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Contemporary Natural History and Management of Nonobstructive Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND Left ventricular outflow tract gradients are absent in an important proportion of patients with hypertrophic cardiomyopathy (HCM). However, the natural course of this important patient subgroup remains largely unresolved.

OBJECTIVES The authors systematically employed exercise (stress) echocardiography to define those patients without obstruction to left ventricular outflow at rest and/or under physiological exercise and to examine their natural history and clinical course to create a more robust understanding of this complex disease.

METHODS We prospectively studied 573 consecutive HCM patients in 3 centers (44 ± 17 years; 66% male) with New York Heart Association functional class I/II symptoms at study entry, including 249 in whom left ventricular outflow tract obstruction was absent both at rest and following physiological exercise (<30 mm Hg; nonobstructive HCM) and retrospectively assembled clinical follow-up data.

RESULTS Over a median follow-up of 6.5 years, 225 of 249 nonobstructive patients (90%) remained in classes I/II, whereas 24 (10%) developed progressive heart failure to New York Heart Association functional classes III/IV. Nonobstructive HCM patients were less likely to experience advanced limiting class III/IV symptoms than the 324 patients with outflow obstruction (1.6%/year vs. 7.4%/year rest obstruction vs. 3.2%/year provocable obstruction; $p < 0.001$). However, 7 nonobstructive patients (2.8%) did require heart transplantation for progression to end stage versus none of the obstructive patients. HCM-related mortality among nonobstructive patients was low (n = 8; 0.5%/year), with 5- and 10-year survival rates of 99% and 97%, respectively, which is not different from expected all-cause mortality in an age- and sex-matched U.S. population ($p = 0.15$).

CONCLUSIONS HCM patients with nonobstructive disease appear to experience a relatively benign clinical course, associated with a low risk for advanced heart failure symptoms, other disease complications, and HCM-related mortality, and largely without the requirement for major treatment interventions. A small minority of nonobstructive HCM patients progress to heart transplant. (J Am Coll Cardiol 2016;67:1399–409) © 2016 by the American College of Cardiology Foundation.

Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease with vast clinical and phenotypic heterogeneity, including a broad hemodynamic spectrum comprising left ventricular (LV) obstruction under resting conditions, dynamic (labile) gradients in patients without rest obstruction, but also patients in whom gradients are absent both at rest and with provocation (i.e., nonobstructive HCM) (1-12). Within this hemodynamic continuum, most attention has historically focused on those patients with outflow obstruction, given that subaortic gradients are the most common

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

CMR = cardiac magnetic resonance

EF = ejection fraction

HCM = hypertrophic cardiomyopathy

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricle

NYHA = New York Heart Association

VF = ventricular fibrillation

mechanism responsible for heart failure symptoms in this disease, and for which specific treatment options are available (such as surgical myectomy or, selectively, alcohol septal ablation) to reverse this process and restore quality of life and expectation of longevity (1-4,7,8,13-17).

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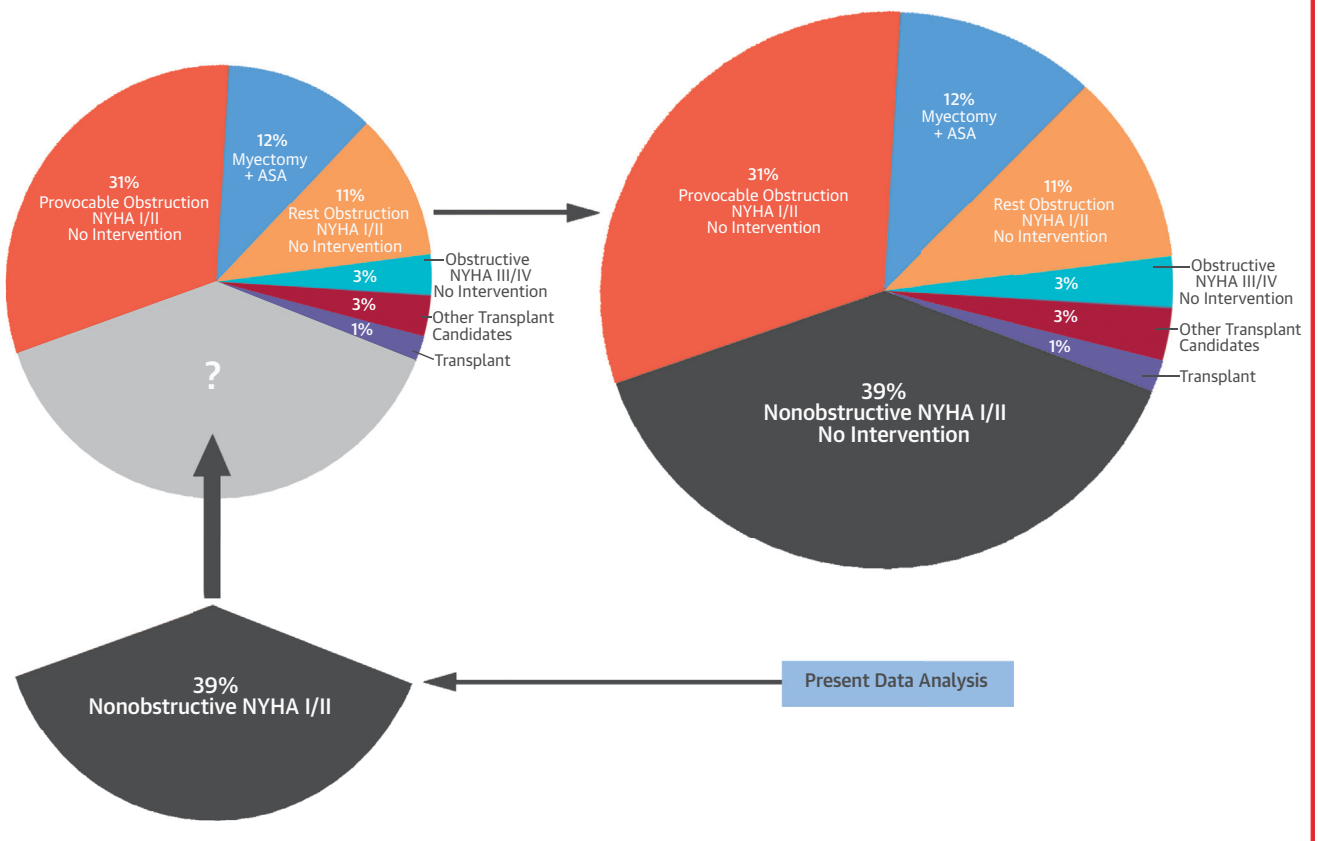
However, understanding the natural history of nonobstructive HCM has been impaired by a sparse literature and failure to define this hemodynamic state in a standard fashion (11-13,18-22). Yet, it has been our clinical intuition that patients with nonobstructive HCM only uncommonly present with advanced heart failure requiring major treatment interventions (**Central Illustration**).

