Hypertrophic Cardiomyopathy: Risk Factors for Life and Living Benefits Insurance

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Background.—The clinical course of hypertrophic cardiomyopathy (HCM) is highly variable. Patients may remain asymptomatic throughout life, develop progressive and ultimately fatal heart failure, or die prematurely due to sudden death. This article reviews Western and Asian literature on HCM, including recent studies of large, regionally based cohorts that reflect the full spectrum of disease. The intent is to estimate HCM-related morbidity and mortality rates in the general population and identify risk factors for life and living benefits insurance.

Results.—Clinical studies have identified risk factors that are associated with a higher incidence of sudden death, such as non-sustained ventricular tachycardia, left ventricular wall thickness, and family history of sudden death. For many of these factors, there was a nonlinear relationship between mortality risk and the number of risk factors (ie, each additional risk factor was associated with a disproportionately greater risk of sudden death). Natural history studies of patients with HCM reported total HCM-related mortality rates of 1.8% per year for ages 5 to 15 years, 1.0% to 1.5% for ages 16 to 75 years, and 4.7% for ages above 75 years. Sudden death rates varied from 0.5% to 1.5% per year for most age groups, with children and adolescents experiencing sudden death rates near the top of this range. With regard to morbidity, patients progressed from New York Heart Association functional class I or II to III/IV at a rate of 1% to 2% per year, with higher progression rates in people aged 65 years or older. Risk varied with genotype and was generally similar in Western and Asian populations.

Conclusion.—Despite improvements in diagnosis and treatment, HCM is still associated with considerable morbidity and mortality.
foundly influenced by early, biased referral patterns, which focused on severe cases. While this circumstance is not unique to HCM, it is more substantial in this disease than in many other more common medical conditions. Since the initial description by Teare in 1958, most information regarding the natural history of HCM has come from a few major referral centers, largely in the United States, Canada, and the United Kingdom. These studies reported mortality rates of 2% to 6% per year, with the highest rates in the young. However, these high mortality rates included considerable referral bias because tertiary care centers treat more severely affected patients whose clinical course is less favorable than that of patients in the general population. In contrast, studies from regionally based populations reported death rates of approximately 1% per year, and limited data from the United States, Italy, and Japan suggested that total HCM-related mortality rates for asymptomatic people could be as low as 0.3%, 0.6%, or 0.9% per year, respectively. Previous articles in the Journal of Insurance Medicine by Ten Cate and Iacovino also suggested a more favorable prognosis.

This article reviews the literature on HCM, including recent studies of large, regionally based cohorts that reflect the full spectrum of disease. The intent is to estimate HCM-related morbidity and mortality rates in the general population and to identify risk factors for life and living benefits insurance.

**DIAGNOSIS**

HCM is diagnosed in adults when there is echocardiographic evidence of a hypertrophied, nondilated LV with a wall thickness of 15 mm or greater (upper limit of normal, 12 mm) in the absence of another cardiac (eg, hypertension, aortic stenosis) or systemic disease that could produce a similar degree of hypertrophy. Hypertrophy may be confined to the base, apex, specific segments, or involve the entire LV myocardium. A minority of adults with more favorable genetic mutations (see "Genetics") do not develop LV hypertrophy until middle-age. Between 25% and 30% of cases also have narrowing of the LV outflow tract, which is formed by the interventricular septum and the anterior leaflet of the mitral valve. This form of HCM is known as hypertrophic obstructive cardiomyopathy.

HCM is diagnosed in children when LV wall thickness is more than 2 standard deviations above the mean. Based on the available data, it appears likely that most genotype-positive (gene carriers), phenotype-negative (no clinical manifestations) children will develop LV hypertrophy by the time they are fully-grown. Thus, a normal echocardiogram at younger ages does not exclude the disorder. Among children with existing LV hypertrophy, the degree of hypertrophy progresses from childhood into adolescence in about 70% of cases, and the magnitude of progression can be considerable. LV wall thickness can continue to increase between ages 20 to 40 years but to a lesser degree.

The magnitude of LV wall thickening in a clinically identified population (20–22 mm) usually permits unequivocal diagnosis, although more modest degrees of hypertrophy (15–20 mm) are also frequently encountered. More subtle phenotypic (manifest by clinical signs or symptoms) expression with borderline wall thicknesses (13–15 mm) in the absence of LV outflow tract obstruction creates diagnostic ambiguity. When such findings arise in highly trained athletes, differentiation from benign physiological hypertrophy may be difficult but potentially resolvable with noninvasive clinical assessment or genetic testing (see later subcategory on Athletic Heart Syndrome).

The ECG is abnormal in 85% of people with HCM. The most common abnormalities are ST-segment and T-wave changes, followed by evidence of LV hypertrophy, with QRS complexes that are tallest in the mid-precordial leads. Giant negative T-waves in mid-precordial leads are characteristic of HCM involving the apex in Japanese patients; in the West this pattern may be found with HCM.
Table 1. Genes Associated with Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency (%)</th>
<th>Onset</th>
<th>Degree of LV Hypertrophy</th>
<th>Risk of Sudden Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-myosin heavy chain</td>
<td>35–40</td>
<td>Adolescence</td>
<td>Variable</td>
<td>High in some families</td>
</tr>
<tr>
<td>Troponin T</td>
<td>15–20</td>
<td>Middle age</td>
<td>Variable</td>
<td>Variable, middle age</td>
</tr>
<tr>
<td>α-tropomyosin</td>
<td>10–20</td>
<td>Adolescence</td>
<td>Mild</td>
<td>High</td>
</tr>
<tr>
<td>Myosin-binding protein C</td>
<td>5</td>
<td>Adolescence</td>
<td>Generally low</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Involving segments other than the apex. Abnormal Q-waves occur in 20% to 50% of cases. P-wave abnormalities indicate left atrial enlargement.13

