

openheart Factors influencing long-term heart failure mortality in patients with obstructive hypertrophic cardiomyopathy in Western Sweden: probable dose-related protection from beta-blocker therapy

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ABSTRACT

Objective In order to avoid effects of referral bias, we assessed risk factors for disease-related mortality in a geographical cohort of patients with hypertrophic obstructive cardiomyopathy (HOCM), and any therapy effect on survival.

Methods Diagnostic databases in 10 hospitals in the West Götaland Region yielded 251 adult patients with HOCM (128 male, 123 female). Case notes were reviewed for clinical data and ECG and ultrasound findings. Beta-blockers were used in 71.3% of patients from diagnosis (median metoprolol-equivalent dose of 125 mg/day), and at latest follow-up in 86.1%; 121 patients had medical therapy alone, 88 short atrioventricular delay pacing and 42 surgical myectomy. Mean follow-up was 14.4±8.9 (mean±SD) years. Primary endpoint was disease-related death, and secondary endpoint heart failure deaths.

Results There were 65 primary endpoint events. Independent risk factors for disease-related death on multivariate Cox hazard regression were: female sex ($p=0.005$), age at diagnosis ($p<0.001$), outflow gradient ≥ 50 mm Hg at diagnosis ($p=0.036$) and at follow-up ($p=0.001$). Heart failure caused 62% of deaths, and sudden cardiac death 17%. Late independent predictors of heart failure death were: female sex ($p=0.003$), outflow gradient ≥ 50 mm Hg at latest follow-up ($p=0.032$), verapamil/diltiazem therapy ($p=0.012$) and coexisting hypertension ($p=0.031$), but not other comorbidities. Neither myectomy nor pacing modified survival, but early and maintained beta-blocker therapy was associated with dose-dependent reduction in disease-related mortality in the multivariate model ($p=0.028$), and final dose was also associated with reduced heart failure mortality ($p=0.008$). Kaplan-Meier survival curves analysed in initial dose bands of 0–74, 75–149 and ≥ 150 mg metoprolol/day showed 10-year freedom from disease-related deaths of 83.1%, 90.7% and 97.0%, respectively ($p_{\text{trend}}=0.00008$). Even after successful relief of outflow obstruction by intervention, there was survival benefit of metoprolol doses ≥ 100 mg/day ($p=0.01$).

Conclusions In population-based HOCM cohorts heart failure is a dominant cause of death and on multivariate

Key questions

What is already known about this subject?

► Much research on patients with hypertrophic cardiomyopathy (HCM) has come from tertiary centre populations with possible referral bias for patients with a malignant family history. In those populations sudden cardiac death (SCD) has been an important proportion of disease-related mortality. Major risk factors for SCD include extreme cardiac hypertrophy, cardiac syncope and a malignant family history. Left ventricular outflow tract obstruction is considered a minor risk factor.

What does this study add?

► This study on a complete geographical cohort of patients with obstructive HCM, and long and 100% complete follow-up, shows that heart failure caused a majority (62%) of disease-related deaths, and that SCD only constituted 17% of deaths. Furthermore, this study is the first to demonstrate on multivariate analysis the independent risk factors specifically for heart failure death: female sex, verapamil/diltiazem therapy, coexisting systemic hypertension and outflow gradient ≥ 50 mm Hg. Thus, risk factors for heart failure death are different from those for SCD. This study also suggests that pharmacotherapy with beta-blockers in doses similar to target doses for dilated cardiomyopathy is associated with reduced risk of heart failure death in a dose-dependent fashion.

analysis beta-blocker therapy was associated with a dose-dependent cardioprotective effect on total, disease-related as well as heart failure-related mortality.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is often associated with a dynamic muscular

Key questions

How might this impact on clinical practice?

► American Heart Association guidelines suggest that symptom-free left ventricular outflow tract obstruction need not be treated, but our results indicate that in obstructive HCM there is survival benefit from pharmacotherapy with beta-blockers, even in those patients where interventional treatment has reduced gradient to <30 mm Hg. Furthermore, our results suggest that other risk factors like systemic hypertension need optimal control, and that perhaps calcium channel blockers should be avoided in this patient group.

outflow tract obstruction, and tertiary centres report that outflow tract obstruction is a risk factor for both more rapid symptomatic deterioration and death.¹ Nevertheless, the American Heart Association (AHA) guidelines for treatment of HCM suggest that left ventricular outflow tract obstruction (LVOTO) without symptoms does not necessarily need treatment.² Whereas LVOTO is not considered a major risk factor in the AHA 2011 guidelines,² it is included in the latest European Society of Cardiology algorithm for assessing risk of sudden cardiac death (SCD).³ Most studies on risk factors have emanated from specialised tertiary centres subject to possible referral bias. Therefore, we studied the long-term outcome of patients with hypertrophic obstructive cardiomyopathy (HOCM) in an unselected complete geographical cohort in order to assess risk factors for adverse outcome. No long-term prospective randomised trials of the effect of currently used therapy on survival have been performed so far, thus we included possible effect on survival of drug therapy, myectomy and pacing in the analysis.