Since 2003, we have consistently evaluated HCM patients without outflow gradients at rest by performing exercise (stress) echocardiography to define the nonobstructive form of this disease in physiological terms (7). This strategy created the unique opportunity to define a potential gap in the natural history of the HCM spectrum, by revisiting and clarifying in contemporary terms the clinical consequences of this important HCM patient subgroup without outflow gradients. Nonobstructive HCM is currently incompletely defined and understood within the heterogeneous disease spectrum.

METHODS

STUDY POPULATION. We initially evaluated and considered for this study 599 consecutive HCM patients, eligible for exercise testing, with New York

CENTRAL ILLUSTRATION Evolution in Understanding the Natural History Profile of HCM



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(Left) The present data demonstrate that the vast majority of patients with nonobstructive HCM do not develop severe progressive heart failure to NYHA functional classes III/IV or require consideration for transplantation (i.e., the missing sector). **(Right)** With the missing sector of the pie inserted, the clinical course in HCM becomes complete, with about 40% of the cohort represented by stable nonobstructive HCM in classes I/II. ASA = alcohol septal ablation; HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association.

Heart Association (NYHA) functional class I or II symptoms, and prospectively evaluated between July 1, 2003 and December 30, 2007 at 3 HCM referral centers (Tufts Medical Center, Boston, Massachusetts; Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; and Azienda Ospedaliera Careggi, Florence, Italy) (Online Figure). Excluded from the study were patients with known atherosclerotic coronary artery disease (≥50% narrowing in ≥1 epicardial vessel), previous septal myectomy or alcohol septal ablation, and those with advanced heart failure symptoms in NYHA functional classes III/IV at initial evaluation (to permit a prospective assessment of outcomes and development of limiting symptoms). In addition, patients with a phenocopy of HCM, such as Noonan syndrome, Fabry disease, and lysosomal-associated membrane protein 2, *LAMP2,* cardiomyopathy, were excluded by clinical diagnosis and/or targeted genetic testing. Of the 599 patients, 26 had no or limited clinical follow-up (<3 months). Therefore, the final study group comprised 573 patients.

The most recent clinical assessment was obtained by hospital visit or telephone contact up to January 1, 2014. The median duration of follow-up was 6.8 years (interquartile range: 5.4 to 8.1) from study entry, when the baseline echocardiogram was performed in each participating center. Patients signed statements, approved by the internal review boards of participating institutions, agreeing to the use of their medical information for research. Each author had full access to and took responsibility for the integrity of the data, and agreed to the paper, as written.

ECHOCARDIOGRAPHY. Standard echocardiographic studies were performed under basal conditions with commercially available instruments. Clinical diagnosis of HCM was on the basis of demonstration by 2-dimensional echocardiography and/or cardiac magnetic resonance (CMR) of a hypertrophied and nondilated LV (wall thickness ≥13 mm), in the absence of another cardiac or systemic disease capable of producing a similar degree of hypertrophy. Peak instantaneous LV outflow tract gradient was measured at rest (in the left lateral decubitus position) with continuous wave Doppler interrogation directly parallel to the outflow tract in the apical views under direct visualization (23). Care was taken to differentiate Doppler waveform signals from LV outflow tract and mitral regurgitation jets (7,23).

EXERCISE ECHOCARDIOGRAPHY. Patients with outflow gradients ≥50 mm Hg at rest did not undergo exercise testing due to the lack of clinical significance attributable to provoking even higher gradients (7). Patients with gradients <50 mm Hg at rest underwent symptom-limited exercise (stress) testing with echocardiography on a standard Bruce protocol or ergometer with 12-lead electrocardiogram, blood pressure, and heart rate monitoring, as previously described (7). Immediately after exercise, patients were placed in the left lateral decubitus position and peak instantaneous LV outflow tract velocities were measured using the apical window. Patients with apical HCM, LV apical aneurysm, or the end-stage phase (ejection fraction [EF] <50%) were considered as nonobstructive, although they were not subjected to exercise testing on the basis of our previous experience that patients with such morphology are not capable of developing outflow gradients.

CMR STUDIES. CMR studies were performed with a 1.5-T clinical CMR scanner (Phillips Gyroscan ACS-NT, Best, the Netherlands; Sonata or Avanto, Siemens Medical, Erlangen, Germany) in 360 patients. Breath-hold cine steady-state free-precession sequences were performed in horizontal long-axis, vertical long-axis, and contiguous short-axis slices with full coverage of the LV and slice thicknesses of 10 mm with no gap. Short-axis cine stacks were obtained parallel to the atrioventricular groove, covering the entire LV chamber. Late gadolinium enhancement (LGE) images were acquired 10 to 15 min after intravenous administration of 0.2 mmol/kg gadolinium-diethylenetriamine pentaacetic acid using breath-held segmented inversion-recovery sequence.

The CMR-LGE images reported in this study were part of a previous multicenter, CMR-based outcome study and, therefore, the methodology used for analyzing LGE, including intraobserver and interobserver reproducibility, has been previously reported in detail (24). Briefly, 2 experienced readers blinded to patient profiles and clinical outcome first assessed the LV short-axis stack of LGE images visually for the presence of LGE. Quantification of LGE was then performed on all LGE-positive studies by manually adjusting a grayscale threshold to define areas of visually identified LGE. These areas were then summed to generate a total volume of LGE and were expressed as a proportion of total LV myocardium (% LGE). This visual grayscale thresholding method is associated with good reproducibility: intraobserver coefficient of variation 5.9 ± 1.1%; interobserver coefficient of variation 6.3 ± 1.2%; concordance correlation coefficient ρ_c 0.996, with minimal bias (bias: -0.1 g; 95% confidence interval [CI]: -3.5 to 3.3) (24).

