THE INVERTED U-SHAPED RELATION BETWEEN THE RISK OF SUDDEN CARDIAC DEATH AND MAXIMAL LEFT VENTRICULAR WALL THICKNESS IN HYPERTROPHIC CARDIOMYOPATHY.

Running title: Maximal wall thickness and sudden death in HCM

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is associated with sudden cardiac death (SCD). Some studies have shown an association between risk of sudden death and left ventricular maximal wall thickness (MWT), but there are few data in patients with extreme hypertrophy. The aim of this study was to determine the relation between MWT and the risk of SCD.

Methods and results: This is a multicentre, retrospective, longitudinal cohort study of 3673 adult (≥16 years) patients, previously used to develop and validate a risk prediction model for SCD (HCM Risk-SCD). There was an inverted U-shaped relation between MWT and the estimated 5 year risk of SCD. In patients with MWT≥35mm [n=47; mean age 33 years; 81% male] there was a single SCD end-point (annual rate 0.2%; 95% CI: 0.03, 1.60) and three additional cardiovascular events during a median follow-up of 9.5 years. Compared to patients with MWT≤14mm, those with MWT≥35mm did not have a higher risk for SCD (HR 0.22; 95% CI 0.03, 1.65), cardiovascular death (HR 0.66; 95% CI 0.26, 1.67) or all-cause mortality (HR 0.73; 95% CI 0.32, 1.69).

Conclusions: The risk of SCD has a complex, non-linear relationship to MWT. The pathophysiological mechanisms behind this observation require further study but ICD implantation should not be guided solely on the severity of left ventricular hypertrophy.

KEYWORDS: hypertrophic cardiomyopathy; sudden cardiac death; implantable cardioverter defibrillator; risk prediction model

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is an inherited myocardial disorder characterised by increased left ventricular wall thickness which is not solely explained by abnormal loading conditions.[1] The clinical perception is that the more severe the hypertrophy, the higher is the risk of sudden cardiac death (SCD)[2] and left ventricular maximal wall thickness (MWT) is one of several clinical features used to guide prophylactic implantable cardioverter defibrillator (ICD) therapy.[1-3] However, patients at the most severe end of the hypertrophy spectrum are under-represented in clinical studies[4,5] and their assumed high risk status is based on extrapolation of data from other patient subgroups. A recent multicentre study reported that patients with left MWT ≥35mm were not at higher risk of SCD compared to patients with lesser hypertrophy,[6] echoing the findings of an earlier cohort study.[7]. The aim of this study was to examine the relation between MWT and the risk of SCD.

METHODS

Study design and overview

This is a retrospective, multi-centre, longitudinal cohort study conducted by the Hypertrophic Cardiomyopathy Outcomes Investigators (www.HCMRisk.org). The relation of SCD risk and MWT was illustrated using the HCM Risk-SCD model,[8] and survival analysis was used to examine how the observed SCD end-points compared to the risk estimates. The phenotype, genotype and outcomes of patients with extreme MWT (≥35mm) are described to corroborate the risk estimates and survival analysis.

The study conforms to the principles of the Helsinki declaration. The sponsors of this study did not have a role in study design, data collection, analysis, and interpretation. COM, FJ, RO and PE had access to all data and final responsibility to submit the manuscript. The authors from each participating centre guarantee the integrity of data from their institution. All investigators have agreed to the manuscript as written. Author contributions can be found in the supplementary files. Patients at A Coruña University Hospital (Spain), Unit of Inherited Cardiovascular diseases at the 1st Department of

Cardiology (Athens), University Hospital Virgen de la Arrixaca (Spain), and Monaldi Hospital (Italy) provided written informed consent. The ethics committees at Heart Hospital (UK), and Institute of Cardiology at the University of Bologna (Italy) were informed, but approval was not required under local research governance arrangements.

Study population and participating centres

The study cohort consisted of consecutively evaluated patients with HCM from six European centres. HCM was defined as a maximum left ventricular wall thickness ≥15mm unexplained by abnormal loading conditions[1] or in accordance with published criteria for the diagnosis in relatives of patients with unequivocal disease.[9] All patients were ≥16 years of age, with no history of ventricular fibrillation or sustained ventricular tachycardia.

A risk prediction model for SCD (HCM Risk-SCD) was previously derived from this retrospective, multi-centre longitudinal cohort study of 3675 patients using the Cox proportional hazards model and internally validated using bootstrapping. Univariable Cox regression models were fitted for each continuous predictor to test the assumption of linearity with the outcome. To develop the final risk model, multivariable Cox regression models were fitted with all predictors and quadratic terms for the continuous predictors where non-linearity was found. Of eight pre-specified predictors, age, MWT, left atrial diameter, left ventricular outflow tract gradient, family history of SCD, non-sustained ventricular tachycardia, and unexplained syncope were associated with SCD/appropriate ICD shocks at the 15% significance level. MWT was observed to have a nonlinear association with SCD and hence a quadratic term was included for this predictor. These predictors were included in the final model used to estimate individual probabilities of SCD at 5 years. Procedures for collecting clinical data, the detailed clinical characteristics of this cohort and the methods used to develop the risk model have been reported previously.[8] Since the publication of HCM Risk-SCD, two patients (including one

affected by a SCD end-point) were found to have a metabolic disorder and were excluded from the current study.

