Factors influencing outcome in patients with obstructive hypertrophic cardiomyopathy

Effects of pharmacotherapy, pacing and surgical myectomy

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Factors influencing outcome in patients with obstructive hypertrophic cardiomyopathy. Effects of pharmacotherapy, pacing and surgical myectomy

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The cover image is the hand of a child making a stop sign. I want it to symbolize that it is time that under-treatment of hypertrophic obstructive cardiomyopathy, in particular inadequate treatment of women with this disease, should stop. I hope my thesis will contribute towards achieving that goal.

To all Kurdish women who fougth against the Islamic State (IS) for the sake of humanity but unfortunately those women are forgotten by the world!

ABSTRACT

Background: Most studies on risk factors for disease-related mortality in hypertrophic cardiomyopathy (HCM) have emanated from specialized tertiary centres which are subject to possible referral bias. About one quarter of HCM-patients have outflow obstruction in the left ventricle, hypertrophic obstructive cardiomyopathy (HOCM). Myectomy has been recommended as "gold standard" treatment for obstruction in American Heart Association (AHA) guidelines from 2011, and short atrio-ventricular delay pacing (pacing) is not considered. European Society of Cardiology Guidelines 2014 recommended pacing only to patients who are ≥65 years of age with co-morbidities. Therefore, it appeared appropriate to study the long-term outcome of patients with HOCM in complete geographical cohort in order to assess risk factors and survival of different therapies.

Methods: In Paper I the total cohort of 251 HOCM patients (128 male, 123 female) with a mean follow-up of 14.4±8.9 years were studied for risk factors for disease-related mortality, and the effect of therapy (Conservative = no, or only medical, therapy n=121; pacing n=88; and myectomy n=42). In Paper II and IV we have compared the effect of pacing and myectomy on mortality (Paper II), and by a case-control methodology compared the complications and cost-effectiveness of those two methods (Paper IV). In Paper III we have studied the relationship between sex and risk-factors for disease-related death.

Results: *Paper I*: There were 65 disease-related deaths. 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). Sudden cardiac death caused 17%, and heart failure 62%, of disease-related deaths. 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). Neither myectomy nor pacing modified survival, but early and maintained beta-blocker therapy was associated with dose-dependent reduction in disease-related death. Beta-blockers were used in 71.3% of patients from diagnosis. Kaplan-Meier survival curves analyzed in initial dose bands of 0-74, 75-149 and ≥150 mg metoprolol/day showed 10-years freedom from disease-related deaths of 83.1%, 90.7% and 97.0%, respectively (p-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). *Paper II*: Post-intervention follow-up was 12.9±8.7 years and 12.2±5.0 years, in myectomy and pacing respectively. Both intervention treatments improved New York Heart Association (NYHA) class and outflow gradients significantly and equally, without survival inferiority for pacing (log-rank p=0.43). Survival after diagnosis was not different to that in patients only treated conservatively either (p=0.51 pacing/conservative; p=0.39 myectomy/conservative). Re-intervention in patients ≥18 years at procedure was needed due to return of the outflow gradient in 3.5% of paced vs 15.6% myectomy patients. Pacing therapy was equally effective in patients aged 13-64 years (n=44), as in patients ≥65 years (n=44). *Paper III*: At diagnosis the median age of females was 11 years higher than for men. Females had a higher disease-related mortality than males (log-rank, p=0.003). Excess female deaths were caused by chronic heart failure, Hazard ratio (HR) 3.76 [1.85-7.66; p=0.0003] in the age-matched group, and by myocardial infarctions (p=0.029). There was no sex-bias in respect to interventional procedures, but a lower proportion of females received beta-blocker therapy initially (64% versus 78%, p=0.011), and in a smaller dose (p=0.006). Verapamil/diltiazem was used in 17.1% females compared to 7.8% of males (p=0.034), and HR for heart failure deaths with verapamil/diltiazem therapy was 4.20 [1.72- 10.23; p=0.002] in the age-matched groups of both sexes. *Paper IV*: There were fewer peri-procedural complications in the pacing-group compared to myectomy-group (3.2% in pacing and 35.5 p<0.001). During follow-up pacemaker was implanted in 35.5% of myectomy-group for atrioventricular block, 9.7% peri-operatively, and 25.8% during late follow-up. Furthermore, the pacing group had a superior freedom from all types of re-interventions, 90.3% versus 61.3% in myectomy-group (p=0.003). Pacing patients had a significant shorter in-hospital stay and costs compared to myectomy.

Conclusions: 1) Heart failure was a dominant cause of death in this unselected geographical cohort of HOCM patients. Independent risk factors for disease, and specifically heart failure-related deaths, were female sex, age and persisting LVOT-obstruction. 2) Beta-blocker therapy aiming for doses of at least 150 mg/day metoprolol equivalents would be beneficial even in asymptomatic LVOT-obstruction. 3) Short atrio-ventricular delay pacing as a simple, cost-effective procedure with low rate of perioperative complications, and a low need for later re-interventions, was not inferior to myectomy in the relief of LVOTO and should thus be considered a valid option to treat patients with HOCM. 4) Early recognition in females, with a more liberal, and earlier, use of adequate treatment to optimize gradient-control and diastolic function, might improve the outcome in females with HOCM.

Key Words: Hypertrophic obstructive cardiomyopathy; myectomy; pacing; beta-blocker; survival; sex and re-intervention rate.

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LIST OF PAPERS

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I Davood Javidgonbadi, Bert Andersson, Nils-Johan Abdon, Maria Schaufelberger, Ingegerd Östman-Smith. Factors influencing long-term heart failure mortality in patients with obstructive hypertrophic cardiomyopathy in Western Sweden: probable dose-related protection from beta-blocker therapy.
Open Heart 2019; 6:e000963. doi:10.1136/openhrt-2018-000963

II Davood Javidgonbadi, Nils-Johan Abdon, Bert Andersson, Maria Schaufelberger, Ingegerd Östman-Smith. Short atrioventricular delay pacing therapy in young and old patients with hypertrophic obstructive cardiomyopathy: good long-term results and a low need for reinterventions.
Europace 2018;20:1683-1691(e-publication (2017) doi:10.1093/europace/eux331)

III Davood Javidgonbadi, Maria Schaufelberger, Ingegerd Östman-Smith. Factors contributing to excess female mortality in hypertrophic obstructive cardiomyopathy.
Manuscript

IV Davood Javidgonbadi, Bert Andersson, Nils-Johan Abdon, Ingegerd Östman-Smith. Morbidity and resource usage after myectomy or pacing-treatment in hypertrophic obstructive cardiomyopathy: a case-control study.
Manuscript

CONTENTS

ABBREVIATIONS

AV	Atrioventricular
ACE	Angiotensin Converting Enzyme
AF	Atrial Fibrillation
AHA	American Heart Association
AL	Amyloidosis
AMP-kinase	Adenosine Monophosphate-Activated Protein Kinase
ARB	Angiotensin Receptor Blockers
ASA	Alcohol Septal Ablation
ASH	Asymmetric Septal Hypertrophy
ATP	Adenosine Triphosphate
bpm	beat per minute
CABG	Coronary Artery Bypass Grafting
CFC	Cardio-Facio-Cutaneous
CMR	Cardiac Magnetic Resonance Imaging (CMRI)
CRT	Cardiac Resynchronization Therapy
CT	Computed Tomography
DDD	Dual-chamber pace
ECG	Electrocardiogram
EF	Ejection Fraction
ES	End-Stage
ESC	European Society of Cardiologists
FU	Follow-Up
G+P-	Gen positive and Phenotype negative
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
HOCM	Hypertrophic Obstructive Cardiomyopathy
HR	Hazard Ratio
ICD	Implantable Cardioverter Defibrillator
IHSS	Idiopathic Hypertrophic Subaortic Stenosis
IQR	Interquartile Range
LA	Left Atrium
LAD	left atrium diameter
LBBB	Left Bundle Branch Block
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
LVAD	Left Ventricular Assist Devices
LVEDD	Left Ventricle End-Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy

LVOT	Left Ventricular Outflow Tract
LVOTO	Left Ventricular Outflow Obstruction
LVPW	Left Ventricle Posterior Wall
MELAS	Acronym for a constellation of findings that includes mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes
MERFF	Myoclonic epilepsy with ragged red fibers
MIBG	Metaiodo-Benzyl-Guanidine
MPATHY	Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy
MRA	Mineralocorticoid Receptor Antagonists
MYBPC3	Myosin-Binding Protein C 3
MYH7	Beta-Myosin Heavy chain 7
MYL3	Myosin Light chain 3
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PICP	Propeptide of type I procollagen C-terminal
PRKAG2	Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma 2
Pro-BNP	Pro-Brain Natriuretic Peptide
PVC	Premature Ventricular Contraction
RV	Right Ventricular
SAM	Systolic Anterior Movement
SCD	Sudden Cardiac Death
SD	Standard Deviation
TEE	Transesophageal Echocardiography
TNNI3	Troponin I3
TNNT2	TroponinT3
TPM1	Tropomyosin alpha-1 chain
TTE	Transthoracic Echocardiography
TTR	Transthyretin
VDD	Ventricle sense and pace
WOR	Wash Out Rate

INTRODUCTION

Background at start of project

Most studies on risk factors for death due to hypertrophic cardiomyopathy (HCM) have emanated from specialized tertiary centres subject to possible referral bias toward patients with a malignant family history for Sudden Cardiac Death (SCD).[1, 2] HCM mortality has been studied in geographical cohorts as well[3] but with several shortcomings such as failure to document details of medical treatment or failure to differentiate the type of death (i.e. sudden arrhythmia, failure or embolism-related).[3] Type of mortality is important because risk factors for sudden death and heart failure death are different.[4] Thus, these existing studies can neither provide information on the natural history, nor of treatment effects[3] and have many patients "lost to follow-up".[5] Short atrio-ventricular (AV) delay pacing has been removed from considerations as a first choice in the American Heart Association (AHA) guidelines for hypertrophic obstructive cardiomyopathy (HOCM) treatment,[6] and European Guidelines from the European Society of Cardiology (ESC) 2014 recommends pacing only to patients who are elderly, at high risk if undergoing septal reduction, or patients who do not want to undergo surgery and have a mild hypertrophy.[7]

During my clinical work in the Västra Götaland region I had observed a good effect of short AV-delay pacing on left ventricular outflow tract (LVOT) gradient and on the clinical status of the patients. Therefore, I wished to study the long-term outcome of patients with HOCM in an unselected complete geographical cohort with 100% follow-up in order to assess risk factors and possible effect on survival of drug therapy, myectomy and pacing for adverse outcome, without possible interference of referral bias.

The historical background of the disease entity hypertrophic cardiomyopathy

A Swiss physician with name Théophile Bonet (1620–1689), and a pathologist who refined Bonet's work with name John Baptiste Morgagni (1682–1771), were the first who described the HCM disease.[8] According Coats and Hollman "Bonet first wrote: "A coachman died suddenly in his carriage whose heart was larger than that of any bullock, another sudden death of a heart far exceeding its natural bulk." Morgagni later recalled another case: "Often troubled with palpitations particularly in the night, an oppressive pain in the chest sometimes was afraid of a swooning and at other times of suffocation, the circulation of the blood being obstructed from the left ventricle into the artery."[8] This should be the first evidence of the recognition of LVOTO in HCM.[9] Laennec (1781–1826) introduced the term hypertrophy, which means increased nutrition [Greek: hyper = over, trophe = nourishment], affecting the left ventricle, right ventricle or both, with or without dilatation.[8, 10]

Vulpian described HCM, as "idiopathic hypertrophic subaortic stenosis" in 1868, according its anatomical abnormality[11] followed by comparable reports in 1869 by Liouville and Hallopeau[12, 13] in the Medical Gazette of Paris. Brock from England reported

a century later three cases of LVOT hypertrophy and proposed systemic hypertension as primary reason.[14] The British pathologist Robert Donald Teare in 1958 was credited as the person who discribed the disease. He reported 8 cases of young patients between the ages of 14 and 44 years, 7 of whom died suddenly, and one died six hours post-mitral valvotomy. In a supplement to the same article, he described a ninth patient, who was the brother of one of the patients; both he and his sister had died suddenly. This seems to be the first recognition of the familial nature of sudden death as part of the HCM. The heart showed asymmetric septal hypertrophy which he named "a muscular hamartoma of the heart". He described the first histological pattern of the disease as, "the pathological picture is one of bizarre and disorganized arrangement of muscle bundles associated with hypertrophy of individual muscle fibers and their nuclei."[15] "Pseudoaortic stenosis" is another name which was introduced by Bercu et al. in 1958, because of similarity to clinical findings and presentation to aortic stenosis. In one case they reported post-mortem findings of a patient with clinically diagnosed as aortic stenosis and he was referred for aortic valvulotomy. During the operation, the surgeon found completely normal aortic valve cusps and difficulty to explore the left ventricle outflow tract because it was "too small to admit the surgeon's finger".[16] Severe myocardial hypertrophy post-mortem was seen in the patient who died shortly after surgery.[16]

In 1961, Brockenbrough described the increase in gradient after ventricular ectopics as a diagnostic means to differntiate HOCM from valvar aortic stenosis.[17] In aortic stenosis the obstruction is persistent but in HCM, the obstruction in the LVOT is dynamic (orifice narrows during systole and relaxes during diastole).[17] Brockenbrough et al. hypothesised that the beat after a PVC give a more forceful contraction, will narrow the orifice of the LVOT further. They concluded a higher gradient across the LVOT post-PVC will be accompanying with a louder murmur, this became known as the Brockenbrough-Braunwald-Morrow sign.[18] In 1963, Braunwald et al. described the non-obstructive form of HCM for first time.[19] They found 14 asymptomatic patients, who even with having left ventricular hypertrophy, a fourth heart sound, sharp arterial pulses, and systolic murmur, did not have evidence of LVOTO.[19] In 1964 the obstructive form of HCM was described as idiopathic hypertrophic subaortic stenosis (IHSS) by Eugene Braunwald, Morrow, Pierce and colleagues.[20-22]

Abbasi et al. in 1972 reported that M-Mode echocardiography may be used to diagnose non-obstructive HCM by demonstrating hypertrophy.[23] Asymmetric septal hypertrophy or ASH term by Henry and colleagues in 1973[24] on the basis of the echocardiographic was another progression of different names to HCM. The noninvasive hemodynamic assessment and quantitative measurements of the pressure gradient across the LVOT using continuous-wave Doppler were validated against the invasive measurements obtained in the catheterization laboratory in the late 1980s.[25, 26]

Hypertrophic cardiomyopathy

Definition

HCM is defined by the presence of increased left ventricular (LV) wall thickness, ≥15 mm in patients and ≥13 mm in first-degree relatives of probands with unequivocal

HCM, which is not solely explained by abnormal loading conditions (e.g. valvular disease or systemic hypertension). The hypertrophy can be present in any segments of LV, as measured by any cardiac imaging technique.[7]

The Prevalence

The prevalence of unexplained increase in LV wall thickness has been reported up to 0.23% in adults in different populations in the US, Europe, Asia and Africa and is similar in different racial groups.[7] The prevalence can be as high as 1 in 200 (0.5%) of all people when Cardiac magnetic resonance imaging (MRI) is used as diagnostic modality.[27] The prevalence of clinically diagnosed disease in childhood is much lower, 2.9 per 100 000 in Finland.[28]

Aetiology

Mutations in cardiac sarcomere protein genes, an autosomal dominant trait, in adolescents and adults cause 60% of HCM-cases.[29, 30] Beta-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) mutations explain the majority of cases; less usually affected genes are cardiac troponin I and T (TNNI3, TNNT2), tropomyosin alpha-1 chain (TPM1) and myosin light chain 3 (MYL3).[7] Patients with a sarcomere protein mutation present earlier, have a higher prevalence of family history of HCM and sudden cardiac death (SCD),[30, 31] have more severe hypertrophy, microvascular dysfunction and myocardial fibrosis[32] with a poorer prognosis than those without an mutation. These reports are based on small numbers of patients, with inconsistency between studies, and are few by the rarity of individual mutations.[33-39] Multiple sarcomeric protein mutations as compound mutations (5%) tend to present earlier with a severe phenotype.[40-42] HCM with histology identical to sarcomeric HCM also occurs with malformation syndromes (Noonan, LEOPARD, Costello, CFC (cardiofaciocutaneous).[43, 44]