GENETICS

It has been estimated that 1 in 500 people have HCM, thus making this impairment a relatively common genetic disorder. Approximately 90% of cases are inherited via an autosomal dominant mechanism, and the rest are sporadic (non-inherited) gene mutations that involve the same genes as familial HCM.10,14

Mutations have been identified in 9 sarcomeric contractile and/or structural protein genes: β-myosin heavy chain, myosin-binding protein C, troponin T, α-tropomyosin, Troponin I, essential and regulatory light chain, cardiac actin, and titin. Additional HCM-related mutations will be identified in the future since all of the known gene defects together explain only two-thirds of HCM cases that are diagnosed clinically.10 These mutations result in myocyte disarray, LV hypertrophy, arrhythmias, and chronic heart failure. The pathophysiology has not been completely determined. In many cases, abnormal proteins are incorporated into the sarcomere complex, which appear to poison the contractile apparatus and reduce myocyte contractility.15 Table 1 displays current information regarding the common mutations.16,17,18,19

The genetic diversity of HCM is complicated by intragenic heterogeneity: each of the 9 affected genes can have different mutations, with a total of more than 100 individual disease-causing mutations identified thus far. Most are missense mutations in which a single amino acid is substituted with a different amino acid. Studies have also documented non-penetrance (gene carriers with no clinical manifestations, ie, no symptoms and a normal echocardiogram and ECG) in up to 25% of some families.14 Certain mutations (eg, troponin T, β-myosin heavy chain) confer a greater risk of sudden death even with no or minimal LV hypertrophy on echocardiography.14,20 Thus, depending on the genotype (specific genetic mutation) and other genetic and environmental factors, there can be wide variation in clinical manifestations and prognosis.21 Even within the same family, some carriers of an HCM mutation have symptoms at a relatively young age, whereas others with the identical mutation may not develop clinical manifestations until middle or old age.15

Late-onset Mutations

One of the more benign mutations involves myosin-binding protein C. Niimura et al22 determined the age-specific penetrance of HCM in a cohort of 212 people with the myosin-binding protein C mutation who were treated at medical centers in Canada, the United Kingdom, and the United States. Cardiac hypertrophy did not develop until older ages (eg, only 58% of those under the age of 50 years had LV hypertrophy), in comparison to mutations caused by other HCM genes that were almost completely expressed by the second or third decade of life. Deaths from cardiac causes did occur in the cohort, and 34 of 36 cardiac deaths were sudden (often during vigorous exercise), but the deaths occurred at older ages compared to other HCM-related
mutations. Thus, delayed penetrance of the myosin-binding protein C mutation may account for its more favorable prognosis. From an insurance perspective, this means that echocardiography will not identify some young and middle-aged applicants who carry the myosin-binding protein C gene.

Part of the explanation for the different outcomes reported in some studies involving Japanese versus Western populations may be the prevalence of different mutations. Doi et al.23 followed 14 patients living in Kochi prefecture, Japan, who had a mutation of the myosin-binding protein C gene. Cardiac hypertrophy was present in 90% of the cohort (mean LV wall thickness, 21±3 mm), and none had apical cardiomyopathy. During follow-up of 5±5 years, (range, 0.1 to 13 years), no sudden deaths were observed, although 4 patients gradually progressed to heart failure. In contrast, Western patients with HCM have a higher frequency of β-myosin heavy-chain and troponin T gene mutations, both of which are associated with earlier onset of symptoms and sudden death.10 According to personal correspondence with Dr. Taishiro Chikamori, Tokyo Medical University (November 2000), these data are consistent with the view that end-stage cardiomyopathy (heart failure) is common in Japanese with HCM, but sudden death is uncommon.

Future Uses of Genetic Tests

Investigation of these genetic defects has focused largely on high-risk cases with early onset of LV hypertrophy and poor survival. In the future clinicians will use genotyping to estimate risk of sudden death10 and to resolve ambiguous diagnoses, such as with patients with borderline or modest increases in LV wall thickness.11 DNA-based diagnosis will also lead to the identification of more children and adults with preclinical HCM (carriers of an HCM mutation who have not yet developed clinical manifestations), usually in the context of genetic testing in families with a history of HCM.14

RISK FACTORS FOR SUDDEN DEATH AND HEART FAILURE

The incidence of sudden death is much higher in males under the age of 30 years.24 Rates of sudden death equalize during middle age, and at older ages the incidence is higher in females.1 The reasons for these differences are not well understood.

Risk Factors Associated with Sudden Death

Table 2 lists the risk factors that have been consistently associated with sudden death in patients with HCM.4,19 It is debatable whether the underlying cause of sudden death is abnormal conduction due to fiber disarray, myocardial ischemia,28 or abnormal peripheral vascular responses, but the final event is ventricular fibrillation, sometimes preceded by ventricular tachycardia.4,20

Also listed in Table 2 are factors that have not been consistently associated with sudden death, including:

- **LV outflow tract obstruction**—Early angiographic studies focused on the obstructive component of HCM (hypertrophic obstructive cardiomyopathy), characterized by a LV outflow tract pressure gradient of 30 mm Hg or greater.29 The preponderance of evidence indicates that the presence or magnitude of LV outflow tract obstruction does not correlate with prognosis,1,20,30 except if there is marked LV outflow tract obstruction.

