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# Hypertrophic Cardiomyopathy in Tuscany: Clinical Course and Outcome in an Unselected Regional Population

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***Objectives.*** **Our aim was to study a population of patients with hypertrophic cardiomyopathy from the well defined geographic region of Tuscany in central Italy, a group virtually free of selective referral bias and therefore probably closely representative of the true patient population with this disease.**

***Background.*** **Most available information on clinical course, natural history and prognosis of hypertrophic cardiomyopathy is based on data generated from tertiary referral centers and therefore constitutes a potentially biased perspective of the disease process in this complex and diverse condition.**

***Methods.*** **The study group comprised 202 patients aged 1 to 74 years (mean ± SD 41 ± 17) at initial diagnosis and followed up for 1 to 30 years (mean 10 ± 5).**

***Results.*** **Largely with the use of single or multiple drug therapy, the vast majority of patients (n = 154 [76%]) were asymptomatic or mildly symptomatic and in stable or improved condition over the period of follow-up, whereas the remaining patients (n = 48 [24%]) experienced deterioration, had substantial functional impairment or died. Of the 13 patients (6%) who died of cardiovascular causes related to hypertrophic cardiomyopathy, 11 had progressive congestive heart failure (including 6 in the end-stage phase) and only 2 died suddenly. The annual mortality rate for cardiovascular disease was 0.6% and that due to sudden cardiac death was only 0.1%; the cumulative survival rate was 97%, 95% and 92%, respectively, at 5, 10 and 15 years of follow-up. Atrial fibrillation proved to be a relatively common (n = 57 [28%]) and particularly unfavorable clinical feature, with premature death occurring in 9 of the 57 patients. The cumulative survival rate after 15 years was 76% for patients with atrial fibrillation versus 97% for patients with sinus rhythm. Syncope occurred in 33 patients (16%) but did not appear to be of prognostic significance.**

***Conclusions.*** **In an unselected regional population, hypertrophic cardiomyopathy had a relatively benign prognosis inconsistent with its prior characterization as a generally progressive disorder, based primarily on the experience of selected referral institutions. Sudden unexpected cardiac death was distinctly uncommon, although a sizable proportion of patients (particularly the subset prone to atrial fibrillation), did experience clinical deterioration.**

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Hypertrophic cardiomyopathy is a primary cardiac disease, often genetically transmitted, with a diverse clinical and morphologic expression and characterized by unexplained left ventricular hypertrophy (1–17). Most previous studies of this disease, based on populations from large tertiary referral centers of highly selected patients, have reported a severe prognosis due largely to unexpected sudden cardiac death (18–32).

However, some studies (33–35) have suggested that a more benign clinical profile and prognosis may be characteristic of the overall hypertrophic cardiomyopathy disease spectrum. This is a potentially critical perception because it may have an important effect on our concepts of the disease process in hypertrophic cardiomyopathy and specifically on those issues related to treatment strategy and risk stratification for premature cardiac death (36). Consequently, in the present study we took advantage of a unique opportunity to describe the clinical features and long-term outcome of hypertrophic cardiomyopathy in a large group of unselected, consecutively identified patients assessed longitudinally in a well defined regional population from the Tuscany region in central Italy over the last 30 years.

**Patient selection.** Ospedale di Careggi is a large community-based multispecialty hospital in Florence, Italy with >3,000 inpatient beds and large outpatient departments. For ~60 years this institution has served the Florence metropolitan area (population 1 million), as well as the surrounding geographic region of Tuscany (total population ~3.5 million within 25,000 square miles). At the time of diagnosis and during the follow-up period, study patients were living either in Florence, other parts of Tuscany or in immediately adjacent regions of Umbria (with the exception of five who were from other parts of Italy). Diagnosis and treatment was generally consistent throughout the period of follow-up, with one cardiologist (F.C.) assuming primary responsibility for the management of each patient. Although cardiac surgery is available in this region of Italy, specialized operative care for patients with

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obstructive hypertrophic cardiomyopathy (septal myotomy–myectomy) (37,38) has not been readily accessible. The diagnosis of hypertrophic cardiomyopathy was based on echocardiographic identification of a hypertrophied, nondilated left ventricle (wall thickness ≥15 mm) in the absence of another cardiac or systemic disease capable of producing the magnitude of left ventricular hypertrophy present in that patient (1,4,16). In patients evaluated before echocardiography was introduced into our clinical practice in 1977, the diagnosis of hypertrophic cardiomyopathy was made by virtue of the typical clinical, electrocardiographic (ECG), phonocardiographic, hemodynamic and angiographic findings (2,18,20,21) and was subsequently confirmed by echocardiography (4).

