

## Syncope and Risk of Sudden Death in Hypertrophic Cardiomyopathy

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**Background**—The prognostic significance of syncope has not been investigated systematically in hypertrophic cardiomyopathy, and treatment strategies have been based largely on intuition and experience.

**Methods and Results**—We assessed the relationship between syncope and sudden death in 1511 consecutive patients with hypertrophic cardiomyopathy. Unexplained (n=153) or neurally mediated (n=52) syncope occurred in 205 patients (14%). Over a 5.6±5.2-year follow-up, 74 patients died suddenly. Relative risk of sudden death was 1.78 (95% confidence interval 0.88 to 3.51,  $P=0.08$ ) in patients with unexplained syncope and 0.91 (95% confidence interval 0.00 to 3.83,  $P=1.0$ ) in those with neurally mediated syncope compared with patients without syncope. In multivariable analysis, the temporal proximity of unexplained syncope to initial patient evaluation was independently associated with risk of sudden death ( $P=0.006$ ). Patients with unexplained syncope within 6 months before the initial evaluation showed a 5-fold increase in risk compared with patients without syncope (adjusted hazard ratio 4.89, 95% confidence interval 2.19 to 10.94), a relationship that was maintained throughout all age groups (<18, 18 to 39, and ≥40 years). Older patients (≥40 years of age) with remote episodes of syncope (>5 years before initial evaluation) did not show an increased risk of sudden death (adjusted hazard ratio 0.38, 95% confidence interval 0.05 to 2.74).

**Conclusions**—In the present large cohort of patients with hypertrophic cardiomyopathy, unexplained syncope was a risk factor for sudden death. Patients with syncopal events that occurred in close temporal proximity to the initial evaluation showed a substantially higher risk of sudden death than patients without syncope. Older patients with remote syncopal events did not show an increased risk. (*Circulation*. 2009;119:1703-1710.)

**Key Words:** syncope ■ death, sudden ■ cardiomyopathy, hypertrophic

A syncopal episode of unexplained origin is often regarded as a marker of high risk for sudden death and a criterion for prophylactic implantation of a cardioverter-defibrillator (ICD) in patients with hypertrophic cardiomyopathy (HCM).<sup>1-6</sup> Nevertheless, 50 years after the first modern description of this disease, the prognostic implications of syncope in HCM have not been addressed systematically in sufficiently large patient populations. Therefore, in proposing management recommendations for HCM patients with syncope, recent expert consensus guidelines have relied largely on clinical intuition rather than data-based evidence.<sup>1,7</sup>

mechanisms that are potentially responsible for this symptom,<sup>8-12</sup> the infrequency of syncopal episodes, and the low rate of sudden death in the disease, as well as the relatively uncommon occurrence of HCM in cardiological practice.<sup>3-5,13,14</sup> Because of these issues, we have investigated the clinical implications of syncope in an HCM cohort of >1500 patients followed up over a substantial period of time.

### Methods

#### Study Population

A total of 1511 consecutive patients with HCM, evaluated between 1983 and 2005 at the Ente Ospedaliero Ospedali Galliera (Genoa, Italy), University “La Sapienza” (Rome, Italy), University of Bologna (Bologna, Italy), Tufts–New England Medical Center (Boston, Mass), Ospedale Rivoli (Torino, Italy), and Minneapolis Heart Institute Foundation (Minneapolis, Minn), were enrolled in the

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Major obstacles to assessment of the prognostic significance of syncope in HCM arise from the diversity of

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**Table 1. Characteristics of the 1511 HCM Study Patients at Initial Evaluation, According to Presence or Absence of a History of Syncope**

