

# Impact of Sex on Clinical Course and Survival in the Contemporary Treatment Era for Hypertrophic Cardiomyopathy

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**Background**—The relation of sex to clinical presentation and course in hypertrophic cardiomyopathy (HCM) remains incompletely resolved. We assessed differences in clinical outcomes between men and women within our large HCM cohort.

**Methods and Results**—Of 2123 consecutive patients, a minority (38%) were women who were diagnosed with HCM at older ages or referred for subspecialty evaluation later than men ( $50 \pm 19$  versus  $44 \pm 16$  and  $55 \pm 18$  versus  $49 \pm 16$ ;  $P < 0.001$ ). Women more commonly developed advanced New York Heart Association class III/IV symptoms (53% versus 35% in men;  $P < 0.001$ ), predominantly secondary to outflow obstruction. While end-stage heart failure with systolic dysfunction (ejection fraction  $< 50\%$ ) was similar in men (5% versus 4% in women;  $P = 0.33$ ), women were 3-fold more likely to develop heart failure with preserved systolic function (7.5% versus 2.6%;  $P = 0.002$ ). Sudden death events terminated by defibrillator therapy were similar in women (0.9%/year) versus men (1.0%/year; hazard ratio, 0.92; 95% CI, 0.6–1.5;  $P = 0.73$ ). HCM mortality was uncommon, with identical rates in both sexes (0.3%/year; hazard ratio, 1.5; 95% CI, 0.7–3.4;  $P = 0.25$ ). Age-adjusted all-cause mortality also did not differ between women and men (1.7% versus 1.3%/year; hazard ratio, 1.32; 95% CI, 0.92–1.91;  $P = 0.13$ ).

**Conclusions**—Survival was not less favorable in women with HCM. Contemporary treatments including surgical myectomy to reverse heart failure and defibrillators to prevent sudden death, were effective in both sexes contributing to low mortality. However, despite more frequent outflow obstruction, women with HCM are underrecognized and referred to centers later than men, often with more advanced heart failure. Greater awareness of HCM in women should lead to earlier diagnosis and treatment, with implications for improved quality of life. (*J Am Heart Assoc.* 2019;8:e012041. DOI: 10.1161/JAHA.119.012041.)

**Key Words:** heart failure • hypertrophic cardiomyopathy • implantable defibrillator • sex • surgical myectomy

The past 25 years have witnessed a transformation in our understanding and management of hypertrophic cardiomyopathy (HCM). Once thought to be a rare disorder with high rates of sudden and heart failure–related death, we now recognize HCM to be a relatively common, global disease compatible with normal or extended life expectancy attributable to contemporary treatment strategies.<sup>1–7</sup>

HCM is inherited as an autosomal dominant disease and characterized by vast clinical and phenotypic heterogeneity.<sup>8–11</sup> However, historically, women have been underrepresented in HCM clinical cohort reports, and there is some

uncertainty as to whether women with this disease are at greater mortality risk from heart failure or other disease complications.<sup>12–18</sup> Therefore, we have taken this opportunity to access our large database to evaluate whether there are sex-related differences in clinical presentation or outcome for patients with HCM.

## Methods

The 2123 study patients were evaluated consecutively at the Tufts HCM Institute from 2001 to 2016. For the overall cohort, median follow-up duration from study entry (initial clinical evaluation at Tufts) to most recent contact (or death) was 3.9 (interquartile range, 2.0–6.9; mean,  $4.7 \pm 3.5$  years) years, encompassing 10 188 patient-years. The most recent clinical assessment was obtained by hospital visit or telephone contact. The authors declare that all supporting data are available within the article.

## Definitions

*Clinical diagnosis of HCM* was based on the 2-dimensional echocardiographic and/or cardiovascular magnetic resonance identification of a hypertrophied nondilated left ventricle (wall

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## Clinical Perspective

### What Is New?

- There is significant delay in hypertrophic cardiomyopathy diagnosis in women, on average 6 years later than in men. Left ventricular outflow obstruction is more common and responsible for more advanced heart failure symptoms.
- Therapeutic options are equally effective in women and in men with hypertrophic cardiomyopathy, including implantable defibrillators terminating potentially lethal ventricular tachyarrhythmias, or septal myectomy (and alcohol septal ablation) for relieving outflow obstruction and averting heart failure morbidity and death.
- Contemporary therapeutic strategies contribute importantly to low mortality. No significant differences were evident between men and women regarding either hypertrophic cardiomyopathy death or age-adjusted all-cause mortality.

### What Are the Clinical Implications?

- Greater awareness of hypertrophic cardiomyopathy in women is needed to allow for earlier diagnosis and treatment, particularly for progressive heart failure.
- Management strategies are equally effective in women and men and should be implemented for sudden death prevention and heart failure reversal to permit extended survival and quality of life.

thickness  $\geq 13$  mm) in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident.<sup>1</sup> Patients with known phenocopies of HCM (eg, Fabry, LAMP2, PRKAG2, or amyloidosis) were excluded. Atherosclerotic coronary artery disease was defined as  $\geq 50\%$  narrowing in  $\geq 1$  epicardial artery by coronary arteriogram or CT angiography.

**Advanced heart failure:** New York Heart Association (NYHA) functional class III or IV heart failure symptoms, refractory to maximum medical management, due to either outflow obstruction or, alternatively, evolution to the end stage in the absence of outflow obstruction with reduced (or preserved) ejection fraction.

**Sudden cardiac death:** unexpected sudden collapse occurring  $< 1$  hour from the onset of symptoms in patients who had previously experienced a relatively stable or uneventful clinical course.

**Heart failure-related death:** event occurring in the context of cardiac decompensation and progressive disease course before death, particularly if complicated by pulmonary edema, evolution to the end stage, and/or requiring hospitalization for heart failure.