Phenocopies triggered by other genetic disorders occur in 5-10% of adult HCM patients. These include: inborn errors of metabolism (Glycogen storage disease ex; Pompe, Danon, AMP-kinase (PRKAG2), Carnitine disorder, Anderson-Fabry), neuromuscular diseases (Friedreich's ataxi, FHL-1 = four and a half LIM domains protein 1), and mitochondrial diseases (MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, and MERFF (myoclonic epilepsy with ragged red fibers). Other non-genetic conditions that mimic genetic forms of the disease, for example, senile transthyretin (TTR) and light chain (AL) amyloidosis can be diagnosed in some patients.[45, 46]

Pathogenesis of disease progression

The diversity of causal genes and mutations causing a common phenotype of HCM suggest that multiple mechanisms of pathogenesis of HCM are perhaps causing a final common pathophysiology. The mechanisms have been described in four different sets by Marian and Braunwald: Mutation as primary defect, Molecular Events as secondary (Intermediary), Histological as tertiary and Clinical as Quaternary Phenotypes.[47] To facilitate different phases of HCM in patients for clinicians, a framework for systematic clinical staging of HCM in four stages with special weight on diagnosis, pos-

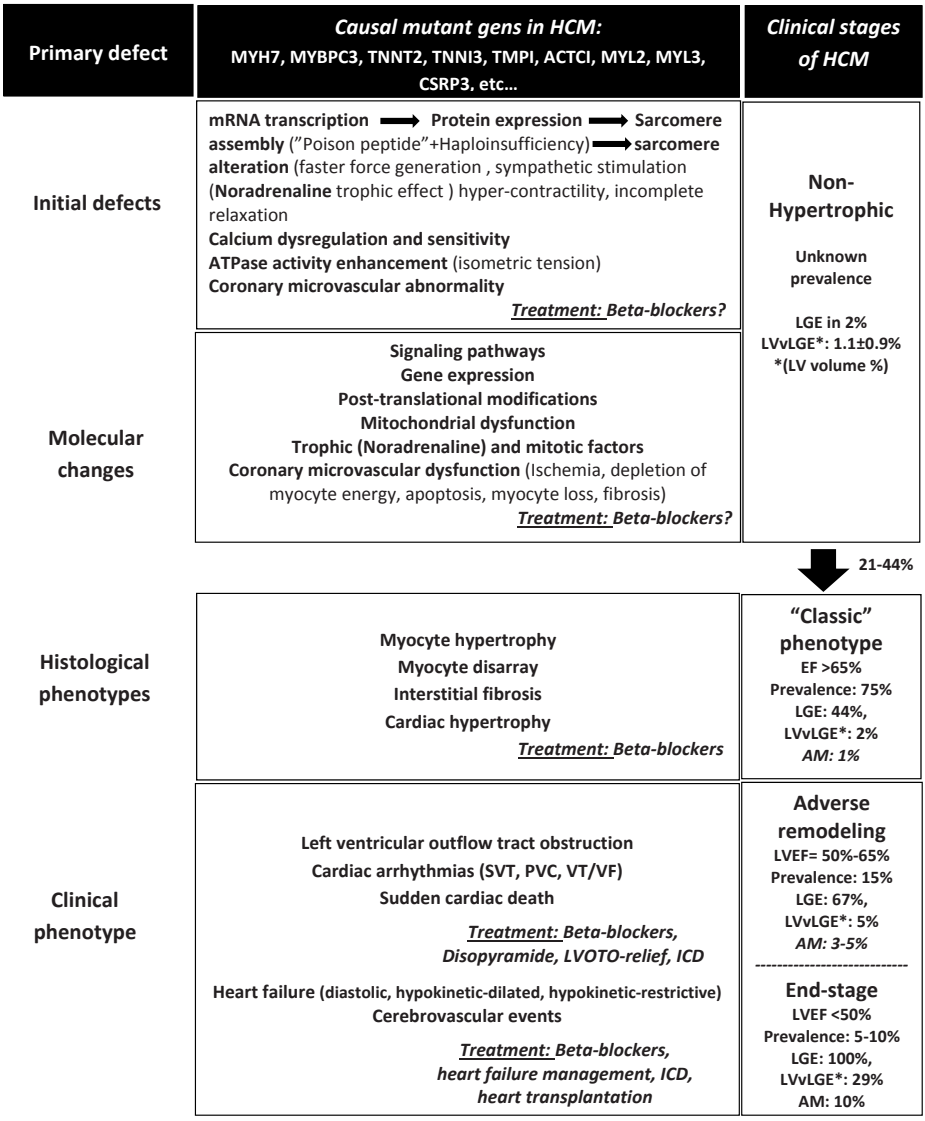
sible mechanisms, management challenges, and aims for future investigation has been proposed by Olivotto at al.[48]: these are well-defined as non-hypertrophic, classical HCM-phenotype, adverse remodeling, and manifest dysfunction.[48] See Figure 1 for a comprehensive description of all stages (modified from[47-49]).

Stage I: Non-hypertrophic stage of cardiomyopathy (phenotype negative phase)

Non-hypertrophic in this stage is a combination of primary defects and secondary molecular changes.[47] This stage is described by the absence of LV hypertrophy in genetically positive individuals, examined during systematic family screenings.[48] A significant minority of genotype-positive individual seems to never develop the disease at all and the rest can develop left ventricular (LV) hypertrophy as late as the 6th or 7th decade due to age-related onset and partial penetrance.[6, 50] However, even in childhood HCM 53% of cases have sarcomere mutations, in 13% the disease presented in infancy.[51]

In a Dutch study a clinical diagnosis of HCM was made at first cardiological evaluation, in 24% of mutation carriers (Mean age 39.3±17.6), and between first and second evaluation (Mean duration; 2.9±1.6 years) the phenotype-positive rate rose to 44%.[52] Age related disease penetrance was diagnosed in 41% of mutations carriers and males were more often affected than females ($p=0.04$).[53] In this stage electrocardiograph (ECG) abnormalities as Q-waves (18% compared to 3% in controls) and repolarization abnormalities (T-wave inversion and ST-segment depression) were significantly more widespread in mutation carriers than in mutation-negative individuals.[54] Some echocardiographic abnormalities have been reported at this stage, such as decreased LV relaxation, increased systolic contraction, abnormalities of mitral valve, and some degrees of left atrial (LA) enlargement.[55, 56] Type I collagen precursors, a fibrosis marker, were significantly higher in mutation carriers without LV hypertrophy and in subjects with overt HCM than in controls (31% and 69% higher, respectively; $p<0.001$).[57 58] HCM patients with very mild phenotype may have changed coronary microvascular function.[59] Myocardial crypts (1-6/patient) were identified by CMR in 19 of 31 (61%) genotype-positive/phenotype-negative patients.[60] As many as 16% genotype-positive with negative echocardiography examination appear to have some degree of LV hypertrophy on CMR.[6] In conclusion nonhypertrophic is not equivalent with phenotype-negative.[48]

Mechanisms of disease (Stage I) When the first "disease gene" for HCM was identified[61, 62] the finding led to the concept that mutations in genes encoding cardiac contractile and Z-disk proteins in sarcomere have been credibly shown to cause HCM.[43, 63, 64] The mechanisms of disease in HCM however remain only partly understood. Proposed mechanisms include (1) a dominant negative function (i.e. a "poison peptide", wherein the mutant gene encodes a protein that interferes with the function of the normal allele in a concentration-dependent manner); (2) haplo-insufficiency (in MYBPC3) (causing inadequate quantity of the normally functioning sarcomere protein which can be attributed to cell surveillance mechanisms); (3) impaired myocardial energetics and decreased energy reserve[64-67] and/or (4) the roll of modifier genes (as responsible for the variation in hypertrophic expressivity) and environmental factors, important in de-



AM=Annual mortality, EF=Ejection fraction, LV=Left ventricle, LGE=Late gadolinium enhancement, LVv=Left ventricle volume, SVT=supraventricular tachycardia, PVC=premature ventricular contraction, VT/VF=ventricular tachycardia/fibrillation, LVOTO=Left ventricle outflow obstruction, ICD=Implantable Cardioverter Defibrillator
Modified from: Ostman-Smith, Clin Sci (Lond), 1981 sep, 3; 265-72, Olivotto et al, Circ Heart Fail. 2012 Jul 1;5(4):535-46, Marian et al, Circ Res. 2017 Sep 15;121(7):749-770

Figure 1. Pathogensis and treatment of hypertrophic cardiomyopathy.

termining an "awakening" of the phenotype.[48, 67, 68] Diastolic abnormalities in pre-LV hypertrophy in HCM-causing mutations, may be due to adverse effects on cardiomyocyte intracellular calcium and energy handling.[50, 57] The prognosis in this stage is unclear, but apparently favorable, possibly similar to that of the healthy people.[6, 48, 69]

No evidence-based treatment is available for non-hypertrophic HCM. HCM is a phenotype with a heterogeneous genetic substrate where hypertrophy is considered a pathophysiologic compensatory response, usually caused by mutations of the sarcomeric proteins. The results of studies underline that energy conservation within the myocyte can be an important therapeutic target to try to prevent progression of pathological hypertrophy, and to prevent progressive fibrosis development.[65, 70, 71] There is evidence that noradrenaline acts as a "myocardial hypertrophy hormone".[72] In animal models non-selective, and $beta_1$-selective, beta-receptor blockers have been shown to block the trophic effects of noradrenaline on heart muscle and to block or reduce compensatory hypertrophy showing that the effect is mainly mediated via $beta_1$-receptors.[49, 73, 74] Thus, although HCM is a genetic condition, these results suggest it may be possible to modify with beta-blockers the pathophysiological cascade leading to increased cardiac muscle hypertrophy.

Stage II: The "Classic" HCM Phenotype

"Classic" HCM phenotype is defined as fully expressed hypertrophic phenotype and hyperdynamic LV (ejection fraction [EF] >65%), in the absence of extensive fibrotic changes.[48] About 80% of adult HCM patients belong to this stage.[75] The distribution of LV hypertrophy is usually regional and asymmetrical, typically involving the basal septum and anterior wall, but may affect any segment of the LV including the papillary muscles or even the right ventricle.[48, 69] Cardiac hypertrophy and other abnormalities such as autonomic nervous system abnormalities, atrial remodeling, crypts, coronary myocardial bridging, mitral valve abnormalities, subaortic, mid-ventricular and right ventricular outflow obstruction are presented in this stage.[56, 76-80] The classic features of HCM are myocardial disarray, microvascular remodeling, and interstitial fibrosis at the microscopic level.[64, 81]

The left ventricle in "classic" HCM is characterized by small or normal-sized cavity and hyper-contractility (EF averaged 71%).[48, 75] In this stage with the changes in the geometry of LV including septum hypertrophy, apparent mitral valve abnormalities and enhanced contractility, dynamic LVOTO occurs in about 70% of HCM patients.[69] Diastolic dysfunction is almost always present. Diastolic dysfunction of severe degree is less common and generally occurs in patients with severe LVOTO, substantial LV hypertrophy and restrictive pathophysiology in the end-stage HCM.[59, 69, 75, 82] Late gadolinium enhancement (LGE) at CMR is presented between 50-71% of HCM patients with "classic" phenotype and occupies a median of 2-10% of the LV.[58, 75, 83] But levels of serum C-terminal propeptide of type I procollagen (PICP) were significantly higher in HCM patients with overt hypertrophy and patients with gen-positive and phenotype negative (G+P-) sarcomeric mutation than in controls (69% and 31% higher, respectively; $p<0.001$) which suggesting collagen deposition as a profibrotic marker preceding the advance of the left ventricular hypertrophy or fibrosis evident on CMR.[57]

Mechanisms of disease in "classic" HCM phenotype (Stage II) HCM-causing gen-mutations trigger a cascade of changes in the myocytes as shown in Figure 1.

In this stage LV hypertrophy is in response to:

1: In relation to the question of how non-hypertrophic HCM progresses to hypertrophy there is evidence that noradrenaline acts as a "myocardial hypertrophy hormone"[72] and excess ATP use that required to generate isometric tension within the sarcomere causes LV hypertrophy.[43, 65, 84, 85] Noradrenaline released from cardiac sympathetic nerve terminals induce compensatory cardiac hypertrophy in animals[49, 86, 87] and those results have been confirmed in biochemical model[88] and in myocyte cell culture from rats.[89, 90] High level of myocardial noradrenaline,[91] and increased cardiac arteriovenous difference in noradrenaline concentration as a result of impaired noradrenaline neuronal re-uptake and metabolism proves increased noradrenaline exposure of myocytes in HCM-patients.[92] Furthermore, reduced myocardial adrenoceptor density, related to a downregulation secondary to increased myocardial concentration of noradrenaline has been observed in HCM-patients.[93]

Pace et al. reported a correlation between sympathetic activity and cardiac anatomy (i.e. degree of hypertrophy), diastolic function and LVOT-gradient in HCM-patients using [123I]-Metaiodo-benzyl-guanidine wash-out rate.[94] In animal models non-selective, and $beta_1$-selective, beta-receptor blockers have been shown to block the trophic effects of noradrenaline on heart muscle and to block or reduce compensatory hypertrophy showing that the effect is mainly mediated via $beta_1$-receptors.[49, 73, 74] Regarding HCM in children and adolescents, retrospective well-matched cohort studies showed that beta-blocker dose correlated with a significant reduction in mortality both due to reduction in the risk of sudden arrhythmia and to risk of heart failure related death.[4, 95, 96] In this stage beta-receptor blocker, by reducing rate x pressure product which is closely and linearly related to myocyte oxygen consumption, improves the myocyte's energy balance

2: Damage to the mechanisms that turn off contraction at low cytosolic [Ca^{2+}], leading to inadequate relaxation with diastolic dysfunction as result while increasing energetic compromise is described as another mechanism.[48, 84, 97, 98] Ca^{2+} sensitization significantly changed the shape of ventricular action potentials, causing in shorter effective refractory periods, greater beat-to-beat variability of action potential durations, and increased dispersion of ventricular conduction velocities. It was suggested these effects produced an arrhythmogenic substrate, cardiac remodeling and, possibly, apoptosis.[48, 99] But the link between mutation and hypertrophy has not been established.[98]

3: Sarcomeres and their Z-disk apparatuses act as centers of mechano-sensation/transmission/transduction,[100] and changed sarcomere mechanics due to faster movement, hypercontractility and impaired relaxation,[101] and irregular sarcomere contractile status responsible for the persistent increase in sympathetic stimulation in patients with HCM as mentioned above[49, 76] may cause LV hypertrophy.

4: Genetically regulated remodeling of the small coronary vessels with microvascular dysfunction is a potent long-term predictor of progression to LV function impairment.[32, 59, 69] Most patients with "classic" HCM phenotype are clinically stable and may never undergo significant degrees of adverse remodeling or disease progression during their life (Figure 1).[6, 69] Symptoms can include dyspnea on effort, angina, atypical chest pain, syncope, SCD, palpitations and paroxysmal atrial fibrillation (AF).[6] Individuals with severe LVOTO or restrictive physiology have severe functional limitation.[102] Adult HCM patients have an annual cardiovascular mortality around 1%.[6, 69] SCD rates are low in this stage of disease, but a subclass of patients remain at high risk and should be addressed by appropriate checkup.[6, 7] Relief of symptoms is the first step of management in this stages as well as relief of LV outflow obstruction, prevention of SCD and cardiac comorbidity, clinical examination for signs of disease progression and control of conventional risk factors such as inactive lifestyle, hypertension, dyslipidemia, obesity and diabetes.[6, 7] Pharmacological management in this stage consists of beta-blockers, calcium channel blockers, disopyramide, and amiodarone for control of symptoms, LV obstruction, and arrhythmias.[6, 7]

Stage III: Adverse Remodeling (Clinical phenotype)

Adverse remodeling is defined[48] by the presence of negative structural changes, overlaid to the "classic" HCM phenotype, with increasing LV fibrosis and deteriorated function (i.e. an LVEF of 50-65%), with relatively well-kept clinical and hemodynamic stability.[48] This seems to represent 15% to 20% of adult HCM patients, a smaller percentage of whom will finally progress to manifest dysfunction and heart failure.[69, 75, 103, 104] Adverse changes often occur progressively over years or decades.[69, 104, 105] and may lead to overt dysfunction, advanced heart failure and ventricular arrhythmia in a brief span of time at any age, including infancy and adolescence.[10, 106, 107] Severe HCM progression is particularly more prevalent in patients with complex compound sarcomere gene mutation heterozygosity genotypes.[42, 64] This transitional stage of disease progression is based on a combination of several adverse features of ventricular remodeling, like reduced LVEF,[75, 105] marked atrial dilatation,[108] moderate to severe diastolic dysfunction,[102, 109] moderate areas of LGE on CMR,[105] severe microvascular dysfunction,[59] thinning of the LV walls,[104] occurrence of AF[110] spontaneous reduction or loss of LVOTO,[104, 111] and LV apical aneurysms.[112] The higher accumulation of these changes, the more likely is a transition from a "classic" HCM phenotype to adverse transformation.[48] In HCM patients with low-normal LVEF values of 50-65% (15% of a cohort of 310 consecutive patients), LGE was present in 67%, and constituted a median of 5% of the LV mass, and it was 100% in patients with an EF <50%, in whom it constituted 29% of the LV volume. In patients with an EF of 66% or more LGE occurred in 44% of cases with a median of 2% of the LV volume[75].

