European Heart Journal Advance Access published September 15, 2010

European Heart Journal
doi:10.1093/eurheartj/ehq308

CLINICAL RESEARCH

Sudden death in hypertrophic cardiomyopathy: old risk factors re-assessed in a new model of maximalized follow-up

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Received 18 February 2010; revised 8 June 2010; accepted 23 July 2010

Aims In hypertrophic cardiomyopathy (HCM), the following five risk factors have a major role in the primary prevention of sudden death (SD): family history of SD (FHSD), syncope, massive wall thickness (MWTh) >30 mm, non-sustained ventricular tachycardia (nsVT) in Holter monitoring of electrocardiography, and abnormal blood pressure response to exercise (aBPRE). In HCM, as a genetic cardiac disease, the risk for SD may also exist from birth. The aim of the study was to compare the survival curves constructed for each of the five risk factors in a traditional follow-up model (started at the first presentation of a patient at the institution) and in a novel follow-up model (started at the date of birth). In an additional analysis, we compared the survival rate in three subgroups (without FHSD, with one SD, and with two or more SDs in a family).

Methods and results A total of 1306 consecutive HCM patients (705 males, 601 females, mean age of 47 years, and 193 patients were <18 years) evaluated at 15 referral centres in Poland were enrolled in the study. In a novel method of follow-up, all the five risk factors confirmed its prognostic power (FHSD: $P = 0.0007$; nsVT: $P < 0.0001$; aBPRE: $P = 0.0081$; syncope: $P < 0.0001$; MWTh $P > 0.0001$), whereas in a traditional method, only four factors predicted SD (except aBPRE). In a novel model of follow-up, FHSD in a single episode starts to influence the prognosis with a delay to the fifth decade of life ($P = 0.0007$). Multiple FHSD appears to be a very powerful risk factor ($P < 0.0001$), predicting frequent SDs in childhood and adolescence.

Conclusion The proposed concept of a lifelong calculated follow-up is a useful strategy in the risk stratification of SD. Multiple FHSD is a very ominous risk factor with strong impact, predicting frequent SD episodes in the early period of life.

Keywords Hypertrophic cardiomyopathy • Sudden death • Risk factors

Introduction

Heart disease induced by gene mutation starts to damage myocardium (morphologically and/or electrophysiologically) at the moment a patient is born. In a genetic cardiac disease, the risk for sudden death (SD) may also begin to affect from birth or even *in utero* (prenatal phase). An adequate example is the arrhythmogenic risk in long-QT syndrome.[1–3] In this genetic heart disease, it has been[1–3]

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proposed to perform a survival analysis with follow-up from the moment of birth. In hypertrophic cardiomyopathy (HCM), the disarray as arrhythmogenic substrate is generated before birth, whereas fibrosis as arrhythmogenic co-factor developed mainly during life. However, in pathomorphological examination in infants who died suddenly apart from extensive disorganization of myocytes, small foci of replacement fibrosis were evident.[4] Alternations in collagen fibre morphology, consisting of thickening and increased numbers of struts, weaves, and perimysial coils, were similar to those of children and adults with HCM.[4] Collagen fibres also appeared disorganized in their arrangement, particularly in areas of abnormal myocyte arrangement. Importantly, HCM infants who died <5 months of age had already showed greater than normal amounts of total and interstitial collagen.[4]

Left ventricular (LV) hypertrophy may appear at birth but usually may develop in different stages of life. In HCM, several risk factors for SD have been identified. The following five risk factors have a major role in the primary prevention of SD: family history of sudden death (FHSD), syncope, massive wall thickness (MWTh) >30 mm, non-sustained ventricular tachycardia (nsVT) in Holter monitoring of electrocardiography (ECG), and abnormal blood pressure response to exercise (aBPRE).[5–9] The occurrence of some of these factors is age-dependent, due to gradual phenotypic development. In contrast, FHSD (if present) influences survival unfavourably at the moment of birth. Unfortunately, FHSD is an unstable risk factor because it may appear in a latter stage of life. Some patients do not have family members who have suffered SD until they have achieved maturity, for instance, when one of their siblings dies.

In HCM studies analysing the impact of genetic mutation on survival, the follow-up was started at the moment of birth.[10,11] Different mutations may influence the prognosis variably (so-called malignant or benign mutations) when studying pedigrees with those mutations. However, detailed analyses performed in unrelated subjects have failed to confirm the presence of malignant or benign mutations. Importantly, there are some other gene modifiers[12–14] that must be activated in conjunction with the original disease causing mutation or disease expression occurs.

In clinical (non-genetic) studies, the prognostic impact of age has been recently taken into consideration in the analysis of syncope[14] and MWTh >30 mm.[15] The methodological approach was very simplified, because the analyses were performed with patients stratified according to three age-determined subgroups.[14,15] The calculated approach, to start the follow-up at the moment of birth, seems to be more precise. An additional advantage of this method is the opportunity to compose the study group including children and adults (full-age spectrum analysis of HCM patients). Importantly, an episode of SD may occur very early.[16–18] Additionally, some risk factors of SD have a prognostic power in young patients, below 30 years of age.[15,19]

It has been postulated that some risk factors need quantitative characteristics.[20] The episode of unexplained syncope has been quantitatively assessed, and the prognostic importance was associated with only recent episodes.[14] Moreover, it is suggested that the prognostic power of FHSD may depend on the number of family members who died suddenly.[21–23] Accordingly, the aim of the study was to test this hypothesis by comparing three subgroups (without FHSD, with one SD, and with two or more SDs in a family). Additionally, we compared the survival curves constructed for each of the five risk factors in a traditional follow-up model (started at the first presentation of a patient at the institution) and in a novel follow-up model (started at the date of birth).