Variable	Overall Patient Population	Patients With Unexplained Syncope	Patients With Neurally Mediated Syncope	Patients Without Syncope	<i>P</i> *
No. of patients	1511	153	52	1306	
Age, y, mean±SD (median)	46±19.7 (47)	47±18.9 (47)	51±17.0 (56)	46±19.9 (47)	0.12†
Male sex, n (%)	927 (61)	85 (56)	25 (48)	817 (63)	0.03†§
Family history of sudden death, n (%)	288 (19)	36 (24)	17 (33)	235 (18)	0.01†§
NYHA functional class III or IV, n (%)	168 (11)	20 (13)	10 (19)	138 (11)	0.09†§
LVOT obstruction, n (%)	442 (29)	53 (35)	16 (31)	373 (29)	0.29†§
Maximal LV wall thickness, mm, mean±SD	20±5.5	22±6.1	20±4.6	20±5.5	<0.001†
Extreme LV wall thickness (≥30 mm), n (%)	111 (7)	16 (10)	2 (4)	93 (7)	0.20‡
LV end-diastolic cavity dimension, mm, mean±SD	45±7.1	44±6.6	46±6.9	45±7.1	0.19†
Left atrial dimension, mm, mean±SD	43±8.5	45±8.1	45±7.4	43±8.5	0.008†
Treatment, n (%)					
None	489 (32)	26 (17)	16 (31)	447 (34)	<0.001†
β-Blockers	616 (41)	70 (46)	26 (50)	520 (40)	0.14†
Calcium antagonists	380 (25)	57 (37)	14 (27)	309 (24)	0.001†
Amiodarone	97 (6)	14 (9)	7 (13)	76 (6)	0.03†
Diuretics	182 (12)	25 (16)	11 (21)	146 (11)	0.02†

NYHA indicates New York Heart Association; LV, left ventricular; and LVOT, LV outflow tract.

\**P* values refer to differences among 3 groups (patients with unexplained syncope, patients with neurally mediated syncope, and patients without syncope).

†One-way ANOVA.

‡Fisher exact test.

§ $\chi^2$  Test for heterogeneity.

study. Initial evaluation (baseline) was defined as the time of first visit to an institution participating in the study.

### Definitions of Syncope and Sudden Death

Syncope was defined as a sudden and brief loss of consciousness associated with a loss of postural tone and a spontaneous recovery.<sup>15,16</sup> At the participating HCM referral centers, detailed descriptions of the features and circumstances related to each syncopal event were systematically obtained from each patient, and syncope was classified as follows: (1) "Neurally mediated" (also termed "neurocardiogenic" or "vasovagal") when it occurred in circumstances that may lead to reflex-mediated changes in vascular tone or heart rate, such as a rapid change in posture, emotion, micturition, defecation, cough, or other similar conditions<sup>7,15,17</sup>; and (2) "unexplained" (of unknown origin) when it occurred in circumstances not clearly consistent with a neurally mediated event, ie, without apparent explanation at rest or during ordinary daily activities, or during an intense effort.<sup>7,15–18</sup> Unexplained syncope was classified as "recurrent" when 2 or more of such episodes occurred. None of the patients in the present study had syncopal episodes due to diseases other than HCM, such as epilepsy or pulmonary embolism, or due to clearly documented bradyarrhythmias or supraventricular tachyarrhythmias.

Sudden cardiac death was defined as natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour of the onset of acute symptoms.<sup>19,20</sup> Death was also classified as sudden if it occurred unexpectedly but was unwitnessed, such as in bed overnight.<sup>21,22</sup> Ventricular fibrillation during follow-up, either interrupted by the discharge of an ICD or documented at the time of aborted cardiac arrest, was regarded as equivalent to sudden death.<sup>23</sup>

### Diagnosis and Evaluation

The diagnosis of HCM was based on echocardiographic demonstration of a hypertrophied and nondilated left ventricle (LV; wall thickness  $\geq 15$  mm in adults, or the equivalent relative to body surface area in children) in the absence of another cardiac or systemic disease that could produce a comparable magnitude of LV hypertrophy.<sup>21</sup> The greatest thickness measured at any site in the LV wall was considered to represent the maximal wall thickness.<sup>21</sup> LV end-diastolic cavity and left atrial dimensions were assessed from the derived M-mode echocardiogram. LV outflow tract obstruction was considered present when the peak instantaneous outflow gradient estimated by continuous-wave Doppler was  $\geq 30$  mm Hg under basal conditions.<sup>22,24</sup>

### Statistical Analysis

To calculate mortality rates, the number of patients who died during follow-up was divided by the total number of person-years accumulated during follow-up in the study population or in each subgroup. For calculation of overall rates of death, follow-up time was considered to be the interval from the initial evaluation to death or, in surviving patients, to most recent evaluation. For calculation of cause-specific mortality rates, follow-up data for patients who died of causes other than HCM were censored at death; 95% confidence intervals (CIs) for mortality rates were calculated with the assumption of an underlying Poisson distribution of rare events. Rates were compared among subgroups of patients by  $\chi^2$  test for heterogeneity, Fisher test, or the  $\chi^2$  test for trend, as appropriate. Survival curves were constructed according to the Kaplan–Meier method.