MATERIALS AND METHODS**Patient population**

Adult cardiac care for the 1.6 million inhabitants of West Götaland Region is provided by 10 hospitals (listed in the Acknowledgements section). We searched all hospital diagnostic databases for adult inpatients and outpatients attending hospital from January 2002 to December 2013 with diagnostic codes relating to a diagnosis of HCM, and reviewed the case notes on site to identify those with HCM and outflow tract obstruction (HOCM). Diagnosis of HCM was based on standard clinical criteria as defined previously.⁴ Patients were categorised as HOCM if they had a verified LVOT pressure gradient of ≥ 30 mm Hg at rest.³ During the study period, 1142 patients had a verified diagnosis of primary HCM, and from that group 251 patients (128 male, 123 female) fulfilled the HOCM criteria.

Therapy modalities employed

Patients were initially treated medically, and 121 patients remained on medical therapy only, but 130 required interventions, 88 with short atrioventricular delay pacing and 42 with myectomy (flow chart in online supplementary

figure S1). Detailed comparisons of haemodynamic and symptomatic outcomes, and of survival, between myectomy and pacing in this cohort have been published and showed equivalent efficacy.⁵ Consequently, in this study we examined the risk factors for disease-related death in the total HOCM group. Type and dose of beta-blocker and calcium-blocker therapy were recorded. For statistical comparison, all beta-blocker doses were converted to equivalent doses of metoprolol (the beta-blocker most commonly employed: 48.6% metoprolol, 22.7% bisoprolol, 7.5% propranolol and 6.7% atenolol). The conversion used was metoprolol 100 mg=propranolol 80 mg⁶=bisoprolol 5 mg=atenolol 50 mg.

Clinical measures collected

Clinical features (including proposed risk factors and comorbidities), ECG and echocardiographic measurements, implantable cardioverter-defibrillator (ICD) therapies and type of medical therapy and dose used were documented at diagnosis, and at latest follow-up visit.

Cause of death

Vital status was censored on 28 February 2015. The Swedish unique personal identification number allowed us to establish causes of death by death certificates from the National Board of Health and Welfare, in addition to case note review. No patient was lost to follow-up. The primary endpoint was a composite of total cardiac mortality, heart transplantation and fatal embolic stroke of presumed cardiac origin together referred to as 'disease-related death'.

Statistics

Analysis was carried out by SPSS statistical software, V.22.0 (IBM). The majority of the variables studied did not show a normal distribution, and accordingly those data are presented by median (IQR). Statistical comparisons of paired continuous variables were made by Wilcoxon signed-rank test, and for paired binary data with McNemar test. Survival was analysed by Kaplan-Meier curves and the log-rank test, and comparative analysis of risk factors for the endpoint was carried out by univariate and multivariate Cox proportional hazards method. Variables were selected for multivariate analysis if univariate p values were ≤ 0.20 . The number of variables was restricted to six at a time in our multivariate models in order to have adequate statistical power, and were analysed with backward selection. All tests were two sided, and p values < 0.05 were considered statistically significant; variables with $p < 0.10$ on multivariate analysis were kept in multivariate models. Correlations were analysed with Pearson's correlation coefficient for continuous variables and Spearman's rho for categorical data. For intergroup comparisons in online supplementary tables, Mann-Whitney U test was used for continuous variables, and two-tailed Fisher's exact test and χ^2 test for categorical variables as appropriate.

Table 1 Characterisation of total cohort at diagnosis and at latest follow-up (n=251), shown as median (IQR) when not otherwise specified

	At diagnosis	At latest follow-up	P value
Total follow-up (years)		13.2 (12.4)	
Age	56 (27)	70 (23)	
Age, male (n=128)	51 (24)	64 (21)	
Age, female (n=123)	62 (20)	75 (18)	
Body mass index	26 (6)	27 (7)	0.001
NYHA class (mean±SD)	2.2 (0.73)	1.8 (0.73)	<0.001
NYHA class ≥III (%)	40.4	15.8	<0.001
Family history of SCD (%)	15.1		
History of syncope (%)	25.4		
Transthoracic echocardiogram and ECG measurement:			
Septum (mm)	19 (6)	19 (5)	0.56
LVPW (mm)	13 (4)	12 (5)	0.48
Wall thickness ≥30 mm (%)	3.4	0.8	0.45
LVEDD (mm)	43 (9)	43 (7)	0.50
Ejection fraction (%)	69 (15)	63 (10)	<0.001
LVOT gradient rest (mm Hg)	65 (57)	16 (36)	<0.001
Left atrium diameter (mm)	41 (15)	48 (11)	<0.001
Sokolow-Lyon index (mm)	3.3 (1.8)	3.1 (2.0)	0.62
QTc (ms)	436 (45)	449 (49)	<0.001
Atrial fibrillation (%)	4.0	30.6	<0.001
Other comorbidity (proportion in %):			
Systemic hypertension	13.5	37.5	<0.001
Diabetes mellitus	5.6	13.5	<0.001
Coronary artery disease	3.6	13.1	<0.001
Chronic kidney disease	1.2	4.0	0.016
Chronic obstructive pulmonary disease	6.8	8.8	0.063

Interindividual paired values are compared with Wilcoxon signed-rank test, normally distributed values with paired t-test and binary data with McNemar test, with proportion positive indicated in per cent. Bold text high-light statistically significant findings.