Study outcomes

The primary study end-point was SCD defined as a composite of witnessed sudden cardiac death with or without documented ventricular fibrillation, death within one hour of new symptoms, nocturnal deaths with no antecedent history of worsening symptoms, aborted SCD or an appropriate ICD shock.[10]

Secondary study end-points for exploratory analyses were as follows:

a) Cardiovascular death defined as a composite of SCD, death from heart failure (death preceded by signs and/or symptoms of heart failure, including cardiogenic shock), stroke, pulmonary or peripheral arterial embolisation, death from a cardiac procedure or myocardial infarction, or orthotopic heart transplantation for end-stage heart failure, as previously described.[10]

b) All-cause mortality defined as a composite of cardiovascular death (as defined above) and any other cause of death.

General statistical methods

All statistical analyses were carried out using STATA (versions 11 and 13). Variables are expressed as mean ± standard deviation (SD), median (25th percentile - 75th percentile) or counts and percentages as appropriate. Least squares linear regression was used to assess the relation of MWT groups to continuous variables. Chi-squared tests were used to assess the relation of MWT to categorical variables.[11] The Bonferroni correction was applied as a multiple testing correction strategy.

MWT as a continuous variable and the estimated probability of SCD at 5 years

The relation between MWT as a continuous variable (mm) and 5-year SCD risk was examined graphically. The risk was calculated using the HCM Risk-SCD model[8] for all MWT values observed in the study (ranging from minimum to maximum), with continuous variables set to their mean value

for the study cohort and dichotomous variables set to 0 (absence) and 1 (presence) to show the effect on risk estimates.

Statistical models examining the relation of MWT in 5mm subgroups to clinical outcomes

In accordance to previous studies, outcomes were examined in 5mm MWT subgroups.[4-6] The Cox proportional hazards model was used to examine SCD using the HCM Risk-SCD predictor variables.[8] The same variables were used in two additional Cox proportional hazards models to explore the relation of MWT to the secondary study outcomes (cardiovascular death and all-cause mortality). The follow-up time for each patient was calculated from the date of their first evaluation to the date of reaching the primary end-point, or death from another cause, or to the date of their most recent evaluation. The annual event rate was calculated by dividing the number of patients reaching the endpoint by the total follow-up period for that end-point. The cumulative probability for the occurrence of an outcome was estimated using the Kaplan-Meier method. Data were assumed to be missing at random and values for the missing predictors were imputed using multiple imputation techniques based on chained equations as previously described.[8]

Genetic data

The cohort was not systematically tested for mutations of sarcomere myofilament genes. The results of *ad hoc* genetic testing of patients with extreme hypertrophy are presented. In the absence of evidence to the contrary (e.g. lack of co-segregation with disease in a family), variants previously reported in the literature as mutations were considered disease causing. The pathogenicity of unreported sequence variants was determined by *in silico* prediction methods and where possible co-segregation analysis.

RESULTS

Baseline clinical characteristics

The study population consisted of 3673 patients with mean MWT 19.6±5mm (minimum: 7mm [diagnosis of HCM on the basis of familial criteria]; maximum: 43mm; figure 1). Thirteen patients

(0.35%) had missing MWT data at baseline (patterns of missing data have been reported elsewhere[8]). The baseline clinical characteristics are shown in table 1. The associations of baseline clinical characteristics to MWT are illustrated in figure 2 (continuous variables) and figure 3 (categorical variables).

Follow-up characteristics and clinical outcomes in the entire cohort

The 3673 patients were followed-up for a total of 24,298 patient-years (median 5.7 (2.8 - 9.2) years). The annual rate of SCD end-points was 0.8% (95% CI 0.7, 0.9) with a 5-year cumulative incidence of 3.7% (95% CI 3.1, 4.5). The annual rate of cardiovascular death was 1.7% (95% CI 1.5, 1.9) with a 5-year cumulative incidence of 7.0% (95% CI 6.1, 8.1). Cardiovascular deaths (n=414) consisted of 197 SCD events, 91 heart failure deaths, 47 cardiac transplants and 79 other cardiac deaths. The annual all-cause mortality (556 end-points) was 2.3% (95% CI 2.1, 2.5) with a 5-year cumulative incidence of 9.0% (95% CI 8.1, 10.1).

MWT as a continuous variable and the estimated probability of SCD at 5 years

The estimated risk of SCD at 5 years had a non-linear relation to MWT as shown in figure 4. The inverted U-shape of this relation means that the estimated risk of SCD increases with worsening hypertrophy to reach plateau and declines thereafter. The inverted U-shaped curve becomes more pronounced with increases in prognostic index i.e. with higher risk of SCD. This suggests that, for a specified change in MWT there appears to be a variable change both in the magnitude and direction of SCD risk depending on other risk predictors e.g. an increase in MWT from 20 to 25mm is associated with a higher increase in the risk of SCD when other high risk features are present (high prognostic index).

Relation of MWT in 5mm subgroups to SCD and additional exploratory analyses

The Kaplan-Meier curves showing the cumulative incidence of the SCD end-point, cardiovascular deaths, and all-cause mortality in 5mm MWT groups are shown in figure 5. The effect of 5mm increments in MWT on the primary study outcome (SCD) and the secondary exploratory outcomes (cardiovascular deaths and all-cause mortality) was examined in three multivariable Cox proportional

hazards models shown in table 2. Compared to HCM patients with MWT≤14mm, patients with MWT≥35mm did not have a significantly higher risk for SCD, cardiovascular death or all-cause mortality.