Mechanisms of disease in Stage III Myocardial fibrosis in this stage is suggested to be the long term consequences of microvascular ischemia, leading to myocyte death, fibrosis,[107, 113] metabolically inefficient contractions resulting in possibly aggravating myocyte energy depletion in the long-term,[114] triggering apoptosis and collagen deposition[42] and consequently impairment of LVEF. The patterns and location of myocardial fibrosis are greatly similar across the spectrum of LVEF values, despite quantitative differences, supporting the opinion of a continuum in the generation of fibrosis.[75]

In patients with HCM fibrosis expressed as LGE is associated with an increased prevalence of ventricular tachyarrhythmias and sudden death.[115-117] This observation is in line with the substantial rate of arrhythmia- related death observed in patients entering the end-stage phase with remodeling and scarring of the LV.[107] Clinically this stage can vary from mild to severe manifestations by heart failure symptom without LVOTO, impairment of cardiopulmonary exercise test, elevated natriuretic peptides,[118] onset of atrial fibrillation[110] and high risk for SCD.[119]

The total cardiac mortality in HCM has been estimated to 3-5 % per year when various risk factors were considered.[48] In this stage close clinical observation with CMR, cardiopulmonary testing, serial proBNP titration and TnT may be beneficial, possibly allowing for preventive management.[105, 120-122] Adequately designed, prospective randomized trials to test which therapeutic strategies may have a potential impact on HCM progression are lacking. It is reasonable to consider well-timed implementation of treatments like angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (only in dilated end-stage, not in patients with heart failure and small cavity with LVOTO), beta-blockers, diuretics and ICD to prevent SCD.[6, 7, 123]

Stage IV: Overt Dysfunction or End-stage (ES) HCM

In this stage HCM patients have severe functional deterioration of the LV (LVEF <50% at rest), extreme degrees of myocardial fibrosis and remodeling with hemodynamic decompensation and severe adverse outcome.[48, 106, 107] Patients in this stage were younger at diagnosis, had a larger LV cavity, had more severe symptoms, more commonly had a family history of ES than other patients with HCM.[107] Those patients had a complex genotypes with multiple mutations in 13% of ES compared with 5% of the negative ES-HCM patients in a cohort of 181 HCM patients with preserved LV ejection fraction.[124] Progressive LV wall thinning occurs in around 10%-15% of HCM patients in tertiary centres, and may be marked and more common in those with severe (>3 cm) left ventricle hyperthropy (LVH) at initial evaluation.[107, 125]

The clinical worsening occurs over nearly 5-6 years. LV dimension changes over time with a regression of LV wall thickness about 25% (from 20-15 mm, on average) at a rate of 1.0 to 2.0 mm per year, LV end-diastolic cavity dimension increases about 20% (from 45-55 mm, on average) at a rate between 1 and 4 mm per year, and a parallel increase in end-systolic dimension can be demonstrated. EF may decrease from >70% to <45%.[104] This subset corresponds with so-called “end-stage” HCM, representing about 5%-10% of patients in most cohorts from tertiary centres.[48, 107]

Two types of changes are observed according to the morpho-functional manifestations of HCM in this progressive phase:

Hypokinetic-dilated form of ES-HCM, increased volume and spherical remodeling of the LV is the character of this phase[48] and in rare cases, this variant may be hard to differentiate from DCM. The diagnosis of HCM relies either on earlier documentation of asymmetrical LV hypertrophy or family history of HCM.[48, 69, 106, 107] This kind of diagnostic dilemma is rarely a problem, as the degree of dilatation in HCM is never as manifest as that of DCM, and focal hypertrophy is often present.[48] In this stage the

LVOTO are absent, but other changes like right ventricle dysfunction and pulmonary hypertension are common.[6, 42, 106, 107]

Hypokinetic-restrictive form of ES-HCM, a small and stiff LV with extreme diastolic dysfunction, with mildly or moderately impaired LVEF, resembling primary restrictive cardiomyopathy are characteristics of this phase.[102, 106, 126, 127] Some degree of remaining asymmetrical hypertrophy is apparent, as a result of progressive fibrous substitution and thinning; marked bi-atrial dilatation and AF are almost regularly present.[59, 127] The decline in LVEF (<50%), and progression of symptoms are slow processes (mean duration 14 years).[107]

The clinical outcome in this phase is severe, Harris et al. reported 11% mortality rate per year and 10% appropriate defibrillator interventions per year in patients awaiting donor hearts.[107] Kubo et al. reported that the 5-year survival rate from all-cause mortality, cardiac transplantation, or ICD discharge was 56.4%.[127] Biagini reported 9.2% SCD per year in this patient category.[102] On the other hand less than 2% of patients have required cardiac transplantation or have died in severe heart failure before the age of 50.[48]

Many patients can be stabilized by using the heart failure guidelines strategies with beta-blockers, low-dose diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists, ICD-implantation and anticoagulation in case of AF and apical aneurysm to prevent cerebrovascular events.[6, 7] Cardiac resynchronization therapy (CRT) did not show a useful effect in this group of patients.[128] Hypokinetic-restrictive subtype heart failure in HCM is more common than the dilated type[127] with low cardiac output on the basis of restrictive filling at presentation.[102, 106] They are more severe to recognize and treat, as they may not benefit or tolerate from the ordinary heart failure therapies[48] or left ventricular assist devices (LVAD) because of small cavities and quite well-maintained contractile function.[129] Early hemodynamic evaluation and oxygen consumption stress testing is important to avoid missing a window for transplantation.[130, 131]

Diagnosis of HCM

HCM is defined by the presence of a left ventricular (LV) wall thickness, ≥15 mm in patients and ≥13 mm in first-degree relatives of probands with unequivocal HCM, which is not solely explained by abnormal loading conditions (e.g. valvular disease or systemic hypertension). The hypertrophy can be present in any segments of LV, as measured by any cardiac imaging techniques like echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography (CT).[7]

Lesser degrees of wall thickening (13-14 mm) are presented in genetic and non-genetic disorders. To diagnose HCM in these cases requires evaluation of other signs like family history, ECG abnormalities, non-cardiac symptoms and signs, laboratory tests and multi-modality cardiac imaging.[7] The diagnosis of HCM in children needs an LV wall thickness more than two standard deviations greater than the expected mean for age and body size (z-score ≥2, where a z-score is defined as the number of standard deviations from the population mean).[132]

The following features challenge the diagnosis of HCM:

- Late phase of the disease with a dilated and/or hypokinetic left ventricle and LV wall thinning.
- Physiological hypertrophy in individual based on intense athletic exercise.
- Patients with co-existent other pathologies.
- Elderly with isolated basal septal hypertrophy.

Most individuals with HCM have a normal lifespan and are asymptomatic, but some develop symptoms, often many years after the presence of ECG or echocardiographic sign of LVH. Patients with structural and functional abnormalities can develop a variety of symptoms, which are related to heart failure, or arrhythmias and may include fatigue, dyspnea, chest pain, palpitations (supraventricular and ventricular arrhythmias), presyncope or syncope.[7] HCM is associated with a wide collection of clinical signs and hemodynamic abnormalities. Based on site and extent of cardiac hypertrophy, HCM patients can advance one or more of abnormalities like: LVOTO, mitral regurgitation, myocardial ischemia, diastolic dysfunction.[7]

HCM with obstruction

HCM is often associated with muscular LVOTO and then named hypertrophic obstructive cardiomyopathy (HOCM). A resting or exercise provoked LVOT gradient is present in 70% of patients with HCM[133] and is an independent predictor of poor prognosis with higher risk of sudden death,[96, 134] impaired functional status, and increased risk of heart failure.[6, 135]

Mechanism of LVOT obstruction

The identification of factors that contribute to the development of LVOTO was facilitated by the advent of 2D echocardiography. Subaortic (i.e. LVOT) obstruction in HCM is due to systolic anterior motion (SAM) of the mitral valve with anterior leaflet approaching or contacting the ventricular septum in mid-systole. This creates mechanical impedance to blood flow as it exits the heart, resulting in a pressure gradient between the LV cavity and the aorta. Increased LV systolic pressures are recorded just below the level of the mitral valve leaflet-septal coaptation, while the systolic pressures above this point are similar to those in the aorta. The presence of SAM-septal contact at rest or with provocation will produce a pressure gradient of 30 mmHg or greater.

There are multiple morphologic alterations of the LVOT area and mitral valve that contribute to the development of SAM-septal contact, including: Narrowed diameter of the LVOT due to increased septal wall thickness, apically positioned papillary muscles that tether the mitral valve plane toward the ventricular septum, elongated anterior leaflet of the mitral valve.

As high velocity blood is ejected from the LV during systolic, the mitral valve is pulled or “dragged” toward the ventricular septum (Venturi effect), creating outflow tract obstruction.[136-138] SAM usually involves only the anterior mitral valve leaflet, but the posterior leaflet and chordal structures may also be involved. When SAM of the

mitral valve occurs, a gap may appear between the apposition of anterior with posterior mitral leaflet, which often produces posteriorly directed mitral regurgitation.[138] The magnitude of LVOT pressure gradient measured at cardiac catheterization correlates well with Doppler velocities and with the duration of SAM-septal contact. For this reason, there is usually no reason for patients to undergo catheterization to assess outflow tract gradients, unless the measurements on echocardiographic assessment are ambiguous.[139] LVOT obstruction can occur associated with any septal wall thickness. In patients with normal or mildly increased septal wall thickness, the mechanism for outflow obstruction is usually due to elongated anterior mitral valve leaflet. This is clinically relevant since those patients who are symptomatic despite drug therapy with elongated mitral valve leaflet should be considered for surgical myectomy with limited septal resection with mitral valve repair (i.e. plication), rather than percutaneous approach with alcohol septal ablation.[140] There is often an area of scarring at the site of repetitive SAM mitral-septal contact (contact lesion).[141]

Some patients with LVOT gradients of ≥50 mmHg have mild or no symptoms. Factors that aggravate LVOTO may increase or induce symptoms of exercise limitation, syncope, and/or ischemic chest pain.[142] In contrast to posteriorly directed mitral regurgitation, the presence of a central or anteriorly directed mitral regurgitation jet suggests the presence of intrinsic mitral valve disease such as mitral valve prolapse, torn chordae, or mitral annular calcification,[138] which may have a different jet direction and should be evaluated further with transesophageal echocardiography (TEE), particularly if the patient is a candidate for invasive septal reduction therapy since this may require repair of the mitral valve at the time the outflow tract gradient is relieved.

Dynamic nature of LVOTO

Defined as an LVOT gradient ≥30 mmHg occurs at rest in about 30% of patients. Provocation can induce obstruction in about 40% of patients, in response to conditions increasing LV contractility, decreasing LV afterload, or reducing LV systolic volume via a reduction in LV preload. In about 30%, there is no sign of LVOTO at rest or provocation.[133]

A variety of manoeuvres and medications can result in induction/increase of LVOTO like manoeuvres that reduce preload (chamber size), decrease afterload, or increase LV inotropy.

- Dehydration, sudden taken of the upright position, the Valsalva maneuver, amyl nitrite inhalation, and certain medications (i.e. diuretics, dihydropyridine calcium channel blockers, etc.) can induce reduction of preload.
- Situations associated with increased inotropy include, exercise, infections with fever, isoproterenol/dobutamine infusion, or post-extrasystolic potentiation (i.e. increased inotropy after an extrasystolic beat).[7]

Other HCM variants

In addition to the classic description of HCM with or without LVOTO, a variety of other HCM variants exist, some of which are managed quite differently than classic HCM.

Mid-cavity obstructive HCM

Mid-ventricular (i.e. mid-cavity) obstruction is an important morphologic variant of HCM, which arises from different anatomic and hemodynamic circumstances.[80, 143] The most common HCM morphology associated with mid-cavitary obstruction occurs due to the apposition of septum and lateral wall with a small, hyperdynamic cavity. In these patients the intracavitary "gradient" does not usually produce clinically significant symptoms, although beta blockers appear to be the most reasonable therapy in symptomatic patients.

Mid-cavity obstruction in HCM can also be due to the systolic apposition of hypertrophied papillary muscle and the lateral wall at the level of the mid-LV, producing two distinct LV chambers (i.e. proximal and distal with an "hour glass" shape LV), and associated with an LV apical aneurysm of varying size.[80] This phenotypic subgroup of HCM patients is uncommon, present in approximately 2% of patients with HCM.[144] These patients may have limiting symptoms similar to patients with typical isolated LVOT obstruction. Clinical examination reveals the typical signs of dynamic obstructive HCM (e.g. a systolic murmur that accentuates with exercise or a change to an upright posture). The diagnosis is made with echocardiography, left ventriculography, or cardiovascular magnetic resonance (CMR).[145]

Mid-cavity obstruction with LV apical aneurysm

HCM with mid-ventricular obstruction, affects approximately 10% of HCM patients.[146] HCM with midventricular obstruction and coexisting akinetic or aneurysmal (maximum dimension, 10 to 66 mm)[112] apical chamber affects even less patients (1-3% of all individuals with HCM).[146, 147] Patients with midventricular obstruction are significantly more expected to develop an apical aneurysm compared to those without an intracavitary gradient (28% versus 1.8%, $p<0.001$).[146] This represent a different phenotype than apical HCM with LV hypertrophy confined primarily to the apex. Those patients are at increased risk of ventricular arrhythmias (including sudden cardiac death [SCD]), thromboembolic events, appropriate ICD intervention, and advanced heart failure.[6, 143, 146, 148] For these reasons, it is important to recognize and consider primary prevention ICD and anticoagulation treatment to prevent stroke in this unique phenotype of HCM.

Apical HCM

In this uncommon morphologic variant of HCM the hypertrophy predominantly involves the apex of the LV.[149, 150] These patients may have mid-ventricular obstruction without LVOT-gradient.[112, 150] The prevalence of apical HCM has been difficult to quantify, but among patients with HCM apical form were found in 41% in Chinese,[151] 15% in Japanese[152] and 1-3% in non-Asian patients.[112, 152, 153] However, Chikamori et al. reported distal pattern of hypertrophy in 13% of Japanese and 11% of Europeans HCM patients, suggesting that there may not be significant differences in prevalence of apical HCM between Asians and other racial groups.[154] Most patients with apical HCM present with no or mild symptoms, although presentation with angina, HF, myocardial infarction, AF or ventricular fibrillation has been reported.[112, 150] Symptoms are often mild, but a minority of patients have refractory symptoms of dyspnea, angina, and presyncope or syncope due to diastolic dysfunction and low cardiac output.

Typical features of apical HCM include:

- Audible and palpable fourth heart sound, reflecting impaired LV relaxation
- ”Giant” negative T-waves on ECG, particularly in the left precordial leads
- ”Spade-like” configuration of the LV cavity at end-diastole on imaging
- Associated apical wall motion abnormalities which may include hypokinesis and aneurysm formation[150]

The diagnosis of apical HCM can be made with echocardiography, left ventriculography, computed tomography, or most accurately with CMR.[145]

Apical HCM patients are managed in the same way as for most patients with HCM with medical therapy. Patients with apical HCM do not have sign of LVOT or mid-cavity obstruction, septal reduction therapy is not an option. Lethal ventricular arrhythmias have been reported in patients with apical HCM.[155, 156] In one study SCD, resuscitated cardiac arrest, and/or defibrillator discharge was observed in 6% of patients with apical HCM during a follow-up of 78 months.[157] Risk stratification for ventricular tachyarrhythmias and SCD is the same as for other patients with HCM.

