performance.[56,57] Neverthe-

less, men and women do not differ significantly with respect to the rate of death from HCM, including sudden death.[57]

HEART FAILURE AND OUTFLOW OBSTRUCTION

For 90% of patients with chronic, drug-refractory disability from heart failure, the primary cause is left ventricular outflow obstruction (at rest or with exercise), which leads to markedly elevated left ventricular pressures and secondary mitral regurgitation.[1-4,58] Heart failure in patients with HCM is often accompanied by pulmonary hypertension, diastolic dysfunction, and absence of an increase in stroke volume with exercise and is potentially exacerbated by extrinsic factors (e.g., obesity)[6,55-59] (Fig. 4). The rate at which subaortic gradients at rest lead to progressive heart failure is about 5% per year, although paradoxically, some patients have large gradients with little or no symptoms over long periods of time, sometimes even to an advanced age.[6,48,55,58]

Pharmacologic therapy is the first option and the mainstay of treatment in patients with obstructive HCM. Many such patients have a favorable response to pharmacologic therapy, with symptom control and a restored quality of life for varying periods of time.[2,3,6,60] Cardioactive medications administered to mitigate symptoms of heart failure, chest pain, or both in patients with obstructive HCM traditionally include atrioventricular nodal blocking agents and disopyramide; additional drugs for the treatment of HCM have not been introduced in more than 30 years.[55,60-62]

Beta-adrenergic blocking agents (atenolol, metoprolol, and propranolol) and calcium-channel blockers (verapamil and diltiazem) have inconsistent effects on the resting gradient, although exercise-provoked obstruction can be blunted by inhibiting sympathetic stimuli with beta-blockers.[4] The negative inotropic properties of disopyramide (administered with a beta-blocker) can reduce resting gradients and symptoms in some patients for substantial periods of time.[60] Although pharmacologic treatment for mechanical impedance to left ventricular outflow can result in variable degrees of symptom relief, there is little evidence that drug therapy alone fundamentally alters the natural history of HCM over the long term or is responsible for left ventricular remodeling.[55,61,62]

Patients with disabling symptoms and an im-

paired quality of life (generally consistent with New York Heart Association class III or IV) due to long-standing left ventricular outflow obstruction at rest or with physiological provocation (gradient, ≥50 mm Hg) are candidates for primary transaortic septal myectomy or, in selected patients, alcohol septal ablation, most appropriately performed in high-volume, multidisciplinary HCM centers in accordance with ACC–AHA consensus guidelines[6,63-73] (Fig. 4). Selected patients with less severe symptoms have been considered candidates for myectomy performed in high-volume surgical centers.[63,64]

Recommendations for invasive treatment options, including myectomy, are usually based on a personal history of exertional dyspnea that adversely affects quality of life, although cardiopulmonary exercise testing is useful in clarifying the degree of functional limitation when historical assessment is uncertain.[55] Although a number of traditional, but largely nonphysiological strategies (e.g., amyl nitrite inhalation, the Valsalva maneuver, and isoproterenol infusion) have been used, exercise (stress) echocardiography[44,74] is the preferred method to provoke left ventricular outflow gradients (when absent at rest), for the purpose of excluding or identifying additional surgical candidates (Fig. 4).

Extended myectomy, performed to abolish the gradient and mitral regurgitation, involves muscular resection from the basal ventricular septum[75] (which can range widely in thickness), frequently accompanied by remodeling of the mitral valve with plication to decrease slack and mobility, reconstruction of submitral intraventricular structures, or both.[63,64,68,69,71,73] Myectomy has been performed successfully in both children and adults (average age, 45 to 50 years) and is now established as one of the safest open-heart procedures, with an operative mortality of 0.4% in centers with a high volume of obstructive HCM cases,[65] representing a 95% reduction in mortality from 35 years ago. The risk of operative death is increased by a factor of 12 when myectomy is performed in centers with a lower volume of such cases.[76]

By abolishing subaortic gradients and normalizing left ventricular and pulmonary arterial pressures, myectomy permanently reverses symptoms of heart failure (regardless of their prior duration), restoring quality of life in 90 to 95% of patients, including more than 70% who become completely asymptomatic.[3,6,63,64,66-72] In addition, myectomy is associated with long-term survival equivalent to that in the general population, including a possible reduction in the risk of sudden death.[55,66]

Lack of symptomatic relief after the gradient is abolished is uncommon but is usually associated with compromising coexisting conditions, massive hypertrophy leading to postoperative systolic or diastolic dysfunction, or persistent atrial fibrillation.[71,77] The progress in surgical management has provided an impetus to expand access to myectomy, including in India and China,[13,14] as well as in Europe, where this operation has been underused.[78]