Methods

Study population

A total of 1306 consecutive HCM patients with traditional follow-up of 5.6 ± 4.3 years (705 males, 601 females, mean age of 47 years, and 193 patients were <18 years) evaluated at 15 referral centres in Poland were enrolled in the study. Importantly, 98% of the patients in this study were not related to one another. The diagnosis of HCM was based on the echocardiographic demonstration of a hypertrophied and non-dilated left ventricle (wall thickness ≥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. Left ventricular outflow tract (LVOT) gradients were determined using pulsed and continuous wave Doppler from the apical three- and five-chamber views. The peak LVOT gradient was determined using the modified Bernouilli equation: gradient $=4V^2$, where V is the peak aortic outflow velocity. The LVOT gradient >30 mmHg was detected in 418 patients (32%).

Sudden death was defined as natural death due to cardiac causes, heralded by an abrupt loss of consciousness within 1 h of the onset of acute symptoms. Death was also classified as sudden if it occurred unexpectedly and was also unwitnessed, such as while in sleep in bed overnight. Ventricular fibrillation during follow-up, either interrupted by a discharge of an implantable cardioverter-defibrillator (ICD) or documented at the time of aborted cardiac arrest, was regarded as equivalent to SD.

Based on the data published previously, five clinical features were defined as risk markers for sudden cardiac death:

(1) *Non-sustained ventricular tachycardia*. Three or more consecutive ventricular extrasystoles at a rate of ≥120 b.p.m., lasting for <30 s (353 patients, 27%) in Holter monitoring of ECG.
(2) *Abnormal exercise blood pressure response*. A rise in systolic blood pressure from baseline to peak exercise of <25 mmHg or a fall of >10 mmHg from baseline or the maximum achieved blood pressure. The presence of an abnormal response was only considered as a risk factor in patients aged <40 years of age (418 patients, 32%).
(3) *Family history of premature sudden death*. History of sudden cardiac death in relatives (274 patients, 21%).
(4) *Unexplained syncope*. When it occurred in circumstances not clearly consistent with a neurally mediated event, i.e. without apparent explanation at rest or during ordinary daily activities, or during an intense effort (366 patients, 28%).
(5) *Severe left ventricular hypertrophy*. The LV wall thickness in any myocardial segment of ≥30 mm in two-dimensional echocardiography (235 patients, 18%).

Statistical analysis

SAS statistical software (version 8.2, SAS Inc., Cary, NC, USA) was used for the statistical analysis. Parametric and non-parametric analyses of variance (Student's *t*-test or Wilcoxon test) were used for comparisons between continuous variables; Pearson's χ^2 or Fisher's exact test was used for dichotomous variables. Survival estimates were calculated using the Kaplan–Meier method, and their relation to risk factors was

determined using log rank for trend. Survival curves were constructed for each of the five risk factors in the traditional follow-up model (started at the first presentation at the institution) and in the novel follow-up model (started at the date of birth). The magnitude of risk was calculated using the Cox regression model with 95% confidence interval.

A *P*-value of <0.05 was considered significant. All *P*-values were two-sided.

Results

In the present study, the number of patients with SD or equivalents was 161. Statistical results are presented in all figures.

Family history of sudden death appears to be a powerful risk factor of SD in a lifelong follow-up, both in the simplest dichotomized analysis (0 = no SD or 1 = at least 1 SD; *Figure 1A*) or in a more advanced classification with three categories (0 = no SD, 1 = 1 SD, and 2 = 2 or more SDs; *Figure 1B*).

In both variants of the analysis, FHSD appears to be an important risk factor, especially when two or more SD episodes occurred in a family (very rapid reduction of survival in *Figure 1B*). In the traditional model of follow-up calculation, FHSD appears also to be an important risk factor (*Figure 2A* and *B*). *Figures 3–6* show the significance of the remaining risk factors, analysed in the traditional (*Figures 3A–6A*) or novel model of follow-up (*Figures 3B–6B*).