LVEDD, left ventricle end-diastolic diameter; LVOT, left ventricular outflow tract; LVPW, left ventricle posterior wall; NYHA, New York Heart Association; SCD, sudden cardiac death.

RESULTS

Characterisation of the cohort

Mean follow-up was 14.4±8.8 years (mean±SD) and median follow-up 13.2 (IQR=12.4) years. Findings at the time of diagnosis and at latest follow-up are shown in [table 1](#). The sex distribution was even, but females were generally older. Initial medical therapy consisted of beta-blocker in 69.7%, verapamil/diltiazem in 10.8% and in 1.6% beta-blocker and calcium-blocker were combined; 17.9% of patients did not receive any initial pharmacotherapy. During follow-up there was improvement in New York Heart Association (NYHA) class with therapy, and

reduction in resting LVOT gradient at rest to a median of 16 mm Hg. However, 21% had resting gradients remaining ≥50 mm Hg, and 33% ≥30 mm Hg at latest assessment. Atrial size and incidence of atrial fibrillation had increased at latest follow-up.

Primary endpoint

There were 65 primary endpoint events (53 cardiac deaths, 4 heart transplants, 8 embolic deaths) during follow-up consisting of a total of 3614 patient-years. Only 11 deaths (17%) were attributed to SCD, with an annual rate of 0.37% during the first 10 years of follow-up. The majority of deaths were due to heart failure (62%), with myocardial infarct (8%) and embolic strokes (12%) being less common. There were 25 non-cardiac deaths in the cohort.

ICD implantations

Sixteen patients (6.4%) had received ICD implantation (4 secondary, 12 primary prevention). There was one appropriate discharge in 149 patient-years, that is an appropriate annual discharge rate of 0.67%.

Medical therapy employed

Beta-blocker use increased from 71.3% at diagnosis to 86.1% at latest follow-up, with no significant differences between intervention and non-intervention groups (online supplementary table S1). The beta-blocker dose prescribed initially had no significant correlations to NYHA class, chest pain, syncope, outflow gradient or severity of cardiac hypertrophy (correlation coefficients between -0.053 and 0.144 for all). Hence, patients with the most advanced disease did not receive lower doses. The median initial dose prescribed was 125 mg metoprolol/day, and at latest follow-up was 150 mg/day for patients given beta-blockers. Verapamil/diltiazem therapy was given in median doses of 240 (IQR=80) mg/day, and altered only from 12.4% of patients to 12.7% at latest follow-up. For other medication, see online supplementary table S1.

Cox hazard analysis of risk factors

Risk factors at presentation for subsequent disease-related death Among risk factors significantly associated with outcomes on univariate analysis were age at diagnosis, female sex, coronary artery disease and a resting LVOT gradient ≥50 mm Hg. In the multivariate analysis of the whole group, those risk factors except coronary artery disease remained as significant independent risk factors. Comorbidities and accepted risk factors for SCD were not significant risk factors for total disease-related deaths ([table 2](#)).

Risk factors that were significantly associated with disease-related mortality were also significantly associated with all-cause mortality (online supplementary table S2).

For *heart failure deaths* female sex and age were independent risk factors on multivariate analysis ([table 2](#); univariate risk factors, see online supplementary table S3).

Table 2 Risk factors/protective factors at diagnosis for disease-related and heart failure death on Cox hazard regression