Between 1963 and 1992, 221 consecutive patients diagnosed as having hypertrophic cardiomyopathy at our institution were evaluated clinically on two or more occasions and followed up for ≥1 year. Nineteen were excluded because at the time of initial evaluation they showed 1) associated valvular or congenital heart disease (n = 5); 2) symptomatic and hemodynamically significant coronary artery disease documented by arteriography (n = 5); or 3) systemic hypertension defined as blood pressure ≥170/100 mm Hg (n = 9). Therefore, the final study group consisted of 202 patients with hypertrophic cardiomyopathy. Of the 202 patients, 155 were from separate and distinct pedigrees and completely unrelated. The remaining 47 patients were from 18 other families, each of which contributed two to four patients to the cohort.

Initial clinical evaluation was defined as the time when the diagnosis of hypertrophic cardiomyopathy was first confirmed. The most recent clinical assessment was obtained during 1992. Ages at initial evaluation were 1 to 74 years (mean ± SD 41 ± 17); 22 (11%) were <20 years and 30 (15%) were >60 years. Ages at most recent evaluation were 13 to 82 years (mean 52 ± 16). Follow-up period from initial diagnosis was 1 to 30 years (mean 10.1 ± 5); 139 patients (68%) were men.

The vast majority of our patients (n = 176 [87%]) were initially identified as having hypertrophic cardiomyopathy at our institution, usually in the outpatient clinic. The diagnosis of hypertrophic cardiomyopathy was made most commonly because of the onset of cardiac symptoms or the occurrence of acute events such as atrial fibrillation, syncope, or peripheral embolism, or identification of an abnormal ECG. No patient was included solely on the basis of a diagnosis made during a systematic pedigree analysis (39). Patients were followed up in a standard fashion at ~1-year intervals with clinical examination, two-dimensional echocardiogram, 12-lead ECG, 24- to 48-h ambulatory (Holter) ECG and treadmill exercise test. Cardiac catheterization and angiography were performed in 57 patients.

**Echocardiography.** Echocardiographic studies were performed with the use of commercially available instruments. Extent and distribution of left ventricular hypertrophy was assessed from the two-dimensional echocardiogram as previously described (4). Magnitude of basal subaortic gradient was estimated with continuous wave Doppler study (40) or by the magnitude and duration of mitral valve systolic anterior motion in patients studied before the introduction of Doppler echocardiography at our institution (1).

**Definitions.** *Congestive heart failure.* Heart failure was defined in the context of two distinctive profiles: 1) substantial functional limitation with evidence of marked pulmonary congestion, often associated with pulmonary edema, but with intact left ventricular systolic function; and 2) end-stage phase (41–43), characterized by progressive heart failure and left ventricular wall thinning (≥5 mm), relative cavity enlargement or decreased ejection fraction. These patterns of severe heart failure in hypertrophic cardiomyopathy are distinct from the more common functional limitation associated with exertional dyspnea in the presence of intact systolic function.

*Sudden death.* Sudden cardiac death was defined as an unexpected nontraumatic event occurring <1 h from the onset of symptoms. Unexpected cardiovascular collapse occurring unexpectedly in the context of severe congestive heart failure or peripheral embolization was not regarded as sudden death.

**Medical treatment strategies.** Medical therapy was directed toward control of symptoms, arrhythmias, outflow obstruction and prevention of peripheral embolization. Patients with angina pectoris or symptoms of congestive heart failure, or both, were treated with beta-adrenergic blocking agents (usually nadolol, 80 to 160 mg/day) if obstruction was present or with calcium channel blockers (usually verapamil, 240 to 360 mg/day, or nifedipine, 30 to 60 mg/day) if obstruction was absent. With severe congestive symptoms, diuretic agents (e.g., furosemide, thiazides) or an angiotensin-converting enzyme inhibitor (captopril) were often administered.

Asymptomatic patients did not receive drug treatment except in the presence of additional clinical variables regarded as risk factors, such as severe outflow obstruction or ventricular tachycardia; amiodarone was administered in low doses (200 mg/day) to patients with sustained or multiple and repetitive runs of ventricular tachycardia on Holter ECG. In patients with atrial fibrillation, sinus rhythm was usually restored by direct current cardioversion, in association with amiodarone, and after anticoagulation was achieved with warfarin.