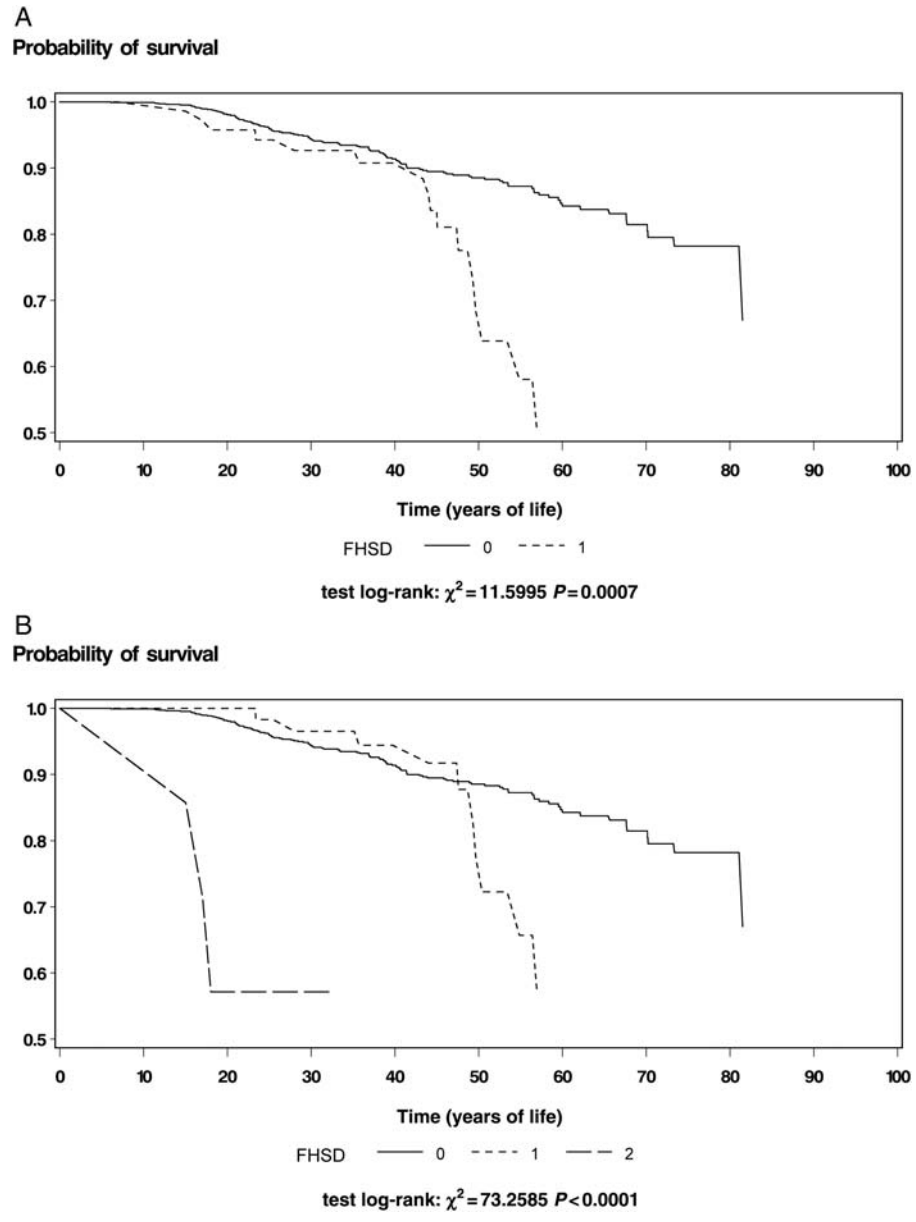

Figure 1 (*A*) Prognostic role of family history of sudden death (without episode vs. any episode) in novel follow-up model. (*B*) Prognostic role of family history of sudden death (without episode vs. one episode vs. two or more episodes) in novel follow-up model.