Variable	B	SE	Exp(B)	95% CI Exp(B)	P value
<i>Univariate Cox hazard analysis disease-related death</i>					
Female sex	0.756	0.258	2.136	1.288 to 3.542	0.003
Age at diagnosis	0.045	0.008	1.046	1.028 to 1.063	<0.001
NYHA class ≥III vs ≤II	0.198	0.251	1.218	0.745 to 1.994	0.432
Body mass index	-0.047	0.032	0.954	0.896 to 1.016	0.143
Systemic hypertension, Yes versus No	0.554	0.366	1.740	0.850 to 3.565	0.130
Diabetes mellitus, Yes versus No	0.677	0.469	1.968	0.785 to 4.938	0.149
Coronary artery disease, Yes versus No	1.430	0.530	4.178	1.479 to 11.807	0.007
Atrial fibrillation, Yes versus No	0.101	1.013	1.107	0.152 to 8.059	0.920
Chronic kidney disease	0.624	0.738	1.866	0.439 to 7.926	0.398
Chronic obstructive pulmonary disease	0.419	0.430	1.521	0.654 to 3.534	0.330
Family history of SCD, Yes versus No	0.596	0.415	1.814	0.804 to 4.095	0.152
History of syncope, Yes versus No	0.222	0.298	1.248	0.697 to 2.237	0.456
History of chest pain, Yes versus No	0.124	0.253	1.131	0.687 to 1.859	0.624
Septum (mm)	-0.023	0.029	0.977	0.924 to 1.033	0.417
Septum:cavity ratio	-0.813	0.997	0.44	0.063 to 3.131	0.415
Left ventricle wall:cavity ratio	-0.078	1.484	0.925	0.050 to 16.96	0.958
Max wall thickness (mm)	-0.022	0.028	0.978	0.925 to 1.035	0.445
Max wall thickness ≥30 vs <30 (mm)	0.222	0.720	1.248	0.304 to 5.120	0.758
Left ventricle posterior wall (mm)	0.029	0.047	1.029	0.939 to 1.128	0.540
Initial LVEDD	0.008	0.017	1.008	0.974 to 1.042	0.660
Initial ejection fraction (%)	-0.819	1.137	0.441	0.047 to 4.095	0.471
Left atrium diameter (mm)	0.023	0.014	1.023	0.995 to 1.053	0.112
LVOT gradient (mm Hg)	0.002	0.003	1.002	0.996 to 1.008	0.511
LVOT gradient at rest ≥30 vs <30 (mm Hg)	0.632	0.361	1.880	0.927 to 3.814	0.080
LVOT gradient at rest ≥50 vs <50 (mm Hg)	0.587	0.281	1.804	1.031 to 3.133	0.038
Beta-blocker, Yes versus No	-0.735	0.256	0.479	0.298 to 0.812	0.004
Beta-blocker dose (mg/day)	-0.006	0.002	0.994	0.991 to 0.997	0.001
Beta-blocker ≥100 vs <100 (mg)	-1.121	0.291	0.330	0.191 to 0.581	<0.001
Verapamil/diltiazem use, Yes versus No	0.891	0.320	2.441	1.314 to 4.553	0.005
Verapamil/diltiazem daily dose (mg/day)	0.003	0.001	1.003	1.001 to 1.006	0.014
Statin treatment, Yes versus No	-0.856	0.441	0.425	0.179 to 1.008	0.052
<i>Multivariate Cox hazard analysis, disease-related death (93% complete data)</i>					
Female sex	0.823	0.292	2.278	1.286 to 4.036	0.005
Age	0.039	0.009	1.039	1.021 to 1.058	<0.001
LVOT gradient at rest ≥50 vs <50 (mm Hg)	0.631	0.301	1.879	1.042 to 3.388	0.036
Beta-blocker dose (mg/day)	-0.004	0.002	0.996	0.992 to 1.000	0.028
<i>Multivariate Cox hazard analysis, heart failure death (93% complete data)</i>					
Female sex	0.763	0.387	2.145	1.005 to 4.581	0.049
Age	0.060	0.014	1.062	1.034 to 1.091	<0.001
Beta-blocker dose (mg/day)	-0.005	0.003	0.995	0.990 to 1.001	0.080

Significant negative values of B suggest reduction in risk. Bold text high-light statistically significant findings.

LVEDD, left ventricle end-diastolic diameter; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; SCD, sudden cardiac death.

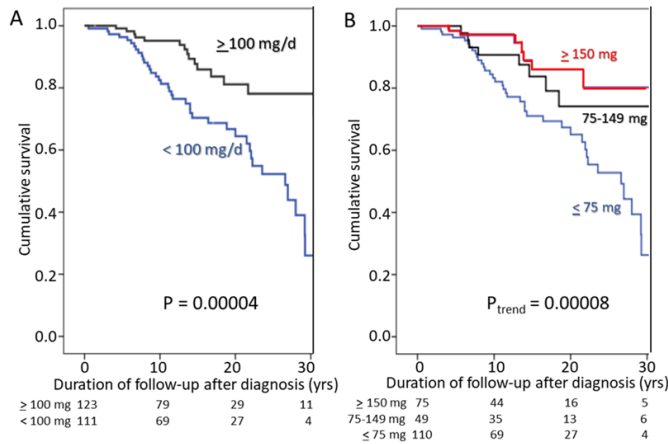


Figure 1 (A) Kaplan-Meier survival curve illustrating freedom from disease-related death in patients with initial beta-blocker dose 0–99 mg/kg, that is, less than the total cohort median dose of 100 mg metoprolol equivalents/day (blue curve), or equal to or greater than 100 mg/day (black curve), who on log-rank testing have significantly superior survival ($p=0.00004$). (B) Kaplan-Meier survival curves showing freedom from disease-related death in patients receiving 0–74 mg/day (blue curve), 75–149 mg/day (black curve) or ≥ 150 mg/day (red curve) in metoprolol equivalents, with increasing daily dose showing significant trend of improvement ($p=0.00008$). The numbers below the curves indicate the number of patients remaining in the survival curves.