On the basis of ACC–AHA and European consensus guidelines, percutaneous alcohol ablation with myocardial contrast echocardiography has become the primary alternative to myectomy. Alcohol ablation has the advantages of being a less invasive procedure and requiring a shorter hospital stay.[2,6,79-82] This procedure is usually reserved for selected patients of advanced age with severe symptoms that are refractory to drug therapy who are not candidates for myectomy (because of coexisting conditions or insufficient motivation for surgery) and who do not require coronary-artery bypass grafting or valve replacement. The targeted (iatrogenic), alcohol-induced transmural infarct mimics the effects of myectomy on gradient and symptoms by virtue of basal septal thinning and outflow-tract enlargement, although 10% of patients who undergo alcohol ablation require a pacemaker for heart block; the arrhythmic burden may be increased in vulnerable patients[2,6,79-82] because of septal scarring. Ten percent of patients require repeat ablation, and unfavorable anatomy of the left ventricular outflow tract and septal perforator artery may limit treatment efficacy.

Successful alcohol septal ablation depends on high operator volume and technical expertise in a multidisciplinary HCM center, with appropriate patient selection, an emphasis on the minimal effective alcohol dose and infarct size, and mandatory reporting similar to that for other catheter-based therapies.[79] At centers that meet these criteria, procedural mortality can be as low as 1%, with survival rates that are similar to those for myectomy.[79,82]

HEART FAILURE WITHOUT OBSTRUCTION

Patients without the capacity to generate outflow gradients both at rest and with exercise (i.e.,

those with nonobstructive HCM) account for one third of patients referred to centers that specialize in the treatment of HCM. Such patients are largely in stable condition, usually with preserved systolic function, only mild heart failure symptoms or none, and a generally favorable prognosis.[44] Cardioactive drugs (primarily beta-blockers and verapamil) have beneficial effects on symptoms in a substantial proportion of these patients over variable periods of time. Exertional dyspnea is probably due to diastolic dysfunction with impaired relaxation and filling or restrictive physiology, although echocardiographic indexes may not reliably reflect these abnormal hemodynamic features.[83]

A minority of patients without obstruction at rest or on physiologic provocation (about 10%) have progressive end-stage heart failure that is refractory to maximum medical management and may ultimately become candidates for heart transplantation[44,55,84,85] (Fig. 4). Many such patients have unique phenotypic remodeling with transformation to systolic pump failure (ejection fraction, <50%), often associated with enlarged ventricular chambers and increased end-diastolic and end-systolic volumes, as well as regression of hypertrophy due to diffuse myocardial replacement scarring on MRI that is probably the result of microvascular ischemia.[20,45,55,85] About half of patients with end-stage heart failure have preserved systolic function and minimal ventricular remodeling in the presence of diastolic dysfunction.[86]

Few factors predict end-stage heart failure, other than extensive fibrosis associated with a borderline ejection fraction[87] and a family history of end-stage disease.[55] Treatment with the aldosterone antagonist spironolactone does not reduce the symptom or scar burden.[61]