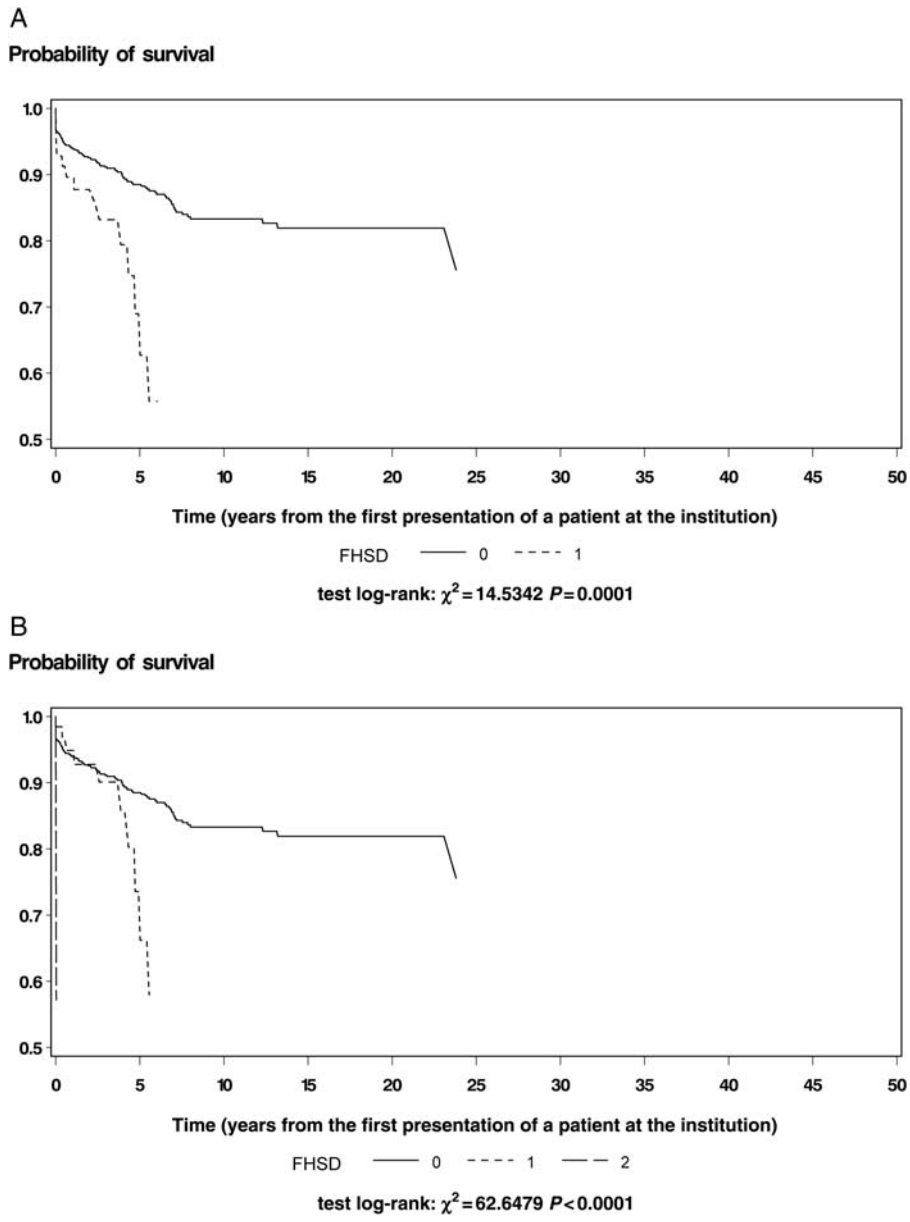

Figure 2 (*A*) Prognostic role of family history of sudden death (without episode vs. any episode) in traditional follow-up model. (*B*) Prognostic role of family history of sudden death (without episode vs. one episode vs. two or more episodes) in traditional follow-up model.

In the novel method of follow-up, all the five risk factors confirmed the prognostic power, whereas in the traditional method, only four factors predicted SD (except the aBPRE).

Family history of sudden death in a single episode starts to influence the prognosis with a delay to the fifth decade of life. Multiple FHSDs appear as very powerful risk factors, predicting frequent SDs in childhood and adolescence. The remaining four risk factors begin to influence the prognosis more or less progressively from the end of the second decade of life. The survival curve in patients with syncope featured a plateau between 55 and 65 years of life.

The relation between survival from SD and the number of additional risk factors is shown in *Table 1*. There was a significant trend towards increased mortality, with increasing numbers of risk factors.

Discussion

Fifty years after Teare's description of HCM, the identification of patients at high risk for SD still remains a challenge. In an analysis of the five major risk factors, the positive predictive accuracy for SD is low,[23] and thus new risk factor has been searched.[24] Important obstacles to the development of accurate prediction models are the complexity and variability of the underlying arrhythmogenic substrate.[5] A crucial aspect of the management of patients with HCM is an assessment of each individual patient's profile risk for