- **Pattern of hypertrophy**—There is generally no association between the pattern of hypertrophy (asymmetric, concentric, apical or eccentric) and survival.21

- **Abnormalities on electrophysiologic testing**—The role of invasive electrophysiologic testing is controversial because abnormalities elicited by programmed stimulation have very low specificity in the absence of symptoms or a history of sustained or nonsustained ventricular tachycardia.20 Current electrophysiologic
Table 2. Risk Factors for Sudden Death in Patients with Hypertrophic Cardiomyopathy*

Consistently associated with sudden death
- Prior cardiac arrest
- Implantable cardioverter-defibrillator
- Dilated left ventricle (indicating heart failure)
- Family history of sudden death
- Sustained ventricular tachycardia
- Recurrent episodes of nonsustained ventricular tachycardia²⁶,²⁷,²⁸
- Left ventricular wall thickness of 30 mm or greater†
- Abnormal blood pressure response to exercise³

New York Heart Association functional class III or IV
- Onset of symptoms or hypertrophy during childhood
- Age <35 years
- Syncope
- Palpitations
- Atrial fibrillation
- Left atrial enlargement (higher risk of atrial fibrillation)
- Cardiac pacemaker (for arrhythmias or LV outflow tract obstruction)
- Strenuous exercise or work
- HCM plus coronary heart disease²⁷
- Unfavorable genotypes (troponin T, β-myosin heavy chain)
- Septal myotomy-myomectomy, alcohol septal ablation

Not consistently associated with sudden death
- Left ventricular outflow tract obstruction
- Pattern of hypertrophy
- Abnormalities on electrophysiologic testing

* Most factors increase risk of sudden death. Some increase risk of death due to stroke (eg, atrial fibrillation) or heart failure (eg, dilated LV).
† Risk increases with the magnitude of LV wall thickness, with highest risk for LV wall thickness of 30 mm or greater.
‡ Failure of blood pressure to rise at least 25 mm Hg during exercise, or a fall in blood pressure of more than 15 mm Hg; used only for subjects aged 40 years or younger.²⁸

Index of Risk Factors for Sudden Death

Elliott et al²⁷ reported the incidence of sudden death in 368 patients with HCM seen in a London tertiary referral center. Mean age was 37±13 years (range, 14 to 65 years), 239 were male, and mean follow-up was 3.6±2.5 years. None of the subjects had a history of sustained ventricular arrhythmia, cardiac arrest, or treatment with amiodarone for more than 50% of their follow-up. A history of chest pain was present in 11% of subjects, atrial fibrillation (AF) in 3%, New York Heart Association (NYHA) functional class (Table 3) III/IV in 3%, and peak LV outflow tract gra-

dient of greater than 30 mm Hg in 22%. The diagnosis of HCM was made an average of 4 years prior to referral.

Four risk factors for sudden death were identified:

Table 3. New York Heart Association Functional Classification of Heart Disease

<table>
<thead>
<tr>
<th>Functional Class</th>
<th>Limitation of Physical Activity</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Slight</td>
<td>With heavy physical exertion</td>
</tr>
<tr>
<td>III</td>
<td>Marked</td>
<td>With ordinary activities</td>
</tr>
<tr>
<td>IV</td>
<td>Marked</td>
<td>At rest</td>
</tr>
</tbody>
</table>
Table 4. Estimated Annual Mortality Experience in 368 Patients with Hypertrophic Cardiomyopathy During 6-year Follow-up, by Number of Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Subjects (%)</th>
<th>Sudden Death Rate</th>
<th>Expected Death Rate*</th>
<th>Total Death Rate</th>
<th>Mortality Ratio (%)²</th>
<th>Excess Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>55</td>
<td>0.009</td>
<td>0.00448</td>
<td>0.01299</td>
<td>290</td>
<td>9</td>
</tr>
<tr>
<td>1 or 2</td>
<td>33</td>
<td>0.012</td>
<td>0.00448</td>
<td>0.01650</td>
<td>370</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.033</td>
<td>0.00448</td>
<td>0.03701</td>
<td>830</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.157</td>
<td>0.00448</td>
<td>0.16104</td>
<td>3600</td>
<td>157</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0.00448</td>
<td>0.00448</td>
<td>340</td>
<td>10</td>
</tr>
<tr>
<td>0 or 1</td>
<td>88</td>
<td>0.010</td>
<td>0.00448</td>
<td>0.01473</td>
<td>340</td>
<td>10</td>
</tr>
<tr>
<td>2 or more</td>
<td>12</td>
<td>0.053</td>
<td>0.00448</td>
<td>0.05775</td>
<td>1300</td>
<td>53</td>
</tr>
</tbody>
</table>

* Expected annual death rate during 6-year follow-up was estimated as 0.00448 per the 1997 U.S. Population Life Table, based on the initial age and gender distribution of the cohort.

¹ Total annual death rate is sudden death rate plus expected death rate.

² Annual mortality ratio is 100 x (total death rate/expected death rate).

1. Non-sustained ventricular tachycardia (3 or more consecutive ventricular beats, lasting for less than 30 seconds) during 48-hour ECG monitoring.

2. Abnormal blood pressure response during treadmill exercise (failure of systolic blood pressure to rise at least 25 mm Hg during exercise, or a fall in blood pressure of more than 15 mm Hg; patients were exercised to exhaustion), used only for subjects aged 40 years or younger.

3. Maximum LV wall thickness of 30 mm or more.

4. Family history of sudden death (sudden cardiac death in 2 or more first-degree relatives before age 40) plus history of syncope. This combination was chosen because neither family history of sudden death nor history of syncope was independently associated with sudden death (in contrast to what has been reported in many studies).