Influence of therapy choice on survival

Neither pacing nor myectomy reduced disease-related deaths significantly, whereas use of beta-blocker therapy started at diagnosis was associated with reduced risk on univariate Cox hazard analysis ($p=0.004$). The association with outcome appeared to be dose dependent with reduced risk with increased daily dose ($p=0.001$) and dose dependency remained significant in the multivariate analysis ($p=0.028$; [table 2](#)), also for heart failure deaths specifically ([table 2](#); [online supplementary table S3](#)). The HR between early beta-blocker use and non-use was 0.49 (95% CI 0.30 to 0.81), $p=0.006$. Freedom from disease-related deaths for patients given ≥ 100 mg/day was significantly better than for those given 0–99 mg/day (log-rank: $p=0.00004$; [figure 1A](#)), as was all-cause survival, $p=0.00005$ ([online supplementary figure S2](#)). There were no significant differences in comorbidities between patients in 0–99 mg/day and ≥ 100 mg/day groups ([online supplementary table S4](#)). The survival curves of patients given no beta-blocker ($n=74$) were overlapping the curves of patients given 25–74 mg/day ($n=36$; $p=0.67$; [online supplementary figure S3](#)) and these patients were combined in a 0–74 mg/day group. Survival curves depicting three dose ranges: 0–74 mg/day, 75–149 mg/day and ≥ 150 mg/day of metoprolol equivalents, the middle band encompassing the median dose, show the benefit of larger doses of beta-blocker most clearly. There was a significant log-rank for trend in reduced risk of disease-related deaths with increased dose ($p=0.00008$; [figure 1B](#)). The 10-year freedom from disease-related

deaths for the three dose bands, 0–74, 75–149, ≥ 150 mg/day, was 83.1%, 90.7% and 97.0%, respectively. The 20-year proportions were 65%, 74% and 86%, respectively. The 10-year freedom from disease-related deaths of patients without beta-blocker therapy was 81.7%. Analysis of total mortality confirmed a similar pattern (log-rank $p_{\text{trend}}=0.00009$), with 10-year all-cause survival of 78.7%, 88.8% and 91.1% in respective dose bands.

Verapamil therapy, on the other hand, was associated with increased risk on univariate analysis ($p=0.014$; [table 2](#)).

Predictors of disease-related death at latest follow-up

On univariate Cox hazard analysis, female sex, age, NYHA class $\geq \text{III}$, a gradient remaining ≥ 50 mm Hg and a smaller left ventricle end-diastolic diameter were associated with a significantly increased risk. Progression to dilated end stage was observed in only 4%. Larger beta-blocker dose was associated with lower risk of disease-related death also at latest follow-up ($p=0.018$). Verapamil/diltiazem was a risk factor on univariate, but not multivariate analysis. Neither use of amiodarone, disopyramide, ACE inhibitor nor spironolactone showed any significant influence on survival. Also at latest follow-up a higher beta-blocker dose remained an independent predictor associated with reduced risk of disease-related death in multivariate analysis ($p=0.021$). Comorbidities were not independent predictors in the multivariate model ([table 3](#)).

For *heart failure death*s specifically, female sex, verapamil/diltiazem therapy, coexisting systemic hypertension and outflow gradient ≥ 50 mm Hg remained independent risk predictors, whereas beta-blocker dose reduced risk ($p=0.008$) in the multivariate model ([table 3](#); for univariate results see [online supplementary table S5](#)).

Multivariate analysis of risk factors, therapies and comorbidities in relation to total *all-cause mortality* is shown in [online supplementary table S6](#). The risk predictors for total all-cause mortality were similar as for disease-related deaths: female sex, age, LVOT gradient ≥ 50 mm Hg and maximal wall thickness. Higher daily dosage of beta-blockers was associated with better survival also on multivariate analysis for total mortality ($p=0.008$).

Beta-blocker and postintervention gradient

Patients not receiving early beta-blockers had significantly higher proportion of disease-related deaths, if post-treatment gradient was ≥ 30 mm Hg (10-year proportion 39.1%) than with gradients < 30 mm Hg (10-year proportion 7.4%; $p=0.002$). Accordingly, we analysed whether the apparent protective effect of beta-blockers was present only in patients with a residual gradient of ≥ 30 mm Hg after initial therapy. This appeared not to be the case as shown in [figure 2A,B](#).

Some patients with good relief of outflow tract obstruction after interventional procedures had beta-blocker therapy reduced after intervention. We therefore explored whether postintervention beta-blocker dose influenced survival, and found that a beta-blocker dose

Table 3 Predictor factors/protective factors for disease-related and heart failure death on Cox hazard regression as recorded at latest follow-up

