Archives of Cardiovascular Disease xxx (xxxx) xxx—xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

CLINICAL RESEARCH

Management and outcomes of hypertrophic cardiomyopathy in young adults☆

Gestion et résultats de la cardiomyopathie hypertrophique chez les jeunes adultes

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Received 31 July 2020; received in revised form 29 November 2020; accepted 22 December 2020

KEYWORDS
Hypertrophic cardiomyopathy;

Summary
Background. — Management of young adults with hypertrophic cardiomyopathy (HCM) is challenging.

Abbreviations: ABPR, abnormal blood pressure response; ESC, European Society of Cardiology; GEREMY, GEnetic REgister of hypertrophic cardioMYopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVWT, left ventricular wall thickness; MACE, major adverse cardiac events; MRI, magnetic resonance imaging; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; OR, odds ratio; REMY, REgister of hypertrophic cardioMYopathy; SCD, sudden cardiac death; SVT, sustained ventricular tachycardia.

☆ Tweet: Major cardiac events, mostly arrhythmic in origin, are common at 4.4 years in young adults (16—25 years) with hypertrophic cardiomyopathy, especially if obstruction and in women in REMY, the French HCM registry.

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https://doi.org/10.1016/j.acvd.2020.12.006

Please cite this article as: É. Baron, N. Karam, E. Donal et al., Management and outcomes of hypertrophic cardiomyopathy in young adults, Arch Cardiovasc Dis, https://doi.org/10.1016/j.acvd.2020.12.006

Young;
Sudden death;
Implantable cardioverter defibrillator;
Prognosis

Aims. — To evaluate the profile of young adults (16—25 years) with HCM included in the French prospective HCM registry.
Methods. — Patients were compared according to occurrence of major adverse cardiac events (MACE), comprising sudden cardiac death (SCD) events (implantable cardioverter defibrillator [ICD] discharge, SCD, sustained ventricular tachycardia), atrial fibrillation/embolic stroke, heart failure hospitalisation and unexplained syncope, at a mean follow-up of 4.4 ± 2.2 years.
Results. — At baseline, among 61 patients (20.5 ± 3.0 years; 16 women, 26.2%), 13 (21.3%) had a prophylactic ICD, 24.6% a family history of SCD, 29.5% obstruction, 86.0% magnetic resonance imaging myocardial fibrosis, 11.8% abnormal exercise blood pressure and 52.8% a European Society of Cardiology (ESC) 5-year SCD score < 4% (24.5% ≥ 6%). At follow-up, 15 patients (24.6%; seven women; all with fibrosis) presented 17 MACE, comprising: SCD events (n = 7, 41.2%; including three patients with an ICD, five with at least one SCD major classical risk factor and an ESC score ≥ 5% and two with no risk factors and an ESC score < 4%); atrial fibrillation/stroke (n = 6, 35.3%); heart failure (n = 1, 5.9%); syncope (n = 3, 17.6%). An ICD was implanted in 11 patients (four for secondary prevention), but in only 61.5% of patients with a score ≥ 6%. Only obstruction significantly increased MACE risk (odds ratio 3.96; P = 0.035), with a non-significant trend towards a lower risk in men (OR 0.29; P = 0.065).
Conclusions. — In young adults with HCM, MACE are common in the short term, especially in obstructive HCM and women, mostly arrhythmic in origin. Prophylactic ICD implantation is frequent and does not strictly follow the guidelines, while the use of European/USA guidelines is helpful but imperfect in identifying SCD risk.

MOTS CLÉS
Cardiomyopathie hypertrophique ;
Jeune ;
Mort subite ;
Défibrillateur automatique implantable ;
Pronostic