When the relative predictive ability of the 4 risk factors was analyzed in subjects in NYHA functional class I (where most insurance applicants would be classified), the most powerful predictor of sudden death was the combination of family history of sudden death plus history of syncope, followed by maximum LV wall thickness, non-sustained ventricular tachycardia, and abnormal exercise blood pressure response in subjects aged 40 years or younger. Six subjects with no risk factors died suddenly; 2 had significant coronary heart disease (CHD), 1 patient had chest pain that was unresponsive to treatment, 2 had a family history of sudden death but no other risk factors (LV wall thickness, 23 mm and 27 mm, respectively), and 1 patient had a LV outflow tract gradient of 121 mm Hg and left atrial dilatation.

Table 4 displays estimated annual mortality experience due to sudden death based on a comparison with general population mortality rates. Mortality ratios varied from 290% (no risk factors) to 3600% (3 risk factors). Noteworthy is the relative relationship between the mortality ratio and the numbers of risk factors. Compared to having no risk factors (mortality ratio, 290%), the mortality ratio with 1 (370%), 2 (830%), and 3 (3600%) risk factors was about 1.3 times higher, 3 times higher, and 12 times higher, respectively. Likewise, the mortality ratio was 4 times higher in subjects with 2 or more risk factors (1300%) compared to those with zero or 1 risk factor (340%). Thus, there was a nonlinear relationship between mortality risk and the number of risk factors. Mortality experience in an insurance context would be some-
what more favorable than indicated in Table 4 because underwriters would generally decline or load applicants with other serious impairments (eg, CHD) or other significant risk factors that were not included in this study but which are listed in Table 2.

**Left Ventricular Hypertrophy**

Spirito et al assessed the relationship between the magnitude of LV hypertrophy and mortality in 480 patients (mean age, 47 years; range, 1 to 89) with HCM who visited medical centers in Italy and the United States. Ninety-three percent were NYHA functional class I or II, and 7% were functional class III or IV. Sixty-five deaths occurred during mean follow-up of 6.5 years: sudden death, n = 23; heart failure, n = 15; and stroke or noncardiac causes, n = 27. Of the 23 subjects who died suddenly, 91% were functional class I or II. Twenty percent of those who died suddenly were taking amiodarone.

Figure 1 displays annual HCM-related mortality rates by cause and LV wall thickness. This information is especially useful for classifying insurance risk because echocardiographic reports are often available to the underwriter. For sudden death, there was a strong correlation between risk and LV wall thickness, with the rate of sudden death almost doubling from each wall thickness subgroup to the next. The highest risk was for LV wall thickness of 30 mm or greater (mortality rate, 1.8% per year). Prognosis was least favorable for young patients with a wall thickness of 30 mm or greater (data not shown). No sudden deaths occurred in subjects with a LV wall thickness of 15 mm or less. Death due to heart failure showed less correlation with wall thickness; the mortality rate was zero for LV wall thickness of 15 mm or less, and averaged 0.5% per year for wall thicknesses of 16 mm or greater. Multivariate analysis was also performed. After adjusting for wall thickness, sudden death was not related to functional class or LV outflow tract obstruction. Heart failure deaths were related to wall thickness, functional class, and LV outflow tract obstruction.

**Index of Risk Factors Plus Left Ventricular Hypertrophy**

Elliott et al updated their previously cited study from a London tertiary referral center by reporting the relationship between an index of risk factors and the magnitude of left ventricular hypertrophy. The cohort included 630 patients of mean age 37±16 years, with mean follow-up of 59 months. Some subjects had an implantable cardioverter-defibrillator (ICD).

Definitions for some of the 4 risk factors for survival were slightly different compared to the original report:

- Non-sustained ventricular tachycardia (3 or more consecutive ventricular beats, lasting for less than 30 seconds) during 48-hour ECG monitoring
- Abnormal blood pressure response during treadmill exercise (failure of systolic blood pressure to rise at least 25 mm Hg during
exercise, or a fall in blood pressure of more than 10 mm Hg; patients were exercised to exhaustion), used only for subjects aged 40 years or younger

- Family history of sudden death (sudden cardiac death in 2 or more first-degree relatives before age 40);
- Recurrent unexplained syncope (2 or more episodes within 1 year of the initial echocardiographic measurement of LV wall thickness)

Figure 2 displays annual HCM-related mortality rates by left ventricular wall thickness and number of risk factors (Elliott et al)

Figure 2. Annual HCM-related mortality rate (includes cases of sudden death prevented by ICD discharge), by left ventricular wall thickness and number of risk factors (Elliott et al)

due to heart failure was higher than in most studies, perhaps because the cohort was more representative of the natural spectrum and course of disease.

A history of chronic or paroxysmal AF was present at the initial evaluation in 21 subjects. Thirty-six additional patients developed AF during follow-up; increased left atrial size (40 mm or greater) and age greater than 45 years were independent predictors of greater risk of subsequent AF. Survival was much poorer in patients with a history of paroxysmal or chronic AF, with most deaths occurring after 10 years of observation and in association with progressive heart failure. For the 15-year follow-up, the mortality rate among subjects with a history of AF was 2% per year, 10 times higher than that of subjects without a history of AF at the initial evaluation or during follow-up (0.2% per year). The authors concluded that chronic or paroxysmal AF is a marker of more advanced disease. This is useful information for insurers because AF is one of the risk factors that can be identified at the time of underwriting via an ECG or a physician’s statement.

Risk Factors in Other Studies

Maron et al followed 277 patients with HCM who were seen at a regional clinic in the United States. Mean age at diagnosis was 47 ± 22 years (range, 1 month to 86 years). Circumstances that led to the diagnosis of HCM included cardiac symptoms (n = 174; 91% NYHA functional class I/II, 9% functional class III/IV), a newly detected heart murmur
or abnormal ECG (n = 82), and family history of HCM (n = 21). Follow-up was 8±7 years. In adult patients, hypertrophy was most frequently confined to 1 segment of the LV wall.