Variable	B	SE	Exp(B)	95% CI Exp(B)	P value
<i>Univariate Cox hazard analysis for disease-related death</i>					
Female sex	0.756	0.258	2.136	1.288 to 3.542	0.003
Age at follow-up	0.018	0.008	1.018	1.003 to 1.034	0.016
NYHA class \geq III vs \leq II	0.862	0.340	2.369	1.218 to 4.609	0.011
Body mass index	0.000	0.002	1.000	0.995 to 1.005	0.989
Systemic hypertension, Yes versus No	0.476	0.251	1.609	0.984 to 2.632	0.058
Diabetes mellitus, Yes versus No	0.108	0.363	1.114	0.547 to 2.271	0.766
Coronary artery disease, Yes versus No	0.448	0.322	1.566	0.834 to 2.940	0.163
Atrial fibrillation, Yes versus No	0.051	0.126	0.950	0.742 to 1.216	0.681
Chronic kidney disease	0.074	0.479	1.077	0.422 to 2.752	0.877
Chronic obstructive pulmonary disease	0.403	0.402	1.496	0.681 to 3.289	0.316
Septum (mm)	0.021	0.031	1.021	0.961 to 1.086	0.500
Max wall thickness (mm)	0.047	0.031	1.049	0.988 to 1.113	0.121
Left ventricle posterior wall (mm)	0.073	0.050	1.075	0.975 to 1.186	0.146
LVEDD (mm)	-0.047	0.023	0.954	0.912 to 0.998	0.040
Ejection fraction (%)	-0.049	0.996	0.952	0.135 to 6.706	0.961
Left atrium diameter (mm)	-0.004	0.020	0.995	0.996 to 1.035	0.824
LVOT gradient (mm Hg)	0.013	0.003	1.013	1.007 to 1.018	<0.001
LVOT gradient at rest \geq 30 vs $<$ 30 (mm Hg)	0.016	0.006	1.016	1.004 to 1.028	0.008
LVOT gradient at rest \geq 50 vs $<$ 50 (mm Hg)	1.526	0.270	4.600	2.710 to 7.810	<0.001
Myectomy	0.086	0.148	1.090	0.815 to 1.458	0.562
Pacemaker therapy	0.073	0.253	1.076	0.655 to 1.766	0.773
QTc (ms)	0.001	0.021	1.001	0.972 to 1.031	0.940
Beta-blocker dose (mg/day)	-0.003	0.001	0.997	0.995 to 1.000	0.018
Verapamil/diltiazem use, Yes versus No	0.918	0.308	2.504	1.368 to 4.582	0.003
Verapamil/diltiazem dose (mg/day)	0.003	0.001	1.003	1.001 to 1.006	0.011
Amiodarone use, Yes versus No	-0.141	0.391	0.868	0.411 to 1.862	0.723
Disopyramide use, Yes versus No	-0.552	0.467	1.736	0.697 to 4.333	0.237
ACE inhibitor use, Yes versus No	-0.057	0.279	0.945	0.547 to 1.631	0.838
Spironolactone use, Yes versus No	-0.029	0.157	0.972	0.714 to 1.322	0.855
Statin treatment, Yes versus No	-0.759	0.401	0.468	0.213 to 1.028	0.059
Implantable cardioverter-defibrillator (ICD)	-1.196	0.598	3.305	1.023 to 10.678	0.046
<i>Multivariate Cox hazard analysis, disease-related death (96.8% complete data, 3.2% missing)</i>					
Female sex	1.197	0.389	3.310	1.543 to 7.100	0.002
Age	0.024	0.011	1.025	1.003 to 1.047	0.025
LVOT gradient at rest \geq 50 vs $<$ 50 (mm Hg)	1.262	0.374	3.533	1.697 to 7.355	0.001
NYHA class \geq III vs \leq II	0.846	0.383	2.330	1.100 to 4.934	0.027
Beta-blocker dose (mg/day)	-0.005	0.002	0.995	0.991 to 0.999	0.021
<i>Multivariate Cox hazard analysis, heart failure death (96.8% complete data, 3.2% missing)</i>					
Female sex	1.036	0.352	2.819	1.414 to 5.620	0.003
LVOT gradient at rest \geq 50 vs $<$ 50 (mm Hg)	0.014	0.007	1.014	1.001 to 1.028	0.032
Systemic hypertension, Yes versus No	0.726	0.336	2.066	1.069 to 3.995	0.031
Verapamil/diltiazem use, Yes versus No	1.036	0.414	2.817	1.251 to 6.343	0.012
Beta-blocker dose (mg/day)	-0.005	0.002	0.995	0.991 to 0.999	0.008

Significant negative values of B suggest reduction in risk. Bold text high-light statistically significant findings.

ACE, angiotensin converting enzyme; LVEDD, left ventricle end-diastolic diameter; LVOT, left ventricular outflow tract; NYHA, New York Heart Association.