**Table 2. Overall and Cause-Specific Mortality According to Different Categories of Syncope**

Variable	Death Due to Any Cause				HCM-Related Death (Sudden Death, HF, or Stroke)				Sudden Death			
	No. of Deaths (%)	Incidence per 1000 Person-Years (95% CI)	Relative Risk (95% CI)	P	No. of Deaths (%)	Incidence per 1000 Person-Years (95% CI)	Relative Risk (95% CI)	P	No. of Sudden Deaths (%)	Incidence per 1000 Person-Years (95% CI)	Relative Risk (95% CI)	P
Without syncope (n=1306)	182 (14)	24.6 (21.2–28.5)	1 (Reference)		131 (10)	17.7 (14.8–21.0)	1 (Reference)		61 (5)	8.2 (6.3–10.6)	1 (Reference)	
Unexplained syncope (n=153)	22 (14)	29.4 (18.4–44.5)	1.19 (0.74–1.90)	0.44	15 (10)	20.0 (11.2–33.0)	1.13 (0.64–1.97)	0.65	11 (7)	14.7 (7.3–26.2)	1.78 (0.88–3.51)	0.08
Unexplained and recurrent syncope* (n=63)	10 (16)	34.6 (16.6–63.6)	1.41 (0.69–2.67)	0.30	6 (10)	20.8 (7.6–45.2)	1.18 (0.47–2.76)	0.70	3 (5)	10.4 (2.1–3.4)	1.26 (0.32–4.15)	0.52†
Neurally mediated syncope (n=52)	10 (19)	37.8 (18.1–69.4)	1.53 (0.76–3.02)	0.19	8 (15)	30.2 (13.1–59.5)	1.71 (0.77–3.60)	0.14	2 (4)	7.6 (0.9–27.2)	0.91 (0.00–3.83)	1.0†

HF indicates heart failure.

\*These 63 patients represent a subgroup of the 153 patients with unexplained syncope.

†Fisher exact test.

To assess the role of a history of syncope as an independent predictor of death due to any cause or sudden death, a set of multivariate Cox proportional-hazards models were fitted to the data. The following variables were included as covariates in all models: Age at initial evaluation (3 categories: <18, 18 to 39, and ≥40 years old), family history of sudden death, New York Heart Association functional class, magnitude of LV wall thickness, LV outflow obstruction, end-diastolic cavity dimension, and left atrial cavity dimension. Only episodes that occurred before the first evaluation were considered, and a history of syncope was included in the model as a binary variable (yes=1, no=0). Interaction between each of the variables retained in the final model and syncope was assessed by evaluation of the change in the likelihood of the model when the appropriate interaction term was introduced. In a subsequent analysis, patients with a history of syncope were subgrouped according to the time interval between the most recent episode of unexplained syncope and initial evaluation, and the risk of sudden death was compared in the patient subgroups by use of the statistical models reported above. The small number of patients and events in the subgroup with recent syncope did not permit us to support or refute the proportionality assumption, although inspection of the log plot of –log cumulative survival against time failed to provide evidence of a major departure from proportionality.

In each of the models used in the statistical analyses, all variables were initially included as covariates, and those not significantly ( $P>0.10$ ) associated with outcome were removed from the model in a stepwise procedure based on the likelihood ratio test. All  $P$  values are 2-sided. SPSS statistical software (SPSS, Chicago, Ill) was used for most calculations.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Baseline Clinical Characteristics and Follow-Up

At initial evaluation, 153 patients had a prior history of unexplained syncope (118 at rest or during ordinary activity and 35 during intense effort), 52 had syncope with features consistent with neurally mediated origin, and 1306 did not have a history of syncope. Baseline characteristics of these patients are summarized in Table 1.