The apical variant has a better prognosis than other forms of HCM. In one series of 105 patients with apical HCM overall estimated survival was 95% at 15years.[150]

Right ventricular obstruction

RV obstruction in HCM is very uncommon. This is usually a result of mid-systolic contact of prominent right ventricular muscle bundles located in the RV outflow tract region. If present, RV obstruction can be a cause of symptoms such as exertional dyspnea similar to left-sided obstruction. The approach to treatment is similar to the standard approach to treatment for patients with HCM and LVOT obstruction. Patients who remain symptomatic after a trial of medical therapy with AV nodal blocking agents can be considered for surgical intervention to relieve right-sided obstruction, usually by resection of accessory RV muscle bundles in the outflow tract area.[158, 159]

Obstructive HCM in elderly patients

HCM can be diagnosed initially in patients of advanced age as in the Framingham Heart Study, among 1862 unrelated individuals, with average age of 60 years, who did not have hypertension or aortic valve disease, 3% had unexplained increase in LV wall thickness. Sarcomeric contractile protein gene mutations were found in only 18% of these individuals.[160] A sigmoidal configuration to the basal septum is observed with increased frequency in elderly individuals and may occur as part of the cardiac remodeling associated with aging.[161] In addition, the likelihood of identifying a mutation may be lower in late-onset HCM than in earlier onset HCM.[162, 163] Older patients are more likely to have comorbidities (e.g. coronary heart disease, aortic stenosis, etc.) that may also require treatment. Regardless of the age at diagnosis, patients with increased LV wall thickness and LVOT obstruction may develop symptoms. The approach to the treatment of symptomatic LVOT obstruction is the same regardless of age (i.e. initial medical therapy, pacing and followed by septal reduction therapy if symptoms persist).[7]

Resting and ambulatory electrocardiography in HCM

The ECG is abnormal in most adult HCM patients and shows a variable mixture of LVH, ST- and T-wave abnormalities, and pathological Q-waves, but almost 6% had a normal ECG with a less severe phenotypic expression of HCM as showed by lower wall thickness, LVOTO, symptom progress, complication rates, and cardiac mortality as compared with HCM patients with abnormal ECGs.[164] The ECG is suggested at the first clinic visit in all individuals with known/suspected HCM and should be repeated on every occasion if there is a change in symptoms.[7] The ECG is also a sensitive - however non-specific - early marker of disease in relatives to HCM patients.[165] ECG risk score >5 points is associated with high risk for SCD in adult HCM[166] and in paediatric HCM-patients.[167]

Ambulatory ECG monitoring is recommended at the initial clinical evaluation to assess the risk of SCD and stroke.[7] Asymptomatic non-sustained ventricular tachycardia (NSVT) occurs in 19.5-31% of adults with HCM.[168, 169] Paroxysmal supraventricular arrhythmias occur during ambulatory electrocardiographic monitoring in up to 37% of patients. SVT occurred more commonly in patients with outflow obstruction.[169] Monserrat et al. reported no definite relation between the duration, frequency, or rate of NSVT runs and prognosis at any age: the odds ratio of sudden death in patients ≤30 years of age with NSVT was 4.35 (95% CI: 1.54 to 12.28; p=0.006) compared with 2.16 (95% CI: 0.82 to 5.69; p=0.1) in patients >30 years of age.[168] However, in even younger patients Östman-Smith et al. reported a relative risk of 9.1 (3.6-22.8) for SCD in patients with NSVT at a mean follow-up of 10.9±9.0 years in patients age <19 years at diagnosis.[167]

Echocardiography features in HCM

Echocardiography has a central role in assessment of left ventricular wall thickness, latent obstruction, left atrial enlargement, systolic and diastolic function, associated abnormalities of the mitral valve and left ventricular outflow tract and differential diagnosis. In patients with known or suspected HCM it is essential that all LV segments from base to apex be examined also in short-axis views, ensuring that the wall thickness is recorded at mitral, mid-LV and apical levels.[7]

Assessment of left ventricular wall thickness

Accurate assessment of LV wall thickness can be challenging when hypertrophy is confined to one or two segments, particularly in the anterolateral wall or the LV apex. If a segment is not visualized adequately, LV opacification - using ultrasound contrast agents and/or CMR - should be considered.[170, 171]

Abnormalities of the mitral valve and left ventricular outflow tract

Around one-third of HCM-patients have SAM of the mitral valve leaflets at rest, that results in LVOTO, while another third have latent obstruction, which is only during manoeuvres that change LV contractility and loading conditions.[133, 172, 173] Papillary muscle abnormalities (hypertrophy, anterior and internal displacement, direct insertion into the anterior mitral valve leaflet) and mitral leaflet abnormalities such as elongation or accessory tissue are other morphological features that contribute to

LVOTO.[141, 174] In case of LV cavity gradient, it is important to exclude obstruction that is unrelated to SAM, including sub-aortic membranes, mitral valve leaflet abnormalities and mid-cavity obstruction, mainly when interventions to relieve LV outflow obstruction are considered. Systematic two-dimensional (2D) and Doppler echocardiography is sufficient and in some case in combination with CMR in selected patients.[7]

Assessment of latent obstruction

Identification of LVOTO is important in the treatment of symptoms and evaluation of SCD risk by 2D and Doppler echocardiography during a Valsalva manoeuvre in the sitting and semi-supine position - and then on standing if no gradient is provoked- in all patients.[175, 176] In symptomatic patients if bedside manoeuvres fail to induce LVOTO ≥50 mmHg exercise stress echocardiography is necessary. Pharmacological provocation (dobutamine) which is not physiological and can be poorly tolerated is not recommended. Nitrates should be reserved for patients who cannot perform physiologically exercise test.[177]

Left atrial enlargement

The causes of enlargement of the left atrium (LA) are multifactorial, but the most common mechanisms are impaired diastolic function, SAM-related mitral regurgitation and elevated LV filling pressures.[7] LA size was independently associated with SCD/appropriate ICD shock,[178, 179] and a predictor to AF and thromboembolism.[180]

Assessment of diastolic function

HCM patients often have diastolic dysfunction. Diastolic function measured by Doppler echocardiographic is influenced by loading conditions, age and heart rate. There is no single echocardiographic factor that can be used as a diagnostic hallmark of diastolic dysfunction of LV. Therefore, an all-inclusive evaluation of diastolic function - including Doppler myocardial imaging, pulmonary vein flow velocities, pulmonary artery systolic pressure and LA size - is recommended as part of the routine assessment of HCM (Criteria recommended for establishing diastolic dysfunction in patients with adult HCM are average E/é ratio (>14), LA volume index (>34 mL/m^2), pulmonary vein atrial reversal velocity (Ar-A duration ≥30 msec), and peak velocity of TR jet by CW Doppler (>2.8 m/sec). The parameters can be useful regardless of the presence or absence of dynamic obstruction and MR, except for patients with more than moderate MR, in whom only Ar-A duration and peak velocity of TR jet are still valid.[82] HCM patients with preserved EF and a restrictive LV filling pattern [ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A) ≥2; E-wave deceleration time ≤150 ms] may be at greater risk for adverse outcome.[102, 127, 181]

Systolic function

EF or fractional shortening is usually normal or increased in HCM patients. However, EF is a poor measure of LV systolic performance in HCM.[182] Myocardial longitudinal velocities and deformation parameters (strain and strain rate), derived from Doppler myocardial imaging or speckle tracking techniques, are often impaired despite a normal EF. These parameters may be abnormal before the development of hypertrophy in genetically affected relatives. Myocardial longitudinal deformation is usually par-

ticularly reduced at the site of thickness.[79] At the early phase, longitudinal function may be reduced, despite that circumferential contractility, measured for example with fractional shortening, may have high or supra-normal values. Longitudinal function is of value to differentiate against hypertrophy found in "athlete's heart" which has excellent longitudinal function.

Cardiovascular magnetic resonance features in HCM

Cardiovascular magnetic resonance includes several modalities that provide detailed information on anatomy, function, flow, perfusion, tissue characteristics and differential diagnosis in HCM patients.[183] [184] CMR is superior to transthoracic echocardiography (TTE) in establishing the diagnosis of HCM in patients with poor acoustic windows and poorly visualized LV - such as the anterolateral wall, the LV apex and the right ventricle.[171] [185]

Treatment options in HCM

Pharmacological treatment in HOCM patients

Beta-Blocker

Medical therapy is the primary treatment for control of symptoms that usually occur as chest pain, dyspnoea, palpitations, or as a combination.[7, 186-188] Maximum tolerated doses of non-vasodilatory beta-blockers are used as first therapy to reduce heart rate, prolong diastole, decrease LVOTO especially during activity, and improve myocardial perfusion and oxygen delivery by prolonging diastole.[189, 190] A short time double-blind randomized placebo control trial of propranolol and another beta-blocker (practolol) by Hubner et al. found that a propranolol dosage of 320 mg/day was best to reduce symptoms in patients with HCM.[191] In 1978 Frank et al. found that to block both the chronotrophic and inotrophic effects of beta stimulation (administration of 2.4µg/min of isoproterenol) consistently required daily doses of propranolol of 320 mg/day or more. The optimal doses for a "complete" beta receptor blocking of propranolol for management for HOCM patients in their study was on average 462 mg/day. Time to maximal improvement with medical therapy was 1-6 years (average 2.75), suggesting at least a 2 years observation time to see the maximal effect of medical therapy.[187] Bourmayan et al. reported a significant association between high doses of propranolol (average 391mg/day) and improvement in the Isovolumic relaxation time (IVRT) in HCM patients.[192] In childhood HCM beta-blocker therapy is also associated with improved survival[95] in a dose-related manner,[4, 96] and reduces risk of SCD.[167] There are no randomized long-time beta-blockade studies on mortality in adult HCM patients and at the start of our study, there were no corresponding cohort studies to study the effect of beta-blocker dose on survival in adult HCM. Of the registry studies available, Melacini et al.'s negative study from 2007[109] is often cited, but in that study, only 26% of patients (77/293; 453 patient years) were treated with beta-blockers at an unspecified dose, with a median follow-up 6 years, and they only studied effect on sudden cardiac death. The study had only 17 (10%) end-points and lacked statistical power to detect a protective effect of beta-blockers because only about 1/4 of the patients received beta-blockers.

Lee et al. (2007) found in univariate analysis in a study of 163 patients followed on average 5.3 years, of which 40% received beta-blockers, that beta-blocker use (dose unspecified) had a significant protective effect with a hazard ratio (HR) of 0.25 [95% CI0.08-0.77], p=0.012; the effect did not remain significant in a seven-parameter multivariate analysis,[193] but their statistical power would be insufficient.

Summary of the situation with beta-blocker studies prior to my thesis

Beta-blocker studies of efficacy on mortality are too few, with a small number of patient years, have a short follow-up period, are not randomized and lack information on the doses used.[109, 193] Because beta-blockers are no longer patent-protected, and are inexpensive, drug companies have no interest in funding randomized studies of sufficient duration to see the effect of beta-blockers on mortality in HOCM patients.

Calcium channel blockers

Verapamil/diltiazem in tolerated doses is recommended for symptomatic HOCM patients who are intolerant of, or have contraindications to, beta-blockers, and may also be considered for asymptomatic patients to reduce the LVOT gradient.[7] There is currently no evidence that verapamil/diltiazem improves quality of life or reduces the risk of sudden cardiac death or heart failure in HCM patients. In a series of 120 patients who had received verapamil for HOCM, Epstein et al reported serious side effects in about 7% (pulmonary edema in 8 patients with 3 subsequent deaths).[194] Verapamil may rarely lead to vasodilation resulting in an increase in LVOTO and subsequent deterioration of clinical status, and is therefore not recommended in patients with severe obstruction or elevated pulmonary arterial pressure.[189]

Summary Verapamil/diltiazem is still used in patients with HOCM, but the long-term effects of treatment on sudden cardiac death and heart failure are unclear.

Disopyramide

If medical treatment with non-vasodilator beta-blockers or verapamil does not produce the desired effect on symptoms or gradient, international guidelines recommend the addition of disopyramide.[6, 7, 195] In the largest disopyramide multi-center study with 118 patients, Sherrid et al. (2005) showed that two-thirds of HOCM patients treated with disopyramide could be managed medically with improvement of symptoms and about 50% reduction in LVOT gradient over three years. The incidence of sudden death was lower (non-significantly) in disopyramide-treated patients. They concluded that the disopyramide treatment did not have pro-arrhythmic effect in HCM patients and should be considered before proceeding to surgical myectomy or alternative strategies.[195] Class IA antiarrhythmic drugs have negative inotropic effects and can reduce both resting and provoked LVOT obstruction. Disopyramide also has beneficial effects on diastolic function.[196, 197] Anticholinergic side effects (constipation, urinary retention, and dry mouth) from disopyramide can often be managed with chewing gum, lactulose or dose adjustment, but in the event of severe problems, Mestinon (Pyridostigmine) is a cholinesterase inhibitor with a very favorable safety profile and very infrequent side effects (can cause hypotension) that can be given to reduce side effects with often good effect.[189] Cibenzolin (not registered in Sweden, available on license) has also been used for this indication.[198]

Summary Disopyramide studies are few, with few patient years and have short follow-up times, and one-third of patients have intolerance problems or go to invasive treatment.[195]

Aggressive management of atrial fibrillation

AF is the most frequent arrhythmia in HCM patients with a prevalence of 22-32% in both tertiary[110, 199, 200] and non-referral centres[201] with an incidence for de-novo AF in a general adult HCM cohort about 2% per year.[27, 110, 199, 200, 202, 203] AF is an independent risk factor for cardiovascular death, heart failure, stroke and SCD in HCM-patients.[204-207] Paroxysmal AF is an independent determinant of outcome, including the risk of HCM-related death, SCD[208] and worsened exercise intolerance.[209] The fact that paroxysmal AF in HCM patients may be frequently sub-clinical and therefore untreated is a major risk factor to adverse outcomes.[199, 208] Nevertheless, AF has not been classified as a major risk factor for SCD in the current guidelines.[6, 7] The mechanism of AF in HCM is complex. Myocardial fibrosis with enhanced ectopy in atrial and ventricular myocardium,[210] and increased left atrial pressure and dilatation due to LV-hypertrophy with reduced LV filling properties favour the development of AF. In most HCM patients with LVOT obstruction, mitral valve anatomy and function (Mitral regurgitation in up to 30%) is altered leading to valve insufficiency that further enhances the left atrial volume with adverse remodeling.[200, 211] Aggressive treatment of AF in HCM patients is necessary to avoid complications, and the therapeutic options do not differ from those without HCM. Early detection and therapy of AF is essential with oral anticoagulation even after one single episode of AF. There are no evidence to comparing a rhythm control versus rate control strategy in HCM patients, but sustaining sinus rhythm as long as possible and restoring sinus rhythm as soon as possible is beneficial for both improvement of patients symptoms and hemodynamics.[6, 7]

- Rhythm control
  When hemodynamics are critically impaired urgent cardioversion is indicated.[7] Amiodarone as the best pharmacological option for rhythm control is recommended.[212] However, amiodarone was associated with increased adverse events in patients with severe diastolic dysfunction.[213] Disopyramide used for LVOTO has been found safe in HCM patients[195] and is recommended also for avoiding recurrence of paroxysmal AF (combined with beta-blocker).[6] Beta-blocker as therapy base[7] modulates sympathetic activity, improves ventricular contractility and diastolic dysfunction, reduces the LVOT gradient and the incidence of supraventricular and ventricular arrhythmia.[212] In one retrospective study including 25 HCM-patients loaded on dofetilide for AF-suppression, dofelitide facilitated the management of AF in 21 out of 25 (84%) patients. However, QTc prolongation requiring drug discontinuation in patients with HCM was more common (12%) than among patients who did not have HCM (7.5%).[214] Dofetilide (class III antiarrhythmic) is not available in Europe and is not recommended in HCM patients according to guidelines. There are no systematic data on the use of dronedarone in HCM patients and it is not recommended in HCM.[7]

- Ventricular rate control
  Using beta-blockers and non-dihydropyridine calcium channel antagonists - alone or in combination - is recommended to reach a resting heart rate <100 bpm. The suf-

ficiency of rate control should be evaluated during exercise. In cases of inadequate rate control, AV node ablation and permanent pacing may be considered according ESC guidelines, with the exception that CRT-P (CRT with a pacemaker) may be considered in patients with LVEF <50%. In the absence of significant LVOTO, digoxin (0.125 mg–0.5 mg o.d.), alone or in combination with beta-blockers, may be used to control heart rate in patients with AF and an EF <50%, although evidence on its efficacy in this context are lacking.[7]

- Catheter ablation
  There are few data on catheter ablation for AF in patients with HCM. The technique should be recommended in patients without severe left atrial dilatation, who are unable to take anti-arrhythmic drugs or are symptomatic despite anti-arrhythmic drugs.[215]

Management of patients with drug-refractory LVOT obstruction

For symptomatic and drug resistant HOCM patients, surgical treatment with septal myectomy[21, 216, 217] or short AV-delay pacing[218-222] with apical positioning of the pacing electrode[219, 220, 223] to provide a dysynchrony in the left ventricle, have been used. Since 1995, alcohol septal ablation (ASA) has also been introduced to reduce the gradient through a septal infarction.[224] ASA was not a recommended treatment alternative in Sweden according to the national guidelines during the study period for my thesis project.