**Statistical analyses.** Data were expressed as mean value ± SD. Statistical analyses were performed by using a Student *t* test for comparison of normally distributed data. Univariate analysis for survival and event-free curves were performed by using Kaplan-Meier estimates (44); univariate and multivariate analysis for the assessment of independent risk predictors utilized the Cox regression model (45).

## Results

**Mortality data.** Of the 202 study patients, 13 (6%) died of cardiovascular causes related to hypertrophic cardiomyopathy during the follow-up period; 1 other died in an automobile accident and was excluded from the mortality statistics (Table 1, Fig. 1). Age at death was 31 to 75 years (mean 58); 7 (53%) of those who died were men. Of the 13 cardiovascular deaths, 2 were sudden and unexpected and unrelated to exertion,

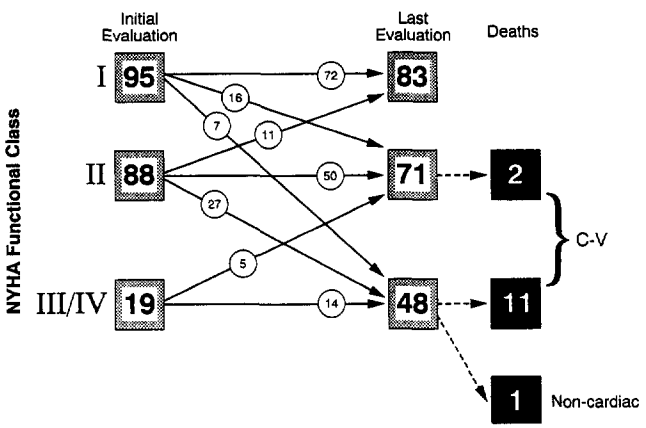
**Table 1.** Demographic, Clinical and Morphologic Data in 13 Patients With Hypertrophic Cardiomyopathy–Related Death

| Pt No./ Gender | Age (yr) At Diagnosis | Age (yr) At Death | Duration of Follow-Up (yr) | Family History of HCM or SD | NYHA Class Initial | NYHA Class Recent | Echo Data at Initial Diagnosis: Max LV Thickness* (mm) | LA (mm) | LVED (mm) | % FS | Hemodynamic Data: Basal LVOTG (mmHg) | PAP (S/D) (mmHg) | Mean PAW (mmHg) | NSVI (Holter) | AF | End-Stage HCM | Cause of Death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1/M | 8 | 32 | 28.0 | 0 | II | II | 18† | 47 | — | 38 | 80 | — | — | 0 | 0 | 0 | SD |
| 2/M | 20 | 48 | 28.0 | HCM + SD | I | IV | 23 | 43 | 45 | 38 | 0‡ | — | — | 0 | C | + | CHF |
| 3/F | 25 | 40 | 23.2 | 0 | II | II | 26† | 53 | 40 | 24 | 100 | 52/12 | — | 0 | P | 0 | SD |
| 4/M | 30 | 31 | 1.0 | 0 | III | III | 24 | 49 | 41 | 39 | 60 | 60/34 | 29 | 0 | 0 | 0 | CHF‖ |
| 5/F | 34 | 55 | 21.3 | 0 | II | III | 29 | 56 | 37 | 43 | 0§ | 35/12 | 16 | 0 | C | + | CHF |
| 6/M | 40 | 53 | 12.7 | HCM + SD | II | IV | 30 | 52 | 41 | 29 | 32 | 55/25 | — | + | C | + | CHF |
| 7/F | 52 | 64 | 12.1 | HCM + SD | III | III | 20 | 38 | 40 | 40 | 0 | 36/15 | — | 0 | P | 0 | CHF‖¶ |
| 8/M | 53 | 72 | 18.8 | 0 | II | III | 20 | 72 | 54 | 25 | 0‡ | — | — | + | C | + | CHF/R.emb. |
| 9/F | 59 | 72 | 13.1 | HCM + SD | IV | III | 30 | 40 | 43 | 25 | 100 | 42/14 | 16 | + | C | + | CHF/stroke |
| 10/M | 59 | 62 | 3.8 | 0 | II | III | 26 | 50 | 44 | 32 | 0‡ | — | — | 0 | C | + | CHF/stroke |
| 11/M | 60 | 73 | 12.8 | 0 | II | III | 28 | 53 | 48 | 41 | 0 | — | — | + | 0 | 0 | CHF |
| 12/F | 66 | 75 | 8.8 | HCM | IV | IV | 30 | 70 | 26 | 61 | 0 | 75/40 | 25 | + | C | 0 | CHF |
| 13/F | 70 | 73 | 2.8 | 0 | II | III | 28 | 47 | 27 | 22 | 100† | — | — | 0 | 0 | 0 | CHF‖ |