Mean follow-up was  $5.6\pm 5.2$  years (median 4.0 years) in the 1511 HCM patients and was similar in patients with and without syncope ( $4.9\pm 4.5$  and  $5.7\pm 5.2$  years, respectively;  $P=0.26$ ). During follow-up, 214 study patients (14%) died, 74 of sudden death, 54 of heart failure, 26 of stroke-related death, and 60 of non-HCM causes. Incidence of death was as follows: Any cause, 25.4/1000 person-years; total HCM-related death, 18.3/1000 person-years; and sudden death, 8.8/1000 person-years. Age at time of sudden death was  $42.2\pm 18.5$  years.

Of the 1511 study patients, 98 (6%) received an ICD, 58 of which were implanted during follow-up. Of these 98 patients, 5 received 1 or more appropriate ICD interventions for ventricular fibrillation during follow-up. Of the 98 patients with ICDs, 29 had a history of unexplained syncope before ICD implantation, including 4 in whom syncope was the sole risk factor. Of these 29 patients with ICDs and unexplained syncope, 4 (14%) received 1 or more appropriate ICD interventions (3 for ventricular tachycardia and 1 for ventricular fibrillation). Of the 4 patients with unexplained syncope as a sole risk factor, 1 received an appropriate ICD intervention for ventricular tachycardia after 4 years of follow-up.

### Syncope and Mortality

Compared with the 1306 patients without syncope, the relative risk of sudden death was 1.78 (95% CI 0.88 to 3.51,  $P=0.08$ ) in the 153 patients with unexplained syncope and 0.91 (95% CI 0.00 to 3.83,  $P=1.0$ ) in the 52 with neurally mediated syncope (Table 2). The relative risk of sudden death in the 63 patients with recurrent unexplained syncope was 1.26 (95% CI 0.32 to 4.15,  $P=0.52$ ).

### Multivariable Regression Analysis

In a set of multivariable Cox proportional-hazard models, age, LV wall thickness, and left atrial size were independently associated with sudden death. Unexplained syncope

**Table 3. Results of Multivariable Cox Proportional-Hazards Analysis of the Relation Between Base-line Clinical Variables and Risk of Death**

Variable	Death Due to Any Cause (214 Events)			HCM-Related Death (154 Events)		Sudden Death (74 Events)	
	No. of Patients†	Relative Risk (95% CI)	<i>P</i>	Relative Risk (95% CI)	<i>P</i>	Relative Risk (95% CI)	<i>P</i> ‡
Age, y			0.29		0.41		0.001
<18	145	*		*		1 (Reference)	
18–39	408	...		...		0.59 (0.30–1.15)	
≥40	947	...		...		0.30 (0.15–0.59)	
Sex			0.001		0.01		0.65
Males	921	1 (Reference)		1 (Reference)		*	
Females	579	1.66 (1.25–2.20)		1.53 (1.09–2.15)		...	
Family history of sudden death			0.29		0.46		0.12
No	1217	*		*		*	
Yes	283	...		...		...	
NYHA functional class			<0.001		<0.001		0.56
I–II	1333	1 (Reference)		1 (Reference)		*	
III–IV	167	2.19 (1.50–3.19)		2.48 (1.60–3.85)		...	
Unexplained syncope			0.77		0.96		0.09
No	1348	1 (Reference)		1 (Reference)		1 (Reference)	
Yes	152	1.07 (0.69–1.66)		1.02 (0.60–1.73)		1.75 (0.91–3.37)	
LVOT obstruction			0.02		0.22		0.29
No	1061	1 (Reference)		*		*	
Yes	439	1.40 (1.05–1.86)		...		...	
LV wall thickness, mm			0.03		<0.001		0.06
Up to 10	19	1 (Reference)		1 (Reference)		1 (Reference)	
11–15	249	0.56 (0.07–4.37)		0.25 (0.30–2.06)		0.38 (0.04–3.36)	
16–19	455	0.88 (0.12–6.58)		0.57 (0.07–4.32)		0.79 (0.10–6.47)	
20–24	490	0.83 (0.11–6.21)		0.55 (0.07–4.21)		0.81 (0.10–6.54)	
25–29	177	0.98 (0.13–7.47)		0.72 (0.09–5.62)		0.93 (0.11–7.88)	
30–34	80	1.69 (0.22–13.07)		1.48 (0.19–11.62)		2.05 (0.24–17.28)	
≥35	30	1.94 (0.21–17.87)		1.67 (0.18–15.45)		0.66 (0.04–11.20)	
LVED dimension, mm (continuous variable)	1500	1.02 (1.00–1.04)	0.08	1.02 (1.00–1.04)	0.12	*	0.20
LA dimension, mm (continuous variable)	1500	1.03 (1.01–1.05)	<0.001	1.03 (1.02–1.05)	<0.001	1.03 (1.00–1.06)	0.04

LA indicates left atrial; LVED, LV end-diastolic; LVOT, LV outflow tract; and NYHA, New York Heart Association.