Follow-up characteristics and clinical outcomes in patients with extreme hypertrophy

The 47 patients (1% of the cohort) with MWT≥35mm had longer follow-up (median 9.5 (4.8 - 13.3) years) than the rest of the cohort (median 5.6 (2.8 - 9.2) years). During a total of 445 patient-years, four patients with MWT≥35mm died from cardiovascular causes (one suddenly, two from heart failure and one from systemic embolisation; table 3). All observed cardiovascular deaths in patients with MWT≥35mm occurred beyond 5 years of follow-up. The annual rate of the SCD end-point was 0.2% (95% CI 0.03, 1.60) with a 10-year cumulative incidence of 3.0% (95% CI 0.4, 20.0). The annual rate of cardiovascular death was 0.9% (95% CI 0.3, 2.6) with a 10-year cumulative incidence of 10.0% (95% CI 0.3, 29.0). A single patient with MWT≥35mm died from non-cardiac causes (complications of viral respiratory tract infection after 4.8 years of follow-up). The annual all-cause mortality rate was 1.1% (95% CI 0.5, 2.7) with a 10-year cumulative incidence of 12.0% (95% CI 0.5, 31.0).

Sarcomeric protein gene mutations in patients with extreme hypertrophy

Genetic testing was carried out in 37 (79%) patients with MWT≥35mm. Sarcomeric protein gene mutations were detected in 16 patients (43%). Mutations in myosin-binding protein C *(MYBPC3)* and/or β-myosin heavy chain *(MYH7)* mutations were detected in 13 (81%) of the 16 mutation positive patients and one patient (6%) was double heterozygote. The sarcomeric protein gene mutations and clinical characteristics of the 16 genotype positive patients are shown in supplementary table 2. Variants of unknown significance are also shown in the supplementary data. Of the remaining 31 patients (21 mutation-negative and 10 not genetically tested), 2 (6%) received a pacemaker during follow-up and none had evidence of pre-excitation. The baseline clinical characteristics of mutation-positive and mutation-negative patients, and patients who were not genetically tested are shown in supplementary table 3.

DISCUSSION

Until very recently, it was assumed that the risk of SCD in patients with HCM increased in direct proportion to the severity of hypertrophy.[2,4,5] This study shows that the relationship between SCD risk and MWT is more complex than previously thought in that risk increases with worsening hypertrophy to reach plateau and declines thereafter. Contrary to received opinion, the incidence of SCD in patients with extreme hypertrophy may not be very high in the absence of other clinical risk factors.

There is no clear explanation for the inverted U-shaped relation of MWT to SCD. All patients with HCM have the structural substrate for ventricular arrhythmias. Disarray and cardiac hypertrophy support re-entry[12] and arrhythmias are often triggered by premature ventricular ectopics.[13] It is also likely that sustained ventricular arrhythmias are precipitated only when transient phenomena (e.g. myocardial ischemia secondary to left ventricular outflow tract obstruction) reduce the threshold for arrhythmogenesis.[13,14] Patients at the extremes of the MWT spectrum may have a very high arrhythmia threshold or be less exposed to transient functional modulators. We cannot exclude the coexistence of other unknown protective factors that operate at the extremes of the MWT spectrum and confer a survival advantage. Advanced tissue characterisation techniques using CMR or PET may further our understanding of the arrhythmogenic substrate in HCM.[15]

In this study patients with extreme hypertrophy experienced few clinical events despite longer follow-up. These data are in keeping with the limited literature on hypertrophy of this severity. In one study of 30 patients with MWT≥35mm, there was only one SCD end-point after a mean follow-up of 6 years (approximate event rate: 0.6%/year; 95% CI 0.08, 3.9).[7] In a more recent multivariable analysis which examined the temporal association of unexplained syncope to SCD, 30 patients with MWT≥35mm were found to have a similar risk of SCD to patients with MWT≤10mm (hazard ratio: 0.66; 95% CI 0.21, 17.87).[6] In all published studies, the confidence intervals associated with the risk estimates are wide due to small numbers which is an inherent limitation when studying the extremes of the phenotypic spectrum.

Since 2003, international guidelines have considered MWT≥30mm as a risk factor for SCD,[2,3] but the data to support this recommendation are conflicting (figure 6).[4-6,10,16-24] In this context, our findings suggest that ICD implantation should not be based solely on the severity of left ventricular hypertrophy and that a more global SCD risk assessment which integrates other risk factors should be used.

In this study the typical patient with MWT≥35mm was a young male and the prevalence of LVOTO≥50mmHg, non-sustained ventricular tachycardia, left atrial dilation, NYHA class III/IV and unexplained syncope was less than other MWT subgroups. The comparatively small left atrial size and good functional capacity in this subgroup may be related to the lower prevalence of significant left ventricular outflow tract obstruction.[17,21,22] Even though most patients were <40 years of age, MWT≥35mm was not exclusively seen in young patients. The male preponderance is not unique to this patient subgroup, and may relate to sex hormone receptor gene variations, social factors or diagnostic bias. [25,26]

We hypothesised that the genetic substrate in patients with MWT≥35mm might differ from patients with lesser degrees of hypertrophy. However, the overall prevalence of sarcomeric protein gene mutations in patients with MWT≥35mm was comparable to that reported in recent pooled analysis of unselected cohorts of unrelated HCM patients and was similarly dominated by *MYH7* and *MYBPC3* mutations.[27] In addition, none of the observed mutations has been consistently linked with MWT≥35mm. Complex genotypes have been associated with severe hypertrophy,[28-30] but this study shows that the reverse is not true as the majority of cases MWT≥35mm was not linked to a complex genotype. HCM with extreme MWT can be a feature of some glycogen storage diseases and it is conceivable that some patients had undiagnosed metabolic disorders. However, the lack of

electrocardiographic evidence of pre-excitation, the low prevalence of permanent pacemaker implantation and the relatively benign natural history make diseases such as Danon and PRKAG2 related cardiomyopathy[31] unlikely causes for the phenotype in mutation-negative patients. It is more likely that other genomic and environmental modifiers are responsible for the severe phenotypic expression.