*Site of maximal thickness was the ventricular septum except for Patient 2, in whom posterior free wall thickness predominated. †Data based on postoperative echocardiogram in two patients with myotomy-myectomy; all other data are from the preoperative echocardiogram. ‡Estimated with continuous wave Doppler echocardiography (40); all other outflow gradients were measured at cardiac catheterization, except in Patient 11, whose gradient was assessed by M-mode echocardiography with respect to magnitude and duration of systolic anterior motion of the mitral valve. §A 60-mm Hg gradient was provoked at cardiac catheterization; provocable gradients were not elicited in the other three patients without a basal gradient at catheterization. ‖Clinical course included one or more episodes of acute pulmonary edema. ¶Also, with cardiovascular complications of bacterial endocarditis. AF = atrial fibrillation; C = chronic; CHF = congestive heart failure; D = diastolic; Echo = echocardiographic; F = female; FS = fractional shortening; HCM = hypertrophic cardiomyopathy; LA = left atrium; LV = left ventricular; LVED = left ventricular end-diastolic dimension; LVOTG = left ventricular outflow tract pressure gradient; M = male; Max = maximal; NSVT = nonsustained ventricular tachycardia; NYHA Class = New York Heart Association functional class; P = paroxysmal; PAP (S/D) = pulmonary artery pressure; PAW = pulmonary artery wedge pressure; Pt = patient; R.emb. = renal embolism; S = systolic; SD = sudden death; — = data not available; + = present; 0 = absent.

occurring when the patients were 32 and 40 years of age (15 and 8 years, respectively, after septal myotomy-myectomy); both patients were mildly symptomatic before death. The other 11 deaths were related to congestive heart failure, including 3 in patients whose final event (despite anticoagulation) was peripheral embolism. Six of these 11 patients had morphologic and functional evidence of the end-stage phase of hypertrophic cardiomyopathy (41–43).

**Figure 1.** Changes in functional symptomatic state between the initial and most recent clinical evaluation in 202 patients with hypertrophic cardiomyopathy. **Numbers within connecting lines** indicate subsets of patients. C-V = cardiovascular.




Of the 19 clinical variables examined, 4 were significantly associated with cardiovascular mortality by univariate analysis (wall thinning ≥5 mm, fractional shortening <30%, New York Heart Association functional class III or IV at initial evaluation and atrial fibrillation); with multivariate analysis, more advanced functional impairment at initial evaluation was the only independent predictor of cardiovascular mortality ($p < 0.001$).

For the overall study group the 5-, 10- and 15-year cumulative survival rates were 97%, 95% and 92%, respectively (Fig. 2). Over the period of follow-up the overall annual cardiovascular mortality was 0.6%. The annual mortality rate confined to sudden cardiac death was 0.1%.

**Clinical course.** *Symptoms.* Symptomatic state and functional cardiovascular status at the initial and most recent evaluations were compared (Fig. 1). Symptoms during follow-up were most commonly exertional dyspnea with or without fatigue (n = 108) and chest pain (n = 68, 23 with angina and 45 with atypical pain); frequently patients experienced palpitation (n = 95) or syncope (n = 25).

At initial evaluation, 183 patients (91%) were asymptom-

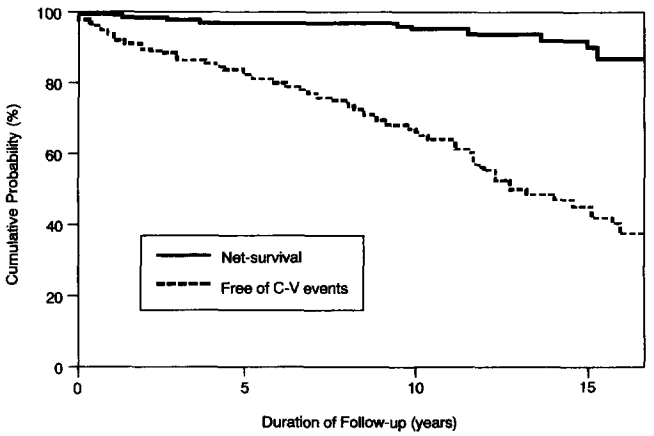



**Figure 2.** Occurrence of hypertrophic cardiomyopathy–related deaths and cardiovascular (C-V) events during the follow-up period in the 202 study patients (Kaplan-Meier estimates). **Top curve,** General cumulative cardiovascular survival. The study design required patients to have ≥1 year of follow-up. **Bottom curve,** Cumulative event-free rate. For each patient, the cardiovascular event that occurred first served as the end point, irrespective of whether the patient subsequently died. The area between the two curves reflects the proportion of patients who have survived one or more cardiovascular events. The major cardiovascular events are detailed in the text.