Twenty-nine HCM-related deaths occurred: sudden death, n = 17; progressive heart failure, n = 4; stroke associated with AF, n = 5; and postoperative complications of septal myotomy-myomectomy, n = 3. Of the 17 sudden deaths, 14 patients had no or mild symptoms prior to death, and 3 were severely impaired. Approximately one-third of sudden deaths occurred before age 30, one-third in middle-age, and one-third after age 60. For the entire cohort, the annual HCM-related mortality rate was 1.3% and the annual sudden death rate was 0.7%. The HCM-related annual mortality rate was also 1.3% for patients diagnosed before age 20. Survival was poorer if subjects had significant symptoms (NYHA functional class III/IV), AF (often associated with embolic stroke), LV wall thickness of 26 mm or greater, or a LV outflow tract gradient of 30 mm Hg or greater. There was a trend toward increasing annual mortality rates for patients followed for 12 years or longer, but mortality estimates were less precise at these later intervals because fewer patients were being followed.

AGE-SPECIFIC MORTALITY RATES

All Ages

Maron et al\textsuperscript{12} reported age-specific mortality rates on 744 subjects in Italy and the United States in one of the world's largest natural history studies of HCM. All patients were initially evaluated at regional medical centers (not at tertiary referral centers, which attract high-risk cases) and, therefore, were more closely representative of the overall disease spectrum. Unfavorable risk factors were present in some patients when the study began. For example, 19% were in NYHA functional class III/IV, and AF was present in 21%.

Eighty-six HCM-related deaths occurred during mean follow-up of 8 years. Risk of sudden death (n = 44) was not confined to young patients, but extended into later phases of life without a statistically significant predilection for any age group. Seventy-one percent of sudden deaths occurred in subjects with no or mild symptoms (NYHA functional class I and II, respectively), and 29% of those who died suddenly had substantial symptoms (functional class III). There was no significant difference in the age distribution of deaths caused by heart failure (n = 31). Stroke-related deaths (n = 11) were more common in older patients, and 10 of the 11 fatal strokes (91%) were associated with a history of chronic or paroxysmal AF. A family history of HCM-related death was reported by 17% of the 86 subjects who experienced an HCM-related death. For the 44 patients who died suddenly, 16% were taking amiodarone, and marked LV hypertrophy (30 mm or greater) was present in 20%. Patients with stroke-related death showed substantially higher LV outflow tract gradients (60±53 mm Hg).

Figure 3 displays annual HCM-related mortality rates by age at initial evaluation and...
cause of death. The rate of sudden or heart failure-related deaths did not vary significantly by age group, but stroke risk was higher in older patients. Total HCM-related mortality rates averaged 1.8% per year for ages 5 to 15 years, varied between 1.0% and 1.5% for ages 16 to 65 years, increased to 3.9% for ages 66 to 75 years, and peaked at 4.7% per year for ages above 75 years. The authors suggested that this pattern—sudden and heart failure-related deaths occurred at all ages and not principally in young people—could be explained by the absence of selection bias.

Semsarian reported the experience of 261 high-risk patients with HCM who were treated at a specialty clinic in Australia over a 5-year period (Table 5). Thirty-four patients (13%) died during follow-up. One-third died during strenuous exercise and all deaths were prior to age 51 years. The high mortality rates for patients aged 30 years and younger in part reflected selection bias because the clinic population included a disproportionate number of high-risk young patients.

Middle Age

Hecht et al reported the course of 31 middle-aged subjects in the United States with HCM and no or minimal symptoms. Mean age was 42±5 years (range, 35–55 years) and mean follow-up was 8 years. The hypothesis was that patients with HCM who had already reached middle age without incurring important cardiac symptoms or clinical events may represent a subgroup that had been selected for a relatively benign life-long clinical course. However, the results did not support this hypothesis. Four sudden deaths occurred, yielding an annual HCM-related mortality rate of 1.7%. Of the 4 patients who died, 1 had diffuse, 1 had localized (1 segment), and 2 had intermediate (2 segments) degrees of LV wall thickening. Maximum LV wall thickness in these 4 patients was 20±2 mm (range, 18–23 mm). Thus, patients who experienced sudden death had relatively mild LV hypertrophy. Three of the 4 patients who died reported palpitations at the last evaluation (1 of whom also had lightheadedness, and another had paroxysmal AF), and the other subject experienced a syncopal episode. All deaths occurred between ages 50 and 65 years, a period of life often perceived to be beyond the greatest risk for such catastrophes. In 3 of the 4 deaths, coronary angiography at the initial evaluation showed the absence of CHD, and there was no history of chest pain in the other patient who died suddenly. Thus, the high death rate was probably not related-undiagnosed CHD. The authors concluded that long periods of stability may still be followed by adverse events later in life.

Older Age

The prevalence of HCM in people older than age 60 years has been estimated at 3%. Some investigators have suggested that HCM in the elderly may be caused by a “benign” process associated with aging rather than the “malignant” LV thickening seen in younger patients. Or, perhaps patients diagnosed at older ages have a disorder that begins in middle age and is compatible with long life. Fay et al described the course of 95 patients in the United States initially diagnosed with HCM at age 65 years or older (mean age at diagnosis, 72±5 years; range, 65 to 90 years). Forty-eight percent had a history of hypertension, symptoms (chest pain, dyspnea
or syncope) were present in 75%, 17% had a history of definite or suspected myocardial infarction, and 16% had associated medical illnesses, including diabetes mellitus, chronic lung disease, cancer and peripheral atherosclerotic disease. The annual mortality rate due to all cardiac causes was 3%. It was not possible to determine a mortality rate due to HCM. Mortality was much higher in patients who were NYHA functional class III at the time of the initial diagnosis (one-year mortality rate, 36%). History of hypertension had no effect on survival.