Surgical treatment with septal myectomy

WP Cleland was the first one who performed surgical myectomy at Hammersmith Hospital, London 1958.[216] The patient, a 42-year-old man, who for six years had symptoms of tight chest pain, syncope and dyspnoea on physical exertion. A systolic gradient of 60 mmHg was measured between the left ventricle and the brachial artery by percutaneous puncture. On suspicion of some form of sub-aortic stenosis it was decided to operate. The pressure measurements on the operating table however showed no outflow-gradient, Cleland was unwilling to continue, but the joining cardiology registrar who had measured the preoperative gradient, advised him to explore. The aorta was opened, with a normal anatomy of aortic valve. The surgeon passed his finger into the left ventricle and an extremely enlarged protruding ventricular septum was found. After excision of a part of the muscle a great deal of hypertrophied muscle remained. After the operation the gradient were almost unchanged, but patient had improvement of symptoms and the result lasted for many years.[216] Glenn Morrow pioneered surgery in hypertrophic cardiomyopathy with sub-aortic ventriculomyotomy after visiting Cleland and Hugh Bentall in London. Morrow performed the procedure in his first two cases in 1960, in a 10-year-old schoolboy and a 33-year-old man with good result,[217] and subsequently in a cohort of highly symptomatic HOCM patients (NYHA class III), with improvement of almost three-quarters to NYHA class I and the rest in NYHA class II.[21] The procedure has been known as the Morrow procedure and has been modified over the years to involve resection of larger area of myocardium. With removal of 5-10 g myocardium from basal interventricular septum, LVOT gradient is usually reduced.[225] Surgical myectomy at tertiary centers has been the gold

standard treatment for most patients with severe symptoms since 1964 with a reduction of LVOT gradient in 90% of patients when performed in expert centres.[6, 225-227]

At the time of myectomy concomitant papillary muscle abnormalities, moderate-to-severe mitral regurgitation and/or significant mitral leaflet elongation may be corrected by surgical procedure.[6, 7] Mayo Clinic data with 289 patients with 6.2 years of follow-up on average reported a 5, 10 and 15-year survival rate of 98%, 96%, and 83%, without reporting the patients lost to follow-up or rate of any re-interventions.[228] Similar results have also been reported by Swiss authors, but they also reported 14% lost to follow-up in which one did not know if patients were alive.[226] In a series of 52 myectomies in children 14.3% of patients needed an additional cardiac surgery re-intervention during a 8.6 year follow-up period.[229] Surgical myectomy has a surgical mortality rate of 0.3-1.1% (per operative or within 30 days of postoperative) and complication rate of about 28% reported from US tertiary centers.[230]

However, studying audited US national statistics for myectomies for all hospitals performing the procedure, the corresponding figures US-wide were 5.9% reported mortality and 30-38% complication rate.[231, 232] In a US registry study of 11248 patients undergoing septal reduction therapy (56.8% myectomy and 43.2% alcohol septal ablation), it was found that during the entire study period of nine years (2003-2011) many centres had low volumes: in 59.9% of institutions only 10 myctomies were performed, and in 66.9% only 10 ASA were carried out. An increase in hospital mortality (15.6%, 9.6% and 3.8%; $p<0.001$), an increased need for permanent pacemaker (10.0%, 13.8% and 8.9%; $p<0.001$) and increased rate of bleeding complications after myectomy (3.3%, 3.8% and 1.7%; $p<0.001$), were found in low volume centers compared to high volume centers when stratified after the first, second and third tertiles of the hospital volume.[233] However, note that even the highest volume tertile (four hospitals with 126 myectomy procedures during nine years of study period) had substantially higher audited operative mortality, 3.8%, than the self-reported figures of 0.3-1.1%,[233] and similarly the 8.9% rate of pacemaker implantation[233] was higher than self-reported figures from Mayo clinic of 2%.[234] One could also observe a low incidence of death and kidney failure after ASA in high volume centers compared to low volume centers.[233]

Summary Thus, the few studies of the long-term results selected to motivate myectomy as the gold standard, are non-randomized and from highly specialized tertiary centers[225] with selected young adult patients under the age of 60 with either many "lost to follow-up",[226] or without information on number of patients "lost to follow-up", or of subsequent need for re-interventions.[228]

Short AV-delay pacing

Hassenstein and Wolter in 1967 reported on two patients with bradycardia who experienced reductions of their left ventricular outflow gradients with pacemaker stimulation of the right ventricular apex. One of their patients was in a critical condition but was dramatically improved and regained consciousness during pacing. They concluded that the increased frequency during pacing caused the gradient reduction due to shortened diastolic intervals.[218] Somewhat later Rothlin and Morcetti investigated

six patients with HOCM and observed a reduction in the mean LVOT gradient from 60 to 15 mmHg when the electrode was placed in right ventricular apex. However, when the electrode was placed close to the pulmonary artery the gradient increased. They concluded that the beneficial effect of right ventricular apical pacing was due to the induced left ventricular block pattern.[219] Hassenstein reported on four cases of pacing in HOCM patients 1975. P-wave triggered pacemakers were implanted and LVOT gradient was decreased by 56% and "subjective complaints inclusively cerebral syncope were remarkable decreased".[220] Duck et al. reported (n=23 patients) a LVOT-gradient reduction of 44% (from 71 to 40 mmHg) with right ventricle apex pacing during heart catheterization and that this was due to an increased outflow tract area during pacing. They could show that those reductions were not caused by a decrease of the stroke volume, but by an enlargement of the effective opening of the outlet.[221] In all these reports the pre-excitation of the left ventricle by stimulating the right ventricular apex, achieving complete ventricular capture by programming a short AV-delay during VDD/DDD stimulation to over-ride intrinsic conduction is important.[220, 221, 223, 235-237]

Optimization of pacing should focus on three key points: ventricular stimulation site, ventricular capture and left AV synchrony.[238] Apex as ventricle stimulation site, showed by Gadler et al. reduced LVOT gradient from 96±33 mmHg to 38±24 mmHg in contrast to unchanged gradient with septal pacing.[223] Berruezo et al. showed that 58% of patients with short AV-delay pacing had fusion between intrinsic conduction and pace activation resulting in lack of improvement in LVOT gradient or symptoms.[239] Optimization[238] of pacemaker recommended during operation was achieved by using temporary pacing in VOO mode at 20 bpm above the patients intrinsic rate to ensure RV apical pacing and complete ventricular capture on 12-lead surface ECG. LBBB configuration and left superior axis deviation on paced QRS complexes is the sign of RV apical pacing. Widest paced QRS duration defined as full capture. Paced QRS duration and morphology which obtained during operation will serve as reference of full ventricular capture during follow-up.[238] To obtained optimal left AV synchrony for full ventricular capture, short AV-delay during VDD/DDD pacing is the best option. AV-delay on the one hand must be short enough to give full capture of the LV from the RV apex, but on the other hand long enough to achieve a maximal atrial contribution to the LV filling as described by Daubert et al.[238] The mechanism of action of AV sequential pacing is not fully clear but some hypothesis explain the beneficial effects include: (i) negative inotropic effect and reduced hyper contractility of the LV, (ii) asynchronous late septal activation and delayed septal thickening, (iii) limitation of abnormal mitral valve motion, (iv) interaction with LV filling, and (v) gradual ventricular remodeling.[238]

In 1999 Kappenberger et al. reported on favorable results of temporary short AV-delay pacing in drug refractory eighty-three HOCM patients (33 female and 50 male) mean age 53 (18-82) years. Patients were included in a prospective study after a pacemaker (DDD) implanted. After an initial double-blind crossover phase of 6 months, patients were reinvestigated at 12 and 36 months. With pacemaker on the LVOT gradient significantly reduced from 72±35 mmHg to 29±24 mmHg ($p<0.01$). At 1 year the effect persisted with a resting gradient of 28±24 mmHg, an improvement in functional

capacity, quality of life, and a significant improvement in dyspnoea and angina. Only patients with reduced initial tolerance had improved in exercise on treadmill. During follow-up of 36 months (mean), 65 (79%) patients continued with pacing alone. [222, 240]

Reports of short AV-delay pacing from the USA showed the same good result in drug refractory HOCM patients. Fananapazir et al. reported in one study of forty-four consecutive patients with drug refractory obstructive HCM-patients who underwent implantation of a DDD pacemaker. Symptoms and exercise durations were improved and LVOT gradient reduced significantly (87±43 mmHg to 38±38) notably, all cardio active drugs were discontinued in all patients before and after pacing.[237] Fananapazir et al. reported a following study of long-term (2.3±0.8 years) results of DDD pacing in 84 drug refractory HOCM patients. They concluded that most of the improvement of clinical and hemodynamic indexes occurs during the first few months of DDD pacing, additional improvement is often observed a year later, and DDD pacing reduces both resting and provokable LVOT obstruction. Furthermore they observed despite the presence of LBBB, DDD pacing reduced LVOTO significantly in all 15 patients with LBBB.[237, 241]

Slade et al. reported the result of short AV-delay pacing (median 65 ms, range 25-125, ms) in 56 patients with a follow-up duration of 11 month. The mean (range) LVOT gradient before implant was 78 (31) mmHg and at follow-up was 36 (25) mmHg giving a reduction of 54%. There was a significant improvement in functional class with 23 (50%) patients achieving NYHA class I. Nine patients (17%) showed no improvement or one had worsening functional status. There was a small but significant ($p<0.02$) improvement in maximum oxygen uptake in the patients who underwent metabolic exercise testing.[242]

A minor American randomized double-blind cross-over study (Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy (MPATHY) of 48 patients significantly confirmed the benefit of pacing treatment to outflow gradient and quality of life, but found no significant improvement in exercise ability.[3] This study is mentioned in the discussion below. Another small non-randomized study compared 20 patients who, based on patient preference, underwent myectomy and 19 patients treated by short AV-delay pacing,[243] in this study, significantly better gradient reduction and greater improvement in exercise capacity were reported in the myectomy group than in the pacing group. The follow-up time in the study, however, was longer for myectomy than patients with pacing therapy, myectomy patients were on average 17 years younger, many sick patients undergoing myectomy were not included in the study (highly selected patients to myectomy), and in addition patients who underwent DDD pacing under study time (1995-1997) were part of a multicenter randomized trial as mentioned above (M-PATHY) with a LVOT gradient reduction by 40% in M-PATHY study,[244] but the same cohort of patients as in M-PATHY in this study had a LVOT gradient reduction by 29%, also a 25% less reduction than in M-PATHY(selection bias). All this may be relevant for their ability to increase exercise capacity and the result of this study. These two studies were probably influential in that short AV-delay pacing was removed from considerations as a first choice in the American Heart Association (AHA) guidelines for HOCM treatment.[6]

More recently long-term observational studies with short AV-delay pacing from Europe have reported good symptom improvement and maintained LVOT gradient reduction with pacing. In a study from Spain by Galve et al. in 2010 fifty drug refractory HOCM patients underwent a dual-chamber pacemaker implantation with a follow-up of 10 years. During follow-up, resting gradients decreased successively (baseline 86±29 final resting gradient 28±24 mmHg), NYHA class improved, as well as exercise tolerance (baseline 281±112 m; 3 months 334±106 m; 1 year 348±78 m; $p<0.0001$).[245] Lucon et al. reported on 51 drug refractory HOCM patients who underwent implantation of DDD pacemakers with or without a defibrillator and were followed for 11.5 years.[246] During follow-up, no patient underwent interventional treatment as myectomy or septal alcohol ablation. NYHA functional class decreased significantly and the LVOT gradient decreased by a mean of 89% at end of follow-up. The 5- and 10-year survival rates were 90% and 65%, respectively.[246] Thus it appears that benefit of short AV-delay pacing on outflow-gradient increases with time, perhaps through beneficial re-modelling. Currently European Guidelines from the European Society of Cardiology 2014 recommends pacing to patients who have a high risk if subjected to septal reduction, patients who do not want to undergo surgery and those who have a mild hypertrophy.[7] One observation of relevance is that chronic pacemaker treatment on other indications has also been shown to lead to a dilated cardiomyopathy with reduced systolic function.[247]

Summary Pacing studies have included few (8-84) patients[248, 43, 241] and elderly patients with short follow-up periods,[222, 237] or are without control groups.[245, 51, 246, 52]

Alcohol septal ablation (ASA)

ASA has recently been used to a greater extent in Europe as it is alleged that it has an effect as good as myectomy[7] but there are no randomized studies. ASA has a higher frequency of complications in the form of atrio-ventricular blocks requiring permanent pacemaker following the procedure (7-20%)[7] compared to myectomy (4%).[249] Re-interventions after ASA for LVOTO occur in about 10%.[119, 250] Quintana et al. reported that patients who are referred to myectomy after ASA with insufficient relief of LVOTO have poorer diastolic function and higher frequency of arrhythmias, a higher frequency of postoperative complete heart block and a higher perioperative mortality rate of 6.2%.[251] As for other treatment options, nothing new has emerged recently.[137]

Shortcomings of studies dealing withy treatment of obstructive HCM

- Non-randomized studies, from tertiary centers with referral bias, without any control group.
- Short follow-up time, this means that long-term effects of therapy (medication, septum reducing treatment and pacing therapy) on the mortality of adult HOCM patients are poorly elucidated.
- Few patients in studies (about 50% of HCM studies have <20 patients in their studies, 7% have ≥50 patients), this gives low statistical power.
- Many “lost to follow-up” or unreported data on “lost to follow-up”.
- Complications and re-interventions are not adequately reported.

- As a result of the above, scientifically robust studies defining best treatments for obstructive HCM are lacking.

In order to see the effect of long-term results of various treatments (pharmacotherapy, surgery or pacemaker) on outflow obstruction in hypertrophic obstructive cardiomyopathy on HCM-related deaths, a long-term follow-up study, with 100% complete follow-up and without the influence of referral bias, is needed. To get enough patient years, we have studied a total geographical cohort throughout the Västra Götaland region with no loss to follow-up and complete documentation of causes of death, to highlight the following issues:

1. Does the treatment of outflow obstruction with surgery have better long-term results than pacemaker treatment?
2. What are the risk factors that affect mortality in patients with HOCM in a geographical cohort?
3. What are the mortality patterns in a geographical cohort of HOCM patients?
4. What is the long-term effect of pharmacological treatment on disease-related mortality?
5. Are there gender differences in mortality among HOCM patients, or is there referral-bias in the gender distribution to tertiary centers? What might be the factors that affect any gender differences?
6. How do complications, and early and late morbidity, compare after surgical myectomy or pacing therapy in a case-control analysis of matched patients?
7. Length of stay at hospital and costs related to myectomy compared to pacing therapy in a case-control analysis of matched patients

Our study is about primary HCM, including Noonan spectrum mutations because this group of mutations has identical histology. Many physicians fail to recognize mild dysmorphology among adult HCM populations. When Jacqueline Noonan visited Bill McKenna´s outpatient clinic for HCM in London, she spotted several unrecognized Noonan patients (W. McKenna, pers communication), and paediatric cardiologists in Västra Götaland have recognized several adult HCM-patients with un-diagnosed co-existing Noonan syndrome in contact screening of familial paediatric cases. Thus many published HCM-studies will likely include patients with unrecognized Noonan-syndrome associated HCM. Patients with storage disorders that have secondary HCM are not included (Danon, Fabry, Familial amyloidosis, Friedreich ataxia and other mitochondrial cardiomyopathies).