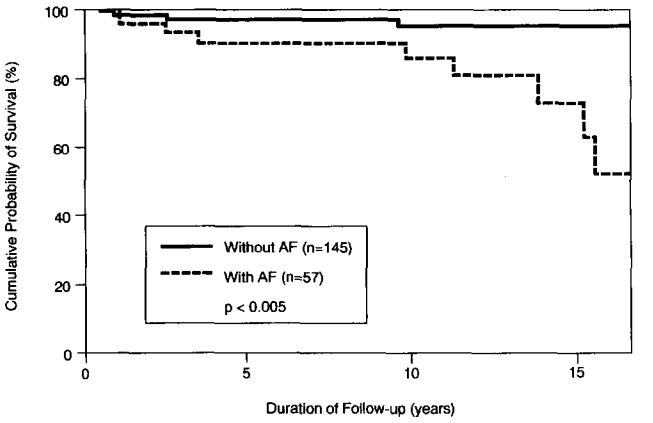



**Figure 3.** Cumulative survival of the 57 study patients who had demonstrated atrial fibrillation (AF) at (or before) initial diagnosis of hypertrophic cardiomyopathy or demonstrated this arrhythmia during the follow-up period versus that of the 145 patients without evidence of atrial fibrillation. Cardiovascular mortality was significantly greater in patients with atrial fibrillation, particularly after 10 years of observation ($p < 0.005$).

atic or had mild symptoms (functional class I or II); 19 other patients (9%) had moderate to severe symptoms (class III or IV). One asymptomatic patient entered the study group by virtue of an episode of ventricular fibrillation from which she was successfully resuscitated. At most recent evaluation, 154 patients (76%) were either asymptomatic or had mild symptoms, including 2 who died suddenly and unexpectedly; 48 other patients (24%) had moderate to severe symptoms, and 11 of these ultimately had heart failure–related death. Therefore, overall longitudinal analysis of the 202 study patients showed that the vast majority (n = 154) had a benign and stable clinical course, including 51 who remained completely symptom-free during follow-up.

Subgroup analysis showed that the condition of 50 (25%) of the 202 patients deteriorated by one or more functional classes; of these 50 patients, 34 who initially had no or mild symptoms eventually had moderate or severe symptoms with an annual deterioration rate of 1.7%. Conversely, only 16 patients (8%) had improvement by one or more functional classes with treatment, including 5 patients with moderate to severe symptoms who later had no or mild symptoms (Fig. 1).

*Cardiovascular events.* Clinical course was also characterized with respect to the occurrence (in 75 patients, 37%) of one or more of the following acute potentially unfavorable cardiovascular events: atrial fibrillation, peripheral embolization, abrupt worsening of congestive symptoms (often with acute pulmonary edema), bradyarrhythmias or conduction abnormalities requiring a permanent pacemaker, bacterial endocarditis or syncope. For the overall study group, the annual cardiovascular event rate was 6% over the follow-up period; event-free rates at 1, 5, 10 and 15 years were 94%, 85%, 69% and 45%, respectively (Fig. 2).

At least one episode of syncope occurred in 33 patients (16%)—before age 25 years in 3 patients and after age 25 in 30. In 10 of the 33 patients, the cause of syncope appeared to be either atrioventricular block (n = 3), sustained ventricular tachycardia (n = 2), atrial fibrillation (n = 2), clinically documented myocardial ischemia with angina and ST-T changes on ECG (n = 2) or exercise-induced hypotension (n = 1) (46). In 19 of the 33 patients, the most recent syncopal spell had occurred >2 years before the last evaluation; only 1 patient died suddenly, although his death occurred 15 years after operation and 7 years after the last syncopal episode.

**Atrial fibrillation.** Of the 202 study patients, 57 (28%) had atrial fibrillation (chronic in 38 and with one to five paroxysmal episodes in 19). Atrial fibrillation was present at or before initial evaluation in 21 patients (mean age 48 ± 15 years, range 20 to 74). The other 36 patients with atrial fibrillation had sinus rhythm at initial evaluation but had atrial fibrillation during the follow-up period (mean age 53 ± 13 years, range 24 to 75). Patients with atrial fibrillation showed impaired survival compared with that of other patients ($p < 0.005$); death most frequently occurred after 10 years of observation and in association with progressive heart failure (Fig. 3).