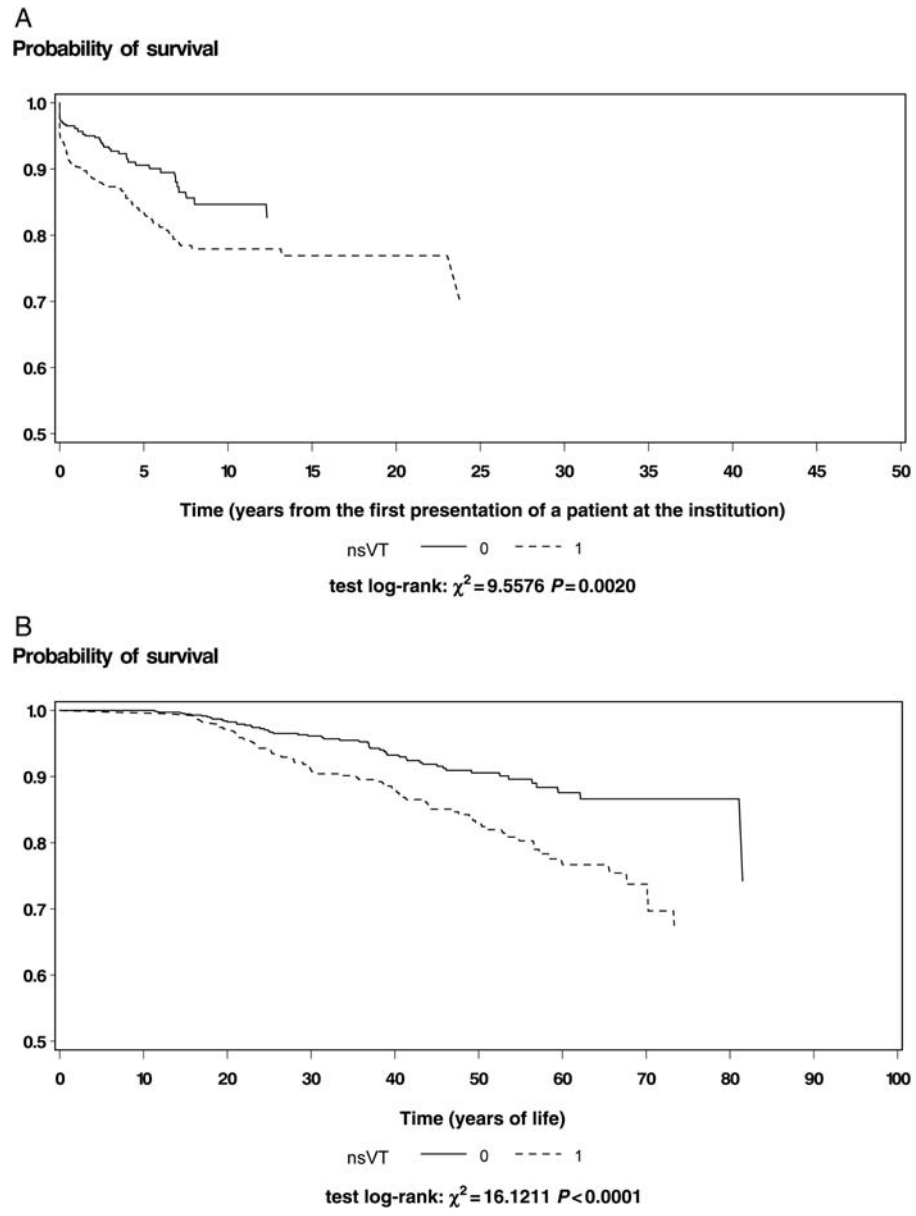

Figure 3 Prognostic role of non-sustained ventricular tachycardia, analysed in traditional (*A*) and in novel (*B*) follow-up models.

SD, so that preventative strategies may be considered. However, preventive ICD, while undeniably effective in aborting SD, is on the other hand unfortunately associated with a considerable morbidity rate, especially in younger patients, and the decision to implant it should not be taken lightly.[25]

Despite decades of investigation, our ability to stratify risk for SD is imperfect as evidenced by the fact that, even among patients with no discernible risk factors, SD occurs at a rate of just below 1% per year. Patients with three or more risk factors appear to have event rates that approach 5% per year, whereas even survivors of prior SD have a rate of subsequent SD of ≈10% per year.

The proposed concept of a lifelong calculated follow-up is a novel and reasonable strategy. Although SD occurs most commonly in children and young adults,[8,16–18] the risk extends across a wide age range through midlife and beyond;[6] therefore, achieving a particular age does not confer immunity to a sudden catastrophe.[7] The youngest children (according to age at presentation) had the worst survival.[17] The disarray and early fibrosis may play an important role as arrhythmogenic substrates.[4] In the study of Shirani *et al.*[4] HCM infants who died <5 months of age had already showed greater than normal amounts of total and interstitial collagen. However, these infants had 3.5 times less collagen than older children, and adults with HCM also suggests a remodelling process in which LV interstitial collagen compartment expands as the ventricular walls thickens during childhood with accelerated growth and maturation. However, similar to the