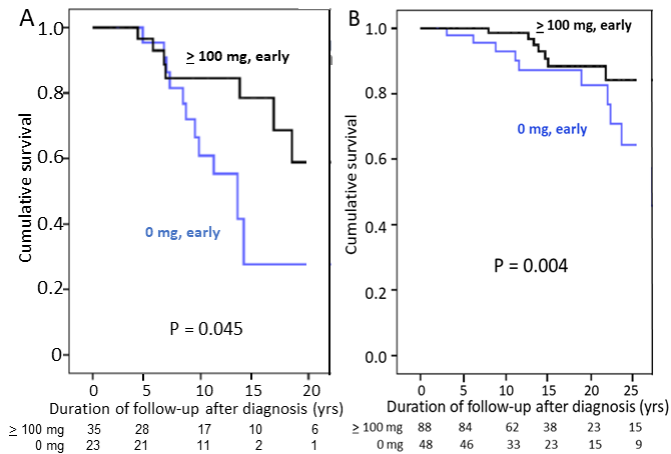


Figure 2 (A) Kaplan-Meier survival curve comparing freedom from disease-related death in patients with residual gradient on treatment ≥ 30 mm Hg in patients with a median initial dose of ≥ 100 mg/day of metoprolol equivalents (black curve) to patients not receiving any beta-blocker (blue curve). There are few patients with gradients ≥ 30 mm Hg, but the difference is nevertheless significant ($p=0.045$). (B) Kaplan-Meier survival curve comparing freedom from disease-related death in patients with residual gradient on treatment < 30 mm Hg in patients with a median initial dose of ≥ 100 mg/day of metoprolol equivalents (black curve) which also has significantly better survival ($p=0.004$) to patients not receiving any beta-blocker (blue curve). The numbers below the curves indicate the number of patients remaining in the survival curves.

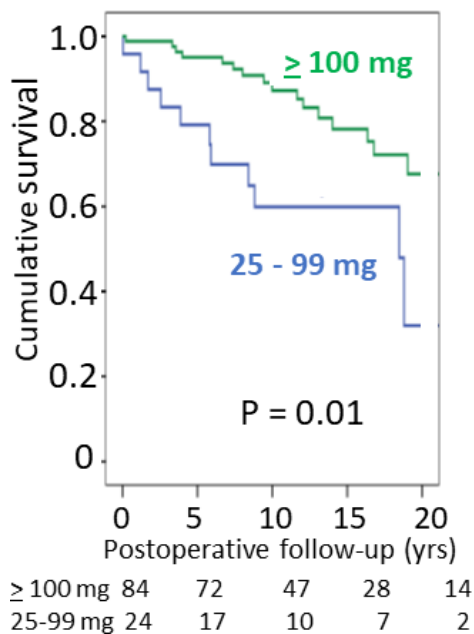


Figure 3 Kaplan-Meier survival curves illustrating postintervention freedom from disease-related death in patients who have received interventional treatment with either short atrioventricular (AV) delay pacing or myectomy related to postintervention dose of beta-blocker therapy. The green curve illustrates survival with postintervention dose of ≥ 100 mg/day of metoprolol equivalents, and the blue curve illustrates the inferior survival with metoprolol-equivalent doses of 25–99 mg/day ($p=0.010$).

≥ 100 mg metoprolol equivalent/day was associated with significantly better outcome than low dose (25–99 mg) (figure 3).

Effect of comorbidities

There was no significant skewing of proportion of patients with comorbidity between patient groups in figure 3 (online supplementary table S7). Furthermore, there was no excess comorbidity in patients who had died a disease-related death (online supplementary table S8).

DISCUSSION

Risk factors for long-term mortality

Age, female sex and an unrelieved LVOT gradient were significant risk factors for disease-related mortality in this study of a geographical cohort of patients with HOCM. These have previously been reported by others.^{1 7–10} It is noteworthy that in our geographical cohort of patients with HOCM, SCD caused a small proportion of disease-related deaths, in spite of a low rate of ICD implantations (6.4%), in contrast to reports from tertiary centres. For example, in a multicentre study of patients with similar age profile as ours, SCD comprised 39% of deaths in the HOCM group, with annual SCD mortality of 0.75%–1.26% in various groups,¹¹ compared with an annual SCD mortality of 0.37% in our study. This may explain why risk factors thought to be important for SCD, such as family history of SCD and maximal wall thickness ≥ 3 cm, failed to show significant impact on total disease-related mortality in our cohort, in contrast to an LVOT gradient ≥ 50 mm Hg. A recent study identified unmet clinical needs in population-based patients with HCM including a 4.3 times excess of heart failure, and that heart failure was more common than SCD and ventricular arrhythmias combined,¹² as in our study. This underlines the importance of evaluating therapies that may reduce non-sudden and heart failure-related mortality in HOCM, like a good control of significant risk factors for heart failure death on multivariate analysis in this study such as systemic hypertension and LVOTO.

Effect of therapy on risk of death

Surgical septal myectomy has long been considered the gold standard treatment for therapy-resistant patients with HOCM,^{2 13 14} and suggested to give superior survival compared with conservative treatment.¹⁵ However, the conservatively treated group was on average 10 years older, and a reduction in cardiovascular mortality in the intervention group could not be substantiated.¹⁵ We have earlier reported that in a geographical cohort of patients with HOCM, neither myectomy nor pacing was significantly associated with improved survival compared with conservative medical therapy, although both treatments improved NYHA class.⁵ In the present study, neither univariate nor multivariate Cox hazard analysis could detect that myectomy or pacing was associated with a survival benefit that was independent of other risk factors such as age (tables 2 and 3). Thus, the only therapy

associated with significant improvement of survival on multivariate analysis in our cohort was beta-blocker therapy. The observed excess mortality in heart failure in patients with HOCM receiving verapamil/diltiazem is concerning but should be interpreted with caution due to the small numbers receiving calcium-blockers. This merits further study in HCM populations with higher use of calcium channel blockers than ours.