Change in Risk with Advancing Age

Years may pass between the diagnosis of HCM and application for insurance. How does risk change with time? Does an applicant retain the mortality rate that applied at the age of diagnosis, or instead assume the mortality rate for attained age? These questions cannot be resolved because cohorts have been too small and follow-up has been for only 6 to 10 years, according to personal correspondence with Barry Marron, MD, Minneapolis Heart Institute (November 2000).

HYPERTROPHIC CARDIOMYOPATHY IN ASIA

Japan

Apical cardiomyopathy was originally described in Japanese patients in 1976 by Sakamoto et al as a morphologic variant of HCM in which hypertrophy is predominantly in the apical region of the LV. It is thought that this variant of HCM is more frequent in Japan than elsewhere. A favorable prognosis was reported after a 10-year follow-up of a small series of 31 mainly asymptomatic patients with apical HCM. Angina developed in only 1 patient and none experienced serious arrhythmia, heart failure or sudden death.

Koga et al reported experience on 314 patients (mean age, 42±15 years) with HCM in a hospital-based study from Kurume, Japan. Follow-up averaged 5±2 years. Patients with other cardiac diseases were excluded from the study. There were 25 sudden deaths and 12 deaths due to heart failure or cerebral embolism. Annual sudden death rates for ages to 29 years, 30 to 49 years, and 50 years and older were, respectively, 4.4%, 1.9%, and 0%. For death due to heart failure or cerebral embolism, annual mortality rates for ages to 29 years, 30 to 49 years, and 50 years and older were, respectively, 0%, 0.6%, and 1.2%. There were no cardiac deaths in patients with apical HCM. Paroxysmal or chronic AF was strongly associated with an increased risk of death from heart failure or cerebral embolism (relative risk, 12.4), but there was no associated risk for sudden death. There was no significant difference in survival between patient groups with or without LV outflow tract obstruction. Ten of the 25 sudden deaths (40%) occurred during or immediately after strenuous exercise, such as running, climbing stairs, or carrying a heavy object.

Maki et al updated the experience of the Kurume, Japan, cohort in their study of 309 patients (mean age, 43 years; range, 10 to 73 years) with HCM. All potential subjects were screened with cardiac catheterization prior to entering the study, and people with CHD, valvular heart disease, or concentric hypertrophy were excluded. Some patients had a history of syncope and nonsustained ventricular tachycardia. A maximal treadmill exercise test was performed on all participants. There were 43 HCM-related cardiac deaths during mean follow-up of 9 years, 28 of which were sudden deaths. Eight of the sudden deaths (29%) occurred during moderate-to-severe exertion. The overall HCM-related cardiac death rate (including sudden deaths) was 1.6% per year, and the sudden death rate was 0.8% per year. For patients who were unable to increase systolic blood pressure at least 24 mm Hg during maximal treadmill exercise testing, the sudden death rate was 3.1% per year. The sudden death rate was 2.0% per year in subjects with a resting LV outflow tract pressure gradient of 30 mm Hg or greater. Syncope was not a statistically significant risk factor, perhaps because this var-
Takagi et al. reported the long-term prognosis of 58 completely asymptomatic adult patients with HCM in Mie Prefecture, Japan. Ninety-five percent were male and mean age was 43±12 years (range, 20 to 71 years). All cases were diagnosed at local hospitals during a routine health examination which detected an abnormal ECG or cardiac murmur (n=28), or during an evaluation for a non-cardiac problem (n=30). Mean LV wall thickness was 12.9±3.0 mm. Three cardiac deaths (1 sudden, 2 due to heart failure) and 1 noncardiac deaths occurred during a mean follow-up of 11±6 years. The annual cardiac mortality rate was 0.9% and the annual sudden death rate was 0.1%. At the most recent evaluation of the 53 survivors, two-thirds were still completely asymptomatic, and the remaining one-third had developed at least 1 new cardiac symptom: cardiovascular functional limitation, n=10; chest pain, n=9; and palpitations, n=12. This study provided an estimate of prognosis for patients at the mild end of the disease spectrum. The outcome was favorable because all patients were asymptomatic, there was no history of syncope, and none of the subjects were at high-risk ages (ie, no children or adolescents). Reliable family history could not be obtained. Noteworthy is that the degree of LV thickening in this asymptomatic cohort was considerably less than what has been reported in most studies of symptomatic patients. Given that LV thickness is strongly predictive of risk, mortality rates would be higher in symptomatic Japanese subjects and/or if LV thickness were greater.

China

Lin et al. reported data from one of the largest studies of Chinese patients with HCM. The cohort included 122 adults (mean age, 62±13 years) who were seen in a single center in Taiwan. Syncope and chest pain were the most common symptoms, one-third of the patients had congestive heart failure, and 10% were NYHA functional class III or IV. Mean follow-up was 3.2 years. There were 4 cardiac deaths (annual HCM-related cardiac death rate 1.0%) and 14 deaths due to non-HCM-related causes.

Lai et al. reported morphologic data on 14 elderly Chinese patients (mean age, 90±5 years) in Taiwan. LV thickening was relatively mild and localized to certain segments of the LV. The authors concluded that the cohort had a milder form of HCM. Xuesu et al. also observed a single extended family in Weihai City (Shandong, China) with 11 cases of HCM, ranging in age from 12 to 68 years.
a permanent pacemaker, endocarditis, or syncope) was 6%.