Total study cohort

Adult in- and outpatient cardiac care for the 1.6 million inhabitants of West Götaland Region is provided by 10 hospitals (Sahlgrenska, Östra, Mölndal, Uddevalla, Trollhättan, Skövde, Lidköping, Alingsås, Borås and Kungälv). We searched all hospital diagnostic databases (Melior data system) for adult patients attending hospital from

January 2002 to December 2013 with ICD diagnostic codes (I42.0, I42.1, I42.2, I42.3 and I 42.8) relating to a diagnosis of HCM, and reviewed the case notes on site (D.J. and I.Ö.S.) to identify those with HCM and outflow tract obstruction (HOCM).We identified 1142 adult patients, out of whom 251 (22%) patients had obstructive HCM with a resting LVOT gradient ≥30 mmHg,[7] with an even sex distribution (128 male age 51years [IQR=27] and 123 females age 62years [IQR=20]). Syncope occurred in 25.4% and 15.1% had a family history of SCD. Among total cohort 75.3% reported symptoms as reason to search health care, 24.7% did not report any symptoms related to HCM (Figure 2A). Co-existing Noonan syndrome was identified in 7 patients (3 females and 4 males).

The average NYHA class was 2.2 (±0.73) at diagnosis, Figure 2B.

Transthoracic echocardiogram measurement showed (median [IQR]): septum 19 [6] mm, LVEDD 43 [9] mm, LAD 41 [15] mm, LVOT gradient at rest 65 [57] mmHg and EF 69% [15]. AF was present in 4% at diagnosis, systemic hypertension in 13.5%, diabetes in 5.6%, coronary artery disease in 3.6% and chronic obstructive pulmonary disease (COPD) in 6.8%. The maximal septal wall thickness was ≥30 mm in 9 (3.4%) of the patients.

Initial medical therapy is shown in Figure 3.

Reasons not to have cardio-protective medication

At diagnosis 74 out of the 251 HOCM-patients (29.5%) did not receive BBL-treatment and for 8 patients data are missing. Calcium blockers – presumably at that time considered just equally effective as cardio-protection – were given to 26 patients i.e, 48 patients did not have cardio-protective medication with either beta-blockers (BBL) or calcium channel blockers (CCB). Among the 48 patients without initial cardioprotective medications (BBL or CCB) 57.8% were symptomatic and their median LVOT gradient was 65 [IQR 46] mmHg.

Among all patients only 4/251 (1.6%) did not tolerate BBL, because of tiredness. In patients who did not receive any BBL at diagnosis we could not find any differences in age and co-morbidities (hypertension, heart rate, AV-block, QRS duration at diagnosis, or presence of COPD or diabetes at diagnosis or at follow-up) compared to patients that were treated with BBL. Of patients treated with calcium-blocker at diagnosis 27% had COPD compared to 7.3% in BBL group (p=0.0008), otherwise there were not any significant differences in age, gender, blood pressure, heartrate, QRS duration or diabetes compared to patients with BBL.

Among those treated actively the initial treatment was always pharmacotherapy and during the study period 121 of the 251 patients (48.2%) did not receive intervention (101 on drug therapy and 20 without drug-therapy). However, 130 required interventions, 88 with short atrioventricular delay pacing and 42 with myectomy. The time from diagnosis until intervention for pacing group was 3.4 [6.3] and myectomy group 4.5 [8.1] years, p=0.20.

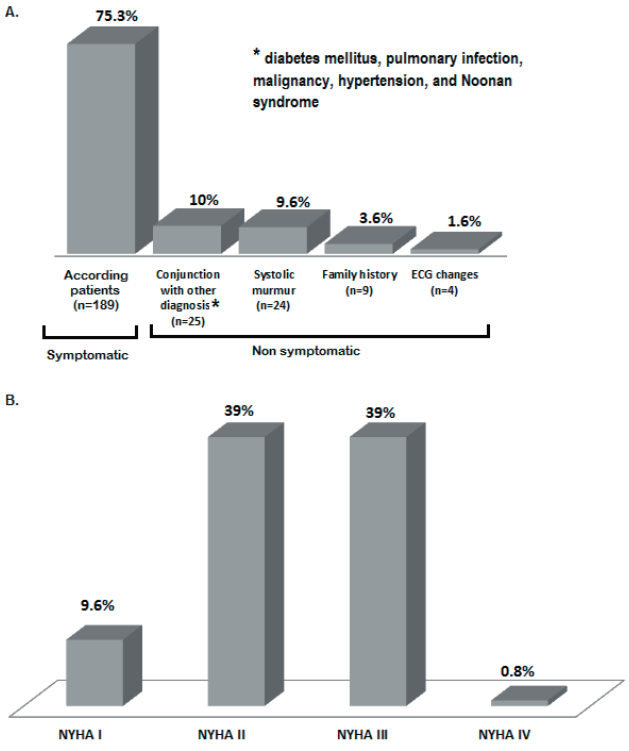


Figure 2. A. Diagnosis according to patients self-reported symptoms. **B**. NYHA class at diagnosis estimated by doctor.

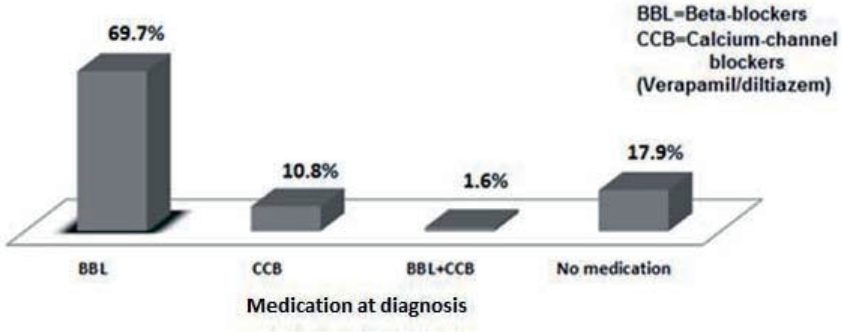


Figure 3. Initial medications.

Vital status was censored on 28 February 2015. Death certificates from the National Board of Health and Welfare were obtained to establish causes of death in addition to case note review. No patient was lost to follow-up. See Table I, Paper 1, for characterization of total cohort at diagnosis.

AIMS

The aims of the studies were:

Paper I

To assess risk factors for HCM-related mortality in a geographic cohort of patients with hypertrophic obstructive cardiomyopathy and any therapeutic effect of pharmacotherapy and interventional therapy on survival.

Paper II

To compare long-term results after treatment of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy with myectomy or with short atrio-ventricular delay pacing

Paper III

To assess the impact of female sex on disease-severity and prognosis. Possible sex-specific risk-factors for disease-related mortality are examined in more detail in this unselected complete geographical cohort of hypertrophic obstructive cardiomyopathy patients.

Paper IV

To compare short- and long-term morbidity following treatment of left ventricular outflow-obstruction in hypertrophic obstructive cardiomyopathy by myectomy or by short atrio-ventricular delay pacing

MATERIAL AND METHODS

Paper I

Subjects and Method

In this complete geographical cohort of 251 HOCM patients we reviewed records for: clinical data, ECG and echocardiographic findings, presence of proposed risk factors and comorbidities, therapy modalities (conservative; with or without medical therapy but without intervention, n=121, pacing n=88, myectomy n=42) as well as recording ICD therapies. The type of all medical therapy used was recorded at, or shortly after, diagnosis and at latest follow-up visit. Type and dose of beta-blocker and calcium-channel blocker (CCB) therapy were documented. For statistical evaluation, all beta-blocker doses were converted to corresponding 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 mg[252] = bisoprolol 5 mg = atenolol 50 mg. The mean follow-up time was 14.4±8.9 (mean±SD) years. Among the 26 patients with CCB, 3 had diltiazem and 23 had verapamil. The dose of diltiazem converted to the same equivalent doses of verapamil as both drugs exhibited consistent efficacy with minimal adverse effects in equivalent doses.[253]

Endpoints 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", and secondary end-points were heart failure death and appropriate shocks from ICD. Other outcome parameters in the total cohort are NYHA class, permanent AF, outflow gradient measured with Doppler and left ventricular wall thickness. NYHA class was assessed by the physician at the initial visit or within three months in 222/251 (88.4%) cases, and by analysis of patient records in 29/251 (11.6%) cases according to NYHA classification criteria.[254]

Paper II

Subjects and Method

As mentioned above 203/251 patients were initially tried on medical therapy; 121 remained in conservative group (16.5% without medications). Of those having insufficient control of gradients or symptoms, 88 patients were treated with short AV-delay pacing (19.3% without cardioprotective medication), and 42 patients underwent a surgical myectomy (19% without cardioprotective medication). For patients aged ≥18 years, first-line procedure was determined by the responsible physician and patient preference. The first choice of intervention for patients <18 years of age was myectomy. Thus among the patients in the cohort, we identified 10 patients who had myectomy after infancy but <18 years of age, but who at last follow-up were adults (n=6) or teenagers (n=4). Furthermore, four patients (all now adults) received pacing therapy <18 years of age: in patients aged 13-17 years where an ICD was indicated (three primary, one secondary prophylaxis) and the device was used also for short AV-delay pacing. Two of the four had had unsatisfactory results from a prior myectomy. Clinical data, ECG and ultrasound measurements were documented at pre-procedure

examination, and at last follow-up visit, as well as medical therapy and interventional procedures during follow-up.

Cardiac surgery (myectomy) was carried out at the Sahlgrenska University Hospital, Gothenburg, and short AV-delay pacing was also undertaken in Uddevalla, Trollhättan and Skövde as well as the Sahlgrenska Hospital.

Dual-chamber permanent pacemakers were implanted in a standardized way with fluoroscopy- and echocardiographic verification that the ventricular electrode tip was placed optimally in the apex of the right ventricle. AV-delay was set under ECG-control to ensure abolition of spontaneous conduction, and then evaluated by echocardiography in order to obtain maximal LVOT gradient reduction without deterioration of diastolic filling.[241] Septal myectomy was performed as described by Robbins and colleagues.[225]

Endpoints The primary endpoint was disease-related death (henceforth: 'cardiac mortality'), in which we included death due to heart failure, arrhythmia, death-certificate classified sudden deaths, bacterial endocarditis (n=1), fatal strokes in patients with AF and due to embolism from a presumed cardiac source, and cardiac transplantation that was considered a death equivalent. The secondary endpoint was re-intervention for residual LVOTO during follow-up. Other outcome parameters in the total cohort are NYHA class, permanent AF; outflow gradient measured with Doppler and left ventricular wall thickness.

Paper III

Subjects and Method

This cohort is identical with the complete geographical cohort in Paper I and Paper II, consisting of 251 patients (128 males and 123 females) who fulfilled the criteria of HOCM and were included in the study. As the women were older than men at diagnosis (with a median difference of 11 years ($p<0.001$), we compared not only total survival but also survival by matching females and males for age at diagnosis, severity of cardiac hypertrophy, severity of LVOTO and treatment category (medical therapy only, short atrio-ventricular delay-pacing or myectomy). We identified 83 pairs that were good matches, with mean difference in age between pairs of 0.2 (1.7) years.

Endpoints The primary endpoint was disease-related death defined as in Paper I and Paper II. Other outcome parameters in the total cohort are NYHA class, permanent AF; outflow gradient measured with Doppler and left ventricular wall thickness.

Paper IV

Subjects and Methods

This cohort is the same unselected complete geographical cohort as in Papers I, II and III. Patients in myectomy-group were significantly younger at procedure as compared to the pacing-group. As age is expected to impact on peri-operative morbidity and possible return of LVOTO, we chose to compare the rates of complication and

morbidity also by case-control methodology, matching patients for age at intervention, LVOT-gradient, maximal wall thickness, and sex if possible. We identified 31 pairs (≥18 years age at procedure) which were satisfactory matches which constituted the case-control group with mean difference in age between pairs of 2.6 (2.0) years (p=0.56).

Clinical characteristics and ECG and ultrasound measurements were documented at pre-procedure, and at follow-up, in addition to peri-procedural (cardiac and non-cardiac) complications and interventional procedures during follow-up. Complications were defined as peri-procedural when occurring during, or in the first 30 days after, intervention.[231] Cardiac and non-cardiac complications were defined as: any complication/re-intervention related to the procedure, perioperatively or during follow-up (Table 2, Paper IV). As further outcome measures the length of stay was determined, and the costs (material, operations- and care-related costs) during the study period were acquired from the National Board of Health and Welfare.

Endpoints were peri-procedural cardiac and non-cardiac complications (within 30 days) and re-interventions during long-term follow-up.

Ethical considerations

The first part of the study is about case note reading/archiving work, extracting data on patients' clinical status, and collecting information on their medical treatment. The risk for the individual was considered very small even though a retrospective journal review always entails an integrity infringement. The benefit for future patients was considered good, which justified the risk to the integrity of the individual patient. Collected data was coded in the database for statistics processing and no individual can be identified in any published information. The study complies with the Declaration of Helsinki and was approved by local ethics committee of the University of Gothenburg (ÖS no 1012-12).

Statistical Methods

For all Papers (I-IV): Parameters without normal distribution are represented with median [interquartile range (IQR)] and normally distributed by mean ± standard deviation. Kolmogorov-Smirnov test has been used for assessing distribution fitting, Mann-Whitney U-test for comparing the groups, Wilcoxon signed rank test for paired data (paired continuous variables) and Fisher's exact and $\chi 2$ two-tailed test for comparing the categorical groups as appropriate. All tests were two sided, and p-values <0.05 were considered statistically significant. Analysis was carried on SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). For each specific Paper, further statistical methods have been used and are described under each Paper.

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

We have used Pearson's correlation coefficient for continuous variables, Spearman's rho for categorical data and McNemar test for comparison between paired data (paired binary data). Kaplan-Meier curves and log-rank test have been used for analysing of survival. Univariate and multivariate Cox proportional hazards method for comparative analysis of risk factors for the endpoint was carried out. For multivariate analysis we selected variables if univariate p-values were ≤ 0.20. In order to have adequate statistical power the numbers of variables were restricted to six at a time in our multivariate models with backward selection analysed. 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

Paper II: *Short atrioventricular delay pacing therapy in young and old patients with hypertrophic obstructive cardiomyopathy: good long-term results and a low need for reinterventions*

Box and Whisker plots were used to display the final result of LVOT gradient after first intervention. Kaplan-Meier curves and log-rank test were used for analyzing of survival and hazard of re-intervention.

Paper III: *Factors contributing to excess female mortality in hypertrophic obstructive cardiomyopathy*

Univariate and multivariate Cox proportional hazards method used for risk comparative risk factors analyzing. Kaplan-Meier curves and log-rank test were used for survival analysis.

Paper IV: *Morbidity and resource usage after myectomy- or pacing-treatment in hypertrophic obstructive cardiomyopathy: a case-control study*

McNemar test was used for comparison between binary paired data and Cumulative hazard was analysed by Kaplan-Meier curves and log-rank test.

RESULTS

Paper I

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

Mean follow-up was 14.4±8.8 years (mean±SD) and median follow-up 13.2 (IQR=12.4) years (Table 1, Paper I for detailed findings at diagnosis). Females were generally older but the sex distribution was even. Beta-blocker use increased during follow-up from 71.3% at diagnosis to 86.1% at latest follow-up ($p<0.001$). The median initial dose prescribed was 125 mg metoprolol equivalents/ day, and at latest follow-up was 150 mg/day for patients given BBL, with no significant differences between intervention and non-intervention groups. Including un-treated patients the population median dose was 100 mg metoprolol/day. The duration of BBL treatment for those who had BBL since diagnosis was 13.3 [11.7] years and for patients who were started later it was 6.0 [3.8] years. The duration between diagnosis and introduction of BBL for those who did not have BBL since diagnosis was 4.0 [10.2] years. 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). Therefore, HCM-patients with the most advanced disease did not obtain lower doses.

Of 4 patients who were considered not to tolerate BBL at diagnosis 2 had BBL-therapy successfully started during follow-up. For more detail see Figure 4.