Résumé
Contexte. — La prise en charge des jeunes adultes atteints de cardiomyopathie hypertrophique (CMH) reste difficile.
Objectifs. — Évaluer le profil des jeunes adultes (16—25 ans) atteints de CMH sarcomèrique et inclus dans le registre prospectif français des CMH.
Méthodes. — Les caractéristiques initiales ont été comparées selon la survenue à 4,4 ± 2,2 ans d'évènements cardiaques majeurs (ECM) : mort subite (MS) (décharge de défibrillateur cardiaque [DAI], MS, tachycardie ventriculaire soutenue) ; fibrillation atriale (FA) ou accident vasculaire cérébral (AVC) ; hospitalisation pour insuffisance cardiaque (IC) ; ou syncope.
Résultats. — À l'inclusion, parmi 61 patients (20,5 ± 3.0 ans ; 16 femmes, 26,2 %), 21,3 % avaient un DAI (n = 13), 24,6 % des antécédents familiaux de MS, 29,5 % une obstruction, 86.0 % une fibrose en IRM, 11,8 % une réponse tensionnelle anormale d'effort, 52,8 % un score ESC de MS à 5 ans < 4 % (24,5 % ≥ 6 %). En fin de suivi, 15 patients (24.6 % ; 7 femmes ; tous avec fibrose) avaient présenté 17 ECM : 7 MS (41,2 % ; 3 patients avec DAI, 5 avec ≥ 1 facteur de risque majeur de MS [FRM] et score > 5 %, 2 sans FRM et score < 4 %); 6 FA/AVC (35,3 %) ; 1 IC (5,9 %) ; 3 syncopes (17,6 %). Un DAI était posé chez 11 patients (4 en prévention secondaire), 61,5 % des patients avec score ≥ 6 %. Seule l'obstruction augmentait le risque d'ECM (OR 3,96 ; p = 0,035), avec une tendance pour un moindre risque chez l'homme (OR 0,29 ; p = 0,065).
Conclusions. — Chez les jeunes adultes avec CMH, les ECM sont fréquents à court terme, en particulier en cas d'obstruction et chez la femme, essentiellement rythmiques. L'implantation d'un DAI prophylactique est fréquente, non strictement basée sur les recommandations internationales, utiles mais imparfaites pour identifier le risque de MS.

Background

Hypertrophic cardiomyopathy (HCM) is the most common cardiac monogenic disorder, with a prevalence of at least 1/500 [1]. Lethal complications are infrequent (each < 1% per year) [2], and include heart failure, ischaemic stroke consecutive to atrial fibrillation and sudden cardiac death (SCD), which may reveal HCM, often in asymptomatic or poorly symptomatic patients (particularly in the young and in competitive athletes) [3]. The management of young

adults with HCM is challenging, with the need to offer optimal protection against SCD along with preservation of quality of life.

Increased prophylactic implantable cardioverter defibrillator (ICD) implantation has contributed to the improved longevity of patients with HCM [4,5]. The decision to implant an ICD for the primary prevention of SCD is currently based on the presence of five major classical risk factors for SCD [6], eventually in association with other relevant markers [7], and/or on a 5-year risk score for SCD proposed by the European Society of Cardiology (ESC) [8]. Several studies have recently been performed to validate and compare these two approaches, with conflicting results [7,9,10], highlighting the difficulty in predicting SCD in HCM. However, most of these studies were conducted in tertiary centres, did not focus on younger adults and did not reflect the real-life management of these patients. Moreover, risk stratification for all major clinical events is particularly important in young adults when considering the risks linked to the ICD implantation procedure and inappropriate shocks, but also the potential impact (psychological, familial, social and professional) of any severe clinical event.

This study aims to assess the clinical profiles and management of young adults with sarcomeric HCM, and the predictive factors for major adverse cardiac events (MACE), using data from the ongoing French national REgister of hypertrophic cardioMYopathy (REMY).

Methods

Inclusion criteria

REMY is a prospective registry on HCM that was initiated in 2010 [11]; it includes adults with HCM (aged $\geq$ 16 years at inclusion) after informed written consent, with a systematic follow-up at 3 years, 5 years and on demand. In REMY, HCM was diagnosed based on the presence of left ventricular hypertrophy ($\geq$ 15 mm in sporadic cases and $\geq$ 13 mm in the presence of a family history of HCM) using any imaging technique (echocardiography, cardiac magnetic resonance imaging [MRI] or computed tomography), unexplained by abnormal cardiac loading conditions (i.e. severe systemic hypertension or significant aortic stenosis $\leq$ 1 cm^2) [8].