Limitations

Even though this is the largest cohort of HCM patients with MWT≥35mm, the number of patients is still small, reflecting the low prevalence of this phenotype. The findings of this study are limited to patients without a history of aborted SCD and exclusion of patients with MWT≥35mm and a previous history of aborted SCD could give the impression of better prognosis. However, patients with MWT≥35mm are also scarce in previously published cohorts with aborted SCD[32,33] and this is an unlikely explanation for the observations of this study. The findings of this study should not be extrapolated to pediatric (<16 years) patients as they were excluded from the study. Furthermore, HCM Risk-SCD estimates use MWT as the sole measure of left ventricular hypertrophy, and the impact of the septal morphology[34] and/or extent of hypertrophy[5] on SCD risk was not examined.

CONCLUSIONS

The risk of SCD has a complex, non-linear relation to MWT in patients with HCM. Patients with MWT≥35mm may have a relatively good prognosis from SCD despite the extreme severity of hypertrophy. The pathophysiological mechanisms behind this observation require further study but ICD implantation should not be guided solely on the severity of left ventricular hypertrophy.

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APPENDIX

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DISCLOSURES

Lorenzo Monserrat is shareholder in Health in Code S.L. Dr. Ortiz-Genga received personal fees from Health in Code S.L. All other authors have no conflicts of interest to declare.

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TABLE 1: Clinical characteristics at baseline evaluation

Baseline characteristic	Study population	Maximal LV wall thickness ≥35mm
Number of patients	3673	47
Male	2347 (64%)	38 (81%)
Age; years	48±16	33±14*
NYHA III/IV	426 (12%)	3 (7%)
Myectomy	34 (1%)	0
Alcohol septal ablation	10 (0.3%)	0
Amiodarone	468 (13%)	7 (15%)
ICD†	42 (1%)	3 (6%)
NSVT	633 (20%)	13 (29%)
LA diameter; mm	44±8	45±7
$LVOTG_{max}$; mmHg	12 (5-49)	16 (8-43)
$LVOTG_{max}$≥50 mmHg	891 (25%)	11 (24%)
LVedd; mm	45±7	40±6
FS; %	41±9	47±11
FHSCD	884 (24%)	15 (32%)
Unexplained syncope	506 (14%)	4 (9%)

LV: Left ventricular, NYHA: New York Heart Association, ICD: implantable cardioverter defibrillator, AF: Atrial fibrillation, NSVT: non-sustained ventricular tachycardia, LA: left atrium, LVOTG: left ventricular outflow tract gradient at rest or Valsalva, LVedd: left ventricular end diastolic dimension, MWT: maximal wall thickness, FS: fractional shortening, FHSCD: family history of sudden cardiac death, SCD: sudden cardiac death.

*Age range: minimum 17.2 years, maximum: 77.3years; Interquartile range: 21.8-41.3 years

† During the study period, a total of 558 (15%) patients were treated with an ICD

TABLE 2: The risk of cardiovascular outcomes and maximal wall thickness in 5mm groups

		Primary outcome			Exploratory analyses					
		Sudden cardiac death			Cardiac death/transplant			All-cause mortality		
Variable		Hazard Ratio	p-value	95% CI	Hazard Ratio	p-value	95% CI	Hazard Ratio	p-value	95% CI
Maximal wall thickness	≤14mm	Baseline group for comparison			Baseline group for comparison			Baseline group for comparison		
	15-19mm	0.93		0.56, 1.54	0.82		0.59, 1.13	0.78		0.59, 1.03
	20-24mm	1.09		0.66, 1.81	0.90		0.65, 1.25	0.93		0.70, 1.23
	25-29mm	1.21	0.02	0.69, 2.13	0.99	0.047	0.68, 1.46	1.04	0.02	0.74, 1.44
	30-34mm	2.13		1.17, 3.89	1.56		0.99, 2.45	1.45		0.96, 2.19
	≥35mm	0.22		0.03, 1.65	0.66		0.26, 1.67	0.73		0.32, 1.69
Age (years)		0.98	0.001	0.97, 0.99	1.01	<0.001	1.01, 1.02	1.03	<0.001	1.02, 1.04
LA diameter (mm)		1.03	0.004	1.01, 1.05	1.05	<0.001	1.04, 1.06	1.04	<0.001	1.03, 1.05
LVOTG$_{max}$ (mmHg)		1.01	0.007	1.001, 1.01	1.001	0.470	0.998, 1.004	1.001	0.452	0.999, 1.003
FHSCD		1.58	0.003	1.17, 2.12	1.27	0.033	1.02, 1.58	1.19	0.081	0.98, 1.45
NSVT		2.44	<0.001	1.74, 3.42	1.83	<0.001	1.43, 2.33	1.48	<0.001	1.20, 1.83
Unexplained syncope		1.99	<0.001	1.44, 2.74	1.58	<0.001	1.24, 2.02	1.54	<0.001	1.24, 1.91

LA: left atrium, LVOTG: left ventricular outflow tract gradient at rest or Valsalva, FHSCD: family history of sudden cardiac death, NSVT: non-sustained ventricular tachycardia. The number of end-points per 5mm subgroup is shown in supplementary table 1.