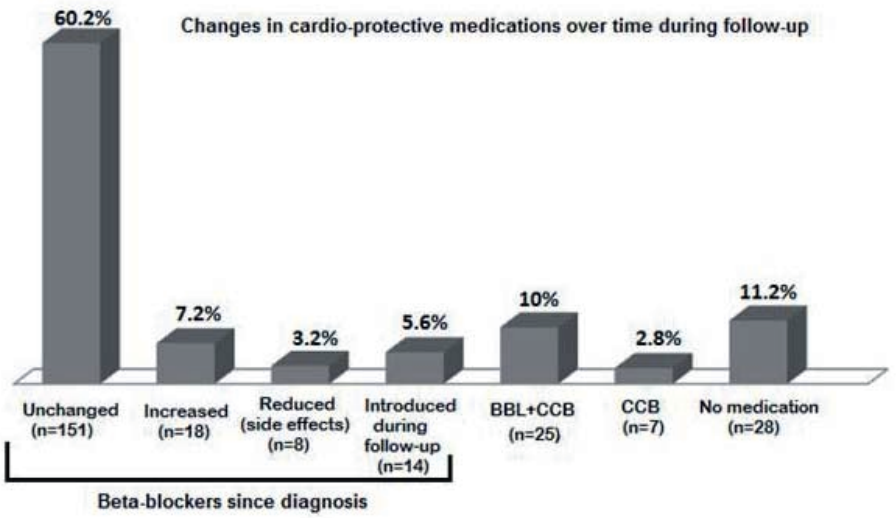


Figure 4. Medication at last follow-up. BBL=Beta-blockers, CCB=Calcium-Channel blockers (verapamil/diltiazem).

Verapamil/diltiazem was prescribed at diagnosis to 12.4% of patients without any significant differences in age, arrhythmia, hypertension, LVOT ≥50 mmHg, COPD, angina, smoking habits or hospital affiliation (University hospital compared to local hospitals) compared to all patients without verapamil/diltiazem therapy. But 17.1% of females were given verapamil/diltiazem at diagnosis compared to 7.8% of males (p=0.034). Verapamil/diltiazem therapy was given in median doses of 240 (IQR=80) mg/day, and proportion prescribed changed only from 12.4% of patients to 12.7% at latest follow-up (p=0.48). For other medication see Supplementary Table S1, Paper I)

Irrespective of the type of therapy applied the New York Heart Association (NYHA) class was improved and the resting LVOT gradient was reduced to a median of 16 mmHg during follow-up. However, 21% had resting gradients remaining ≥50 mmHg (37% in NYHA I, 37% in NYHA II, 26% in NYHA III-IV), and 33% ≥30 mmHg at latest follow-up (33.3% in NYHA class I, 41% in NYHA class II and 25.4% in NYHA class III-IV). The proportion of LVOT ≥50 mmHg was 24% in the conservative, 17% in pacing and myectomy groups (updated data) respectively at last follow-up. Among patients with LVOT gradient ≥50 mmHg at last follow-up only 7.8% had disopyramide as additional medication despite AHA and ESC recommendations. The reason for why more active treatment was not undertaken could not be addressed from records. Atrial size and incidence of AF had increased significantly at latest follow-up. There were 65 primary end-point events (53 cardiac deaths, 4 heart transplants and 8 embolic deaths) during follow-up. SCD occurred in 11 (17%) patients, with an annual rate of 0.37% during the first 10 years of follow-up as estimated only on those patients that received the diagnosis during the study period, Figure 5. Sixteen patients (6.4%) had ICD implanted (4 for secondary, 12 for primary prevention), and during follow-up there was only one appropriate discharge in 149 patient-years, that is an appropriate annual discharge rate of 0.67%.

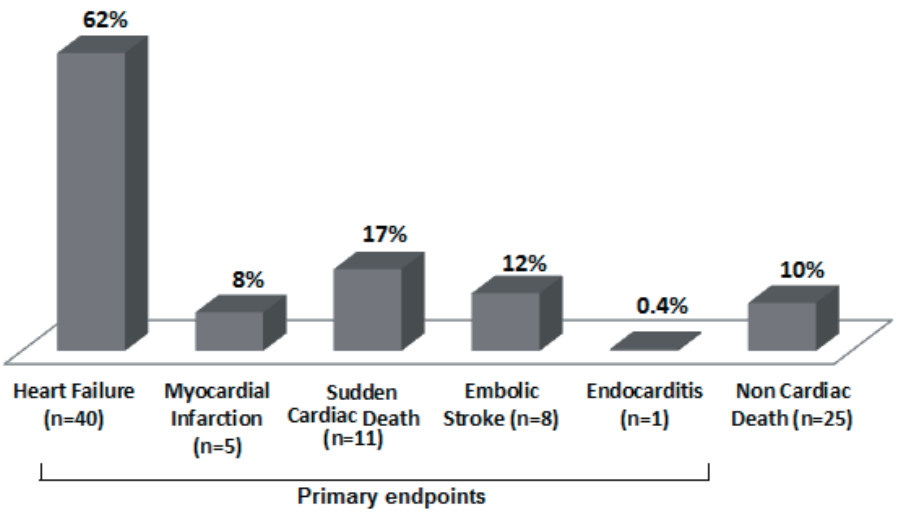


Figure 5. Mortality in total cohort divided by HCM-related and total mortality.

Risk factors at presentation for subsequent disease-related death

On univariate analysis, age at diagnosis, female sex, coronary artery disease and a resting LVOT gradient ≥50 mmHg at diagnosis were significantly associated with endpoints (Table 2, Paper I). Verapamil/diltiazem was a risk factor on univariate, but not multivariate analysis. In the multivariate analysis of the whole group accepted initial risk factors for SCD and comorbidities were not significant risk factors for total disease-related deaths. For multivariate analyses see Table 1.

Table 1. Multivariate Cox hazard analysis influence of initial risk factors

Variable	B	SE	Exp (B)	95% CI Exp (B)	p value
			Disease-related death (93% complete data)		
Female sex	0.823	0.292	2.278	1.286-4.036	0.005
Age	0.039	0.009	1.039	1.021-1.058	<0.001
LVOT-gradient ≥50 mmHg at rest	0.631	0.301	1.879	1.042-3.388	0.036
Metoprolol/metoprolol equivalents dose mg/day	-0.004	0.002	0.996	0.992-1.000	0.028
			Heart failure death (93% complete data)		
Female sex	0.763	0.387	2.145	1.005-4.581	0.049
Age	0.060	0.014	1.062	1.034-1.091	<0.001
Metoprolol/metoprolol equivalents dose mg/day	-0.005	0.003	0.995	0.990-1.001	0.080
			All-cause mortality (93% complete data)		
Female sex	0.805	0.252	2.237	1.367-3.663	0.001
Age	0.050	0.008	1.051	1.035-1.068	<0.001
LVOT-gradient ≥50 mmHg at rest	0.708	0.257	2.029	1.226-3.58	0.006
Metoprolol/metoprolol equivalents dose mg/day	-0.003	0.001	0.997	0.995-1.000	0.064

Predictors of disease-related death at last follow-up

On univariate Cox hazard analysis, female sex, age, NYHA class ≥III, a gradient remaining ≥50 mmHg and a smaller left ventricle end-diastolic diameter were associated with a significantly increased risk for disease-related death (Table 3, Paper I). Development to dilated end stage heart failure was observed in only 4%. Verapamil/diltiazem was a risk factor on univariate, but not multivariate analysis. Neither use of Disopyramide, amiodarone, ACE inhibitor nor spironolactone showed any significant effect on survival. On multivariate model comorbidities were not independent predictors. For risk factors on multivariate analysis (Table 2).

Influence of therapy choice on survival

Neither pacing nor myectomy reduced disease-related mortality significantly see Paper II.[135] Verapamil therapy was associated with increased risk on univariate analysis (p=0.014), whereas use of beta-blocker therapy started early at diagnosis was associated with reduced risk on univariate Cox hazard analysis (p=0.004; Table 2, Paper I).

Table 2. Multivariate Cox hazard analysis of predictors of disease-related death at latest follow-up

Variable	B	SE	Exp (B)	95% CI Exp (B)	p value
		Disease related death (96.8% complete data, 3.2%missing)			
Female sex	1.197	0.389	3.310	1.543-7.100	0.002
Age	0.024	0.011	1.025	1.003-1.047	0.025
LVOT-gradient ≥50 mmHg at rest	1.262	0.374	3.533	1.697-7.355	0.001
NYHA class ≥III	0.846	0.383	2.330	1.100-4.934	0.027
Metoprolol/metoprolol equivalents dose mg/day	-0.005	0.002	0.995	0.991-0.999	0.021
		Heart failure death (96.8% complete data, 3.2% missing)			
Female sex	1.036	0.352	2.819	1.414-5.620	0.003
LVOT-gradient ≥50 mmHg at rest	0.014	0.007	1.014	1.001-1.028	0.032
Systemic hypertension Yes vs No	0.726	0.336	2.066	1.069-3.995	0.031
Verapamil/Diltiazem use Yes vs No	1.036	0.414	2.817	1.251-6.343	0.012
Metoprolol/metoprolol equivalents dose mg/day	-0.005	0.002	0.995	0.991-0.999	0.008
		All-cause mortality (98% complete data)			
Female sex	1.131	0.284	3.099	1.777-5.406	<0.001
Age	0.019	0.008	1.019	1.003-1.035	0.017
LVOT-gradient ≥50 mmHg at rest	0.052	0.015	1.053	1.023-1.083	<0.001
Max wall thickness (mm)	0.071	0.030	1.074	1.013-1.139	0.017
Metoprolol/metoprolol equivalents dose mg/day	-0.004	0.001	0.996	0.993-0.999	0.008

The association with outcome seemed to be dose-dependent with reduced risk with increased daily dose (p=0.001) and dose-dependency persisted significantly in the multivariate analysis (p=0.028; Table 2, Paper I), also for heart failure deaths specifically at last follow-up. The HR (Cox hazard) between early beta-blocker use and non-use of beta-blocker was 0.49 (95% CI 0.30 to 0.81), p=0.006. Freedom from disease-related deaths for patients given ≥100 mg/day metoprolol-equivalent was significantly better than for those given 0-99 mg/day (log-rank: p=0.00004; Figure 1A, Paper I), as was all-cause survival, p=0.00005. Comorbidities were not significantly different between patients in 0-99 mg/day and ≥100 mg/day groups (Supplementary Table S4, Paper I). The survival curves of patients with no beta-blocker initially (n=74) were overlying the curves of patients given 25-74 mg/day (n=36; p=0.67; online Supplementary Figure S3) and therefore these patients were combined in a 0-74 mg/day group. Survival curves representing three dose ranges: 0-74 mg/day, 75-149 mg/day and ≥150 mg/day of metoprolol-equivalents beta-blocker, the middle band including the median initial dose, show the advantage of larger doses of beta-blocker most obviously. There was a significant log-rank for trend in reduced risk of disease-related deaths with increased dose of beta-blocker (p=0.00008; Figure 1B, Paper I and Figure 6 below). The 10-year survival 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 survival from disease-related deaths of patients without beta-blocker therapy was 81.7%. Analysis of total mortality established a similar shape (log-rank p-trend=0.00009), with 10-year all-cause survival of 78.7%, 88.8% and 91.1% in respective dose bands. In the multivariate model beta-blocker dose was associated to reduced risk for chronic heart failure and total mortality (p=0.008) at latest follow-up (Table 2).

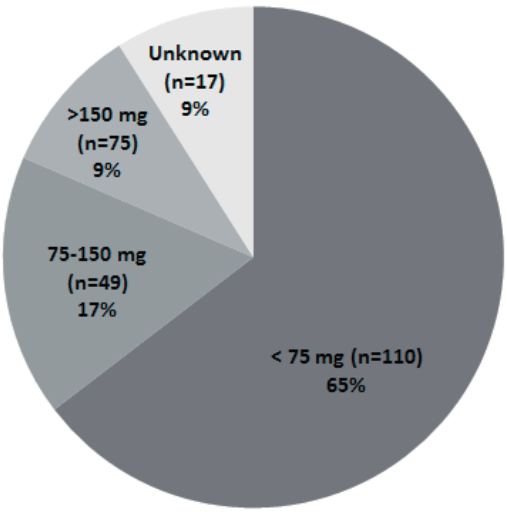


Figure 6. Proportion of disease-related deaths belonging to each dose category (percent).

Beta-blockers and post-intervention gradient

Disease-related mortality was significantly higher in patients who did not receive early BBL if residual gradient was ≥30 mmHg (10-year proportion 39.1%) than if gradient was <30 mmHg (10-year proportion 7.4%; p=0.002). Consequently, we analyzed if the obvious protective effect of BBL was present only in patients with a residual gradient of ≥30 mmHg after initial therapy. This seemed not to be the case as shown in Figure 2AB, Paper I.[255] In this study post-intervention beta-blocker dose ≥100 mg metoprolol/metoprolol equivalent/day was associated with significantly better survival than low dose (25-99 mg) even after interventional procedure (Figure 3, Paper I). There was no significant difference of co-morbidity between patient groups (Supplementary Table S7, Paper I). In addition, there was no additional co-morbidity in HCM-patients who had died a disease-related death compared with survivors (Supplementary Table S8, Paper I).

According to US and European Guidelines, BBL or verapamil may be considered in children and asymptomatic adults with resting or provoked LVOTO, to reduce left ventricular pressures, but need not to be prescribed.[6, 7] We investigated whether beta-blocker therapy was associated with better survival only in symptomatic patients. We found that BBL were significantly associated with better survival on Kaplan-Meier curves both in asymptomatic and symptomatic patients, Figure 7 AB.

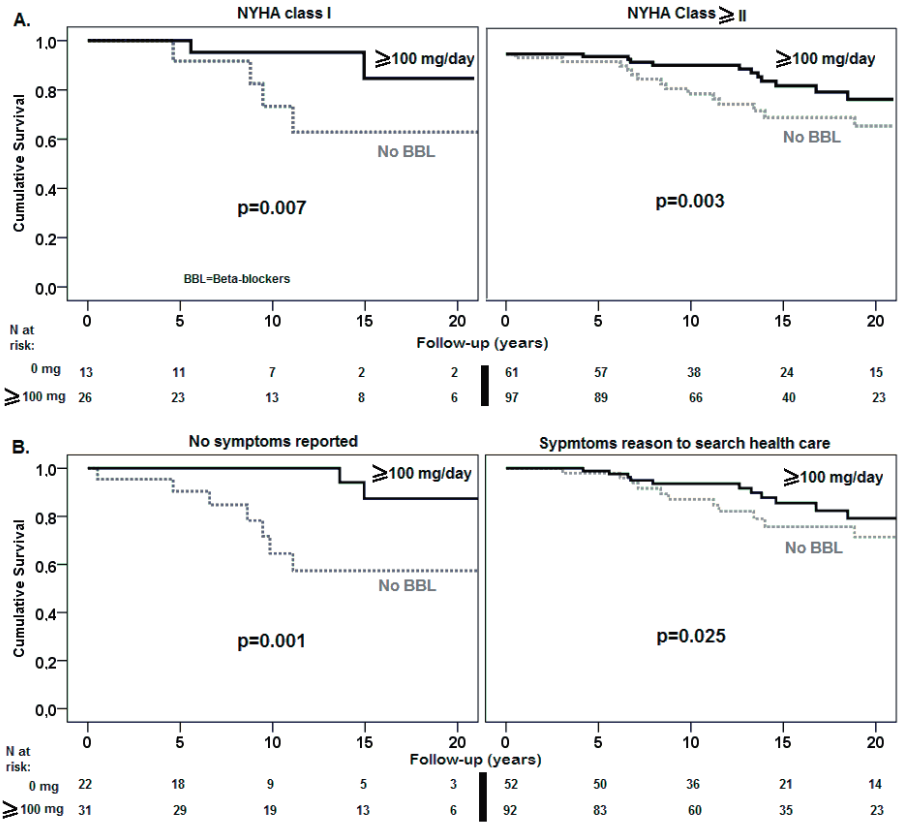


Figure 7. **A**. Beta-blockers with a median dose ≥100mg/day were associated to better survival in patients with all NYHA classification. **B**. Beta-blockers with a median dose ≥100mg/day were associated to better survival in patients who self-reported symptoms at diagnosis.

In Paper I we found that verapamil/diltiazem treatment showed a significant association with increased risk of heart failure related death in univariate (p=0.008) and also in multivariate Cox hazard regression (p=0.012), after correction for other factors such as age, female gender, LVOT gradient ≥50 mmHg, systemic hypertension and beta-blockers (Figure 8).