Benefit of beta-blocker therapy

Beta-blocker therapy reduces LVOT gradient in HOCM, both at rest and during exercise, and improves symptoms, diastolic function and exercise capacity.^{16–21} In childhood HCM, it is also associated with improved survival²² in a dose-related manner,^{23 24} and reduces risk of SCD.²⁵ It has been claimed that beta-blocker therapy does not affect survival in adult HCM,²⁶ although Frank *et al*²⁷ reported particularly low SCD mortality (0.3%) in patients treated with relatively high doses of propranolol, aiming for ≥ 320 mg/day. In another study on 163 consecutive patients, average follow-up of 5.3 years, of whom 40% received beta-blockers, beta-blocker was significantly associated with improved outcome, HR 0.25 (95% CI 0.08 to 0.77), $p=0.0120$.⁹ In a larger recent study that focused on sex differences in survival (3673 patients), beta-blocker therapy (dose unspecified) was associated with a lower all-cause mortality (they were unable to separate cardiac mortality).²⁸ These observations support our finding that beta-blocker therapy emerges as a significantly protective factor for disease-related deaths even on multivariate analysis (tables 2 and 3, and figure 1A,B), confirmed in an all-cause mortality analysis. Previous studies have included both non-obstructive and obstructive HCM, and the effect we observed might be due to gradient reduction or to the doses employed. Findings illustrated in figure 2B make the former mechanism unlikely. Among patients receiving beta-blockers the early median metoprolol dose for survivors was 162.5 mg metoprolol/day, and median latest follow-up dose was 175 mg/day. Thus, the survivor doses are within the range of doses used in the prospective randomised trials on heart failure that have demonstrated metoprolol significantly reduces cardiac mortality.²⁹ A dose effect would tally with studies that show heart rate lowering efficacy of beta-blocker dose correlates to reduction in mortality in patients with heart failure.³⁰

However, our significant results are quite likely also a question of statistical power. Melacini *et al*'s negative study from 2007²⁶ lacked statistical power to detect a protective effect of beta-blockers: out of 293 patients only 26% were treated with beta-blockers, giving at most 456 patient-years, whereas our study has 2613 patient-years on beta-blocker therapy. With our study there are now three studies from patient cohorts of very different ethnic origin that report statistically significant protection from beta-blocker use. The HR for patients with beta-blocker use from diagnosis was 0.49 (95% CI 0.30 to 0.81) in our cohort. Furthermore, the association was dose dependent

(figure 1A,B), suggesting a pharmacological effect and not a chance association.

Therapy with mild or latent obstruction

The finding of an apparent survival benefit of continued adequate beta-blocker therapy even in patients where interventions have reduced gradients to below 30 mm Hg might indicate that this therapy could be protective also in the absence of LVOT obstruction. A prospective randomised trial in non-obstructive HCM has not been performed. The observation that it takes around 5 years for survival curves to diverge significantly (figure 1A) indicates that the effect may be particularly on myocardial preservation perhaps affecting progress of fibrosis, rather than reducing SCD mortality as reported with higher paediatric dosages.²⁵ Lacking controlled trials, it would be desirable that large international registries for HCM should collect and publish data on mortality related to pharmacotherapy, both type and dose.

Incomplete relief of LVOTO

Our results confirm earlier studies that patients in whom therapeutic interventions have failed to reduce the resting gradient below 30 mm Hg have a worse prognosis^{1 3}; the risk is incremental and the prognosis is particularly poor with gradients ≥ 50 mm Hg. This underlines the importance of intensifying treatment even in asymptomatic patients if a sizeable resting gradient remains.

Strengths and limitations

The strengths of this study are the long follow-up and 100% complete cause of death information. Retrospective studies on complete unselected geographical cohorts are the method of choice in identifying risk factors for adverse outcomes, but it is not the method of choice for evaluating the effects of drug therapy, where prospective randomised trials would be preferable. The fact that there is no published prospective randomised drug trial using mortality as endpoint in patients with HCM, not even from supraspecialised centres, testifies to the difficulties in organising such studies. Particular handicap is studying drugs such as beta-blockers that are out of patent so that pharmaceutical companies have no incentive for financial support.

CONCLUSIONS

In this unselected geographical cohort we found that heart failure was a dominant cause of death in HOCM, and showed that female sex, age and persisting LVOT obstruction were important independent risk factors for disease-related, and specifically heart failure-related deaths. The data indicate that beta-blocker therapy would be beneficial even in asymptomatic LVOT obstruction, aiming for doses of at least 150 mg/day metoprolol equivalents. We hope these results will stimulate international collaborative prospective randomised studies of adequate duration of the effect of pharmacotherapy on survival in HCM.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study complies with the Helsinki convention and was approved by the University of Gothenburg Ethics Committee (approval number ÖS1012-12).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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