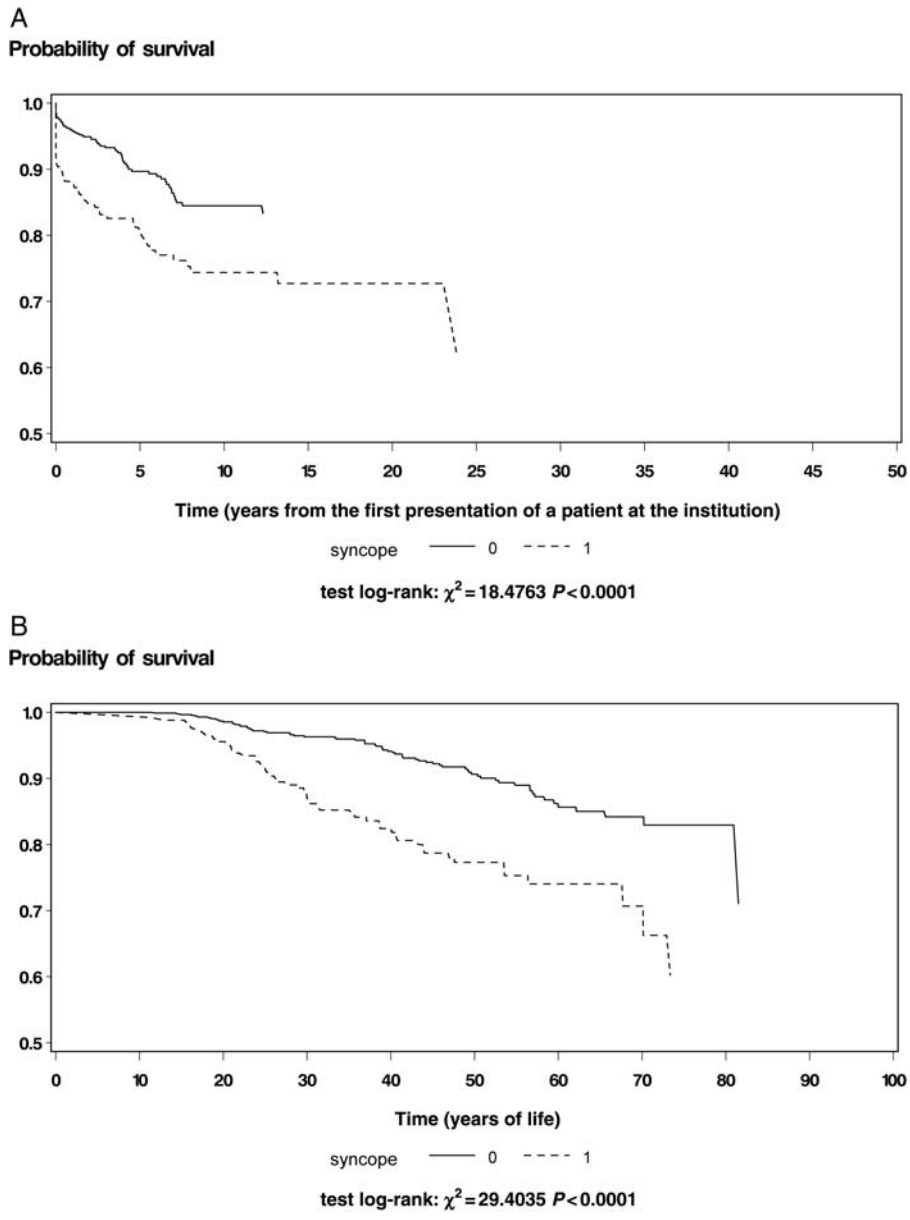

Figure 4 Prognostic role of syncope analysed in traditional (*A*) and in novel (*B*) follow-up models.

older HCM patients, areas of dense perivascular collagen encase numerous abnormal intramural coronary arteries with apparently narrowed lumen, thickened walls, and increased collagen.

In our study, the poorest survival early after birth and during childhood was observed in patients with two or more episodes of FHSD (*Figure 1B*).

A life-saving ICD discharge may occur in a delayed period, in advanced age even 10 years after implantation.[9]

In HCM, stratification of SD risk is based on five major risk factors: FHSD, syncope, nsVT, massive LV hypertrophy (wall thickness >30 mm), and aBPRE. Two of the risk factors FHSD and syncope are theoretically simple to establish by anamnesis. However, some families neither recall the events regarding an ancestor's mode of death nor carried a diagnosis of HCM. In the current study, authors make every effort to complete full-informed FHSD.

The not overwhelmed difficulty was the fact that episodes of FHSD may accumulate during an individual patient's lifetime does not mean that it is present at the time of first evaluation or even at birth.

The verification of the remaining risk factors requires diagnostic investigations: ECG Holter monitoring, echocardiography, and exercise test. There are some weaknesses of this measurement, e.g. Holter findings (even from 48 h) may be false-negative and nsVT may be detected in another Holter monitoring.

Recently, syncope was defined as a unstable risk factor.[14] Accordingly, if an event occurred in close temporal proximity to the initial

