SUPPLEMENTARY DETAILED METHODS

Methods

Study patients Patients attending all Swedish regional pediatric cardiology centers with a diagnosis of hypertrophic cardiomyopathy (HCM) presenting <19 years of age since 1972 were identified retrospectively in 1990-1999 using the diagnostic registry of each center, and. original patient records were reviewed.[1, 2] From 1999 cases were collected prospectively from all Swedish pediatric cardiology centers. Retrospective and prospective patients are compared in *Supplemental Table S1*. Included patients had HCM as defined by a maximal wall thickness >+2SD, and a diastolic septum-to-cavity ratio (sepcavr) or diastolic posterior left ventricular wall-to-cavity ratio (lvcavr) >99th percentile for age,[3] with a non-dilated ventricle with normal or increased systolic contractility in the absence of another cardiac or systemic disease.[4] 77 (48%) had a family history of HCM, and 37 (23%) were associated with a Noonan-group syndrome. HCM secondary to maternal gestational diabetes, endocrine disorders, Friedreich´s ataxia, mitochondrial disease or storage-disorders was not included. Included in this analysis are patients entered up to October 2014, a national cohort of 162 patients with a minimum of two years follow-up in survivors, and average follow-up of 10.9±(SD 9.0) yrs, with a total of 39 patients that had suffered sudden death or resuscitated cardiac arrest (30 sudden deaths, including 12 presenting with sudden death, plus 6 re-suscitated cardiac arrests and 3 appropriate ICD-interventions), together termed SD/CA-group. Patients who presented with sudden death due to clinically unrecognized HCM before 19 years of age (n=12) are included and retrieved from hospital records or the Forensic Medicine national database Rattsbase; some of those had previous ECGs recorded at either pediatric outpatient clinics, or at military mustering, but most of them, and some additional patients diagnosed in the earliest time-period, only had angiographic or post-mortem measurements of LV wall thickness. The 12 presenting with sudden death did not differ in clinical characteristics although a slightly higher proportion were male (85% as compared to 62% for those with SD/CA on follow-up, p=0.27). A total of 155 patients (with 32 SD/CA) had available ECGs, and were used in the assessments of relative risk of different ECG features. 140 patients in the cohort have both ECG- and wall thickness measurements, out of whom 27 had suffered either sudden death/cardiac arrest (n=24) or an appropriate ICD-shock (n=3) (SD/CA-group). Those 140 were used for the uni-and multi-variate Cox-hazard analysis.

Primary end-point Sudden cardiac death/cardiac arrest/appropriate ICD-intervention (SD/CA).

Clinical measures collected All HCM-patients ECG-voltages and other ECG-measures were re-measured in a standardized fashion at entry to the national registry by the registry-holder (IÖS),[1] These measurements were done retrospectively 1990-1999, and prospectively from 2000, as part of studies originally focusing on treatment effects, when many of the patients who subsequently died suddenly were still alive,[16 18] Thus bias was not possible as the ECG risk-score was not published until 2010, and 87% of survivor ECG-measurements, and 84% of SD/CA-ECG-measurements were entered into the registry before 2010. ECG risk-score was later calculated from entered measurements as first described.[5] It was not possible to re-

measure all ECGs blindly for the current study as original ECGs from the earlier decades were no longer accessible, thus the ECG-measures originally entered into the registry had to be used for the calculation of ECG risk-scores. From 2000 ECGs were measured prospectively as patients entered into the registry, and virtually all ECGs were digitally recorded allowing automatic calculation of QRS-duration, QTc, voltages and ST-T-wave deviations by the ECG-machine to be utilized, so bias does not arise and reproducibility is excellent. Original ultrasound measurements, M-mode, and where available, 2-D ultrasound measurements were re-measured where available (IÖS and EF), or otherwise reports in hospital notes were accepted. Detroit Z-scores for maximal wall thickness have been calculated using the Cardio Z app,[6] and septal thickness related to upper limit of normal for age (SEPPER) according to the published formula.[1] However we found that the choice of Z-score had very great influence on values, and whereas we got a normal distribution of Z-score values within ±2 on our normal patients with the Detroit Z-score, we obtained very much higher Z-score values with the Kampmann Z-score[7], with 19% of normal patients having Z-score values >2. Accordingly, only Detroit Z-score values are used. An LVOT gradient >20 mm Hg at rest was considered significant obstruction (LVOTO).[8] Presence of obvious systolic anterior movement of mitral-valve apparatus (SAM) plus a systolic murmur was judged evidence of LVOTO in era before Doppler measurements available. 24h-Holter ECG-recordings were not available in the 1970-ies so Holter data is available only for later patients. Exercise-testing on a bicycle ergometer has been available from the outset, but blood pressure response was not always recorded. Hospital records were scrutinized for information about syncope and family history of sudden death. Latest ultrasound- and ECG measures recorded were retrieved from the hospital records, even for those patients that had entered adult cardiology follow-up, and in the majority last follow-up measurements are obtained within one-two years of the end-point. Medical treatments given, and interventional procedures have been documented. 101 patients (62.4%) received beta-blocker therapy (mostly propranolol or metoprolol, and only 2% received atenolol), 14 (8.6%) had calcium-blocker therapy, and 7 (4.3%) amiodarone. 39 (24.0%) patients received a combination of disopyramide and high-dose beta-blocker. All patients receiving high-dose propranolol or metoprolol received slow-release preparations twice daily. Beta-blocker doses used were converted to propranolol equivalents using the conversion propranolol 80 mg = metoprolol 100mg[9] = bisoprolol 5 mg = atenolol 50 mg.