Cannan et al\textsuperscript{44} reported the rate of disease progression in 37 American patients with HCM (mean age, 59±20 years; range, 1 week to 92 years). Forty-one percent of the subjects were older than age 65 years. During mean follow-up of 8 years, patients progressed from NYHA functional class I to functional class III/IV at a rate of 1.2\% per year, from functional class II to functional class III/IV at 0.0\% per year (only 2 patients began the study in functional class II), and from functional class I or II (again assuming that underwriters might not have enough information to accurately estimate initial functional class) to functional class III/IV at 1.1\% per year.

Fay et al\textsuperscript{36} followed 95 patients in the United States initially diagnosed with HCM at age 65 years or older (mean age at diagnosis, 72±5 years; range, 65 to 90 years). The annual progression rate from NYHA functional class I/II to functional class III/IV was 4.6\%.

Maron et al\textsuperscript{2} observed 277 patients with HCM, who were seen at a regional clinic in the United States. Mean age at diagnosis was 47±22 years (range, 1 month to 86 years). Forty-seven percent of the cohort experienced major health care and/or disabling events during follow-up, such as septal myotomy-myomectomy, heart transplantation, ICD implantation, fatal and nonfatal stroke, and AF. The percentage of patients with significant symptoms (NYHA functional class III/IV) doubled during follow-up.

**Figure 4.** Annual rate of HCM progression to functional class III or IV during 10-year follow-up (Cecchi et al)

**Implantable Cardioverter-Defibrillators and Other Treatment**

**Implantable Cardioverter-Defibrillators**

In patients with HCM who were resuscitated after cardiac arrest or ventricular tachycardia that caused syncope, the incidence of sudden death or ventricular arrhythmia that would generally cause sudden death is approximately 6\% per year.\textsuperscript{4} These deaths occur despite treatment with amiodarone\textsuperscript{4} and beta-adrenergic blockers.\textsuperscript{30} This very unfavorable prognosis stimulated interest in implantable cardioverter-defibrillators (ICD) as means to prevent these deaths.

Maron et al\textsuperscript{45} reported the efficacy of ICD in patients with HCM, who were at high risk for sudden death. The cohort included 128 patients (mean age at implantation, 40±16 years; range, 8 to 82 years) from 19 medical centers in Italy and the United States, who were followed for an average of 3.1 years. Some participants in the study had advanced disease including NYHA functional class III/IV (14\%), prior septal myotomy-myomectomy (9\%), and end-stage cardiomyopathy with LV dilatation (5\%).

The ICD was implanted in 34\% of subjects for secondary prevention of sudden death after resuscitation from cardiac arrest or sustained ventricular tachycardia. Appropriate discharges occurred in 34\% of these patients, with an average discharge rate of 11\% per year (mean follow-up, 4.0 years). In the remaining 66\% of participants, the ICD was implanted prophylactically for primary preven-
tion because of syncope, family history of sudden death due to HCM, nonsustained ventricular tachycardia, or a LV wall thickness of 30 mm or greater. Appropriate discharges occurred in 12% of these subjects, with an average discharge rate of 5% per year (mean follow-up, 2.6 years). This rate was very similar to that reported in other studies of ICD use in high-risk HCM patients.\textsuperscript{44} For the entire cohort, the interval between implantation and initial appropriate discharge ranged from 2 weeks to 9 years (mean, 23 months). Multiple discharges occurred in about 70% of patients. Patients with appropriate discharges were more likely to be younger than age 31 or older than age 55. Stored ECG data indicated that appropriate ICD discharges were triggered by ventricular tachycardia or ventricular fibrillation. Two deaths due to refractory heart failure occurred in patients with end-stage HCM; in each case repeated defibrillator discharges failed to reverse ventricular tachyarrhythmias.

This study indicated that ICD can prevent sudden death in high-risk subjects during mean follow-up of 3.1 years. Given that more than one-third of patients were taking amiodarone at the time of ICD discharge, it highlighted the superiority of ICD (compared to amiodarone) for preventing sudden death. It also confirmed that the occurrence of what would have been sudden death (as measured by appropriate defibrillation shocks) was unpredictable, and that an ICD could lay dormant for long periods of time before intervening appropriately.\textsuperscript{44} Finally, it is important to note that there are complications associated with use of ICD. These include inappropriate discharges (in up to 25% of patients with HCM), broken leads, infection and substantial cost.\textsuperscript{46}

Other Treatment

Interventions for heart failure, such as septal myotomy-myomectomy, pacing, or alcohol septal ablation, may provide symptomatic improvement for patients with obstructive HCM but do not decrease risk of sudden death.\textsuperscript{42,46} Pacemakers are sometimes used to control arrhythmias or to relieve symptoms of LV outflow tract obstruction. This treatment has no impact on the incidence of sudden death.\textsuperscript{11}

ATHLETIC HEART SYNDROME

Between 1% and 2% of elite athletes have a LV wall thickness of 13 to 16 mm. It can be difficult to differentiate these individuals from people who have HCM and only minimal increases in LV wall thickness. This overlap constitutes a “gray zone” between physiologic LV hypertrophy in athletes and morphologically mild HCM. Hypertrophic cardiomyopathy is more likely if there is a family history of HCM, echocardiographic evidence of a small LV cavity dimension, a large left atrial diameter, abnormal diastolic filling patterns, or the presence of pathologic Q waves and ST- and T-wave abnormalities on the ECG. Conversely, an enlarged LV cavity in association with mild LV hypertrophy is indicative of physiologic adaptation to intensive training rather than HCM. These distinguishing features are absent in a small minority of individuals. Regression of the hypertrophy after detraining is the definitive method for differentiating physiologic from pathologic LV hypertrophy. However, athletes are often reluctant to detrain. Measurement of cardiopulmonary gas exchange during exercise testing—peak oxygen consumption greater than 50 ml/kg/min or more than 20% above the predicted maximum value—will often differentiate these 2 conditions.\textsuperscript{49} In the future, clinicians will use genetic tests to resolve uncertainty regarding the correct diagnosis.\textsuperscript{10}