The complementary GEnetic REgister of hypertrophic cardioMYopathy (GEREMY) includes, after informed consent, the genotyped REMY index patients using a custom-made next generation sequencing panel of 12 genes (TruSeq Custom Amplicon Low Input kit; Illumina, Evry, France), which includes 10 sarcomere genes (*MYH7*, *MYBPC3*, *TPM1*, *TNNT2*, *TNNI3*, *CSRP3*, *MYL2*, *MYL3*, *ACTC1* and *LMNA*) and the *GLA* and *TTR* genes. Analysis and interpretation of variants were performed using SEQNEXT (JSI Medical Systems GmbH, Ettenheim, Germany), PolyDiag (Imagine Institute, Paris, France) or Alamut® (Interactive Biosoftware, Rouen, France), and then confirmed by Sanger. In case of a negative study and depending on the patient profile, screening was performed on a larger next generation sequencing panel of 45—80 genes. Genetic variants of unknown significance were not considered.

The relevant government institution (the National Commission on Informatics and Liberty; *Commission nationale de l'informatique et des libertés*) provided clearance (CNIL agreement #909378). These cohorts were set independent of the ongoing European cardiomyopathy registry.

For the purpose of this study, we considered only three large centres in three different regions in France in which extensive follow-up was available (*Hôpital européen Georges-Pompidou* in Paris, *Hôpital Haut-Lévêque* in Bordeaux and *Hôpital Pontchaillou* in Rennes), and only young adults (maximum age 25 years) with HCM of sarcomeric origin (or supposed, after systematic exclusion of amyloidosis and Fabry disease) and no history of SCD or sustained ventricular tachycardia (SVT) were included.

Collected data

REMY and GEREMY use an anonymised electronic case report form hosted by the French Society of Cardiology, with prospective collection of clinical, imaging and laboratory data [12]. Collected data include — at the time of diagnosis and at follow-up — age, family history of HCM and SCD, unexplained syncope, New York Heart Association (NYHA) class and medical treatment at baseline, presence of an ICD, presence of permanent atrial fibrillation and presence and type of mutation. Echocardiographic variables included maximum anteroposterior left atrial diameter, maximum left ventricular wall thickness (LVWT), left ventricular ejection fraction using the biplane Simpson's rule, and maximum instantaneous left ventricular outflow tract gradient either at rest or during a Valsalva manoeuvre; obstruction was defined as a gradient $\geq$ 30 mm Hg, either at rest or during provocation. Non-sustained ventricular tachycardia (NSVT) and atrial fibrillation on 24-hour or 48-hour Holter electrocardiogram monitoring, abnormal blood pressure response (ABPR) at exercise and the presence of myocardial late gadolinium enhancement (LGE) on cardiac MRI were also collected. The 5-year SCD risk score proposed by the ESC was calculated retrospectively at inclusion, as were notified the presence of major classical risk factors for SCD (family history of HCM-related SCD, unexplained syncope, left ventricular hypertrophy $\geq$ 30 mm Hg, presence of NSVT, exercise ABPR). At follow-up, ICD implantation and occurrence of MACE (including SCD or appropriate ICD shock, SVT, atrial fibrillation, ischaemic stroke, hospitalisation for heart failure and unexplained syncope) were reported. Indications for ICD implantation were adopted by consensus of a group of HCM experts, taking into account the published USA/European guidelines at time of decision and the patient clinical profile.

Statistical analysis

Variables are described using means and standard deviations for continuous measures and counts and proportions for categorical measures. Comparisons between groups were performed using the χ^2 test or Fisher's test for categorical variables, and Student's test or the Mann—Whitney—Wilcoxon test for continuous variables. Given the small number of events, it was not pertinent to use a multivariable analysis, so a bivariable analysis based on known predictors in the literature was performed. All *P* values were calculated using two-sided tests, and a significance level of 0.05 was used to declare statistical significance. Statistical analyses were

Table 1 Baseline characteristics of patients according to the occurrence of major adverse cardiac events at follow-up.