Causes of death All Swedish nationals have a unique personal identification number, and if patient was alive or dead was last ascertained on October 6th 2016. Where causes of death were not recorded in hospital notes, they were obtained from death certificates from National Board of Health and Welfare. Apart from the 39 classed as SD/CA-group, there were 17 additional cardiac deaths. No patient was lost to follow-up.

Statistics Statistical analyses were carried out using Statgraphics Centurion XVI, GraphPad Prism v. 6.02, and IBM SPSS Statistics v. 22 software. Categorical data were compared with two-tailed Fisher´s exact test, and continuous variables with Mann-Witney U-test as the majority of parameters were not normally distributed. Survival was analysed by Kaplan-Meier survival curves compared with log-rank test. Comparisons of relative risk for various risk

factors were made both for previously published suggested cut-off values, and where these performed poorly, by analysis of the frequency distribution of the those parameters comparing survivors with individuals in the SCD-group compared to survivors. For the uni- and multivariate analysis of risk-factors with Cox proportional hazards method on the other hand all patients with ECG- and ultrasound data (n=140) were included, even those who had died another type of cardiac death, but sudden death was still used as primary end-point, in order to study how specific various risk factors were for arrhythmia-associated death. Parameters were selected for multivariate analysis if univariate p-values were ≤0.20. The number of variables was restricted to six at a time in order to have adequate statistical power, based on statistician advice, and were analyzed with backward selection. O'Mahony et al, 2014[10] have suggested that one risk-factor per 10 end-points would be appropriate for risk-factor assessment in adult HCM, but they had an annual event rate of 0.81% whereas we had an event rate of 1.7% giving us substantially greater statistical power, and explaining divergence of statistical advice. Those risk-factors not significant in the six-factor analysis were removed and others entered until all had been tested. Only one ECG-parameter and one wall-thickness measure was included in each group-analysis, and bivariate analysis of two ECG-measures or two wall-thickness measures together was used to determine which of the two were the most powerful predictors, as they would have some linkage to each other. The risk-factors included in the AHA risk assessment-model were also re-tested one by one in the final multivariate models, even if they had significance values >0.2 on univariate analysis, and finally the last model was tested with only three or four risk-factors included in the model to obtain the most accurate parameters for the regression. The AHA risk-factors was included as recommended in the 2011 AHA guidelines,[11] with pathological blood pressure reaction not counted as significant risk factors unless other risk factors were present; however nsVT if present was counted as risk factor considering the patients young age.

SUPPLEMENT METHODS REFERENCES

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Supplemental Table S1. **Comparison of retrospective (up to 1999) and prospective cohorts (after 1999)**					
Parameter	Retrospective n=85 Percent/ Median	IQR	Prospective n=77 Percent/ Median	IQR	Mann-Whitney P=value
Male gender	60%		61%		0.62 (n.s.)
Familial HCM	32%		73%		<0.0001
Family history of SD in familial HCM	38%		46%		0.62 (n.s.)
Noonan-spectrum syndrome	41%		14%		0.0001
LVOTO >20 mm Hg at rest	70%		25%		<0.0001
Age at diagnosis (yrs)	5.2	0.3-12.0	9.8	1.1-14.0	0.07 (n.s.)
Septal thickness at diagnosis (mm)	15.0	9.6-20.9	12.1	10.3-16.9	0.49 (n.s.)
SEPPER at diagnosis (%)	181	145-222	144	120-212	0.011
Limb-lead QRS-sum (mV)	10.2	7.1-14.0	8.7	6.4-10.3	0.021
ECG risk score at diagnosis	4	3-8	3	0-6	0.007
LA:aortic ratio	1.33	1.13-1.60	1.32	1.14-1.52	0.69 (n.s.)

Abbreviations: SD=sudden death (at age <40 yrs, and in presence of HCM); LVOTO=left ventricular outflow tract obstruction; SEPPER= septum in % of 95th centile for age; LA=left atrium

Table S2 Calculation of the ECG risk score		
Any deviation in QRS-axis		1 point
Pathological T-wave inversion limb leads		1 point
Pathological T-wave inversion precordial leads*		2 points
ST-segment depression $\geq$ 2 mm		2 points
Dominant S in V_4		2 points
Limb-lead QRS-amplitude sum	$\geq$7.7 mV	1 point
	$\geq$10.0 mV	2 points
	$\geq$12.0 mV	3 points
12-lead amplitude-duration product	$\geq$2.2 mV.s	1 point
	$\geq$2.5 mV.s	2 points
	$\geq$3.0 mV.s	3 points
QTc	$\geq$440 ms	1 point
		Max score=14

*Total score available for T-wave abnormalities is 2 points, i.e. 1 limb lead point is not added on top of precordial points. QTc = corrected QT-interval. Modified from Östman-Smith et al. European Heart Journal, 2010;31:439.

Supplement Table S3 Cox hazard proportional regression multivariate analysis of risk factors in cohort without syndrome-associated HCM –significant risk factors remaining in model				
Only risk factors at diagnosis and early therapy entered				
Parameter	B	SE	Exp (B)	Significance
First limb-lead QRS-sum	0.072	0.033	1.075	**P=0.033**
First SEPPER (septum in % of 95th centile)	0.013	0.003	1.013	**P<0.000**
LVOTO at rest (>20 mm Hg)	0.179	0.108	1.196	P=0.098
Early beta-blocker dose	**-0.323**	0.153	0.724	**P=0.035**
(First ECG risk-score	0.236	0.101	1.266	**0.020**)
Predictors of sudden deaths at late follow-up				
Last ECG risk-score	0.402	0.117	1.495	**P<0.001**
Last Detroit Z-score (maximal wall thickness)	0.381	0.177	1.464	**P=0.031**
Last Beta-blocker dose	**-0.160**	0.069	0.852	**P=0.020**