STATISTICAL ANALYSES. Descriptive statistics. Data are displayed as mean ± SD for continuous variables and as proportions for categorical variables. When continuous variables had skewed distributions

TABLE 1 Demographics, Clinical Features, and Outcomes in 573 HCM Patients Presenting With NYHA Functional Classes I/II Heart Failure Symptoms

		Obstruction		
	Nonobstructive	Provocable	Rest	p Value
Patients	249 (43)	220 (38)	104 (18)	
Age, yrs	41 ± 17	44 ± 18	46 ± 17	0.087
Male	167 (67)	170 (77)	72 (69)	0.044*
Family history of HCM	126 (51)	76 (35)	41 (39)	0.002*
NYHA functional class (study entry)				
I	180 (72)	148 (67)	53 (51)	0.001†‡
II	69 (28)	72 (33)	51 (49)	
Maximal LV thickness, mm	21 ± 6	20 ± 5	23 ± 6	<0.001†‡
LV wall thickness ≥30 mm	22 (9)	11 (5)	16 (15)	0.008‡
LVOT gradient at rest, mm Hg	5 ± 5	11 ± 11	80 ± 27	<0.001
LVOT gradient at rest ≥30 mm Hg	0 (0)	20 (9)	104 (100)	<0.001
LVOT gradient with exercise, mm Hg	17 ± 7	80 ± 42	N/A	<0.001
LA dimension, mm	40 ± 7	41 ± 7	44 ± 8	<0.001†‡
LVED, mm	45 ± 8	44 ± 8	42 ± 7	0.021†
LVEF, %	63 ± 7	65 ± 5	67 ± 6	<0.001
Atrial fibrillation§	48 (19)	50 (23)	34 (33)	0.007†
Paroxysmal	44 (17)	43 (20)	30 (29)	–
Permanent	4 (2)	7 (3)	4 (4)	–
Syncope	41 (16)	38 (17)	13 (13)	0.54
NSVT (ambulatory Holter)	41 (18)	22 (11)	12 (12)	0.11
Family history of HCM sudden death	37 (15)	11 (5)	12 (11)	0.002*
Conventional risk factors‖	0.6 ± 0.7	0.5 ± 0.8	0.4 ± 0.6	0.050†
End-stage HCM; EF <50%	12 (5)	0 (0)	0 (0)	<0.001*
CMR performed	132 (53)	124 (56)	53 (51)	
LGE present	68/132 (52)	42/124 (34)	22/53 (42)	0.019*
% LGE of LV	7.1 ± 9.8	4.3 ± 6.2	5.7 ± 9.6	0.002*
% LGE of LV ≥15%	8/132 (6)	2/124 (2)	2/53 (4)	0.46
ICD	79 (32)	48 (22)	28 (27)	0.055
Genetic testing performed	75 (30)	58 (26)	24 (20)	
Sarcomere mutation identified	40 (53)	32 (55)	14 (58)	0.66
Myosin binding protein-C	17 (23)	16 (28)	6 (25)	–
Beta-myosin heavy chain	13 (17)	10 (17)	3 (13)	–
Troponin T	2 (3)	1 (2)	1 (4)	–
Troponin I	2 (3)	0 (0)	1 (4)	–
Myosin light chain 2	3 (4)	2 (3)	0 (0)	–
Double mutations	3 (4)	3 (5)	3 (12)	–
Medications				
Beta-blocker	116 (47)	113 (51)	68 (65)	0.005†
Calcium-channel blocker	40 (16)	36 (16)	32 (31)	0.003*‡
Disopyramide	1 (0.4)	4 (2)	5 (5)	0.019†
Amiodarone	6 (2)	5 (2)	3 (3)	0.88
ACE/ARB	27 (11)	21 (10)	4 (4)	0.11
Diuretic	20 (8)	8 (4)	8 (8)	0.12
Coumadin	14 (6)	11 (5)	4 (4)	0.79
Duration of follow-up, yrs	6.5 (2.6)	7.1 (2.8)	6.7 (2.9)	0.26

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(follow-up time), data are expressed as median (interquartile range). Student *t* test, 1-way analysis of variance (ANOVA), or Kruskal-Wallis tests were used to assess statistical significance for continuous variables, with chi-square tests used for categorical variables. Variables with a p value <0.05 for univariate associations were entered into a stepwise multivariate Cox proportional hazards model to identify independent predictors. Proportional hazards assumptions were tested graphically before proceeding. Values of $p \leq 0.05$ were considered significant; all are reported as 2-sided. Statistical calculations were performed with Stata (version 11.2, Stata Corp, College Station, Texas).

Survival analysis. The fraction of HCM patients surviving at each follow-up interval was estimated by the Kaplan-Meier method. The expected fraction surviving at each time interval was computed by assigning to each patient the probability of survival after initial evaluation, appropriate to age and sex, on the basis of U.S. Census data. Actual and expected surviving fractions were compared by use of the 1-sample log-rank test, which provides a 95% CI. Endpoints were all-cause mortality and HCM-related mortality, which included: sudden cardiac death (unexpected, within 1 h of witnessed collapse or nocturnal); heart failure death (in the context of progressive cardiac decompensation); and stroke-related death. Appropriate discharges from implantable defibrillators for ventricular fibrillation (VF) or sustained ventricular tachycardia were regarded as aborted sudden deaths.

RESULTS

BASELINE CHARACTERISTICS. Clinical and demographic characteristics of the overall study population of 573 patients are summarized in Table 1. Mean age at study entry was 44 ± 17 years and each patient was in NYHA functional class I or II. A total of 249 patients (43%) had nonobstructive HCM, with gradients <30 mm Hg, both at rest and with physiological exercise, whereas the remaining 324 patients had outflow obstruction ≥30 mm Hg, either at rest (n = 104 patients) or with provocation (n = 220 patients; <30 mm Hg at rest and ≥30 mm Hg following exercise).