Characteristic	Overall ($n = 61$; 100%)	MACE ($n = 15$; 24.6%)	No MACE ($n = 46$; 75.4%)	*P*
Demographics				
Female sex	16 (26.2)	7 (46.7)	9 (19.6)	0.05
Age at inclusion	20.5 ± 3.0	21.7 ± 2.5	20.1 ± 3.1	0.49
NYHA functional class				0.89
Class I	35 (57.4)	8 (53.3)	27 (58.7)	
Class II	21 (34.4)	6 (40.0)	15 (32.6)	
Class III	5 (8.2)	1 (6.7)	4 (8.7)	
Medical treatment				
None	23 (37.7)	0 (0)	23 (50)	0.002
Beta-blocker	35 (57.4)	14 (93.3)	21 (45.7)	0.003
Calcium channel blocker	3 (4.9)	1 (6.7)	2 (4.3)	1.00
ICD implantation	13 (21.3)	6 (40.0)	7 (15.2)	0.07
Echocardiography				
Gradient ≥ 30 mmHg	18 (29.5)	8 (53.3)	10 (21.7)	0.03
LVEF (%)	67 ± 7.5	67.9 ± 8.8	66.7 ± 7.1	0.44
Maximum LVWT (mm)	23.6 ± 7.4	25.5 ± 7.1	23.0 ± 7.5	0.22
LA diameter (mm)	34.5 ± 7.2	36.2 ± 6.6	33.9 ± 7.4	0.22
LVH ≥ 30 mm	17 (27.9)	5 (33.3)	12 (26.1)	0.74
Presence of MRI LGE[a]	37 (86.0)	11 (100)	26 (81.0)	0.31
Risk profile				
ESC score (%)[b]	4.8 ± 3.2	6.9 ± 4.8	4.2 ± 2.3	0.05
ESC score < 4%	28/53 (52.8)	4/12 (33.3)	24/41 (58.5)	0.23
ESC score 4–6%	12/53 (22.6)	3/12 (25)	9/41 (22.0)	1.00
ESC score ≥ 6%	13/53 (24.5)	5/12 (41.7)	8/41 (19.0)	0.14
One classical risk factor[c]	24/57 (42.1)	4/14 (28.6)	20/43 (46.5)	0.39
At least one classical risk factor[c]	39/57 (68.4)	11/14 (78.6)	28/43 (65.1)	0.51
At least two classical risk factors	15 (24.6)	7 (46.7)	8 (17.4)	0.04
Family history of SCD	15 (24.6)	3 (20.0)	12 (26.1)	0.74
Presence of NSVT	6 (9.8)	3 (20.0)	3 (6.5)	0.15
Exercise ABPR[d]	6/51 (11.8)	4/13 (30.8)	2/38 (5.3)	0.03
Negative gene screening[e]	16/52 (30.7)	5/15 (33.3)	11/37 (29.7)	0.02

Categorical data are expressed as number (%); continuous data are expressed as mean ± standard deviation. ABPR: abnormal blood pressure response; ESC: European Society of Cardiology; ICD: implantable cardioverter defibrillator; LA: left atrial; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LVWT: left ventricular wall thickness; MACE: major adverse cardiac events; MRI: magnetic resonance imaging; NSVT: non-sustained ventricular tachycardia; NYHA: New York Heart Association; SCD: sudden cardiac death.

[a] Missing data for 18 patients.
[b] Missing data for eight patients.
[c] Missing data for six patients.
[d] Missing data for 10 patients.
[e] Missing data for nine patients.

performed using R software, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline population

A total of 61 patients (mean age 20.5 ± 3.0 years, range 16–25 years; 45 men; all non-related) were included in the study (Table 1). At inclusion, 56 patients (91.8%) were in NYHA class I or II, no patient presented with permanent atrial fibrillation or a history of SVT and 18 patients (29.5%) had obstructive HCM. Myocardial LGE on MRI was present in 86.0% (37 of 43 patients without contraindication to MRI), exercise ABPR in 11.8% and a family history of SCD in 24.6%. Pathogenic variants on sarcomere genes were identified in 69.2% of patients with available genetic results, on the *MYBPC3* ($n = 18$), *MYH7* ($n = 10$), *TNNT2* ($n = 5$) or *MYL3* ($n = 1$) genes, or on both the *MYBPC3* and *MYH7* genes ($n = 2$). At inclusion, 13 patients (21.3%) had an ICD (all for primary prevention) and 38 (62.3%) were under medical treatment, mainly beta-blockers (92.1%) or calcium channel blockers (7.9%). Concerning SCD risk evaluation, the mean ESC score was 4.8 ± 3.2% (range 1.5–16.7%; < 4% in 52.8%; ≥ 6% in 24.5%), and 15 patients (24.6%) presented with at least two classical risk factors for SCD.

Table 2 Predictors of major adverse cardiac events on univariate and bivariable analysis.