With the reduction in sudden deaths, management of advanced heart failure (including heart transplantation) assumes greater importance in overall disease management.[1,3,44,55,88] Transplantation, for patients in whom this is the remaining definitive option for abolishing heart failure (average age of transplant recipients, 45 years), is associated with a survival rate that is similar to the rate for transplantation in patients with other cardiomyopathies or ischemic heart disease (i.e., 85%, 75%, and 61%, at 1, 5, and 10 years, respectively, according to data from the United Network for Organ Sharing),[84] with potentially superior survival (92% at 5 years) at centers that specialize in the treatment of HCM.[85] Cardiac resynchronization therapy can offer relatively short-term symptomatic relief in some patients before transplantation.[89]
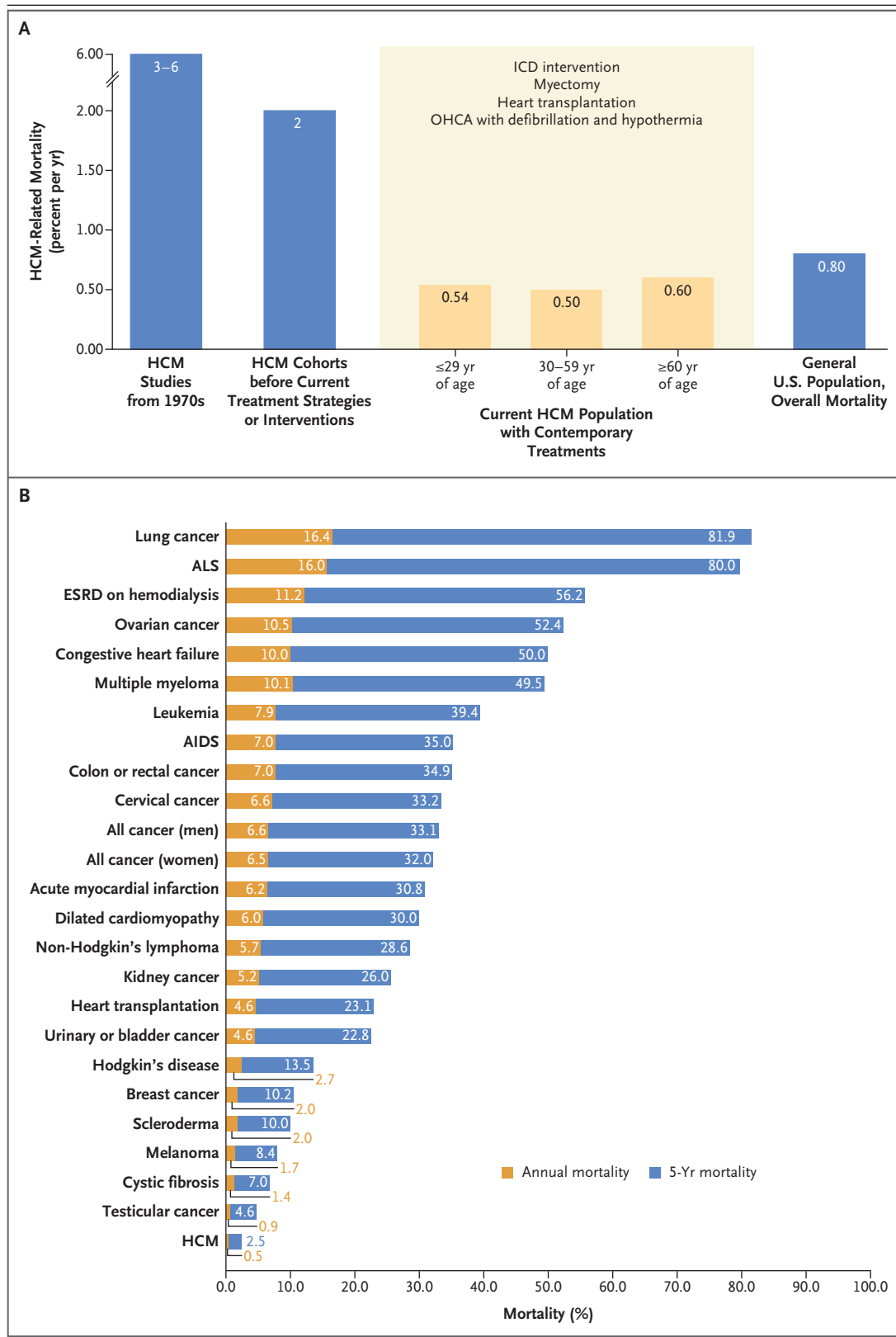
In the current era of treatment for HCM, death directly attributable to heart failure is distinctly uncommon, with most deaths occurring in patients awaiting transplantation, whereas mortality among patients with congestive heart failure unrelated to HCM remains high.[55] Apical myectomy has been reported at one center to be an alternative to heart transplantation for carefully selected patients with severe symptoms of nonobstructive HCM.[67]

ATRIAL FIBRILLATION

Atrial fibrillation is the most common sustained arrhythmia in patients with HCM, accounting for symptoms in about 20% of patients at referral centers (usual age at onset, 50 to 55 years)[90,91] (Fig. 4). Clinically silent episodes are common and predictive of symptomatic atrial fibrillation but with an uncertain risk of stroke.[90] Hemodynamic loading conditions with left atrial enlargement and dysfunction probably confer a predisposition to atrial fibrillation, although the possibility of a primary atrial myopathy has not been excluded.[90,91] Adverse consequences of atrial fibrillation can be related to loss of the atrial contribution to ventricular filling, particularly in the presence of marked left ventricular hypertrophy and diastolic dysfunction.

Repetitive and unpredictable episodes of symptomatic atrial fibrillation requiring cardioversion often impair the quality of life but do not increase the risk of sudden death or progression of heart failure.[90] The frequency of symptomatic atrial fibrillation can be reduced with the use of antiarrhythmic drugs (e.g., amiodarone, sotalol, disopyramide, or dofetilide), catheter ablation, or the maze procedure (involving endocardial incisions that block electrical circuits) combined with myectomy.[90] Transition from paroxysmal to permanent atrial fibrillation is relatively uncommon, occurring in 25% of patients, and with adequate rate control is usually associated with mild or no symptoms.