Table 3: Baseline clinical characteristics of patients with maximal left ventricular wall thickness ≥35mm experiencing cardiovascular end-points

Age (years)	Sex	NSVT	MWT (mm)	LVedd (mm)	LA (mm)	LVOTg (mmHg)	FHSCD	Unexplained syncope	Follow-up (years)	Mutation	CVS end-point
24	Male	No	36	40	44	8	No	No	9.7	MYH7: R723C	Heart failure
29	Male	No	37	47	45	55	Yes	Yes	7.3	None detected	SCD
49	Male	Yes	37	30	42	19	No	No	17.5	Not tested	Systemic embolus
77	Female	No	37	37	50	66	Yes	No	8.1	MYH7: I736T and TNNT2: A28V	Heart failure

NSVT: non-sustained ventricular tachycardia, LA: left atrium, LVOTg: left ventricular outflow tract gradient at rest or Valsalva, LVedd: left ventricular end diastolic dimension, MWT: maximal wall thickness, FS: fractional shortening, FHSCD: family history of sudden cardiac death, SCD: sudden cardiac death, CVS: cardiovascular death. All patients were in NYHA 1-2, and in sinus rhythm at baseline evaluation.

FIGURE LEGENDS

FIGURE 1: The distribution of maximal wall thickness in the study cohort

Patients with MWT<15mm were diagnosed on the basis of familial disease.[9]
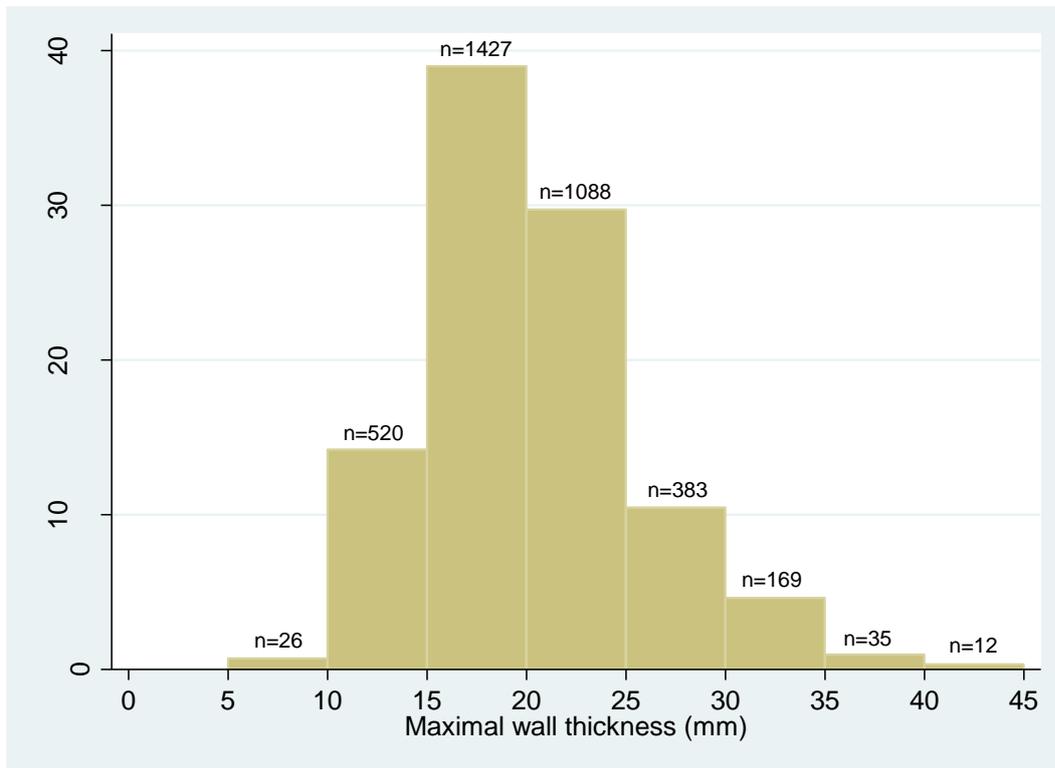
FIGURE 2: Relation of maximal left ventricular wall thickness to age and left atrial diameter