Variable	Univariate analysis		Bivariable analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	0.28 (0.08—0.97)	0.045	0.29 (0.08—1.08)	0.065
Obstruction	4.11 (1.21—14.6)	0.025	3.96 (1.11—14.9)	0.035
Max LVWT	1.04 (0.97—1.13)	0.30		
Exercise ABPR	8.00 (1.35—64.8)	0.027		
Unexplained syncope	3.15 (0.91—11.0)	0.068		
NSVT	3.58 (0.60—21.7)	0.15		
ESC score $\geq$ 4%	3.37 (0.93—14.2)	0.08		
ESC score > 6%	3.04 (0.74—12.3)	0.12		
At least two classical risk factors	4.16 (1.17—15.2)	0.028		

ABPR: abnormal blood pressure response; CI: confidence interval; ESC: European Society of Cardiology; LVWT: left ventricular wall thickness; NSVT: non-sustained ventricular tachycardia; OR: odds ratio.

Cardiac outcomes (MACE)

Over the follow-up (mean duration 4.4 ± 2.2 years; up to 10 years; one patient lost to follow-up), 15 patients (25.0%; seven women) presented 17 MACE at a mean age of 24.5 ± 2.9 years (range 18—29 years). The MACE comprised: seven SCD events (41.2%), which occurred in three patients with a prophylactic ICD at inclusion (one death, one appropriate shock and one SVT overdrive) and four patients without an ICD at inclusion, including two patients who benefited from efficient resuscitation procedures and two patients who had symptomatic SVT (three had subsequent ICD implantation and one patient with SVT refused an ICD); five cases of atrial fibrillation and one stroke without documented atrial fibrillation (six events in total, 35.3%); one hospitalisation for heart failure requiring intravenous diuretics (5.9%); and three unexplained syncope episodes (17.6%).

Prediction of MACE

In our cohort (Table 1), MACE were observed in 43.8% of women (vs. 17.7% of men; $P = 0.05$) and in 53.3% of patients with obstructive HCM (vs. 21.7% of those with non-obstructive HCM; $P = 0.03$). Furthermore, when comparing the MACE ($n = 15$) and non-MACE ($n = 46$) groups, MACE were more frequent in patients with obstructive HCM (53.3% vs. 21.7%; $P = 0.03$) who thus received beta-blocker therapy more frequently (93.3% vs. 45.7%; $P = 0.003$). Furthermore, a family history of SCD, the presence of NSVT, NYHA class and left atrial diameter or maximum LVWT (or LVWT $\geq$ 30 mm) were similar between groups, whereas exercise ABPR was more frequent in the MACE group (30.8% vs. 5.3%; $P = 0.03$). If the presence of LGE on MRI was not more frequent in the MACE group (100% vs. 81% in the non-MACE group; $P = 0.31$), an absence of LGE was never observed in patients with MACE. There was a tendency for patients with a prophylactic ICD at inclusion to present an event more frequently at follow-up (40.0% vs. 15.2%; $P = 0.07$), whereas patients with MACE presented at inclusion with higher ESC scores (6.9% vs. 4.2%; $P = 0.05$) and more often had at least two SCD classical risk factors (46.7 vs. 17.4%; $P = 0.04$). However intermediate ESC scores ($\geq$ 4% and < 6%) and the presence of a single risk factor for SCD did not differ between groups.

On univariate analysis (Table 2), sex (odds ratio [OR] 0.28 for men; $P = 0.045$) and the presence of obstruction (OR 4.11; $P = 0.025$), exercise ABPR (OR 8.00; $P = 0.027$) and at least two classical SCD risk factors (OR 4.16; $P = 0.028$) were significantly associated with outcomes, with a tendency towards association for unexplained syncope (OR 3.15; $P = 0.068$) and an ESC score $\geq$ 4% (OR 3.37; $P = 0.075$). However, on bivariable analysis (Table 2), only two variables emerged as indicators of MACE: obstruction significantly increased the risk of MACE (OR 3.96; $P = 0.035$), and there was a non-significant trend for a decreased risk of MACE in men (OR 0.29; $P = 0.065$).