\*Removed from the final model ( $P>0.1$ ).

†The analysis was performed in 1500 of the 1511 study patients because in 11 patients, an echocardiographic variable was not available (left atrial dimension).

‡For variables removed from the final model, the *P* value is based on a log-likelihood test for reinclusion in the final model.

was associated with an increase in the risk of sudden death similar to that observed in the univariate analysis (relative risk 1.75, 95% CI 0.91 to 3.37,  $P=0.09$ ; Table 3). However, an interaction was found between unexplained syncope and age with regard to the risk of sudden death ( $P=0.052$ ), with unexplained syncope showing a strong effect on sudden death risk in patients <18 years of age (hazard ratio 8.01, 95% CI 2.07 to 31.45,  $P=0.003$ ).

LV outflow obstruction under basal conditions (gradient  $\geq 30$  mm Hg) was not independently associated with sudden death ( $P=0.29$ ). No interaction was found between unexplained syncope and outflow obstruction with regard to the risk of sudden death ( $P=0.09$ ). Syncope during intense effort occurred more frequently in patients with outflow obstruction

than in patients without obstruction (17 [3.8%] of 442 and 18 [1.7%] of 1069, respectively;  $P=0.01$ ). Conversely, unexplained syncope at rest or during ordinary activity occurred with similar frequency in patients with and without outflow obstruction ( $P=0.75$ ), as did neurally mediated syncope ( $P=0.81$ ).

### Proximity of Syncope to Initial Evaluation and Sudden Death Risk

In univariate analysis and in a multivariable model (with age, maximal LV wall thickness, and left atrial dimension included as covariates), the time interval between unexplained syncope and initial evaluation was strongly associated with the risk of sudden death ( $P=0.004$  and  $P=0.006$ , respec-

**Table 4. Multivariable Analysis of the Prognostic Importance of the Time Interval Between Unexplained Syncope and Initial Patient Evaluation at the Participating Institutions**

Variable	No. of Patients†	Sudden Death Events (n=73),* Hazard Ratio (95% CI)	P
Age, y			0.001
<18	145	1 (Reference)	
18–39	408	0.63 (0.32–1.22)	
≥40	947	0.29 (0.15–0.57)	
LV wall thickness, mm			0.04
≤10	19	1 (Reference)	
11–15	249	0.34 (0.04–3.09)	
16–19	455	0.71 (0.09–5.84)	
20–24	490	0.71 (0.09–5.84)	
25–29	177	0.92 (0.11–7.96)	
30–34	80	1.95 (0.23–16.68)	
≥35	30	0.51 (0.03–8.71)	
Left atrial dimension, mm (continuous variable)	1500	1.03 (1.00–1.05)	0.04
Time between unexplained syncope and first patient evaluation			0.006
Without unexplained syncope‡	1349	1 (Reference)	
≤6 mo	53	4.89 (2.19–10.94)	
>6 to 12 mo	16	0 (No events)	—
>1 to ≤2 y	13	2.01 (0.27–14.80)	
>2 to 5 y	19	1.04 (0.14–7.57)	
>5 y	50	0.38 (0.05–2.74)	

\*The analysis was performed in 73 of the 74 patients with sudden death because the date of the most recent syncopal event was not available in 1 patient.

†The analysis was performed in 1500 of the 1511 study patients because in 11 patients, an echocardiographic variable was not available (left atrial dimension).