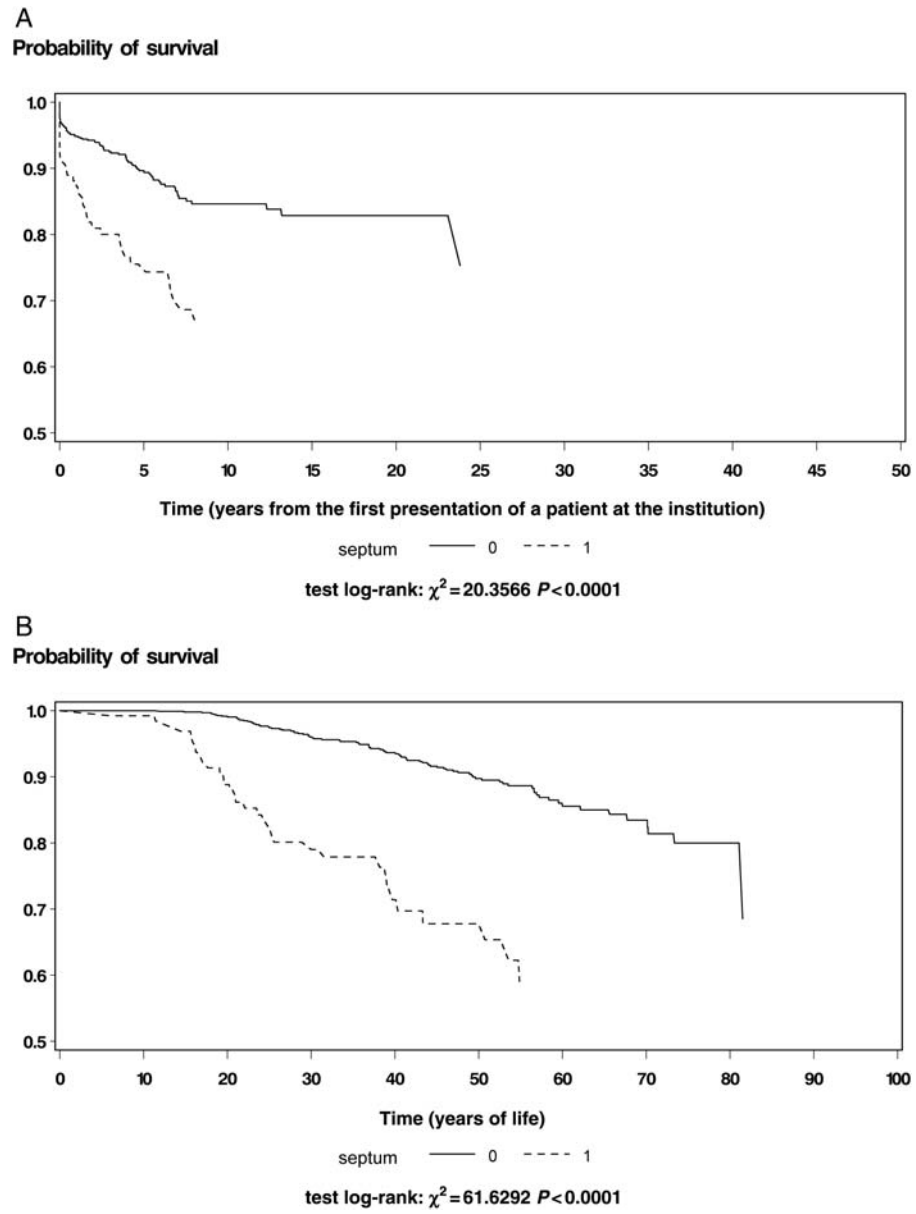

Figure 5 Prognostic role of massive wall thickness <30 mm analysed in traditional (*A*) and in novel (*B*) follow-up models.

evaluation, it showed a substantially higher risk of SD. In contrast, remote syncopal events did not show an increased risk. However, in that study, the follow-up was calculated traditionally. In the present study, the survival curve (long-life follow-up) in patients with syncope featured a plateau between 55 and 65 years of life.

This plateau phenomenon (silent period for SD) seems to correspond with the above-mentioned unstability of prognostic value of syncope. The statistical power of the present study derived from a large number of patients with SD or equivalents (161 subjects) in contrast to the recent study,[14] where 74 patients died suddenly. The higher number of SDs in the present study may be explained by the inclusion of more diseased patients due to referral selection bias.

The traditional starting point of follow-up is usually the first presentation at an investigating institution—referral centre. This moment is delayed when compared with the diagnosis of HCM in a referral centre and significantly delayed when compared with the beginning of the genetic disease.

From patients' point of view, FHSD is the most overwhelming consideration for individual patients. The prognostic role of FHSD varied in the previous studies (significant as an independent factor[26] or significant in combination with syncope[15] or insignificant[21,27]).

Paediatricians have postulated high-rate mortality in HCM diagnosed during infancy and childhood.[28,29] In older studies,[30,31] annual mortality as high as 5% has been described, with overall rates exceeding 50% for subjects presenting during infancy.[20,32] In contrast, meta-analysis prepared by Elliott *et al.*[33] in adults have reported annual mortality rate of from 0.1 to 3.5% in different

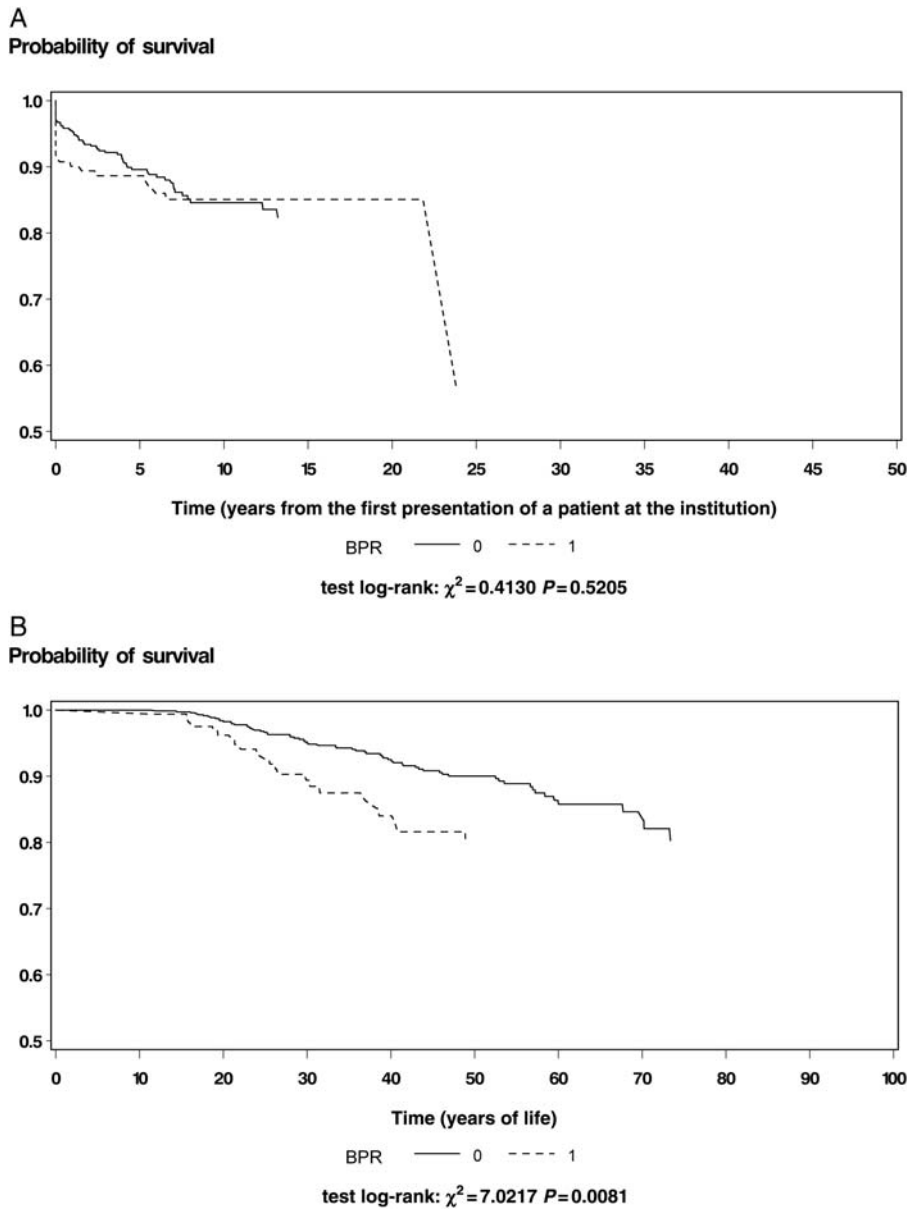

Figure 6 Prognostic role of abnormal blood pressure response to exercise (*B*) analysed in traditional (*A*) and in novel (*B*) follow-up models.