Mean age (years) and left atrial diameter (mm) with 95% CI, for each 5mm MWT subgroup are shown in panel A and B respectively. The p values relate to linear regression.
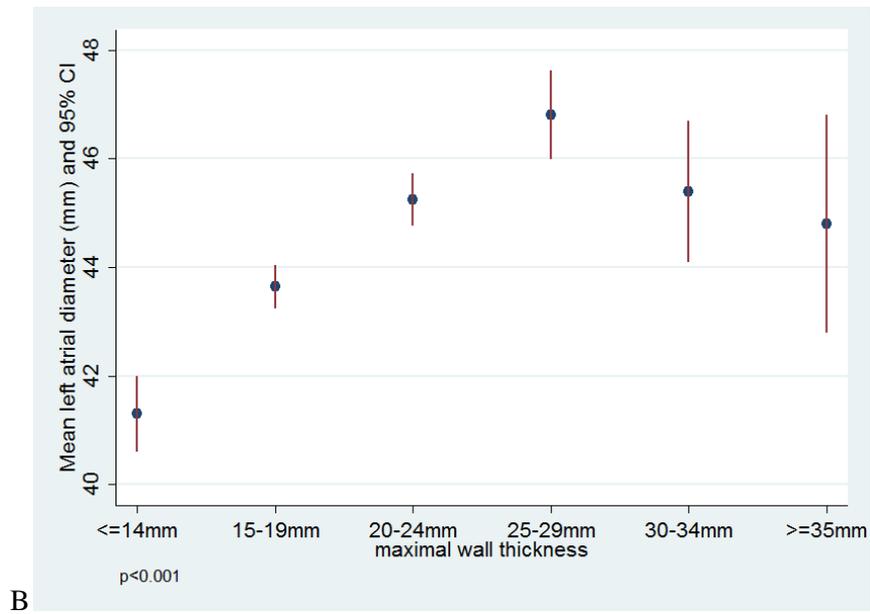
FIGURE 3: The relation of baseline clinical characteristics to maximal left ventricular wall thickness

Proportions (shown on Y-axes) were used to examine the relation of male sex (panel A), NSVT (panel B), LVOTO ≥50mmHg (panel C), family history of SCD (panel D), NYHA III/IV (panel E) and unexplained syncope (panel F) to MWT. The graphs show the proportion for each MWT group, 95% intervals. A chi-squared test for trend was used,[11] and the p value with the Bonferroni correction applied is shown.

FIGURE 4: The relation of the estimated 5-year risk of SCD to maximal left ventricular wall thickness.

The risk of SCD at 5-years was calculated using HCM Risk-SCD with the following predictors kept constant to the cohort mean: age=48years, maximal left ventricular outflow tract gradient=12mmHg, left atrial diameter=44mm.The four curves represent the estimated risk with all possible combinations of NSVT and unexplained syncope, keeping family history of SCD=0. In all cases the risk of SCD increases up to a point and once a plateau is reached, the risk declines. The vertical reference lines represent the 1% and 99% centiles of MWT in this cohort. Variations in family history of SCD also showed the same pattern (plots not shown for clarity).

FIGURE 5: Kaplan-Meier curves showing the incidence of SCD end-points, cardiovascular death and all-cause mortality.

Patients were classified in six 5mm groups on the basis of maximum wall thickness, in accordance to previous studies.[4-6] Panel A shows the cumulative incidence for the SCD end-point. Panel B shows the cumulative incidence for cardiovascular death. Panel C shows the cumulative incidence for all-cause mortality.

FIGURE 6: The risk of SCD and maximal wall thickness ≥30mm in previous survival analyses.

In all studies the number of patients with MWT≥30mm is small, and there is no consistent independent association with SCD.[4-6,10,16-24] The vertical reference line represents a hazard ratio of 1.

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FIGURE 1: The distribution of maximal wall thickness in the study cohort.

FIGURE 2: Relation of maximal left ventricular wall thickness to age and left atrial diameter
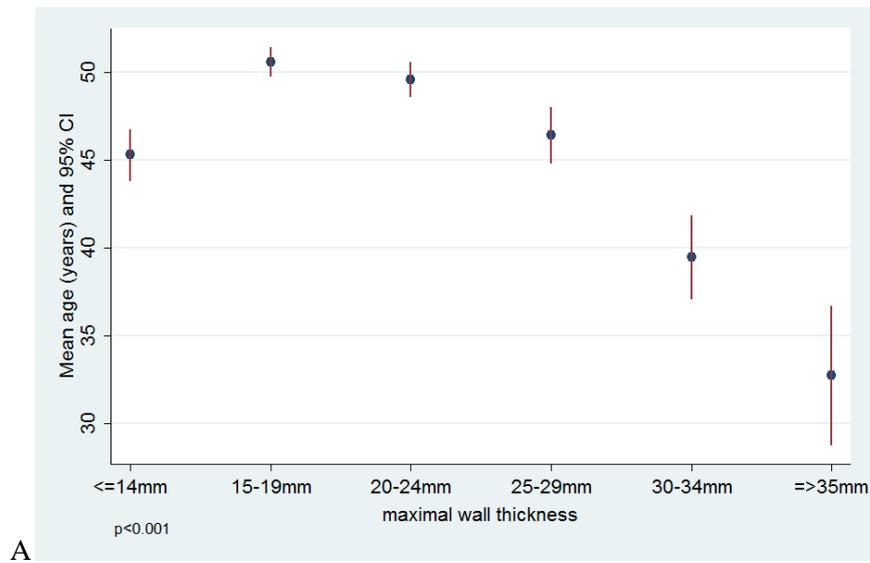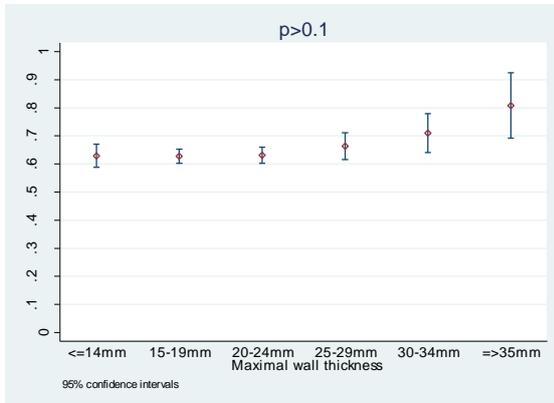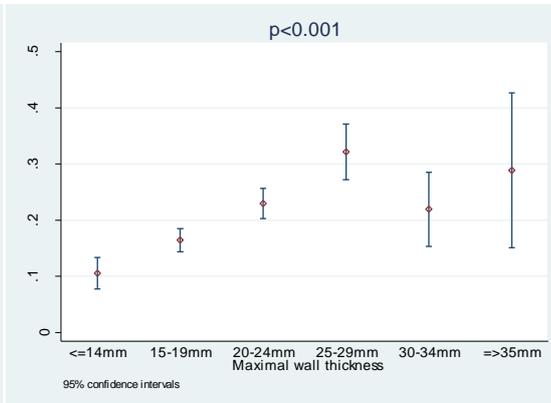