‡All study patients without unexplained syncope, including those with neurally mediated syncope.

tively; Table 4). Patients with recent unexplained syncope (within 6 months before initial evaluation) showed a 5-fold increase in risk compared with patients without syncope (adjusted hazard ratio 4.89, 95% CI 2.19 to 10.94; Table 4). Patients with remote episodes of unexplained syncope (>5 years before initial evaluation) did not demonstrate an increased risk of sudden death compared with patients without syncope (adjusted hazard ratio 0.38, 95% CI 0.05 to 2.74; Table 4). Kaplan–Meier estimates of the proportion of patients with sudden death in the subgroups with a syncopal event at various time intervals from initial evaluation (from ≤6 months to >5 years) and in the group without syncope are shown in Figure 1. Patients with recent unexplained syncope (within 6 months before initial evaluation) also showed an increased sudden death risk throughout all age groups (<18, 18 to 39, and ≥40 years old). Conversely, older patients (≥40 years old) with more distant episodes of syncope did not have an increased risk of sudden death risk (Figure 2; Table 4). No significant differences were found between the 53 patients with recent syncope (within 6 months before initial evaluation) and the 99 patients with more distant syncopal events (>6 months before evaluation) with regard to age, gender, magnitude of LV wall thickness, prevalence of extreme LV hypertrophy (≥30 mm), family history of sudden death, New

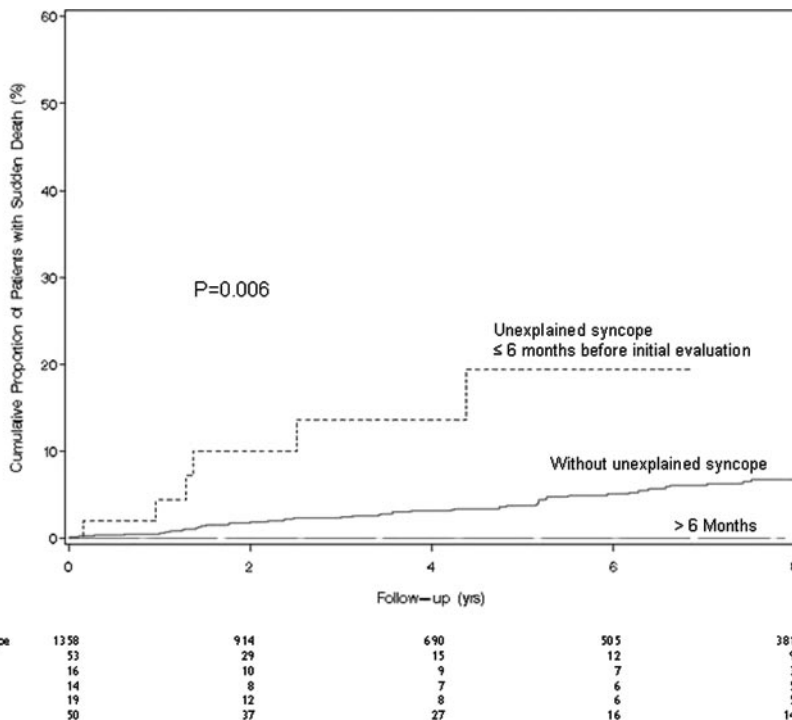
York Heart Association functional class, prevalence of LV outflow obstruction, left atrial size, or the characteristics of the index syncopal episode (ie, the proportion of syncopal events that occurred at rest versus events during intense efforts;  $P \geq 0.1$ ).

### Syncope in Young Patients

Of the 1511 study patients, 147 (10%) were <18 years of age (range <1 to 17 years, mean  $10.8 \pm 5.5$  years). During a follow-up of  $6.5 \pm 5.7$  years, 15 (10%) of these 147 patients died suddenly, and 1 died of heart failure; sudden death incidence was 15.7/1000 person-years (95% CI 8.8 to 25.9). Of the 147 patients, 7 (5%) had experienced unexplained syncope before initial evaluation, including 5 at rest and 2 during intense effort ( $13.6 \pm 3.2$  years of age). Of these 7 young patients with unexplained syncope, 3 died suddenly, and each was in New York Heart Association functional class I. Two of these 3 patients had none of the generally accepted HCM risk factors other than unexplained syncope,<sup>1</sup> and the remaining patient had a family history of sudden death (his only sibling died suddenly at the age of 12 years).