NONOBSTRUCTIVE HCM. Among the 249 patients with nonobstructive HCM, age at study entry was 41 ± 17 years (range 8 to 88), with 111 (46%) <40 years of age. Most were asymptomatic, in NYHA functional class I (n = 180), and 69 were in class II. Maximal LV wall thickness was 21 ± 6 mm (range 15 to 34 mm), including 22 patients with massive hypertrophy (wall thickness ≥30 mm). The LV end-diastolic cavity dimension was 45 ± 8 mm. EF was 63 ± 7% (range 40% to 80%), including 12 patients with EF <50% (Table 1).

HEART FAILURE. After study entry, over 6.5 years (interquartile range: 5.4 to 7.9) of follow-up, 225 of 249 nonobstructive HCM patients (90%) remained in classes I/II, without progression of heart failure, including 151 administered cardioactive medications

(predominantly beta-blockers and calcium-channel blockers) and 74 who remained asymptomatic without medications. Heart failure progression to functional classes III/IV occurred over follow-up in only 24 patients (10%), despite maximal medical management (annual rate 1.6%) (Figure 1, Table 2), including 2 patients with systolic dysfunction (EF <50%) at study entry.

All 24 nonobstructive patients who developed classes III/IV heart failure symptoms were considered transplant candidates. Among these 24 patients, 12 declined or did not qualify for listing, 7 underwent transplantation (6 presently in class I), and 5 remain listed. At the end of the follow-up period, 18 of 24 patients were alive, including 12 who remained in classes III/IV on medical therapy. The remaining 6 patients died, including 4 of heart failure (3 while listed for transplantation and 1 who declined), 1 from complications of transplantation, and 1 from noncardiac causes (Table 3).

Compared with other nonobstructive patients, the 24 patients who progressed to classes III/IV were more likely to be symptomatic at baseline in class II (62% vs. 24%; $p < 0.001$), also to have larger left atria (46 ± 8 mm vs. 39 ± 7 mm; $p < 0.001$), more frequent history of atrial fibrillation (58% vs. 15%; $p < 0.001$), lower EF (60 ± 8% vs. 63 ± 6%; $p = 0.04$), and more extensive LGE (15 ± 14% vs. 6 ± 9%; $p = 0.008$) (Table 2). With multivariate analysis, left atrial size and class II symptoms at study entry were independent predictors for progression of heart failure symptoms to classes III/IV (Table 4).

HCM-RELATED DEATH. Mortality was attributable to HCM in 8 of 249 nonobstructive patients (0.5%/year),

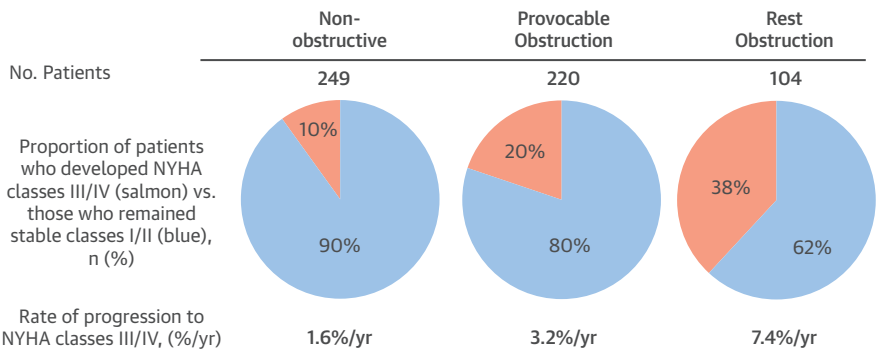
TABLE 1 Continued

		Obstruction		
	Nonobstructive	Provocable	Rest	p Value
Medications				
Beta-blocker	128 (51)	150 (68)	73 (70)	<0.001*†
Calcium-channel blocker	46 (18)	45 (20)	27 (26)	0.28
Disopyramide	4 (2)	12 (5)	7 (7)	0.031†
Amiodarone	18 (7)	17 (7)	6 (6)	0.81
ACE/ARB	25 (10)	14 (6)	10 (10)	0.33
Diuretic agent	35 (14)	25 (11)	10 (10)	0.45
Warfarin	32 (13)	29 (13)	12 (12)	0.92
Major interventions				
Septal myectomy	0 (0)	28 (13)	31 (31)	<0.001
Alcohol septal ablation	0 (0)	4 (2)	3 (3)	0.047†
Heart transplantation	7¶# (3)	0 (0)	0 (0)	0.010*
Resuscitated cardiac arrest	1 (1)	3 (1)	0 (0)	0.41
Appropriate ICD interventions	10‡ (4)	6 (3)	2 (2)	0.66
Progression to NYHA functional classes III/IV	24 (10)	43 (20)	39 (38)	0.002
Mortality	14 (6)	8 (4)	7 (7)	0.43
Non-HCM related	6 (42)	5 (63)	4 (57)	
HCM-related				0.73
Sudden death	3 (21)	2 (25)	2 (29)	
HF	5¶ (36)	1 (13)	1 (14)	

Values are n (%), mean ± SD, or n/n (%). Dashes indicate data are unavailable. *Significant difference between nonobstructive and provocable obstruction. †Significant difference between nonobstructive and resting obstruction. ‡Significant difference between rest and provocable obstruction. §Includes patients with previous history of atrial fibrillation, as well as those who developed atrial fibrillation during the follow-up period. ||Includes family history of HCM sudden death, unexplained syncope, NSVT on ambulatory Holter, or maximal LV thickness ≥30 mm. ¶Includes 1 patient who died 1 year after heart transplantation. #Includes 1 patient who had appropriate ICD intervention prior to heart transplantation.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CMR = cardiac magnetic resonance; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricle; LVED = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; N/A = not applicable; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association.

FIGURE 1 Prevalence and Risk for Advanced Heart Failure in Nonobstructive HCM Patients Compared With Those With Rest or Provocable Obstruction



The proportion of HCM patients who develop NYHA functional classes III/IV symptoms, as well as the rate of heart failure progression, is less among nonobstructive HCM patients than among patients with provocable or rest obstruction. HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association functional class; yr = year.