At initial evaluation, 47 of the 57 patients with atrial fibrillation were asymptomatic or had mild symptoms, and only 10 had moderate to severe symptoms. At most recent evaluation, only 28 patients were asymptomatic or had mild symptoms; 20 had marked symptoms and 9 had died suddenly or prematurely of heart failure. The cumulative survival rate after 15 years was only 76% for patients with atrial fibrillation but 97% for patients with sinus rhythm.

For 181 patients without evidence of atrial fibrillation at initial evaluation, the probability of remaining free of this arrhythmia during the period of observation was 90%, 77% and 69% after 5, 10 and 15 years, respectively (Fig. 4). Cox

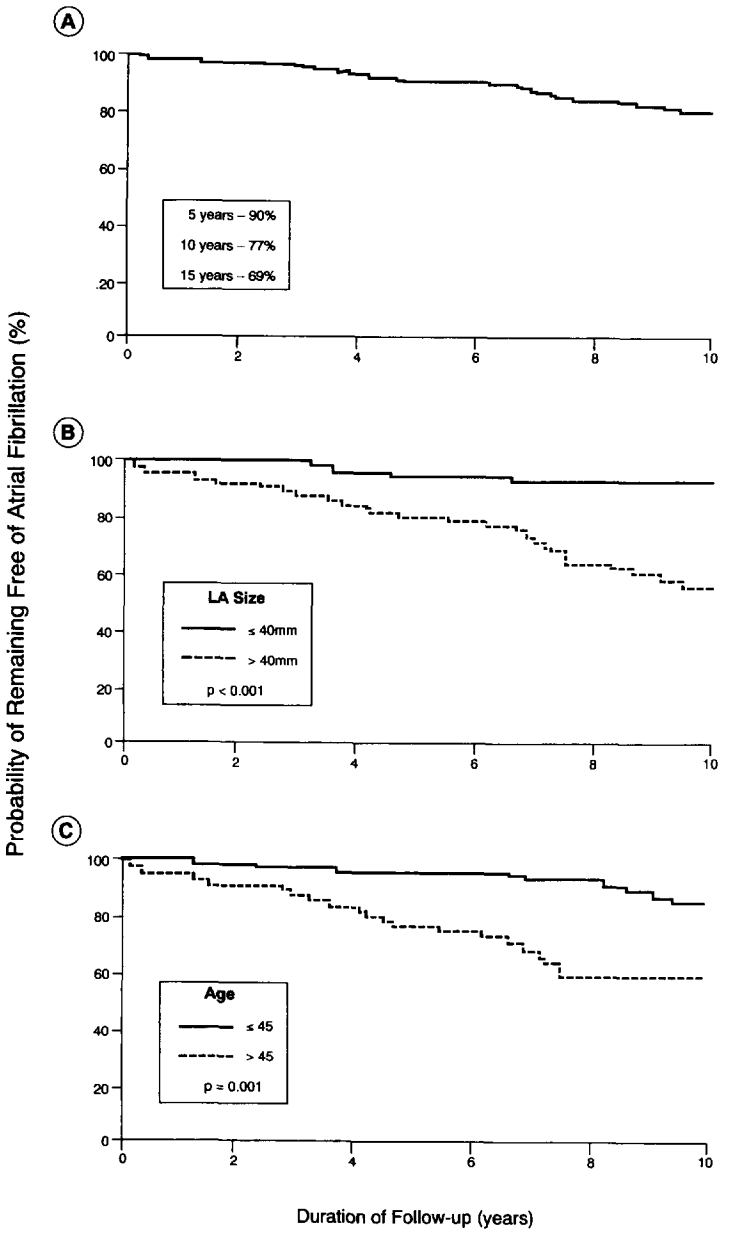



**Figure 4.** Percent cumulative probability (Kaplan-Meier estimates) of remaining free of atrial fibrillation during the follow-up period for those 181 patients without evidence of atrial fibrillation at initial evaluation **(A)**. These data are shown specifically with respect to left atrial (LA) size (≤40 or >40 mm) at initial diagnosis in **B** and with respect to patient age (≤45 or >45 years) at initial diagnosis in **C**.

regression and Kaplan-Meier estimates identified two independent predictors of atrial fibrillation: increased left atrial size (≥40 mm, $p < 0.01$) and older age (>45 years) at diagnosis ($p < 0.002$) (Fig. 4).