**Stroke-related death:** judged as the consequence of an embolic event, usually in the setting of atrial fibrillation.

## Imaging

Transthoracic echocardiographic studies were performed in a standard fashion. Left ventricular (LV) wall thickness was taken as the maximal end-diastolic dimension (usually ventricular septum). Continuous-wave Doppler estimated peak instantaneous LV outflow gradient, with obstruction defined as a subaortic gradient  $\geq 30$  mm Hg. Patients with gradients  $< 50$  mm Hg at rest underwent symptom-limited exercise (stress) testing with echocardiography on a standard Bruce protocol.<sup>9</sup>

Cardiovascular magnetic resonance studies were performed in 1232 study patients with a 1.5-T clinical scanner. Late gadolinium enhancement quantification was performed by manually adjusting the gray-scale threshold to visually define areas of late gadolinium enhancement, which were summed and expressed as the proportion of total LV myocardium.

Genetic testing was performed in 344 patients by commercially available panels that included the most common HCM-associated myofilament-encoding genes. Sarcomere protein variants were classified as pathogenic according to 2015 *American College of Medical Genetics Guidelines*.

This study was reviewed and approved by the Institutional Review Board at Tufts Medical Center, allowing retrospective review of medical records and granting a waiver of informed consent in accordance with 45 CFR 46.116 (d). The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Statistical Analyses

Data are expressed as mean  $\pm$  SD for continuous variables and proportions for categorical variables. Student's t-test or Wilcoxon rank-sum tests addressed statistical significance of continuous variables; chi-square or Fisher exact tests analyzed categorical variables. Tests were 2-sided;  $P < 0.05$  was considered statistically significant.

For survival and event analyses, the fraction of patients at follow-up intervals was estimated using the Kaplan-Meier method. To adjust all-cause mortality for age, Cox proportional hazards regression models were used. Expected fractions surviving at each time after the initial visit were computed by assigning probability of survival (appropriate to age and sex) based on the US general population.<sup>19</sup> Actual and expected survival fractions were compared using 1-sample log-rank tests, which also provide an estimate for the standardized mortality ratio and 95% CI.

End points were total (all-cause) and HCM-related mortality, including sudden, heart failure, and embolic stroke-related death. Appropriate implantable cardioverter defibrillator (ICD) discharges to terminate ventricular fibrillation or sustained rapid ventricular tachycardia were regarded as

**Table.** Demographics and Clinical Features in 2123 HCM Patients by Sex

Parameter	Female Patients (n=794; 38%)	Male Patients (n=1329; 62%)	P Value
Age at diagnosis, y	50±19	44±16	<0.001
Age at first visit, y	55±18	49±16	<0.001
Age at last evaluation, y	60±17	54±16	<0.001
Family history of HCM, n (%)	218 (27)	292 (22)	0.005
Family history—sudden death, n (%)	97 (12)	129 (10)	0.08
Syncope, n (%)	85 (11)	174 (13)	0.11
NSVT on ambulatory monitoring, n (%)	100 (13)	220 (17)	0.01
Maximum LV wall thickness, mm	18.7±4.2	19.1±4.6	0.03
No. (%) with left ventricle ≥30 mm	39 (5)	88 (7)	0.13
No. (%) LV apical aneurysm	25 (3)	48 (4)	0.62
Ejection fraction, %	64±7	63±6	<0.001
Left atrial dimension, mm	40±7	42±7	<0.001
Peak LV outflow gradient, ≥30 mm Hg rest, n (%)	357 (45)	408 (31)	<0.001
Peak LV outflow gradient <30 mm Hg rest, ≥50 mm Hg exercise, n (%)	156 (20)	349 (26)	<0.001
Nonobstructive, n (%)	281 (35)	572 (43)	0.01
LVED, mm	39±7	43±6	<0.001
Contrast CMR			
No. CMR studies	455	777	
No. (%) with LGE	244 (54)	518 (67)	<0.001
% LGE (in patients with LGE)	5.4±5.2	6.0±6.0	0.20
No. (%) LGE ≥15% of LV	16 (4)	52 (7)	0.02
NYHA functional class, initial evaluation, n (%)			
I	214 (27)	618 (47)	<0.001
II	268 (34)	406 (31)	0.28
III/IV	312 (39)	306 (23)	<0.001
No. (%) with atrial fibrillation	197 (25)	348 (26)	0.33
No. (%) with CAD	47 (7)	96 (6)	0.71
No. (%) with HTN	268 (34)	431 (32)	0.56
No. (%) with resistant HTN	5 (<1)	7 (<1)	0.77
Reason leading to diagnosis, n (%)			
Symptoms/event	404 (51)	606 (46)	0.02
Screening due to family history	74 (9)	121 (9)	0.88
Asymptomatic with abnormal ECG or murmur leading to diagnosis	182 (23)	420 (32)	<0.001
Symptoms at first evaluation, n (%)			
Dyspnea	580 (73)	725 (55)	<0.001
Chest pain	210 (26)	289 (22)	0.04
Fatigue	339 (29)	235 (18)	<0.001
Palpitations	129 (16)	159 (12)	0.006
Refractory HF during clinical course, n (%)			
Refractory HF attributable to LVOT obstruction	388 (49)	425 (32)	<0.001