Stroke is the most important sequela of atrial fibrillation, warranting a low threshold for prophylaxis[1-3,6,90,91] with vitamin K antagonists or novel direct oral agents. The risk of embolic stroke is reduced by a factor of 7 when anticoagulant therapy is administered for extended

A

ICD intervention
Myectomy
Heart transplantation
OHCA with defibrillation and hypothermia

HCM-Related Mortality (percent per yr)

3–6	6.00
2	2.00
0.54	≤29 yr of age
0.50	30–59 yr of age
0.60	≥60 yr of age
0.80	

HCM Studies from 1970s

HCM Cohorts before Current Treatment Strategies or Interventions

Current HCM Population with Contemporary Treatments

General U.S. Population, Overall Mortality

B

	Annual mortality	5-Yr mortality
Lung cancer	16.4	81.9
ALS	16.0	80.0
ESRD on hemodialysis	11.2	56.2
Ovarian cancer	10.5	52.4
Congestive heart failure	10.0	50.0
Multiple myeloma	10.1	49.5
Leukemia	7.9	39.4
AIDS	7.0	35.0
Colon or rectal cancer	7.0	34.9
Cervical cancer	6.6	33.2
All cancer (men)	6.6	33.1
All cancer (women)	6.5	32.0
Acute myocardial infarction	6.2	30.8
Dilated cardiomyopathy	6.0	30.0
Non-Hodgkin's lymphoma	5.7	28.6
Kidney cancer	5.2	26.0
Heart transplantation	4.6	23.1
Urinary or bladder cancer	4.6	22.8
Hodgkin's disease	2.7	13.5
Breast cancer	2.0	10.2
Scleroderma	2.0	10.0
Melanoma	1.7	8.4
Cystic fibrosis	1.4	7.0
Testicular cancer	0.9	4.6
HCM	0.5	2.5

Mortality (%)

Figure 5 (facing page). Risk of Death Attributable to HCM.

Panel A shows the decrease in mortality over a period of more than 50 years, encompassing various treatment eras. OHCA denotes out-of-hospital cardiac arrest. Panel B shows mortality associated with HCM with contemporary treatment, as compared with mortality associated with other disorders with current treatments. AIDS denotes acquired immunodeficiency syndrome, ALS amyotrophic lateral sclerosis, and ESRD end-stage renal disease.

periods.[90] With contemporary treatment initiatives, the rate of death associated with atrial fibrillation in patients with HCM is less than 1% per year, and thromboembolism without prophylactic anticoagulation accounts for virtually all such deaths.

OUTCOMES

Early clinical descriptions of HCM included substantial mortality rates (up to 6% per year), largely reflecting the limited management options available at the time. However, with contemporary therapeutic strategies, it is possible to definitively alter the clinical course of this disease. With the use of such strategies, the HCM-related mortality rate can be as low as 0.5% per year (representing a 90% reduction in mortality from 35 years ago), independent of age and including children and young adults, in whom the natural history of the disease has traditionally been the most aggressive[1] (Fig. 5). In a recent study at Tufts Medical Center, in Boston, involving 1700 consecutively enrolled patients with HCM, survival could be directly attributed to major treatment innovations, including implantable defibrillators, in 161 patients (9%).[1] Indeed, most deaths in affected patients are unrelated to HCM, with noncardiac or coexisting cardiac conditions posing the greatest threat to survival, particularly in older patients.

HCM is not characteristically a progressive disorder; two or more major (but treatable) complications develop in only 10% of affected patients during their lifetime.[33] Taken together, the favorable treatment results, obtained largely in multidisciplinary centers specializing in the management of HCM, represent an achievable goal for equalizing the disparities in the care of patients with HCM in many parts of the world.[92]

CONCLUSIONS

Once regarded as a rare condition with an ominous prognosis and limited management options, HCM is now recognized as a worldwide, relatively common, and treatable form of genetic heart disease that often does not affect life expectancy (Fig. 5). The disease is characterized by diverse clinical, genetic, and morphologic features, including a risk of sudden death from arrhythmia, diastolic dysfunction, or left ventricular outflow-tract obstruction, which is the major determinant of progressive heart failure. Clinical diagnosis and treatment have been greatly enhanced by modern imaging techniques (including MRI and exercise [stress] echocardiography to uncover subaortic gradients that are absent at rest) and a refined algorithm for risk stratification.

Contemporary management strategies that influence the natural history of HCM, which are now available for all major complications, offer a more optimistic view of the disease, with a therapeutic armamentarium that includes implantable defibrillators to reduce the risk of sudden death, surgical myectomy (with alcohol septal ablation as a selective alternative) for permanent reversal of heart failure in patients with outflow obstruction, heart transplantation for patients with nonobstructive end-stage disease, and anticoagulant therapy to prevent embolic stroke caused by atrial fibrillation. This management paradigm,[93] driven by innovative clinical science over the past two decades, has greatly improved life expectancy and the quality of life for patients with HCM by reducing the risks of adverse cardiovascular events and death to levels below the levels among patients with other cardiac or noncardiac disorders.[94]

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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