TABLE 2 Comparison of Nonobstructive HCM Patients Who Developed NYHA Functional Classes III/IV Heart Failure During Follow-Up Versus Patients Who Remained in Classes I/II

	Stable NYHA Functional Classes I/II During Follow-Up (n = 225)	Developed NYHA Functional Classes III/IV During Follow-Up (n = 24)	p Value
Baseline characteristics			
Age, yrs	41 ± 17	41 ± 15	0.78
Male	154 (69)	13 (54)	0.16
Family history of HCM	111 (49)	15 (63)	0.22
NYHA functional class			
I	171 (76)	9 (38)	
II	54 (24)	15 (62)	<0.001
III/IV	0 (0)	0 (0)	
Maximal LV thickness, mm	20 ± 6	23 ± 7	0.051
LA, mm	39 ± 7	46 ± 8	<0.001
LVED, mm	44 ± 8	46 ± 6	0.55
LVEF, %	63 ± 6	60 ± 8	0.036
Atrial fibrillation*	34 (15)	14 (58)	<0.001
Maximal LV wall thickness ≥30 mm	18 (8)	4 (17)	0.17
End-stage HCM, EF <50%	8 (4)	4 (17)	0.09
CMR performed	119 (53)	13 (54)	
LGE present	59/119 (50)	9/13 (69)	0.18
% LGE	6 ± 9	15 ± 14	0.013
% LGE of LV >15%	3 (3)	5 (38)	<0.001
Follow-up			
Duration of follow-up, yrs	6.5 (2.6)	7.3 (2.5)	0.91
Mortality	8 (4)	6 (25)	<0.001
Non-HCM	5 (63)	1 (17)	
HCM-related			0.005
Sudden death	3 (38)	0 (0)	
Heart failure	0 (0)	5† (83)	
HCM-related events	8 (4)	9 (38)	<0.001
Heart transplantation	0 (0)	7†‡ (29)	<0.001
Nonfatal sudden death events#	8 (4)	3‡ (13)	0.085

Values are mean ± SD, n (%), or n/n (%). *Includes patients with prior history of atrial fibrillation, as well as those who developed atrial fibrillation during the follow-up period. †Includes 1 patient with HF death and heart transplant 12 months previously. ‡Includes 1 patient with appropriate ICD intervention 12 months prior to heart transplantation. #Includes appropriate ICD interventions and resuscitated cardiac arrests.

Abbreviations as in Table 1.

at 45 ± 12 years of age (range 21 to 61 years of age) (Table 3). Five deaths were directly related to advanced heart failure with progression to NYHA functional classes III/IV (EF <50% in 3; ≥50% in 2), who proved refractory to vigorous pharmacological treatment with angiotensin-converting enzyme inhibitors, diuretic agents, beta-blockers, and calcium-channel blockers. Four of 5 declined, were ineligible, or awaiting heart transplantation; 1 patient died of transplant rejection complications 1 year post-operatively.

Three patients died suddenly of nonobstructive HCM (Table 3), at 40, 58, and 61 years of age. Two of these patients had declined a formal recommendation for primary prevention implantable cardioverter-defibrillator (ICD) therapy on the basis of standard risk factor assessment. The third patient, 40 years of age, received a prophylactic ICD, which proved defective and failed to terminate VF.

ABORTED ADVERSE LIFE-THREATENING HCM EVENTS. Ten patients experienced ≥1 appropriate ICD interventions for ventricular tachycardia/VF (Table 3). Of these, 6 patients had 1 traditional risk factor and 3 patients had 2 or 3, whereas 1 other patient was judged high risk and implanted with an ICD on the basis of a LV apical aneurysm with regional scarring (Table 3). Each of the 10 patients are currently alive 3.3 years after the first ICD intervention at 45 ± 14 years of age, and 7 of them are asymptomatic/mildly symptomatic, including 1 patient who has survived 5.2 years after out-of-hospital cardiac arrest with timely defibrillation and therapeutic hypothermia. The remaining 3 patients had progression to classes III/IV.

Seven patients who progressed to classes III/IV underwent heart transplantation (at 38 ± 16 years of age) as definitive therapy for progressive and unrelenting symptoms, despite aggressive medical management: 2 were in the end-stage phase of HCM at study entry (with class II symptoms); 2 developed systolic dysfunction with end-stage heart failure (EF <50%); and 3 had preserved systolic function (EF ≥50%) (Table 3). Six of the 7 patients are currently alive, 2.3 years post-transplantation.

ATRIAL FIBRILLATION/STROKE. Symptomatic permanent or paroxysmal atrial fibrillation (AF) occurred in 48 nonobstructive patients (19%), including 27 (11%) with previous history of AF and 21 (8%) who developed new-onset AF during follow-up, exclusive of this arrhythmia occurring in the first 30 days following myectomy. Left atrial size in these 48 patients exceeded that in the 201 nonobstructed patients without AF (44 ± 7.4 mm vs. 39 ± 6.6 mm; $p < 0.001$). Nine patients with repetitive AF refractory to medical management underwent radiofrequency ablation with pulmonary vein isolation; 7 were in sinus rhythm at the end of the follow-up and 2 were in permanent AF. Nonfatal thromboembolic stroke occurred in 2 of these 48 patients (4%), both of whom had declined prophylactic anticoagulation. Two other patients, without a history of AF, had nonfatal thromboembolic strokes, both with systolic dysfunction.