Continued

Table. Continued

Parameter	Female Patients (n=794; 38%)	Male Patients (n=1329; 62%)	P Value
Refractory HF in absence of LVOT obstruction	32 (4)	36 (3)	0.10
No. (%) septal myectomy*	283 (36)	347 (26)	<0.001
No. (%) alcohol septal ablations*	89 (11)	58 (4)	<0.001
No. (%) heart transplants	13 (1.6)	18 (1.4)	0.58
Age at heart transplant, y	44±14	48±14	0.43
Primary prevention ICD, n (%)	191 (24)	336 (25)	0.54
Age at ICD implantation, y	42±17	43±16	0.92
Appropriate primary prevention ICD interventions, n (%)	25 (13)	57 (17)	0.20
Resuscitated cardiac arrest, <sup>†</sup> n (%)	14 (1.7)	22 (1.6)	0.86
Sudden death rate, <sup>‡</sup> %/y	0.9%/year	0.8%/year	0.73
ICD-related complications, n (%)	34 (18)	50 (15)	0.45
Inappropriate shock	21 (11)	40 (12)	0.89
Device lead fracture	8 (4)	7 (2)	0.42
Device/lead infection	11 (6)	10 (3)	0.08
Drug therapy, n (%)			
Beta-blockers	657 (82)	987 (74)	<0.001
Calcium antagonists	375 (47)	500 (37)	<0.001
Disopyramide	100 (13)	93 (7)	<0.001
ACE/ARB	229 (28)	391 (29)	0.81
Amiodarone	127 (16)	155 (12)	0.07
Genetic testing performed, n (%)	123 (15)	228 (17)	0.33
Pathogenic mutation	74 (60)	101 (44)	<0.001
MYBPC3	37	51	
MYH7	24	28	
TNNT2	6	6	
MYL2, MYL3	1	3	
TPM1	1	3	
TNNI	3	7	
MYBPC3+TNNI	1	1	
MYH7+MYBPC3	1	2	
NYHA-functional class, last evaluation, <sup>§</sup> n (%)			
I	305 (42)	732 (58)	<0.001
II	365 (50)	480 (38)	<0.001
III/IV	54 (8)	52 (5)	0.002
Nonfatal adverse events, n (%)	56 (7)	93 (7)	1
Deaths, n (%)	70 (9)	65 (5)	<0.001
Age at death, y	67±15	59±5	0.05
Noncardiac death, <sup>  </sup> n (%)	55 (7)	46 (4)	<0.001
Cardiac, non-HCM, <sup>¶</sup> n (%)	4 (0.4)	3 (0.2)	0.68
Unknown, n (%)	2 (0.3)	4 (0.3)	1

Continued

Table. Continued

Parameter	Female Patients (n=794; 38%)	Male Patients (n=1329; 62%)	P Value
HCM-related death, n (%)	13 (1.6)	15 (1.1)	0.33
Sudden	1	4	
Heart failure	6	5	
Posttransplant	2	1	
Postoperative	3	3	
Embolitic stroke death	1	2	
Age at HCM death, y	56±11	53±16	0.54
HCM mortality rate, %/y	0.3	0.3	0.88

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; HF, heart failure; HTN, hypertension; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVED, left ventricular end-diastolic dimension; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association.

\*Includes 15 female and 6 male patients with unsuccessful alcohol septal ablation prior to myectomy.

†Includes 9 female and 4 male patients with subsequent secondary prevention appropriate ICD interventions.

‡Includes sudden death, appropriate ICD intervention, and resuscitated out-of-hospital arrest.

§In 1988 surviving patients.

||Most commonly, pulmonary disease (n=3 men, 8 women), cancer (n=12 men, 6 women), and multiorgan noncardiac comorbidities often associated with advanced age (n=12 women, n=9 men).

\*CAD related in 4 men, postoperative aortic valve replacement in 2 women, and postoperative mitral valve replacement/coronary artery bypass graft in 1 woman.

aborted sudden death events. Statistical calculations were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Results

### Baseline Characteristics

Demographics of the study population are summarized in Table. Among the 2123 study patients, there was a predominance of men with HCM (n=1329; 62%) compared with women (n=794; 38%), which was similar throughout the 15-year study period ( $P=0.13$ ; Figures 1 and 2). At the time of diagnosis, women with HCM were  $50\pm 19$  years of age, an average of 6 years older than men ( $44\pm 16$  years;  $<0.001$ ), and were referred for subspecialty evaluation at older ages than men ( $55\pm 18$  versus  $49\pm 16$  years;  $<0.001$ ). Women represented the majority of patients diagnosed  $\geq 60$  years of age (286 patients [56%] versus 226 patients [44% for men];  $P<0.001$ ) but were less common than men in younger age groups (comprising 26% to 34% of the cohort; Figure 3).

Determinants of the initial HCM diagnosis differed among men and women. In women, heart failure symptoms led to diagnosis most commonly (51% versus 46% in men;  $P=0.02$ ) while in men diagnosis was raised more commonly by an abnormal ECG or for evaluation of a heart murmur (32% versus 23%;  $P<0.01$ ). Family HCM screening led to a diagnosis in a similar proportion of men and women (9% versus 9%;  $P=0.88$ ).

### Morphology

Compared with men, women with HCM had smaller LV end-diastolic and left atrial transverse dimensions ( $39\pm 7$  versus  $43\pm 6$  and  $40\pm 7$  versus  $42\pm 7$ ;  $P<0.001$  for both), with slightly less maximum LV wall thickness (usually in ventricular septum;  $18.7\pm 4.2$  versus  $19.1\pm 4.6$ ;  $P=0.03$ ). There was no significant difference in the prevalence of extreme hypertrophy, that is, LV wall thickness  $\geq 30$ mm (5% in women versus 7% in men;  $P=0.13$ ) nor LV apical aneurysm with regional scarring (3% in women versus 4% in men;  $P=0.62$ ).<sup>20</sup>