Focus on patients with an ICD/SCD

At the end of follow-up, 24 patients (39%) had an ICD, including 13 patients with a prophylactic ICD before inclusion and 11 patients with a de novo implantation — seven for primary prevention and four for secondary prevention (two resuscitated SCD and two SVT). Among those 24 patients, there were 20 patients, in whom the ESC score could be calculated at baseline, comprising eight patients (40%) with a score $\geq$ 6%, six patients (30%) with a score < 4% and six patients (30%) with an intermediate score. Moreover, in the whole group, among the 53 patients in whom the ESC score could be calculated at baseline, 2/28 SCD events (7.1% of the group) occurred among the patients with a score < 4%, 2/12 (16.7%) among those with an intermediate score and 3/13 (23.1%) among those with a score $\geq$ 6%, at a mean follow-up of 4.3, 6.2 and 4.7 years, respectively.

Among the three patients with a prophylactic ICD inserted before inclusion who presented a SCD event at follow-up, all presented at inclusion with at least two major classical risk factors, including one patient with an ESC score of 16.7% along with two pathogenic variants, and two patients with elevated ESC scores (5.3% and 8.2%) and no pathogenic variants. Among the four patients without an ICD who presented a SCD event, one would have got an ICD according to both guidelines (ESC score 5%, three major classical risk factors), one — who carried a malignant *TNNT2* gene mutation — would not have got an ICD according to

Table 3 Characteristics of patients with sudden cardiac death events.

Prophylactic ICD at inclusion	Sex; age at event (years)	ESC score	Presence of major classical risk factors for SCD	Degree of hypertrophy; obstruction (yes/no)	Pathogenic variants
Yes	Male; 25[a]	16.7%	Syncope, LVH, NSVT, ABPR	Yes	*MYBPC3* + *MYH7*
Yes	Male; 18[a]	5.3%	Syncope, ABPR	24 mm; no	None
Yes	Male; 27[a]	8.2%	LVH, NSVT	42 mm; yes	None
No	Female; 24[b]	5%	FH, LVH, ABPR	32 mm; no	*MHY7*
No	Female; 29[b]	2.5%	No	18 mm; no	*TNNT2*
No	Female; 24[c]	9.1%	Syncope	21 mm; yes	*MYH7*
No	Male; 26[c]	2.4%	No	20 mm; no	None

ABPR: abnormal blood pressure response at exercise; ESC: European Society of Cardiology; FH: family history of sudden cardiac death at age < 40 years; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; LVH: left ventricular hypertrophy; NSVT: non-sustained ventricular tachycardia; SCD: sudden cardiac death.
[a] ICD appropriate intervention.
[b] Resuscitated SCD.
[c] Symptomatic sustained ventricular tachycardia.

both guidelines (ESC score 2.5%, no major risk factors) and, finally, among the two patients who presented with symptomatic SVT, both USA and European guidelines would have identified the first as being at high risk and the second as being at low risk (Table 3).

Discussion

Outcomes

Whereas HCM has been qualified as a ''benign'' disease since the wider use of ICDs and myectomy procedures [12], others have highlighted the cumulative burden of HCM with age [13], leading nowadays to controversy about the prognosis of HCM [14,15]. The SHaRE HCM international long-term registry showed that patients with early-onset HCM had more adverse outcomes in the ensuing decades than patients with late-onset HCM, and that young adults had a 4-fold higher mortality in the long term than the general population of a similar age, with a predominance of atrial fibrillation and heart failure late complications [13]. Similarly, the current study showed that MACE are also markedly frequent in young adults with HCM, occurring in almost 25% of patients at an average 4-year follow-up, at an annual incidence of 7 per 100 patient—years, often despite limited (or absent) functional limitation at exercise. Most events (78%) were related to atrial or ventricular arrhythmias, highlighting the importance of adequate preventive measures, such as prophylactic ICD implantation and oral anticoagulation. There was also an 8% incidence of SCD or ICD appropriate interventions, corresponding to an annual incidence of 1.8 per 100 patient—years, which is roughly similar to previous reports [2,4], whereas severe heart failure episodes were infrequent.