LATE GADOLINIUM ENHANCEMENT. Contrast-enhanced CMR was performed in 132 nonobstructive patients (53%). One or more areas of LGE, not confined to a coronary arterial vascular territory, were present in 68 patients (52%), occupying 7.1 ± 9.8% of LV myocardial volume, particularly marked (≥15%) in 8 patients (6%). The extent of LGE at study entry in nonobstructive patients who developed classes III/IV heart failure (and the percentage of

TABLE 3 Nonobstructive Patients With HCM-Related Death or Aborted Life-Threatening Events

Patient no.	Sex	Age: Initial Evaluation (yrs)	Age: Death/ Event (yrs)	NYHA Functional Class: Initial	NYHA Functional Class: Last	AF	Maximal LV Thickness (mm)	LA (mm)	EF (%)	% LGE on CMR	Comment
HCM-related deaths											
Sudden cardiac death											
1	M	58	61	2	2	0	23	46	80	1.4	Declined ICD; syncope
2	M	34	40	2	1	0	18	36	65	–	ICD failure; syncope
3	M	52	58	1	1	0	15	38	65	–	Declined ICD; syncope; NSVT
Advanced heart failure death without transplant											
1	F	36	42	2	3	0	34	42	60	–	Died of HF during transplant evaluation
2	F	42	47	1	4	PAF	17	33	65	–	Died of HF awaiting transplant; LVAD
3	M	38	44	2	4	0	17	52	65	2.5	Died of HF awaiting transplant; LVAD
4	F	41	42	2	3	PAF	24	50	45	–	Died of HF after surgery for atrial thrombus removal
Post-transplantation death											
1	F	18	20	2	3	0	18	38	45	35.6	Died 1 year post-transplantation in setting of transplant rejection
Nonfatal HCM-related major events											
Resuscitated cardiac arrest											
1	M	33	37	1	1	PAF	21	39	75	3.2	Without RF; double sarcomere mutation
Appropriate ICD interventions											
1	F	55	59	2	3	PAF	23	45	70	–	Family history of sudden death; syncope
2	M	57	63	1	1	0	19	40	60	4.3	LV apical aneurysm with regional scarring
3	F	28	35	1	2	0	35	35	70	–	LV ≥30 mm
4	M	26	29	2	2	0	30	43	65	–	Family history of sudden death; LV ≥30 mm
5	M	23	27	1	2	0	19	34	65	–	Family history of sudden death
6	F	25	27	1	1	0	18	37	60	4.8	Family history of sudden death; NSVT
7	F	44	47	2	2	0	28	24	75	24.9	NSVT
8	F	27	30	1	3	0	16	33	60	0	Syncope; listed for transplantation
9	M	53	58	1	1	0	30	36	55	5.5	NSVT, LV ≥30 mm, LV apical aneurysm
Appropriate ICD interventions and heart transplant											
1	M	34	39	1	1	PAF	17	50	60	–	Syncope, NSVT; transplantation 12 months after ICD intervention
Heart transplantation											
1	F	22	29	2	2	PAF	22	51	65	0	Preserved EF
2	F	12	17	2	1	0	18	36	60	0	Preserved EF
3	M	53	55	2	1	PAF	22	55	60	19.8	
4	F	49	57	2	1	PAF	15	47	60	0	Preserved EF
5	M	39	45	1	1	0	15	46	45	15.9	

Dashes indicate that data are not available.

F = female; LVAD = left ventricular assist device; M = male; PAF = paroxysmal atrial fibrillation; RF = risk factors; other abbreviations as in Table 1.

patients with extensive LGE ≥15%) exceeded that in patients who remained in classes I/II over the follow-up period (15% vs. 6%; $p = 0.01$ and 38% vs. 3%; $p < 0.001$, respectively). In addition, among the 26 patients who had or developed end-stage HCM over the follow-up period, 8 underwent CMR, and among these patients, the extent of LGE was significantly greater than in the 60 nonobstructed HCM patients in whom systolic function remained within the normal range (27 ± 14% vs. 4 ± 5%; $p < 0.001$).

Comparison of nonobstructive versus obstructive HCM patients. Compared with patients with rest or provocable obstruction, nonobstructive patients had lower EF and smaller left atrial dimension, but larger LV cavity size, and were more likely to show LGE on contrast-enhanced CMR (Table 1). There was no significant difference between the hemodynamic subgroups with respect to age, extent of LGE, or prevalence of sarcomere protein mutations (Table 1).

TABLE 4 Univariate and Multivariate Analysis for Predictors of Progression of HF Symptoms to NYHA Functional Classes III/IV in 249 Nonobstructive HCM Patients

	Univariate Model		Multivariate Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	1.00 (0.97-1.02)	0.89		
Male	0.62 (0.28-1.40)	0.25		
LA size, mm	1.14 (1.08-1.21)	<0.001	1.09 (1.02-1.17)	**0.01**
Maximal LV thickness, mm	1.05 (0.99-1.12)	0.074		
Ejection fraction, %	0.94 (0.89-1.00)	0.048	0.98 (0.92-1.04)	0.44
Family history of sudden death	0.60 (0.21-1.76)	0.36		
Syncope	2.08 (0.86-5.02)	0.10		
NSVT, 24-h Holter	1.15 (0.39-3.42)	0.25		
History of AF	6.42 (2.79-14.74)	<0.001	1.90 (0.66-5.50)	0.23
Baseline: NYHA functional class II	4.59 (2.01-10.49)	<0.001	2.69 (1.12-6.43)	**0.03**

Bold values are statistically significant.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

ADVANCED HEART FAILURE. Progression of heart failure symptoms from classes I/II to III/IV was significantly less common in patients with nonobstructive HCM (i.e., 10%; 1.6%/year), compared with patients with rest (38%; 7.4%/year; $p < 0.001$), or provocable obstruction (20%; 3.2%/year; $p = 0.002$) (Figures 1 and 2). Seven of 249 nonobstructive patients (2.8%) with severe heart failure underwent transplantation due to severe unrelenting symptoms, a treatment intervention absent in 324 patients with outflow obstruction ($p = 0.01$). In contrast, 66 obstructive patients (20%) with advanced NYHA functional classes III/IV heart failure symptoms underwent myectomy (or, alternatively, alcohol septal ablation) and 61 (92%) improved to classes I/II.

AF before or after the initial visit occurred in 19% of patients with nonobstructive HCM, less than in those with resting obstruction (33%; $p = 0.007$), but not different from patients with provocable obstruction (23%; $p = 0.36$). Occurrence of thromboembolic stroke was similar between patients with nonobstructive (2%) and obstructive (resting 2%; provocable 1%; $p = 0.73$) HCM (Figure 1).