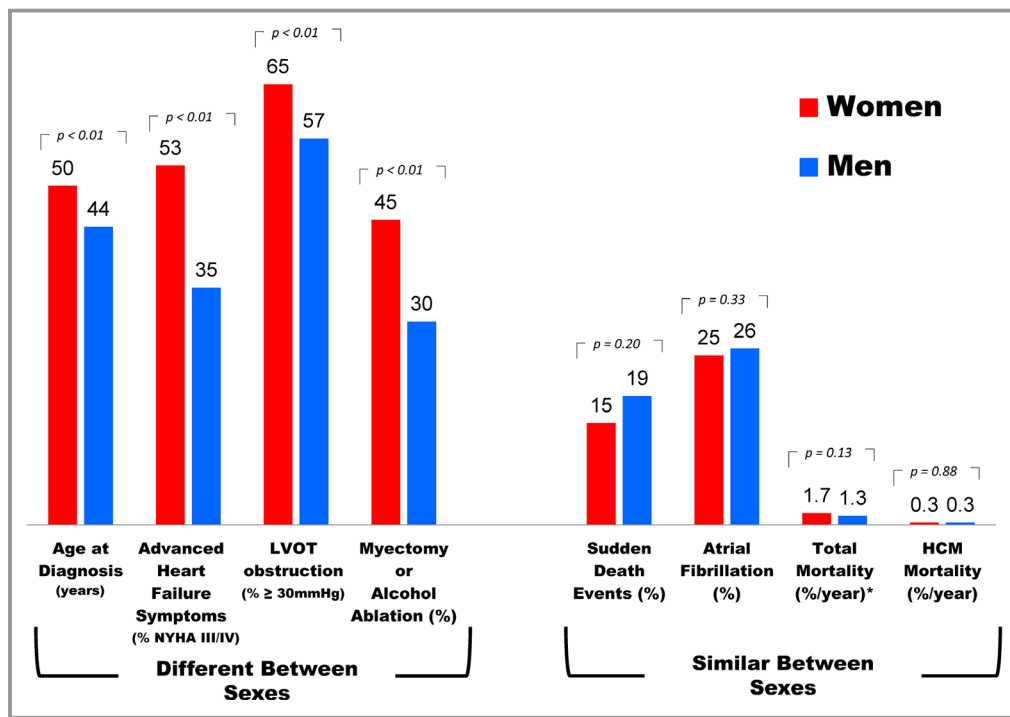
Women more commonly demonstrated dynamic LV outflow tract obstruction caused by mitral valve systolic anterior motion than did men (65% versus 57%;  $P<0.001$ ), present most commonly at rest (45% versus 31% in men;  $P<0.001$ ), and less frequently provoked with stress exercise echocardiography (20% versus 26% in men;  $P<0.001$ ).

A total of 351 patients underwent clinical genetic testing, similar in women and men (15% versus 17%;  $P=0.33$ ). However, women were more likely to have a HCM pathologic (disease-causing) sarcomere variant identified (60% versus 44%), most commonly in the MYBC3 and MYH7 genes (Table).

### Heart Failure

#### Overall by sex

At the time of initial evaluation at our center, women more commonly had heart failure symptoms than men, NYHA functional classes II to IV, characteristically with exertional



**Figure 1.** Clinical and demographic comparison between women and men with hypertrophic cardiomyopathy. LVOT indicates left ventricular outflow tract; NYHA, New York Heart Association functional class.

dyspnea or fatigue, with or without chest pain (73% women versus 53% men;  $P < 0.001$ ). Similarly, during follow-up, women were more likely to develop advanced drug refractory heart failure (NYHA class III/IV, 53% women versus 35% men;  $P < 0.001$ ; Figure 4), an average of 6 years later than in men ( $58 \pm 16$  versus  $52 \pm 14$  years in men;  $P < 0.001$ ). Nevertheless, a substantial proportion of women developed advanced heart failure at a relatively young age, including 48% who were  $< 50$  years of age (range, 14–49).

The rate of heart failure progression was 4.8%/year in women versus 3.4%/year in men (hazard ratio [HR], 1.6; 95% CI, 1.2–2.1;  $P < 0.001$ ; Figure 5) despite greater use of beta-blockers, verapamil, and disopyramide in women (Table). Advanced heart failure symptoms were predominantly secondary to outflow obstruction in 92% of women and 92% of men ( $P = 0.71$ ).

### Obstructive HCM

At initial evaluation, women with obstructive HCM were older ( $58 \pm 16$  versus  $51 \pm 15$  years in men;  $P < 0.001$ ), more symptomatic (NYHA class  $2.4 \pm 0.7$  versus  $2.1 \pm 0.8$  years;  $P < 0.001$ ), and had higher outflow gradients ( $78 \pm 31$  versus  $73 \pm 30$  mm Hg;  $P < 0.001$ ). The proportion of women with obstructive HCM who ultimately developed advanced heart failure symptoms (75% versus 56%;  $P < 0.001$ ), as well as the rate of heart failure progression from NYHA class I/II to class

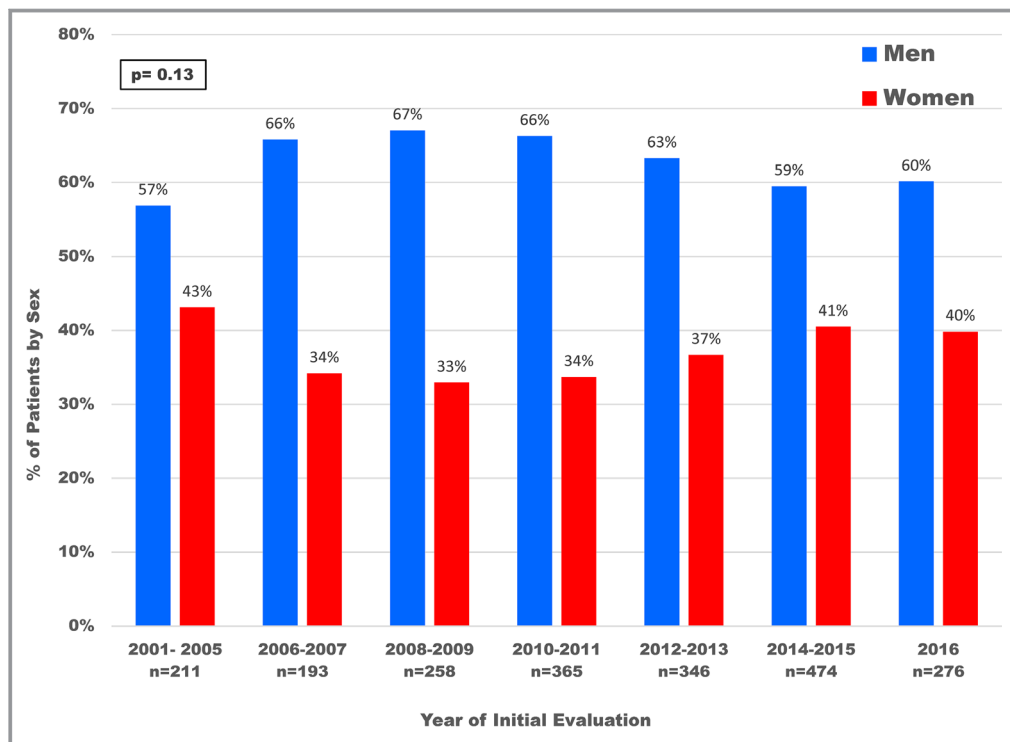
III/IV (7%/year versus 5%/yr;  $P = 0.002$ ) was substantially higher in women than in men.