SUMMARY

Genetics

- HCM is a relatively common genetic disorder.
- A family history of HCM in a parent indicates that approximately half the children will inherit that particular HCM gene.
POKORSKI—HYPERTROPHIC CARDIOMYOPATHY

— However, up to 25% of people who inherit an HCM gene never develop manifestations of disease.
● Risk of sudden death varies with the genotype (specific genetic mutation).
● Patients with the myosin-binding protein C mutation may not develop LV hypertrophy until middle age. Risk of sudden death and heart failure increases once hypertrophy occurs.
● Clinical use of HCM genotyping will increase in the future to identify children and adults with preclinical HCM.

Children and Adolescents are High Risk
● Sudden death rates are highest in children and adolescents.
● Diagnosis at a young age generally indicates symptomatic disease.
● Long-term risk cannot be estimated accurately in children because hypertrophy progresses from childhood into adolescence in about 70% of cases.
● Gene carriers usually develop clinical manifestations by the time they reach adulthood. Thus, a normal echocardiogram at younger ages does not exclude the disorder.

Risk Factors for Sudden Death, Heart Failure, Stroke
● Table 2 summarizes risk factors for sudden death.
● There is a nonlinear relationship between mortality risk and the number of risk factors (ie, each additional risk factor is associated with a disproportionately greater risk of sudden death).
● The most powerful of the 4 risk factors studied by Elliott et al was the combination of family history of sudden death plus history of syncope.
● Risk increases with the magnitude of LV wall thickness.
● Paroxysmal or chronic AF markedly increases risk due to heart failure and stroke.
● Sudden death often occurs in people with few or no symptoms.
● LV outflow tract obstruction is not strongly correlated with prognosis, except if there is marked obstruction.
● There is generally no association between the pattern of hypertrophy and survival.
● Risk is high in people with HCM who engage in strenuous exercise or work.

Age-Specific Mortality Rates
● One of the world’s largest natural history studies of patients with HCM reported total HCM-related mortality rates of 1.8% per year for ages 5 to 15 years, 1.0% to 1.5% for ages 16 to 65 years, 3.9% for ages 66 to 75 years, and 4.7% for ages above 75 years.
— Stroke-related deaths were responsible for the higher HCM-related mortality rates at older ages.
● Sudden death rates vary from 0.5% to 1.5% per year for most age groups, with children and adolescents experiencing sudden death rates near the top of this range.
● Heart failure death rates do not vary a great deal with age.

Japan
● HCM-related mortality rates are generally similar to those reported in Western studies (ie, total HCM-related mortality rates of 1.0% to 1.5% per year, with some variation in the percentage of deaths due to sudden death and heart failure).
● Genetic variation may explain differences in clinical manifestations.
— Japanese are more likely to carry the myosin-binding protein C mutation, with delayed onset of symptoms, a greater risk of end-stage cardiomyopathy, and a comparatively lower risk of sudden death.
— Western populations have a higher frequency of β-myosin heavy-chain and troponin T mutations, both of which are associated with earlier onset of symptoms and sudden death.
China

- Studies have identified families with inheritance patterns similar to those observed worldwide.
- Limited data suggest that HCM-related mortality rates are generally similar to those reported in Western studies.

Treatment

- Amiodarone is often ineffective in preventing sudden death.
- Short-term studies indicate that ICD can prevent sudden death in high-risk patients. It is likely that risk reduction will persist for longer periods.
- It is not possible to predict the future course if sudden death was prevented with ICD. Other unfavorable factors could emerge later in life, such as heart failure or AF.
- Cardiac pacemakers identify patients with serious arrhythmias or obstruction.

Insurance

- Insurers may not receive all of the pertinent history from the applicant and/or the attending physician. For example, underwriters might not learn about a prior syncope attack or a family history of sudden death, and this information is of great prognostic importance for this disease.
- Which applicants with a family history of HCM have inherited the disease?
  - For adults with no symptoms and a normal echocardiogram and ECG, the likelihood of HCM decreases with advancing age. Exceptions regard mutations of the myosin-binding protein C gene, where onset may be delayed until middle age.
  - Children and adolescents may not develop manifestations of HCM until adulthood.
- Life insurance—Mortality rates in asymptomatic people with HCM are somewhere between 0.3% per year (United Kingdom) and 0.9% per year (Japan).
  - However, most people who are currently diagnosed with HCM have symptoms, so mortality rates would be higher than these “best case” estimates.
- Disability, critical illness, and long term care insurance—Some policyholders might file a claim for total and permanent disability if they reach NYHA functional class III or IV.
  - Patients progress from functional class I or II to III/IV at a rate of 1% to 2% per year, with higher progression rates in people aged 65 years or older.
- Health insurance—Medical costs are often high in people with HCM because of complications, such as treatment for heart failure (including septal myotomy-myomectomy or heart transplantation in severe cases), arrhythmias requiring a permanent pacemaker, ICD implantation, peripheral embolism, endocarditis, fatal and nonfatal stroke and AF.

REFERENCES


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