A

B

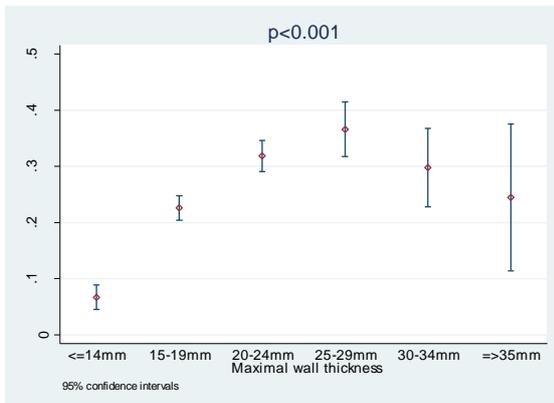**FIGURE 3: The association of baseline clinical characteristics and maximal left ventricular wall thickness**
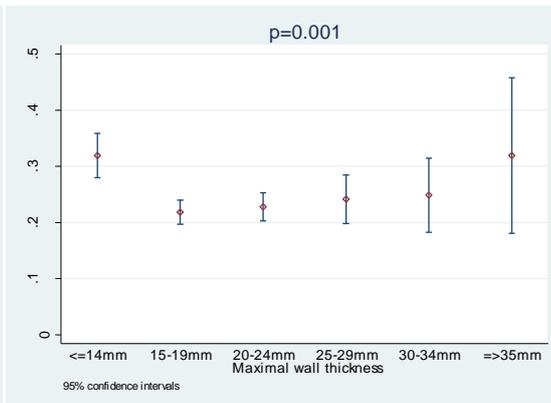
A: Male sex