Consistent with the higher prevalence of heart failure in women, both surgical myectomy (36% versus 26%;  $P < 0.001$ ) and alcohol septal ablation (11% versus 4%,  $P < 0.001$ ) were performed more commonly in women. Of 283 women who underwent septal myectomy with advanced NYHA class III/IV heart failure symptoms, 266 (94%) improved to NYHA class I/II, at the end of follow-up, while 17 patients (6%) were nonresponders with persistent severe heart failure symptoms despite successful relief of subaortic obstruction. Similarly, of the 347 men with obstruction and NYHA III/IV symptoms who underwent myectomy, 335 (97%) improved to NYHA class I/II, and 12 (3%) were nonresponders ( $P = 0.18$ ).

Both men and women demonstrated substantial reduction or abolition of outflow gradients on the most recent echocardiogram  $2.5 \pm 2.0$  years after surgery (from  $67 \pm 40$  mm Hg to  $2 \pm 6$  mm Hg in women versus  $48 \pm 41$  mm Hg to  $2 \pm 7$  mm Hg in men;  $P = 0.86$ ). Operative mortality was low and did not differ between women and men (1.1% versus 0.9%;  $P = 0.56$ ).

Alcohol septal ablation was performed at older ages in 89 women ( $67 \pm 13$  years) compared with 58 men ( $61 \pm 12$ ;  $P = 0.002$ ) usually due to perceived increase in surgical risk or particularly advanced age. Alcohol septal ablation failed to





**Figure 2.** Distribution by sex according to year of initial evaluation in 2123 hypertrophic cardiomyopathy patients.

adequately relieve outflow obstruction and symptoms in similar proportions of men and women treated (17% versus 20%;  $P=0.82$ ), leading to either repeat ablation ( $n=7$ ) or ultimately myectomy ( $n=21$ ).

### Nonobstructive HCM

At initial evaluation, women with nonobstructive HCM were older ( $51\pm 19$  versus  $47\pm 17$  years;  $P=0.003$ ) and more symptomatic than men (NYHA class  $1.6\pm 0.7$  versus  $1.3\pm 0.5$  years;  $P<0.001$ ). The majority of women have remained asymptomatic or minimally symptomatic (NYHA class II) over follow-up (88% of women versus 94% of men;  $P=0.002$ ). However, the proportion of women with nonobstructive HCM who ultimately developed advanced refractory heart failure symptoms (12%) exceeded that of men 2-fold (6%;  $P=0.002$ ).

Development of end-stage HCM with global systolic dysfunction and ejection fraction  $<50\%$  occurred with similar frequency in both sexes (5% women, 4% men;  $P=0.33$ ), although women with no obstruction were 2.8 times more likely to experience advanced drug-refractory heart failure associated with preserved systolic function and ejection fraction  $\geq 50\%$  (7.5% versus 2.6%;  $P=0.002$ ).

A similar proportion of women and men with nonobstructive HCM and unrelenting drug-refractory heart failure symptoms were listed for heart transplant (57% women versus 63% men;  $P=0.80$ ) and ultimately underwent transplant (65%

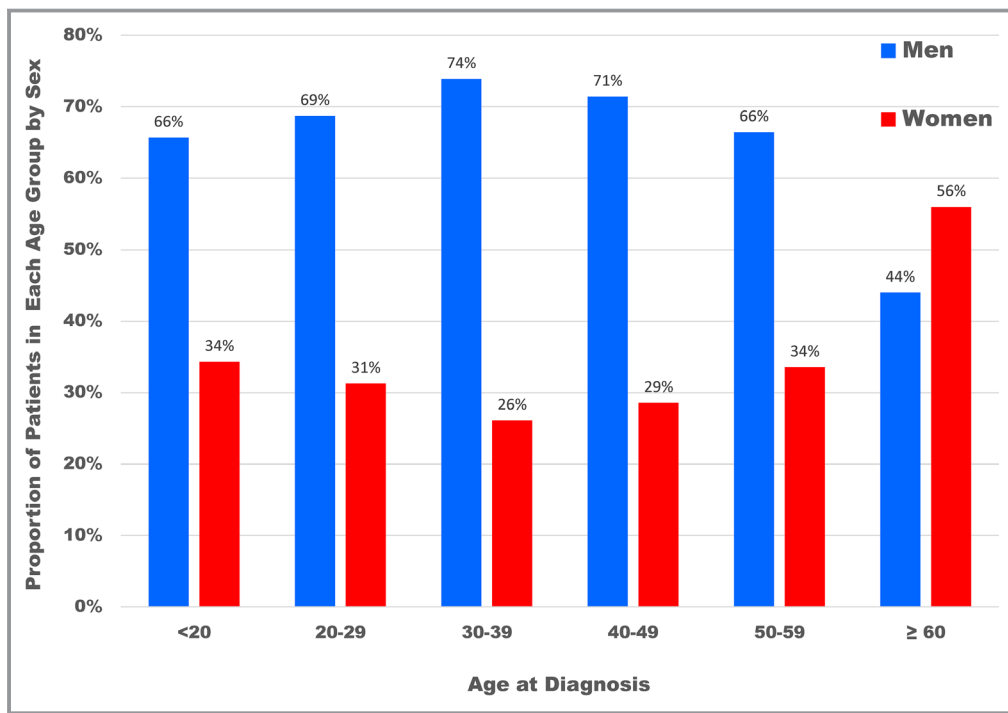
versus 82%;  $P=0.19$ ). Survival following transplant was also similar in both sexes: 85% of women at  $6.4\pm 4.1$  years, and 94% of men ( $P=0.56$ ); each is currently physically active without cardiovascular symptoms.

Eight women died of end-stage heart failure, including 2 with transplant-related complications. Of 6 other patients, 2 died awaiting transplant; 2 were not considered for transplant listing because of medication nonadherence ( $n=1$ ) or irreversible pulmonary hypertension ( $n=1$ ); and 2 patients declined transplant.