**Ambulatory Holter monitoring.** At least one ambulatory ECG recording was obtained in 190 patients. During the initial 48-h recording, 1 to 27 runs of nonsustained ventricular tachycardia (all <10 beats) were identified in 48 patients (25%) but were absent in the 2 patients with sudden cardiac death; an additional 29 patients showed this arrhythmia on a subsequent ambulatory ECG, including 2 asymptomatic surviving patients with long self-terminated runs of 25 and 36 s. Of these 77 patients with ventricular tachycardia, 39 proved to have multiple and repetitive runs on Holter recordings. Syncope occurred with similar frequency in patients with and without nonsustained ventricular tachycardia (14 [18%] of 77 vs. 17 [15%] of 113, p = NS).

**Treatment.** Of the 154 patients who had a stable or benign course, 102 had been treated with cardioactive medications in standard dosages and in a virtually continuous fashion. Each of the 48 patients with severe disease or progressive worsening of symptoms had a trial of medical treatment; five of these patients ultimately had myotomy-myectomy (four had lessening of symptoms) and one other patient underwent valvuloplasty for severe mitral regurgitation but had persistent symptoms.

Amiodarone was administered in 63 patients to manage sustained or multiple and repetitive runs of nonsustained ventricular tachycardia (n = 39), to obtain cardioversion or control or prevent atrial fibrillation (n = 23) or to prevent

recurrence of cardiac arrest (n = 1). None of these 63 patients died suddenly, although progressive heart failure leading to death developed in 6.

**Left ventricular morphology.** Maximal left ventricular wall thickness assessed with echocardiography was 13 to 42 mm (mean 23 ± 5). The predominant area of hypertrophy was most commonly present in the ventricular septum (n = 178 [88%]) but also occurred in the anterolateral free wall (n = 20 [10%]), posterior free wall (n = 2 [1%]) and apex (n = 2 [1%]). Patterns and distribution of wall thickening were diverse: diffuse, involving substantial portions of ventricular septum and free wall (n = 115 [57%]), anterior and posterior septum (n = 30 [15%]); anterior septum alone (n = 31 [15%]) and segments other than the anterior basal septum (n = 26 [13%]) (4).

**Left ventricular outflow obstruction.** On the basis of cardiac catheterization or Doppler assessment (40), 40 patients (20%) had basal outflow obstruction (mean ≥30 mm Hg, range to 110); the remaining 162 patients (80%) had no or a small gradient (<30 mm Hg). Of the 57 patients with cardiac catheterization, 6 showed labile obstruction with basal gradients <30 mm Hg that increased with provocative maneuvers to ≥50 mm Hg (range to 116) (2,47). Cox regression analysis showed no relation between the presence of basal outflow obstruction and cardiovascular death (p = 0.19).

In 38 of the 40 patients with basal outflow tract obstruction, the mechanism by which obstruction occurred under basal conditions was dynamic (due to mitral valve–septal contact). The other two patients showed midcavity muscular obstruction resulting from systolic apposition of septum and papillary muscle (13), associated in one patient with anomalous papillary muscle insertion directly into anterior mitral leaflet (48).

**Family history.** Pedigrees of the study patients were not assessed systematically with echocardiography (40). However, in 86 (43%) of the 202 patients, genetic transmission of hypertrophic cardiomyopathy was evident by virtue of clinical or echocardiographic documentation, or both, of the disease in a relative or by a family history of premature sudden cardiac death (age <50 years) judged to be probably due to hypertrophic cardiomyopathy.

## Discussion

**Impact of patient selection on risk evaluation in hypertrophic cardiomyopathy.** Since the initial clinical descriptions of hypertrophic cardiomyopathy in the early 1960s, most information comprising our knowledge of this disease has emanated from a few large referral centers (18–32). However, patients with hypertrophic cardiomyopathy demonstrate substantial diversity with respect to clinical presentation and prognosis (1–35,49); usually the most severely affected patients or those regarded at increased risk have been selectively referred to such tertiary centers for evaluation and treatment (33,35, 36,49). Therefore, many published reports of patients with hypertrophic cardiomyopathy have probably been unavoidably exposed to a substantial degree of bias in patient selection, and as a consequence the perception of risk in this disease may have been exaggerated (33,36,49).

For these reasons, it is important to access data related to the natural history and prognosis of patients with hypertrophic cardiomyopathy from populations dissimilar to those of the aforementioned referral-based institutions (36,49). It is our expectation that this process will ultimately define in more realistic and accurate terms the overall patient population and disease process in hypertrophic cardiomyopathy.