Prognostic factors

Despite the limited size of the current study population, the presence of an obstruction was strongly associated with an increased risk of MACE. Obstruction has been previously identified as an independent predictor of severe heart failure and SCD in a larger HCM population [16]. A non-significant trend towards an increased risk of MACE was also observed in women. Several studies have shown that middle-aged women with HCM experience shorter survival than men [17,18]; however, such a relationship has not been demonstrated in young adults with HCM. In a previously reported large cohort of HCM adult patients with an average follow-up of > 6 years [19], female patients with HCM had a 50% greater risk than male patients of progression to severe congestive symptoms or death from heart failure or embolic stroke, independent of age and functional class at initial evaluation; they also presented with a 70% greater prevalence of left ventricular outflow obstruction compared with male patients. Because outflow obstruction has been shown to be a powerful independent predictor of adverse outcome caused by heart failure in HCM [8,16], the more frequent occurrence of obstruction in female patients probably contributed importantly to their more adverse long-term outcome. Indeed, that was also the case in the current study, in which 6/16 female patients (37.5%) presented more frequently with an obstructive HCM compared with 12/45 male patients (26.6%). Women may also be prone to disease progression for a variety of physiological factors, and large epidemiological studies of non-HCM populations with secondary forms of left ventricular hypertrophy (including the Framingham study) have consistently reported an increased risk of death and cardiovascular events or a propensity for diastolic heart failure with preserved systolic function in female patients [19].

The current study failed to demonstrate an association between NSVT and MACE, although it has been shown that subjects aged < 30 years with NSVT have a higher risk of SCD [20]. Recent studies have underlined the markedly high frequency of NSVT in patients with HCM. In the SHaRE registry, ventricular arrhythmias occurred in 32% of patients aged < 40 years at diagnosis, but in 1% of those aged > 60 years [13]. The ICD implantation decision may also be influenced by characteristics of NSVT — which were not explored here

— such as concomitant symptoms, occurrence at exercise, rapid heart rate and multiple and repetitive runs [21].

Similarly, the presence and extent of myocardial fibrosis, as demonstrated by LGE on MRI, have been reported as strong risk factors for SCD, heart failure and cardiac mortality in the general population of patients with HCM [22,23]; in the current study, despite the young age of our cohort, LGE on MRI was very common (37/43 patients, 86%) and was not related to a deleterious outcome, but the absence of LGE on MRI should be considered as a reassuring observation as no patients with MACE presented with absence of myocardial LGE on MRI.

Although atrial fibrillation is common in HCM, it has been reported that its occurrence before the age of 30 years is less frequent. However, in the current study, one third of young patients presented with atrial fibrillation. Atrial fibrillation has been associated with a worse prognosis in the young, with increased total mortality, heart failure and stroke [24].

It is known that patients with pathogenic/likely pathogenic sarcomere mutations have a higher risk of adverse outcomes compared with patients without identified mutations [13]. Indeed, in the current study, the prevalence of patients with a pathogenic variant was roughly similar in the no-MACE and MACE groups (26/37, 70.3% vs. 10/15, 66.6% screened patients), but the small number of screened patients should be underlined. Moreover, two patients with multiple pathogenic variants developed MACE, despite one of them having a low ESC score and no major risk factors; such a genetic profile usually carries a worse prognosis [25]. In the SHaRe registry [13], patients with multiple sarcomere gene mutations had the highest risk of transplantation/left ventricular assist device and stroke, whereas patients with mutations in *MYH7* had an up to 3-fold higher risk of MACE than patients with *MYBPC3* mutations. Finally, malignant pathogenic variants have been identified, such as mutations in *TNNT2*, which are thought to account for approximately 15% of familial HCM, and are associated with a particularly severe form of the disease characterised by a poor overall prognosis with a high incidence of sudden death.

Indications for ICD implantation

It has been suggested that the prognosis of young subjects with HCM has greatly improved in recent decades as a result of wider indications for prophylactic implantation of ICDs [12]; this may, however, cause complications, such as inappropriate shocks, which have been reported in up to 27% of patients [26]. The current study concurs with this observation, with a markedly elevated ICD implantation rate in the young (21% at inclusion and 39% at follow-up) compared with a 49% implantation rate in a cohort of younger patients from the USA [5]. In a recent registry of childhood-diagnosed HCM (with a median follow-up of 16 years), the overall risk of SCD was low (< 2% per decade), albeit being the single most common cause of late death, while an ICD was implanted in 21% of the population [27].