### Sudden death

There was no difference in primary prevention ICD placements between women (24%) and men (25%;  $P=0.54$ ), recommended on the basis of  $\geq 1$  HCM risk marker considered major within the individual patient clinical profile. Of 191 women implanted with a prophylactic ICD, 25 (13%) experienced  $\geq 1$  appropriate ICD intervention to terminate ventricular tachycardia/ventricular fibrillation and restore sinus rhythm, compared with 57 men (17%;  $P=0.20$ ). Despite women presenting at older ages, the age at first appropriate ICD intervention was similar in women and men ( $44\pm 15$  years in women versus  $46\pm 17$  in men;  $P=0.53$ ).

Sudden cardiac death, resuscitated out-of-hospital cardiac arrest, and appropriate ICD interventions for ventricular tachycardia/ventricular fibrillation occurred in 5% of women



**Figure 3.** Distribution by sex within each age group at initial hypertrophic cardiomyopathy diagnosis in 2123 patients.

(0.9%/year), versus 6% of men (0.8%/year; HR, 0.92; 95% CI, 0.6–1.5;  $P=0.73$ ). One woman (and 4 men) ultimately died suddenly attributable to HCM (0.1% women versus 0.3% men;  $P=1.0$ ). The only sudden death in a woman was in setting of a LV apical aneurysm (in 2004), well before this abnormality became an established risk marker and ICD indication.<sup>20</sup>

### Atrial fibrillation

Symptomatic atrial fibrillation occurred at similar frequency in women and men (25% versus 26%;  $P=0.33$ ), more frequently paroxysmal in women (86% versus 76%;  $P=0.004$ ). Prophylactic anticoagulation to reduce stroke risk (91% in both groups;  $P=1.0$ ), radiofrequency catheter ablation (17% versus 15%;  $P=0.60$ ), and Maze procedure during surgical myectomy (17% versus 21%;  $P=0.28$ ) were similar in women and men. Over follow-up of  $3.2\pm 2.0$  years, women trended toward less recurrent atrial fibrillation than men after the Maze procedure (19% versus 42%;  $P=0.06$ ), but there was no difference between the sexes after catheter-ablation (76% versus 64%;  $P=0.53$ ). Thirteen women (7%) experienced thromboembolic strokes (one fatal), no different than men (4%;  $P=0.15$ ); only 4 of the 13 occurred on prophylactic anticoagulation.

### Mortality

Of the 794 women with HCM, 724 have survived over the follow-up period; 70 (9%) died (Figure 4). Death attributable to

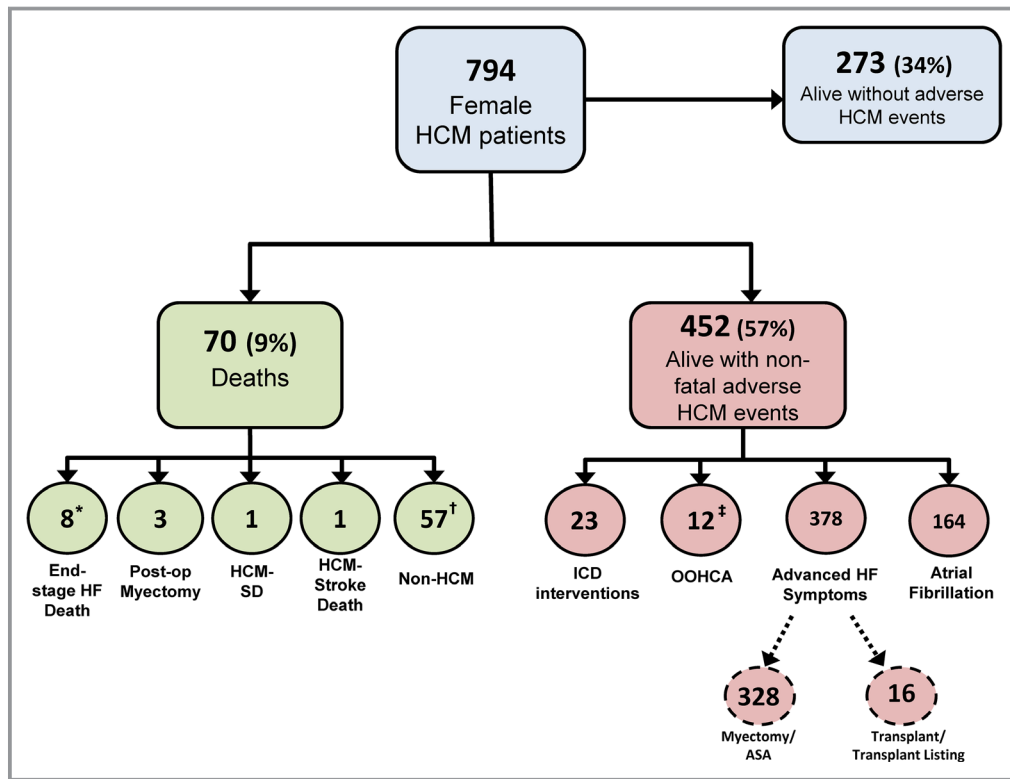
HCM did not differ between the sexes: 13 women (1.6%) at  $53\pm 16$  years of age, compared with 15 men (1.1%) at  $56\pm 12$  years ( $P=0.54$ ), and 0.3%/year in both (HR, 1.5; 95% CI, 0.7–3.4;  $P=0.25$ ). In women, 8 of the 13 deaths were related directly to end-stage heart failure in the absence of LV outflow obstruction, including 6 who had either declined heart transplant, were ineligible, or waitlisted; and 2 others died of transplant-related complications. The other 5 deaths were 1 sudden and arrhythmic (with LV apical aneurysm but without an ICD), 1 attributable to embolic stroke, and 3 postoperatively after myectomy (Table).