In these 7 patients <18 years of age with unexplained syncope, mortality for sudden death was 120/1000 person-years (95% CI 24.4 to 351.4) compared with 13/1000 person-years (95% CI 6.7 to 22.6) in the 140 patients without





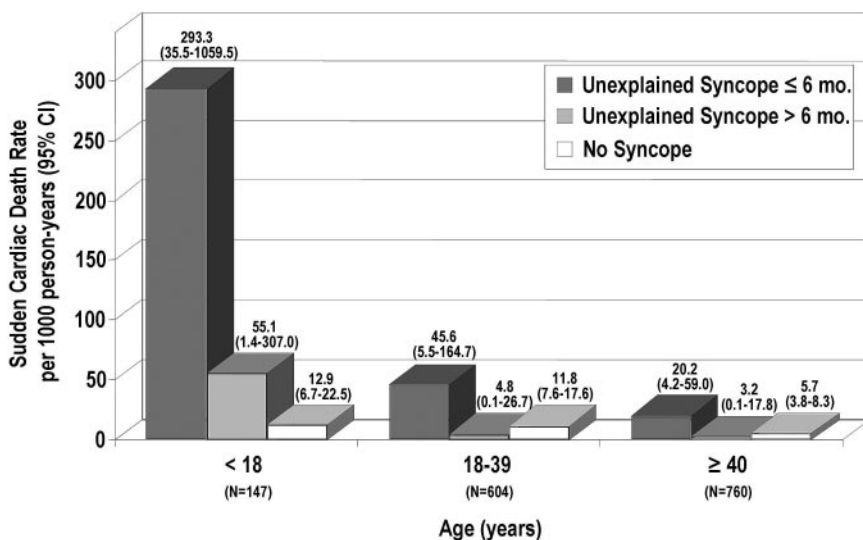
**Figure 1.** Kaplan–Meier estimates of the proportion of patients with sudden death in subgroups with different temporal proximity of unexplained syncopal events to initial evaluation and in patients without unexplained syncope. In the 4 subgroups with syncope >6 months before initial evaluation (reported in Table 4), sudden death events were uncommon, and overlapping survival curves are shown as a single curve.

unexplained syncope ( $P=0.006$ ). Cumulative risk of sudden death for these patients reached 60% at 5 years after initial evaluation.

### Discussion

Syncope is regarded as one of the most difficult clinical presentations in patients with HCM.<sup>1–4</sup> The selection of the most appropriate treatment strategy in patients with syncope has been an even greater challenge since the ICD was proved to be highly effective in preventing sudden death in this disease.<sup>5,6</sup> The present study represents the first systematic investigation of the prognosis of syncope in HCM. We

assembled a cohort of >1500 HCM patients in an effort to clarify the prognostic implications of syncope. We used a strict definition of syncope that included only syncopal events associated with a true loss of consciousness, thereby excluding presyncope and near-syncope. Approximately 15% of our patients had a history consistent with either neurally mediated syncope (also termed “neurocardiogenic” or “vasovagal”) or unexplained syncope (ie, of unknown origin). In the overall study population, neurally mediated syncope was not associated with increased risk of sudden death, and unexplained syncope was associated with a 1.78 relative risk and was of borderline statistical significance ( $P=0.08$ ). Given the diver-



**Figure 2.** Risk of sudden death in relation to age and temporal proximity of unexplained syncope to initial evaluation. Risk of sudden death was increased in all age groups with recent syncope ( $\leq 6$  months). Conversely, risk of sudden death was not increased in adult patients ( $\geq 40$  years old) with more distant syncopal events.

sity of mechanisms potentially responsible for syncope in HCM and the heterogeneity of the disease, we regard this relationship between unexplained syncope and sudden death as clinically relevant. In contrast to previous assumptions,<sup>1-3</sup> recurrent episodes of unexplained syncope did not increase the magnitude of sudden death risk.

When the temporal proximity of unexplained syncope to initial patient evaluation was taken into account, the timing of the event proved to be important. Patients with a recent unexplained syncope (within 6 months before initial evaluation) had a relative risk of sudden death 5-fold higher than patients without syncope, a relationship that was maintained throughout all age groups. This finding supports the clinical intuition of granting stronger prognostic weight to recent unexplained syncopal events, thereby justifying consideration for prophylactic ICD implantation in patients with a history of recent syncope. Of note, a syncopal event within 6 months before the patient's initial evaluation conveyed a long-term increase in risk, because the increase in sudden death rate in patients with recent syncope lasted well beyond a 6-month follow-up (as shown by the survival curve). This finding suggests that particular clinical features of individual patients or characteristics of the syncopal event may have prompted earlier clinical assessment. Thus, HCM patients evaluated soon after an unexplained syncope may represent a selected group at higher risk. The retrospective design of the present study and the small number of events prevented us from confirming this hypothesis.