MORTALITY/EVENT RATES. HCM-related mortality rate in nonobstructive patients was low, 0.5%/year, with a 5- and 10-year survival rates free of HCM death of 99% and 97% (95% CI: 97% to 99% and 95% to 98%, respectively), which are not significantly different from the expected all-cause mortality in the age- and sex-matched general U.S. population ($p = 0.15$), nor different from patients with rest (0.4%/year) or provocable obstruction (0.2%/year) ($p = 0.48$) (Figure 2). In addition, considering heart transplantation as a surrogate endpoint of heart failure death, HCM-related mortality at 5 and 10 years was 98% and 90% (95% CI: 95% to 99% and 82% to 95%, respectively), and also not different from all-cause mortality in the U.S. population ($p = 0.6$). However, the low mortality event rates limit the power of statistical comparisons.

Sudden death, resuscitated out-of-hospital cardiac arrest, and appropriate ICD interventions for ventricular tachycardia/VF occurred in 5.6% (0.9%/year) of nonobstructive patients, which is also similar to patients with rest obstruction (0.6%/year) or provocable obstruction (0.8%/year; $p = 0.51$). Total mortality did not differ significantly among patients with nonobstructive HCM (0.9%/year) compared with those with rest (1.0%/year) or provocable obstruction (0.5%/year; $p = 0.39$).

DISCUSSION

Largely with the introduction of echocardiography in the 1970s, the hemodynamic spectrum of HCM expanded beyond patients with outflow tract obstruction to include those without the capacity to generate subaortic gradients (25). Initially, the nonobstructive form of HCM was characterized by the absence of an outflow gradient due to mitral valve systolic anterior motion using a variety of nonphysiological provocations, some of which date to the inception of the disease and the cardiac catheterization era, including post-premature ventricular contraction response (Brockenbrough maneuver), amyl nitrite inhalation, Valsalva maneuver, and isoproterenol or dobutamine infusion (3,4,10-13,18-23,25). However, these pharmacological and mechanical maneuvers may not reliably measure those outflow gradients that cause the symptoms and functional limitation experienced physiologically by patients during normal daily activities (3,7).

These diagnostic uncertainties have contributed to a potentially confusing circumstance in which the definition of nonobstructive HCM lacked proper standardization and definition. In addition, there has been a remarkable paucity of published papers and data specifically reporting the natural history and management of nonobstructive HCM, even after 50 years of investigation (8,11,12,14,17), particularly when compared with the obstructive HCM subgroup, for which there have been literally hundreds of publications in the last 10 years (2-4,7-9,13,18-20). Indeed, the vast majority of nonobstructive HCM patients appear to have been, in part, ignored within the HCM management discourse, seemingly overwhelmed by a disproportionate focus on the highly visible LV

outflow gradients and associated major management considerations for obstruction (2-4,14-17,26,27), particularly after the introduction of alcohol septal ablation and the myectomy versus ablation debate (27). Indeed, the visibility of nonobstructive disease has historically seemed greatest only in the context of heart transplantation (28-32).

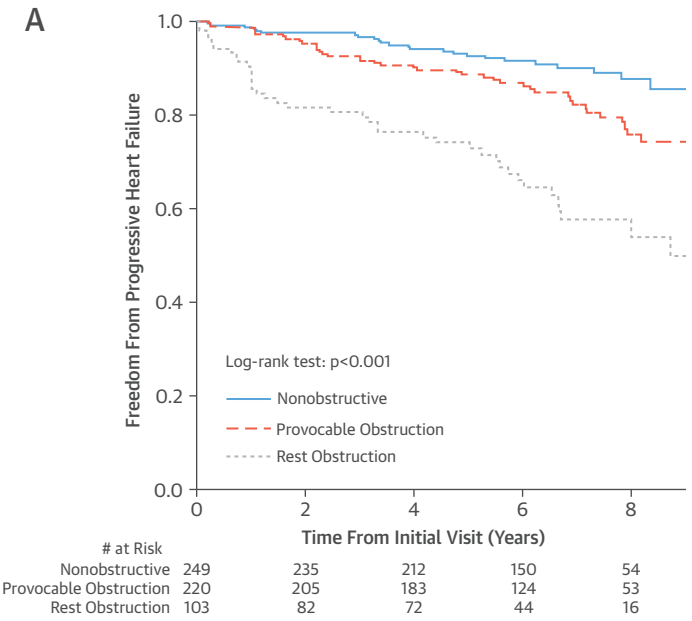
Since 2003, in our 3 centers, we have relied routinely on exercise (stress) echocardiography to induce outflow tract gradients physiologically in those HCM patients without evidence of subaortic obstruction at rest (7). In the process, we believe that we have achieved a more relevant definition of the important subpopulation of nonobstructive patients and, in the process, created an opportunity to clarify the natural history of HCM (**Central Illustration**).

However, in order to permit a true prospective assessment of outcome and development of limiting symptoms among nonobstructive HCM patients, we excluded from the primary study cohort those patients already in classes III/IV at presentation to the participating centers. These nonobstructive HCM patients were preferentially referred for consideration of advanced heart failure management, an observation supported by the fact that about one-third of these patients soon underwent (or were listed for) heart transplantation (Online Table). Therefore, including such highly selected, referral-based patients would not permit a reliable prospective assessment of the heart failure burden among patients with nonobstructive HCM.

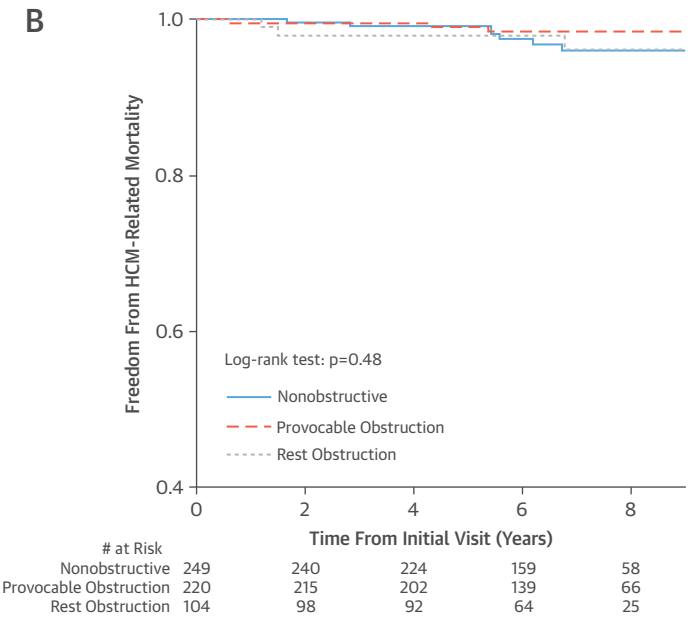
Indeed, on the basis of the present data, over our longitudinal follow-up period we found the HCM-related clinical course to be largely favorable in nonobstructive HCM. Specifically, 90% of these patients experienced little or no functional disability, remaining asymptomatic or mildly symptomatic and, as a group, at low risk for progressive heart failure to NYHA functional classes III/IV (1.6%/year), and with only a small subset developing AF after the initial visit.