When adjusted for age at initial evaluation, there was no difference between women and men in all-cause (total) mortality (1.7%/year versus 1.3%/year; HR, 1.32; 95% CI, 0.92–1.91;  $P=0.13$ ; Figure 4), nor with respect to the mortality expected in an age- and sex-matched general US population ( $P=0.38$  and 0.37, respectively). While unadjusted total mortality in women (9%) exceeded that in men (5%;  $P=0.001$ ), that difference was attributable to a greater number of non-HCM related deaths in women, most commonly chronic pulmonary disease ( $n=8$ ), cancer ( $n=6$ ), or multiple noncardiac abnormalities ( $n=12$ ).

### Discussion

In HCM, there remains some uncertainty as to whether sex differences relate to mortality risk from heart failure or other disease complications.<sup>12–14</sup> Therefore, in the present analysis





**Figure 4.** Flow diagram summarizing clinical outcome of women with hypertrophic cardiomyopathy (HCM). \*Includes 2-post-transplant deaths. †Includes 2 patients in whom the cause of death was unknown and one with resuscitated cardiac arrest 2 years prior to death. ‡Includes 9 with subsequent appropriate defibrillator interventions. HF indicates heart failure; ICD, implantable cardioverter defibrillator; OOHCA, out-of-hospital cardiac arrest; SD, sudden death.

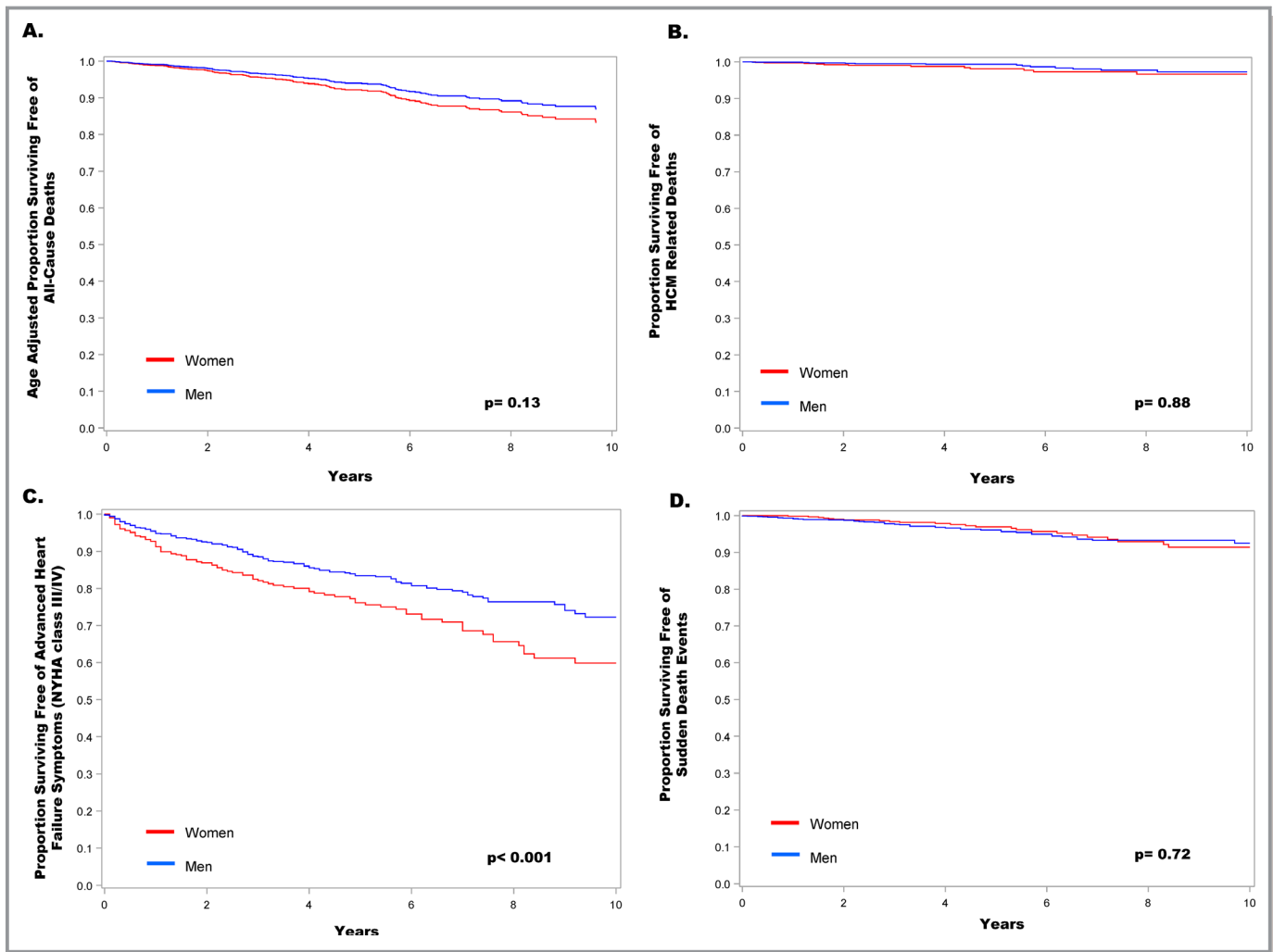
of a large consecutive tertiary referral HCM cohort, we focused on differences in clinical course of heart failure, mortality, and other disease complications in women versus men as well as the effectiveness of contemporary treatments.<sup>1</sup>

Our data showed no difference between men and women with regard to deaths directly attributable to HCM. In addition, we found no significant difference in men and women for total (all-cause) mortality after adjustment for patient age. Notably, the excess absolute number of all-cause deaths observed in women was due largely to comorbid conditions such as obstructive pulmonary disease and cancer. Furthermore, we found no evidence that life expectancy is significantly altered in HCM solely on the basis of sex, given the low HCM-related mortality rates of 0.3%/year in both women and men and lack of difference in mortality for women with HCM compared with the general US population.<sup>19</sup>

Our low mortality rates in women diverge from the portrayal by other HCM investigators in which women are reported to have a generally unfavorable outcome compared with men.<sup>12–14</sup> This discrepancy appears to be largely attributable to differences in study designs and treatment strategies.