B: Non-sustained VT

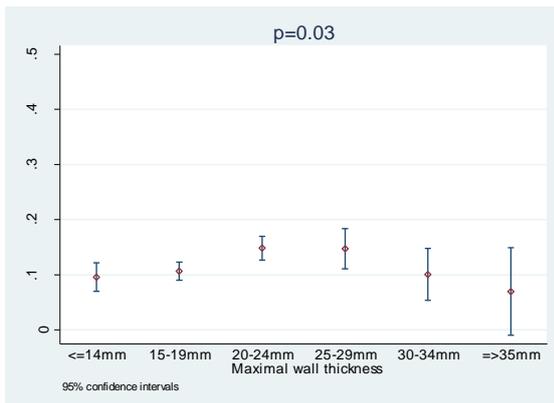C: LVOTO≥50mmHg

D: Family history of SCD
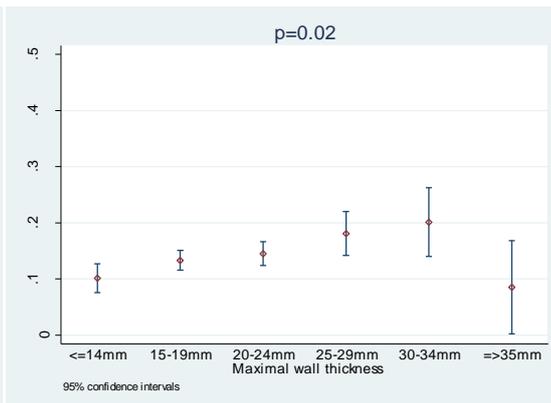
E: NYHA III/IV

F: Unexplained syncope

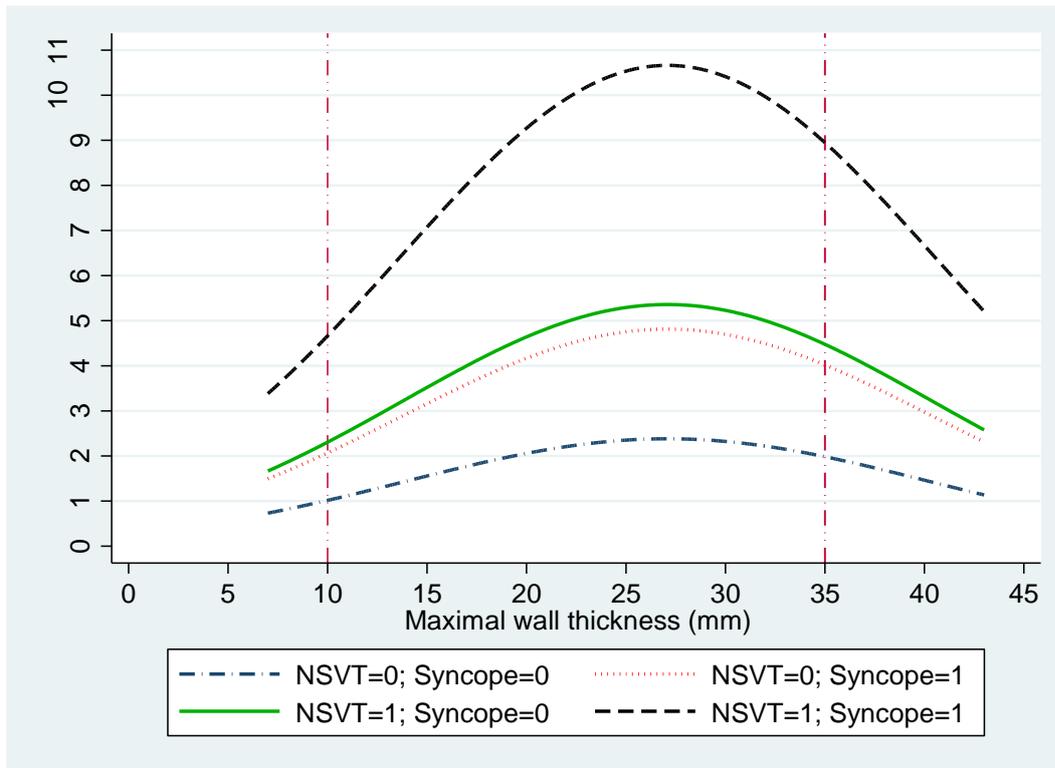**FIGURE 4: The relation of the estimated 5-year risk of SCD to maximal left ventricular wall thickness.**

FIGURE 5: Kaplan-Meier curves showing the cumulative incidence of SCD end-points, cardiovascular death and all-cause mortality
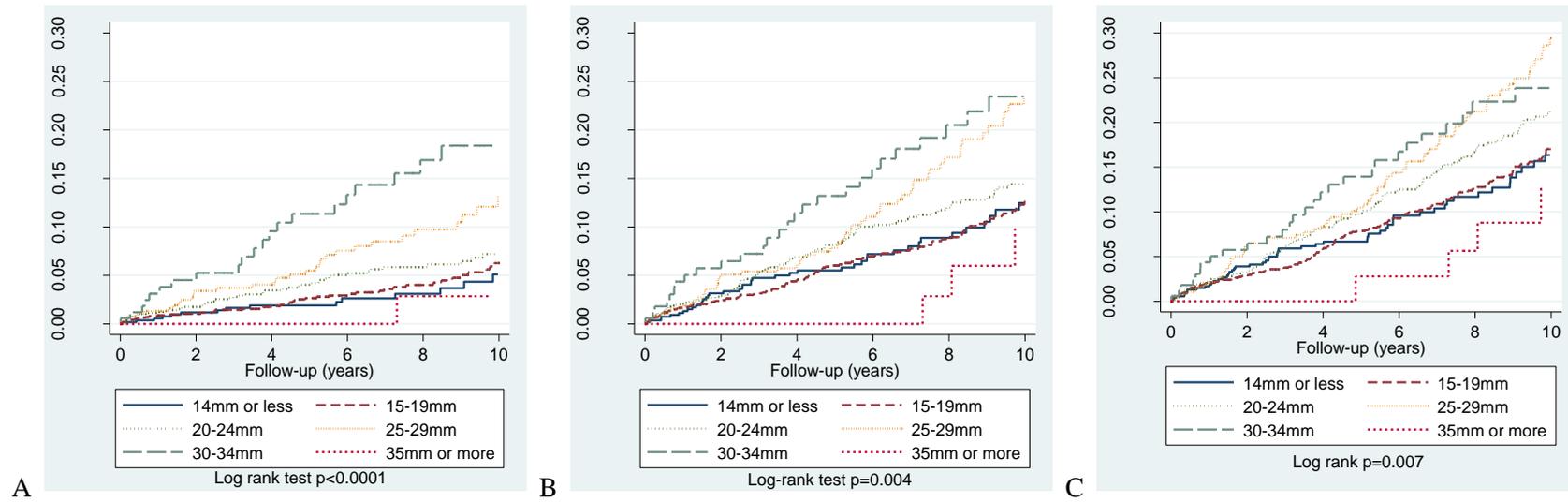
FIGURE 6: The risk of SCD and maximal wall thickness ≥30mm in previous survival analyses.

Reported associations of SCD and MWT>=30mm

current study (n=3673; MV=>35mm)
current study (n=3673; MV 30-34mm)
Efthimiades 2009 (n=166; MV)
Gimeno 2009 (n=1380; MV)
Spirito 2009 (n=1511; MV =>35mm)
Elliott 2006 (n=917; MV)
Dimitrow 2005 (n=151; MV)
Autore 2005 (n=526; MV)
Maron 2003 (n=1101; MV) NS
Olivotto 2003 (n=237; UV) NS
Monserrat 2003 (n=531; MV)
Elliott 2001 (n=630; UV)
Elliott 2000 (n=368; MV)
Spirito 2000 (n=480; MV)

.03   0.125   0.5   1   2   8   30.5

HR with 95% confidence intervals for MWT=>30mm unless otherwise stated (log scale)

UV: univariable; MV: multivariable; NS: non-signficant but HR/95% CI not reported