In contrast, patients with outflow obstruction had 5-fold greater risk for developing such debilitating symptoms and, notably, >90% of these obstructive patients achieved marked improvement in heart failure symptoms following relief of the subaortic gradient and normalization of LV pressures with myectomy (or, alternatively, alcohol septal ablation). This observation underscores the principle that heart failure due to outflow obstruction is a treatable (and reversible) complication of HCM for which there is also a survival benefit (2,3,14). The fact that 20% of our patients with obstruction benefited clinically from septal reduction therapy (33% with rest obstruction) explains, in part, our failure to show a

FIGURE 2 Risk of Heart Failure and HCM-Related Mortality



# at Risk					
Nonobstructive	249	235	212	150	54
Provocable Obstruction	220	205	183	124	53
Rest Obstruction	103	82	72	44	16



# at Risk					
Nonobstructive	249	240	224	159	58
Provocable Obstruction	220	215	202	139	66
Rest Obstruction	104	98	92	64	25

Kaplan-Meier survival curves in 573 HCM patients with comparisons between subgroups. **(A)** Probability of progression to advanced heart failure symptoms (NYHA functional classes III/IV), comparing the nonobstructive with rest and provocable obstructive groups. **(B)** HCM-related mortality comparing nonobstructive with rest and provocable obstruction groups. Of note, survival in obstructive groups is enhanced by a significant proportion who were treated successfully with surgical myectomy or, alternatively, with alcohol septal ablation (i.e., 31% of rest obstruction; 15% of provocable obstruction). Abbreviations as in **Figure 1**.

difference in HCM-related survival between nonobstructive and obstructive patients.

However, we have also identified a small subset of nonobstructive HCM patients (4% of our cohort) who developed progressive and unrelenting heart failure symptoms refractory to pharmacological treatment and who required (or were considered for) heart transplantation as the only available therapeutic option with the potential to restore acceptable quality of life. These transplant candidates constituted 2 distinct subgroups including those with impaired systolic function and various degrees of adverse LV remodeling (i.e., regression of hypertrophy and ventricular chamber enlargement due to diffuse LV scarring) (28–31), as well as patients with preserved EF demonstrating little or no remodeling (29,32,33). Indeed, these latter patients represent a novel subgroup with nonobstructive disease, given that a surprisingly large proportion of HCM transplant candidates in this cohort (i.e., 50%) did not meet our arbitrary EF cutoff for systolic dysfunction.

Those patients who develop advanced progressive heart failure, despite preserved systolic function, expand the spectrum of end-stage heart failure beyond LV systolic dysfunction. Of note, the choice to pursue transplantation in HCM patients with class III symptoms and preserved systolic function is challenging and requires taking into account individual clinical profiles (including results of metabolic exercise testing and invasive hemodynamic data), but ultimately with the greatest weight is given to the clinical history and symptom profile. The basis of the decision to offer heart transplantation to such patients is the recognition that this is the only therapeutic option capable of restoring an acceptable quality of life and longevity to this subgroup of patients (32,33).

Contributing to the low mortality in nonobstructive HCM patients (0.5%/year) was the infrequency of sudden death, attributable to contemporary risk stratification, which has proved effective at identifying high-risk patients who may benefit from ICD therapy (2–4,34–37). Notably, 10 of our patients with nonobstructive HCM had potentially lethal ventricular tachyarrhythmias terminated appropriately by device therapy. Furthermore, of the 3 patients who died suddenly, 2 had declined the ICD, even after receiving a standard recommendation for prophylactic device therapy, and 1 died after his mechanically defective ICD failed to terminate VF. If these 3 patients had elected to undergo ICD therapy (or had an unimpaired device), the HCM-related mortality rate for nonobstructive HCM patients would have been only 0.3%/year.

STUDY LIMITATIONS. Because the present study period largely predated the systematic incorporation of contrast-enhanced CMR into HCM practice, we did not have sufficient data to determine whether LGE was an independent determinant of progressive heart failure in nonobstructive patients as a group. Nevertheless, the amount of LGE at study entry was significantly greater among patients without obstruction who developed advanced heart failure symptoms, an observation consistent with previous reports, which identified extensive LGE as a reliable marker for future development of the end-stage phase (24). Therefore, close longitudinal follow-up for those nonobstructive patients with substantial LGE is prudent, in order to anticipate development of limiting symptoms and/or systolic dysfunction.

CONCLUSIONS

HCM patients without the capacity to physiologically generate LV outflow obstruction, comprising about one-third of the broad HCM hemodynamic spectrum, appear at relatively low risk for developing most HCM-related complications, including progressive drug-refractory heart failure, sudden death, or embolic stroke, and with an HCM-related mortality rate of 0.5%/year (albeit with a small risk for heart transplantation). These novel data complete a significant gap in our understanding of the overall clinical spectrum and natural history of HCM, which is currently dominated by outflow obstruction and its highly visible treatment modalities. In turn, the present observations offer a measure of reassurance to HCM patients with nonobstructive disease.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Nonobstructive HCM carries a relatively low risk of disease-related adverse events, advanced heart failure symptoms, or need for major treatment interventions such as cardiac transplantation.

TRANSLATIONAL OUTLOOK: Further work is necessary to identify specific clinical features that predict progressive heart failure in patients with nonobstructive HCM.

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KEY WORDS heart failure, heart transplant, sudden death

APPENDIX For supplemental material, please see the online version of this article.