For example, in contrast to a report from the Mayo Clinic<sup>12</sup> in which the primary end point was all-cause mortality, in the present study we focused on the clinical course of individual patients with detailed follow-up related specifically to HCM outcome and mortality. It is noteworthy, however, that our present cohort is smaller in size with shorter follow-up,<sup>12</sup> and therefore a trend toward increased all-cause mortality in women cannot be excluded. While both studies have merit and are difficult to compare head to head, we believe our present methodology contributes a unique understanding of contemporary treatment benefit in HCM most importantly resulting in low disease-related mortality. Furthermore, our data, showing low mortality in women attributable to effective management strategies, is supported by another recent Mayo Clinic report showing men and women with similar longevity and symptom relief specifically following myectomy surgery for obstructive HCM.<sup>18</sup>

Therapeutic options that aborted potentially lethal tachyarrhythmic events with implantable defibrillators, or averted heart failure death and morbidity with myectomy (and alcohol septal ablation) or heart transplant, contributed importantly to low HCM-related mortality in women. Indeed, heart failure–related death has become exceedingly rare in HCM (involving only 1% of the women in this cohort) and was virtually



**Figure 5.** Survival free of events in men and women with hypertrophic cardiomyopathy. **A**, Comparison of total (all-cause) mortality adjusted for age. **B**, Comparison of hypertrophic cardiomyopathy-related deaths by sex. **C**, Freedom from development of advanced heart failure symptoms (NYHA class I/II to III/IV). **D**, Freedom from sudden death events (including appropriate defibrillator intervention for ventricular tachyarrhythmias and resuscitated cardiac arrest).

confined to clinical circumstances surrounding heart transplant including listing for transplant. Furthermore, only 1 woman in the study population incurred sudden cardiac death (0.1%), in a patient with an LV apical aneurysm who presented well before this abnormality became an established risk marker and ICD indication in HCM.<sup>20</sup>

We found no evidence of sex-related bias in recommendations for invasive therapeutic options such as myectomy, alcohol septal ablation, catheter ablation for atrial fibrillation, or heart transplant. This experience in HCM contrasts sharply with the management of other cardiovascular diseases, for which women are less likely to be referred for invasive treatment interventions including cardiac catheterization and revascularization for coronary artery disease<sup>21</sup> or ICDs for primary sudden death prevention,<sup>22</sup> anticoagulation and catheter ablation for atrial fibrillation,<sup>23</sup> and heart transplant for end-stage heart failure.<sup>24</sup>

Progression to severe drug-refractory heart failure (classes III-IV) predominated in women because of more frequent underlying LV outflow obstruction (at rest or, less commonly, with exercise provocation).<sup>11</sup> Nevertheless, with surgical septal myectomy (or alcohol septal ablation), both women and men reliably experienced relief of outflow gradients and reversibility of heart failure symptoms; that is, >90% of patients improved by  $\geq 1$  NYHA functional class (with 70% returned to normal activity in class I). Indeed, delayed recognition of HCM can unnecessarily expose many symptomatic women to years of diminished quality of life without the benefit of myectomy (or alcohol septal ablation) and the opportunity to experience extended periods of life without significant functional impairment.<sup>2,3,11</sup> This is particularly relevant considering that about one half of symptomatic women first experienced limiting heart failure symptoms attributable to outflow obstruction at relatively young ages.

While 90% of women with nonobstructive HCM have survived with no or only mild symptoms, they nevertheless more frequently experienced advanced heart failure than did men, including an almost 3-fold greater likelihood associated with preserved systolic function (ejection fraction  $\geq 50\%$ ). This clinical profile in HCM is similar to non-HCM populations in which heart failure with preserved ejection fraction is twice as common in women, although systolic dysfunction occurs in similar frequency by sex.<sup>25</sup>

Less frequent HCM diagnosis in women was associated with a delay in clinical recognition, potentially related to societal bias affecting diagnosis and evaluation of HCM patients by sex.<sup>21,26,27</sup> Given that HCM is a genetic heart disease with an autosomal dominant inheritance pattern, it would be our expectation that women with clinically established HCM should comprise about 50% of the cohort. The fact that only a little more than one third of our patients were women represents significant underrepresentation within the HCM study group. As reported in atherosclerotic coronary artery disease populations and non-HCM congestive heart failure,<sup>21,26,27</sup> early symptoms of angina or atypical chest pain, exertional dyspnea, and fatigue in women are not uncommonly misinterpreted, ignored, or inappropriately attributed to other causes. Women with such complaints may be less likely to seek medical diagnosis and care.<sup>21,27</sup> Also, HCM frequently has been considered a disease more commonly affecting men such as in the competitive athlete population.<sup>1,28</sup> Sex as a determinant of less frequent HCM diagnosis is reminiscent of recent observations that HCM is underrecognized in black patients.<sup>29</sup>

To explain the significant delay in HCM diagnosis and recognition of heart failure symptoms in women (by 6 years on average compared with men), we cannot exclude the possibility that biologic variability or genetic and/or hormonal factors are in part responsible for the timing and onset of heart failure symptoms. Of note, both atherosclerotic coronary artery disease and heart failure with preserved ejection fraction occur in women at more advanced ages than men, usually after menopause and associated with a burden of cardiovascular risk factors.<sup>21,24,25,27</sup> However, our observation that about 50% of women <50 years of age with HCM developed heart failure appears to exclude menopause as a major mechanism for this clinical course.

In conclusion, in this large consecutive HCM patient cohort analysis utilizing effective treatment interventions, we found no compelling evidence that this disease in women was associated with greater heart failure mortality, arrhythmic sudden death, nor other disease-related complications than in men. We have, however, documented a significant delay in HCM diagnosis occurring in women with more frequent heart failure and progression to unrelenting symptoms consistent with NYHA functional class III to IV, predominantly driven by LV outflow obstruction.

Importantly, there were no treatment discrepancies identified between the sexes, and heart failure caused by LV outflow obstruction in women and men was equally amenable to reversal with low-risk surgical septal myectomy. Therefore, these data underscore the importance of increased awareness of HCM in women with implications for earlier diagnosis and effective treatment, and the potential for survival with improved quality of life.

## Disclosures

None.

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