**Study findings.** The present study group of >200 patients with hypertrophic cardiomyopathy was evaluated over a considerable period of time from a well defined geographic region in central Italy. This population is virtually confined to patients with hypertrophic cardiomyopathy who have lived their entire lives in the Tuscany region and consequently is free of the referral patterns that predominate in North America and many parts of Europe. Indeed, our study patients comprise a broad range in age from young children to the elderly, but they also closely resemble previously described patient populations with hypertrophic cardiomyopathy (1,2,4,5,7,15,36,47) with respect to disease expression (e.g., patterns of left ventricular hypertrophy and prevalence of ventricular arrhythmia and subaortic obstruction).

In contrast, in regard to clinical course, the present population with hypertrophic cardiomyopathy differed considerably from the experience of referral centers (18–32). Whereas severe symptoms were initially present in only ~10% of our patients, most other reports (18–21,23,24,33,37) describe marked symptoms in ~50% of patients. Furthermore, our experience was not consistent with the characterization of hypertrophic cardiomyopathy as generally a progressive disorder. More than 70% of the study patients showed relative stability or even improvement in functional state. An important minority, despite treatment, experienced deterioration or death, which was most commonly due to progressive heart failure. The present study patients were generally given medical therapy in a systematic and consistent fashion, with a high level of continuity of care over an extended time period; indications for electrophysiologic testing or surgery were conservative, but amiodarone was administered for multiple and repetitive nonsustained ventricular tachycardia (50). Indeed, we believe that our medical treatment strategies were successful in controlling symptoms in many patients, although not particularly effective in reversing more severe symptoms once these became established.

**Sudden death.** We found the rate of occurrence of sudden cardiac death, to be substantially lower than that previously reported in most large series of patients with hypertrophic cardiomyopathy (18–25,27,29,32). The vast majority of published reports describe mortality rates, due primarily to sudden death (unassociated with severe heart failure) in the range of 2% to 4% (1,2,18–21,23,24,26,31–33) and up to 6% in childhood (27,29,32). In contrast, in the present study, only two

patients died suddenly and unexpectedly over the 1- to 30-year follow-up period, with an annual mortality rate of only 0.1%.

There are several possible explanations for the relative infrequency of sudden cardiac death in our patients. First, the risks inherent in the hypertrophic cardiomyopathy disease process described here may be reduced simply because this particular patient population was subjected to very limited referral selection bias (49). Although possible, at present there is no evidence that a unique genetic substrate exists in the Tuscany region contributing to the relatively benign expression of hypertrophic cardiomyopathy observed. Second, administration of amiodarone to a substantial patient subgroup judged to be at increased risk due to repetitive nonsustained ventricular tachycardia (or atrial fibrillation) may well have contributed importantly to our low frequency of sudden death (50). Finally, we separated the occurrence of pure sudden cardiac death from sudden collapse occurring in the context of severe congestive heart failure, and this methodology may have contributed to the different reported prevalence of sudden death in the present study compared with that in some previous reports (24). Although some investigators (19,51) have suggested that syncope harbors ominous prognostic significance in hypertrophic cardiomyopathy, the present data do not support an unfavorable prognosis for adult patients with hypertrophic cardiomyopathy and syncope. None of the 30 such patients we evaluated had repeated syncopal events or subsequently died suddenly.

**Atrial fibrillation.** Our observation of a relatively high prevalence of premature death due to progressive heart failure (in contrast to true sudden cardiac death) differs from that of many previous reports (18–21,23,24,26–29,31,32). Also, we found that atrial fibrillation was a major risk factor for poor prognosis and was the clinical event with the most important impact on disease progression. Atrial fibrillation developed in >25% of our study group and >50% of patients with this arrhythmia experienced disease progression or died during the study period; indeed, atrial fibrillation occurred in 70% of those study patients who died. Independent risk predictors most strongly associated with the development of atrial fibrillation proved to be left atrial enlargement and older age at diagnosis. These findings support the view that atrial fibrillation in hypertrophic cardiomyopathy is a marker of more advanced disease that may importantly impair clinical course as a result of peripheral embolization or the loss of the atrial systolic contribution to ventricular filling critical to these patients with poorly compliant ventricles (52). In this regard, our observations contrast with those of Robinson et al. (53), who reported similar clinical consequences in patients with hypertrophic cardiomyopathy with or without atrial fibrillation.

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