studies with a mean duration follow-up of 1.8–10.3 years. In a National Australian Childhood Cardiomyopathy Study,[28] the highest mortality was during first 12 months after diagnosis, and the average mortality rate for all subjects was 3.4% and 1.5% in subject diagnosed after the first year of life.

Potential clinical impact

An advantage of the long-life follow-up method is the opportunity to compose the study group including children and adults (full-age spectrum analysis of HCM patients). In HCM, SD may occur in infants and early childhood. The arrhythmogenic substrates generated by disarray or even foci of fibrosis is present at the date of birth.[4] In these circumstances, current study with follow-up from birth date is rational.

Sudden death is one of the most prevalent causes of death in developed countries. Its aetiology varies according to age. Some cardiac diseases may explain SD with minimal or no anatomic findings. However, many cardiac diseases, for example, channelopathies and HCM, have a genetic basis. Therefore, post-mortem genetic analyses (molecular autopsy) are becoming a useful tool to identify the cause of sudden cardiac death and to improve the early diagnosis of asymptomatic carriers among the relatives.[34]

The consideration that more SDs within a family confers greater risk may reduce the chance of random gene modifiers, which may add to the risk inherent with having a mutation. If there is only one family member with HCM who succumbs to sudden cardiac death, it may be their HCM-associated mutation plus some random spontaneous gene modifier or polymorphism

Table 1 The significant trend towards increased mortality, with increasing numbers of risk factors. Hazard ratio was calculated in relation to the group of patients with zero risk factor

Numbers of risk factors	Hazard ratio	95% Confidential limits of HR
One	1.794	(0.94–3.41)
Two	3.355	(1.76–6.36)
Three	6.473	(3.37–12.42)
Four	9.795	(4.60–20.85)
Five	11.992	(1.56–91.83)
$P = 0.0006$ for trend		

that in concert results in that SD. However, if multiple family members suddenly die, then it decreases undesirable chance of a random gene modifier.

Importantly, vast majority of the patients in this study were unrelated to one another.

Limitations of the study

The fact that FHSD may accumulate during an individual patient's lifetime does not mean that it is present at the time of first evaluation or even at birth. To minimize this limitation, we have analysed the information from the patients obtained in last visit.

The main limitation is the fact that majority of our patients survived long enough to be seen at one of the referral centres in Poland. It excludes the possibility that one or more of the risk factors may have such impact that patients died before coming to clinical recognition. However, 193 patients were diagnosed during childhood with a relatively short follow-up period and multiple FHSD appeared as a strong risk factor in a novel follow-up model.

In cases with SD in childhood without hypertrophy, we proposed to perform the post-mortem molecular analysis (see above paragraph) and echocardiographic/genetic analysis in family.

In genetically transmitted arrhythmogenic disease, the model of follow-up from birth was proposed in the analysis of patients with long-QT syndromes.[1–3] This model of follow-up was successfully used in genetic haematological disease.[35,36]

The analysis was retrospective, yet a prospective study from the moment of birth is hard to perform.

The next important limitation is the unavoidable selection bias by referral to tertiary cardiac centres.

The analysis of dose–response of number of sudden cardiac deaths in an individual family may perfectly be normalized by the size of the pedigree. Knowing these denominators may be more insightful than simply counting the number of deaths. However, the number of subjects in an individual family dynamically changed [some members died naturally (not suddenly) and new members have been born]. In all previous studies, the number of FHSD was reported in absolute not normalized to family size manoeuvre.

It is generally (and current study) assumed that fast ventricular tachyarrhythmias that last long enough to cause an ICD to deliver therapy, such as shocks, would progress to ventricular fibrillation and cardiac arrest in the absence of an ICD. However, ICD therapies may not be a surrogate for sudden cardiac death, as episodes may have been unsustained non-fatal events.[37] Fast monomorphic ventricular tachycardial episodes may terminate spontaneously without antitachycardial pacing therapy.

Conclusion

In the novel model of follow-up analysis, all five major risk factors had a prognostic value, whereas in the traditional method of follow-up calculation only four factors predicted SD (apart from the aBPRE).

In the novel model of follow-up, a single episode of FHSD starts to influence the prognosis with a delay to the fifth decade of life. Multiple FHSD appears to be a very powerful risk factor, predicting frequent SDs in childhood and adolescence. The novel model of follow-up provides an opportunity to compare survival rate in children and adults.

Funding

This work was supported by research grant POLKARD I A.4/VII/06 from Polish Ministry of Health.

Conflict of interest: none declared.

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