In contrast to recent syncope, remote episodes of syncope (>5 years before initial evaluation) showed no association with sudden death in older patients. This observation is consistent with the clinical reticence to confer important prognostic implications to a syncopal event that has occurred many years earlier. Because of the wide confidence limits in some patient subgroups, we could not assess the prognostic significance of syncopal episodes within the time frame between recent and remote syncope. Therefore, assessment of the prognostic implications of such syncopal events will continue to rely on the judgment of the managing physician on a case-by-case basis, depending on the patient's overall clinical profile.

The decision to implant an ICD becomes particularly difficult in HCM patients without risk factors other than a recent episode of unexplained syncope. However, in a multicenter study of >500 HCM patients with ICDs, one third of the primary prevention patients with appropriate device interventions for ventricular fibrillation/rapid ventricular tachycardia had been implanted prophylactically on the basis of the presence of only 1 risk factor.<sup>6</sup> Patients who received ICDs with unexplained syncope as the sole risk marker had a 5% annual rate of appropriate interventions compared with an annual rate of 3.5% in the overall study group with primary prevention ICDs.<sup>6</sup> Therefore, the present findings offer additional support for ICD implantation in HCM patients with a recent episode of unexplained syncope as the only marker of increased risk.

The prognostic significance of syncope was also influenced by young age. Although only a small minority of patients <18 years of age in the present study cohort

experienced unexplained syncope (5%), an important proportion of these patients died suddenly during follow-up, with a 60% cumulative risk of sudden death at 5 years. Therefore, the present findings indicate that syncope of unknown origin in adolescents with HCM is predictive of high-risk status, an observation consistent with prior clinical perception.<sup>1</sup> However, given the small number of children and adolescents with unexplained syncope in the present cohort, we advise a measure of caution in interpreting the level of risk for this age group.

Although LV outflow obstruction has been regarded as a potential mechanism for syncope in HCM,<sup>2-4,25</sup> these 2 variables were unrelated in the present study population. However, syncope during effort was significantly more common in patients with LV outflow obstruction than in patients without obstruction, whereas unexplained syncope at rest and neurally mediated syncope showed no relation to obstruction. These findings suggest that syncope may have a hemodynamic basis in some patients with outflow obstruction.

In conclusion, in the present HCM overall cohort, unexplained syncope was a marker for increased risk of sudden death; however, the temporal proximity of syncopal events to patient evaluation proved to be clinically relevant. Recent unexplained syncope was associated with an increased risk for sudden death in all age groups compared with patients without syncope and may justify consideration for prophylactic implantation of a cardioverter-defibrillator. Conversely, remote episodes of syncope were not associated with increased risk in older patients.

## Disclosures

None.

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### CLINICAL PERSPECTIVE

In patients with hypertrophic cardiomyopathy, syncope can be neurally mediated or a warning of dangerous arrhythmias or hemodynamic impairment, but its prognostic significance is not clearly established. We assessed the relationship between syncope and sudden death in 1511 consecutive hypertrophic cardiomyopathy patients; 205 (14%) had a history of unexplained or neurally mediated syncope. Over a 5.6-year mean follow-up, 74 patients died suddenly. Unexplained syncope but not neurally mediated syncope was associated with an increased risk of sudden death (hazard ratio 1.78,  $P=0.08$  compared with patients without syncope). Temporal proximity of unexplained syncope to initial patient evaluation was important. Patients with recent unexplained syncope ( $\leq 6$  months before initial evaluation) showed a 5-fold increase in risk compared with patients without syncope, a relationship that was maintained throughout all age groups. In adolescents, unexplained syncope was associated with a 60% cumulative risk at 5 years. Older patients ( $\geq 40$  years) with remote syncope ( $> 5$  years before initial evaluation) showed no increased sudden death risk. Thus, unexplained syncope is a marker for increased risk in hypertrophic cardiomyopathy, particularly when it occurs in close temporal proximity to patient evaluation. Remote syncopal events are not a marker of increased risk in older patients.

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## Syncope and Risk of Sudden Death in Hypertrophic Cardiomyopathy

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