In 2003, five major risk factors for SCD (family history of SCD, unexplained syncope, maximal LVWT $\geq$ 30 mm, presence of NSVT and exercise ABPR) have been proposed by the American College of Cardiology and the American Heart Association [28] to be used for discussion of ICD implantation in primary prevention, with the need to exclude implantation in the absence of risk factors, to consider an ICD if one risk factor is present and to implant an ICD if at least two risk factors are present. In 2011, those guidelines [6] underlined the need for arbitrators in case of isolated NSVT or exercise ABPR. The list of these arbitrators (mainly young age, presence of obstruction and low left ventricular ejection fraction) was implemented thereafter, and now includes extended fibrosis (> 15% left ventricular mass) on LGE MRI and left ventricular apical aneurysm, each of these being sufficient to consider ICD implantation. However, ICD implantation in all patients with at least one major risk factor leads to a majority of the HCM population undergoing implantation [29], with a relatively low discharge rate (4% per year) [6]. In the current study on young patients, the presence of one or more major classical risk factors for SCD did not influence outcomes. Moreover, the decision for an ICD was based not only on guidelines, but also on clinical judgment, leading to implantation in seven patients to save one patient at a relatively short-term follow-up — a better ratio than when the decision is only based on guidelines [8,29,30].

More recently, a quantitative risk score for SCD at 5 years has been established from a large observational retrospective study [31], considering age, family history of SCD, unexplained syncope, maximum LVWT, magnitude of obstruction, left atrial anteroposterior diameter and presence of NSVT. The systematic calculation of this score, which can be done online on the Web, was then recommended by the ESC to stratify the risk of SCD in sarcomeric HCM and to optimise the indications for ICD for primary prevention. According to European guidelines, an ICD should be considered when the score exceeds 6%, and should not be considered below 4% (with exceptions), whereas it may be considered in case of intermediate score [8].

The current study matches roughly with these recommendations, as 79% of patients with an ESC score < 4% did not receive an ICD, whereas 61.5% of patients with a score $\geq$ 6% were implanted. In fact, all young patients with a SCD event presented with at least one of the following: ESC score $\geq$ 5%, at least two classical SCD risk factors and/or a malignant pathogenic variant.

Study limitations

The REMY register was initiated in 2010, at a time when the latest ESC guidelines introducing the 5-year SCD scoring system were not yet available. The relatively small size of the cohort may have decreased the power to show statistical differences; it also prevented a broad analysis of MACE predictors. It was not possible to consider fibrosis extent on MRI because of the lack of consistency in methodology between centres. An extended follow-up of those patients (currently ongoing) might reveal more prognostic variables, as appropriate use of an ICD up to 10 years after implantation has been documented. This young adult population may present a higher risk of events compared with the general population of young patients with HCM, as they were addressed in three expert HCM centres; for example, about 24% of the study group presented at baseline with an ESC score $\geq$ 6% or at least two major classical SCD risk factors, which is slightly higher than previously published larger and all-age European cohorts, which reported 14% of patients with a score $\geq$ 6%

[10] and 19% with at least two major SCD risk factors [30]. The non-significant result concerning the prognostic role of an ESC score $\geq 6\%$ might be explained by the small number of patients in that group ($n = 13$); however, the prevalence of such a score was more than twice greater in the MACE group (Table 1). Finally, our findings were obtained in a population aged between 16 and 25 years, and might not apply to younger or older patients with HCM.

Conclusions

In this French cohort of young adults with sarcomeric HCM, the occurrence of clinical events in a relatively short term was common, affecting about a quarter of patients, with a markedly high ICD implantation rate (39%). Most of these events were of arrhythmic origin, highlighting the need for prophylactic ICD and/or anticoagulation. Presence of obstruction and female sex were associated with an increased risk of events. In young patients with HCM, proper identification of the risk of MACE/SCD should be based on sex, presence of obstruction and genetic testing, combined with the use of both the ESC score and USA guidelines.

Sources of funding

This work received financial support from Sanofi Genzyme.

Acknowledgments

We are grateful to the French society of cardiology (the promoter and host of the REMY and GEREMY databases) and its staff, mainly Mrs Anne Bacher and Nicole Naccache, for their help and support, data quality control and data collection.

Disclosure of interest

A.H. is advisor to the companies Amicus, Gilead, Myokardia and Sanofi Genzyme. The other authors declare that they have no competing interest.

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