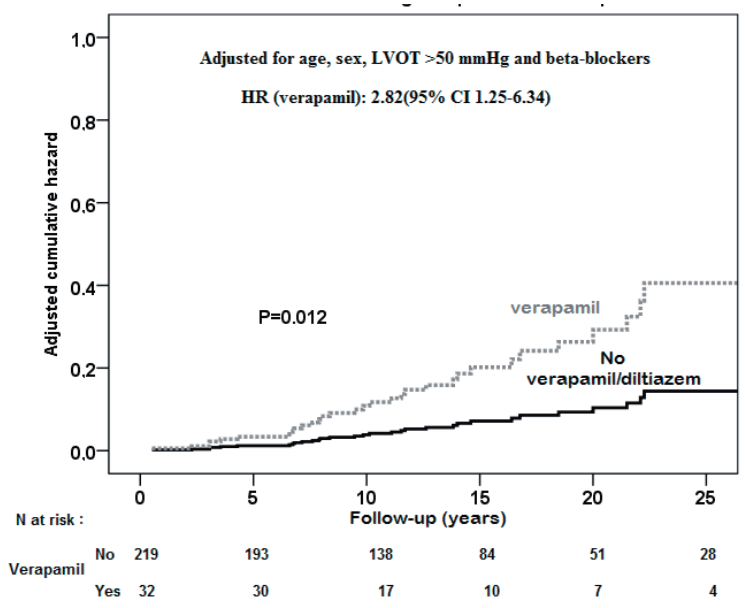


Figure 8. Adjusted cumulative hazard of heart failure death at follow-up according to use of verapamil/diltiazem in total cohort.

Paper II

Short atrioventricular delay pacing therapy in young and old patients with hypertrophic obstructive cardiomyopathy: good long-term results and a low need for re-interventions

This study evaluates the long-term outcome after different therapies for LVOT obstruction. Gender distribution was even between treatment groups. However, pacing patients were significantly older (nearly 25 years) than myectomy patients at the time of intervention. The initial NYHA class tended to be worse in the pacing group compared with the myectomy group (p=0.05). The conservatively treated group on the other hand had a similar age profile as the pacing group, but with less severe septal hypertrophy (p=0.031) and left atrial dilatation (p=0.001). The only difference between the patients that did not need to proceed to an intervention procedure and the

two interventional groups is that the group for whom medical treatment sufficed had significantly higher initial beta-blocker dose, median 200 mg metoprolol-equivalent daily versus 100 mg daily (p=0.002) (Table 1, Paper II).

Effect of therapy

Follow-up was 11.8 [9.1] years for the pacing, 10.5 [12.4] years for the myectomy and 9.5 [9.1] years for the conservative groups respectively.

For distribution of medical therapy treatment in intervention- and non-intervention groups in total cohort see Figure 9.

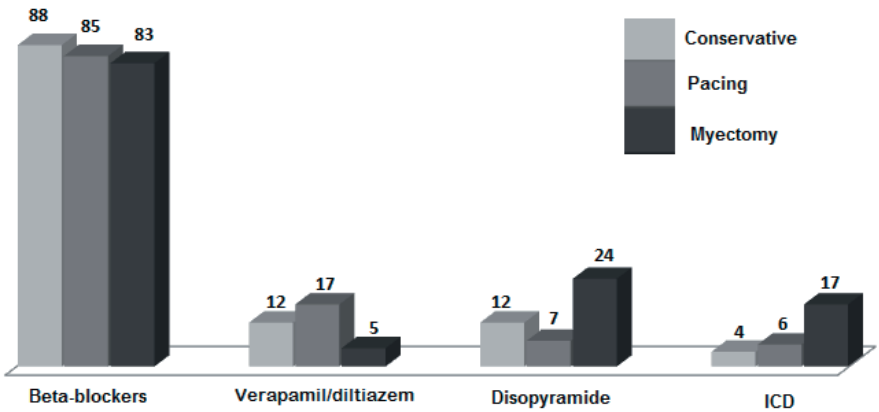


Figure 9. Distribution of treatment in total cohort at last follow-up (percent).

Conservative group

For those who remained on medical therapy only, there was significant improvement in NYHA class (p=0.006), and reduction in outflow-gradient to a median of 23 (43) mmHg (p<0.001), justifying that they did not need interventional therapy. However, in this group 29 (24%) had gradients ≥50 mmHg at last follow-up. Left atrial size increased during follow-up from 40-47 mm (p<0.001), and 40.5% had paroxysmal or chronical AF. The percentage receiving beta-blocker therapy increased from 73%-88%, other medication is detailed in Figure 9. Freedom from cardiac death was 94%, 82%, and 73% respectively (Figure 1, Paper II) at 5, 10, and 20 years in the conservatively treated group, and the survival is not significantly different from the two intervention-groups on log- rank testing (p=0.51 pacing/conservative; p=0.39 myectomy/conservative).

Short atrioventricular delay pacing

Pacing therapy was associated with a lasting reduction in LVOT gradient to a median of 14 mmHg ($p<0.001$), a significant improvement of NYHA class, and a reduction in septal hypertrophy. Patients had a significant increase in LAD during follow-up and 56.8% developed AF (9.1% paroxysmal and 47.7% chronic AF, updated data), which is a high figure compared to only 2 patients (0.8%) with paroxysmal AF at diagnosis. Re-intervention due to residual gradients during follow-up (range 50-120 mmHg) occurred in 3 of 88 patients [3.4%; 1 myectomy, 2 alcohol septal ablation (ASA)]. In the total pacing cohort, 17% had a LVOT gradient ≥50 mmHg at last follow-up, mostly very elderly [median age 82 (IQR 25) years], with AF rendering constant pre-excitation of the ventricle difficult. Annual sudden death mortality was 0.28% and annual cardiac mortality was 2.4% post-procedure in the pacing group, Figure 10.

Pacing in <65 years versus ≥65 years of age

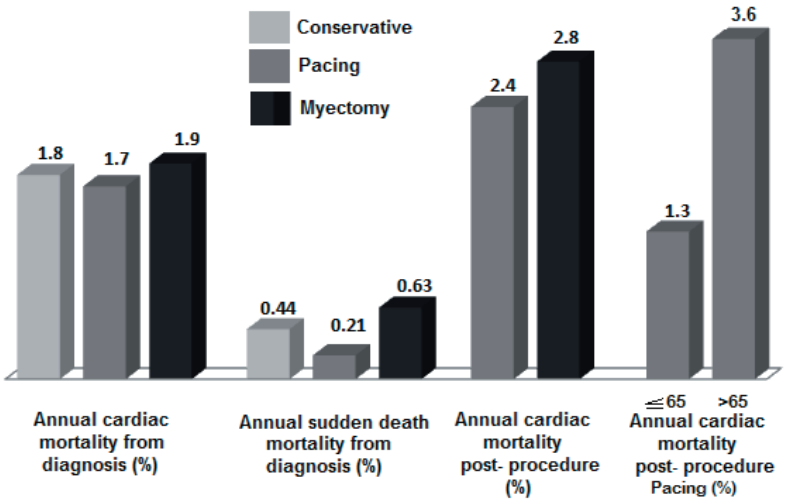


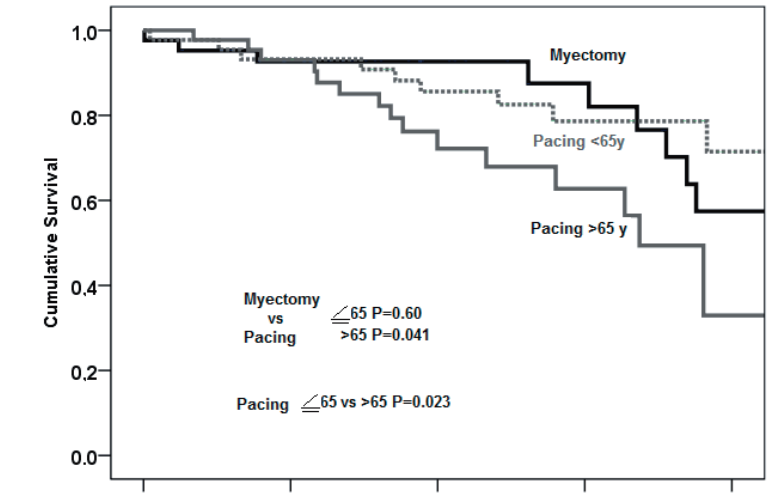
Figure 10. Mortality outcome in total cohort.

In an earlier study it was proposed that the positive effect of pacing occurs only in patients >65 years of age,[244] and in Table 3, Paper II and Figure 10, we therefore compared the results of pacing in patients <65 years and ≥65 years at procedure. There were fewer females among the <65-year-olds ($p=0.0028$). Beta-blocker therapy initially was more common in the younger group ($p=0.023$), among whom BBL therapy increased significantly during follow-up. BBL therapy increased, at last follow-up, in the older pacing group and the difference was no longer significant compared to the younger group. In both age groups, there were significant improvements after pacing in both LVOT gradients ($p<0.001$ for both) and NYHA class ($p<0.001$ for both). The final result for patients aged <65 years was a median gradient of 12 (20) mmHg

(Figure 2, Paper II), and only 9.5% had residual gradient ≥50 mmHg. Post procedural Kaplan-Meier curves show no differences in cardiac-mortality between myectomy and pacing-patients ≤65 years old at procedure, Figure 11 (log-rank p=0.60). Thus the treatment effect of pacing was in no way inferior in patients <65-years-olds. During follow-up cardiac mortality was significantly lower in the younger group on log-rank testing (p=0.006).

Myectomy group

The myectomy group improved the NYHA class (p=0.011), with a final reduction in LVOT gradient (notably though in some cases only after a second re-intervention), to a median of 11 [16] mmHg (p=0.003) (Table 2, Paper II). Initial residual gradients after first myectomy procedure are illustrated in Figure 2, Paper II and were 13 [45] mmHg compared to for pacing 14 [35] mmHg. During follow-up, 21.4% of myectomy patients had a recurrence of LVOT gradient (range 60-110 mmHg) and required a further LVOT intervention to obtain that final result (5 repeat surgery, 1 ASA, and 3 short AV-delay pacing). At last follow-up, 14% had residual gradient ≥50 mmHg. Posterior wall thickness showed a significant decrease (p=0.003). Left ventricular end-diastolic diameter (p=0.002) and left atrial size (p=0.015) increased. Beta-blocker use increased from 76%-83%. Annual cardiac mortality after first myectomy was 2.8%



n. at risk					
Myectomy	42	34	22	16	9
Pacing					
<65	44	40	32	18	8
>65	44	36	18	11	2

Figure 11. Kaplan-Meier survival curves of cardiac mortality from intervention n at risk refers to number of patients left in Kaplan-Meier curves.

(Figure 10), and post-procedure annual sudden death mortality was 0.92% in total myectomy group. Freedom from cardiac death post-procedure at 5, 10, and 20 years were 93%, 93%, and 57%, respectively, in the myectomy group (log-rank pacing/myectomy p=0.43) (Figure 1, Paper II) and survival, i.e. freedom from all-cause mortality was 88%, 88%, and 51%, respectively.

Inter-group comparisons

The conservative group had less good final reduction of LVOT gradient compared both with the pacing group (p=0.013) and the myectomy group (p=0.003) and was the only group with no significant reduction in hypertrophy. Disopyramide therapy was used more commonly in myectomy group (24%) than in pacing group (7%; p=0.016). Survival after time of diagnosis, which for the intervention groups is longer than post-procedural survival, but includes survivor bias in the pre-intervention period for the intervention groups, was illustrated for all treatment groups (log-rank p=0.39-0.71) in Figure 1, Paper II and Figure 10 for outcome after intervention in interventional groups. For mortality outcome see Figure 10 and 11.

We decided to focus evaluations on outcome after pacing and surgery on patients aged ≥18 years at procedure because four of those nine requiring re-intervention after myectomy had the initial procedure at age <18 years (Table 4, Paper II). A new procedure for recurring LVOTO occurred in 15.6% of myectomy patients and in 3.5% of pacing group (log-rank p=0.007). Annual post-procedural cardiac mortality was 1.3% and post-procedural sudden death rate was of 0.16% in pacing patients of age ≤65 years of age, and the figures was 2.2% and 0.48% in ≥18 years myectomy group. There is no difference in relief of LVOTO, prior to any re-intervention, between myectomy (≥18 years) and pacing group (<65 years) (p=0.89), but the conservative group has less good relief (p=0.028) (Figure 2, Paper II).

Survival in patients with diagnosis before and after 2002

Since some of our patients had their diagnoses before 2002, we ascertained if there were any differences in survival between those with diagnosis before and after study start. There was no difference among myectomy or paced patients for diagnosis before 2002 and after (log-rank p=0.53 and log-rank 0.37, respectively). The results also showed no inter-group difference between the groups myectomy and pacing in survival before 2002 (log-rank p=0.50) and after 2002 (log-rank p=0.25).

Paper III

Factors contributing to excess female mortality in hypertrophic obstructive cardiomyopathy

The clinical characteristics in male and female HOCM-patients were compared in the total cohort in Table 1, Paper III, and in the age-matched groups in Table 2, Paper III. Follow-up time was 14.4±8.9 years (mean±SD) after diagnosis in the total cohort with no significant difference between sexes. At diagnosis, AF was more often found in females, who were older but the difference did not reach statistical significance in the age-matched group. Septal thickness, left-ventricular end-diastolic diameter and

left atrium diameter were significantly larger in males than in females, but so was also body surface area, 1.8 [0.30] m² in females and 2.1 [0.25] m² in males (p<0.001).

Bias in medical therapy

Interventional therapies (myectomy and pacing) were used without sex-bias in both sexes. However, males received beta-blocker therapy in a significantly higher proportion, 78% in males compared with 64% in females (p=0.011), the difference was confirmed in age-matched groups (80% versus 66%, p=0.040). Furthermore, the initial daily metoprolol-equivalents beta-blocker dose was significantly lower in females, both in total group, and in age-matched groups (females median 50 mg/day versus males median 100 mg/day p<0.001), and remained significantly lower even when corrected for body weight. In 7.8% of males and 17.1% females (p=0.034) verapamil/diltiazem was used, and when all kinds of calcium-channel blocker therapy were included the difference was even bigger, 19.3% and 36.1%, respectively (p=0.015), in the age-matched group. Disopyramide was prescribed in more males than females (16% versus 7%; p=0.027) during follow-up, but the difference was smaller in age-matched group. The proportion of ICD-implantations was low in both sexes (males: 8.6%; females 4.9%; p=0.24; 9.6% and 6.0% respectively in age-matched groups; p=0.39).

Clinical progress

NYHA class improved in both sexes at follow-up (p<0.001), but the NYHA class was significantly worse in females than males at latest follow-up, also in the age-matched groups (p=0.025). Deterioration of NYHA class to ≥III was 2.1 times more common in females than in males in both the total group (p=0.030), and in age-matched groups (p=0.078). Systemic hypertension (p<0.001), AF (p<0.001) and coronary artery disease (p=0.006) increased during follow-up in the same manner in both sexes in the age-matched groups, but the proportion of diabetes mellitus increased significantly only in males. Median LVOT-gradients decreased significantly in both sexes in the age-matched groups. There was no significant sex-difference in patients with inadequate gradient control: 23% of females and 18% of males had LVOT-gradients ≥50 mmHg at last follow-up (p=0.49). During follow-up LV ejection fraction fell significantly in both sexes (p<0.001), Tables 1 and 2, Paper III.

Mortality

Disease-related deaths occurred in 65 patients (41 in females and 24 in males). Sudden cardiac death occurred in 11 (17%) patients, 4 females, and 7 males. The annual disease-related mortality rate for the total cohort was 1.8%, with 2.4% in females and 1.2% in males, and in the age-matched groups 2.6% versus 1.2%. Figure 1, Paper III, shows in Kaplan-Meier curves freedom from disease-related death comparing the sexes in both total and age-matched groups.

Females had a significantly higher mortality risk compared to males both in total and age-matched groups (log-rank p=0.003; p=0.019); female-to-male HR was 2.10 [95% CI 1.27-3.48] and 2.04 [1.11-3.76] respectively, and the shape of the total and

age-matched respective curves were similar. In age-matched groups 10- and 20 year freedom from disease-related death was 82% and 59% (female) and 93% and 85% (male), respectively.

Figre 12 shows the proportion of disease-related death in both sexes in total and age-matched groups. In the total group, non-cardiac mortality was significantly higher in females, but the same as in males in the age-matched group. The main causes of disease-related deaths are shown in Figure 2, Paper III. Females had an excess mortality in heart failure with a female-to-male HR of heart failure mortality, 3.76 [95% CI 1.85-7.66, p=0.0003] in the age-matched group, and also an excess in fatal myocardial infarctions, five in females, and none in males (Figure 2, Paper III). Cardiac transplantation was performed in three (2.4%) females and one (0.8%) male in the total cohort.

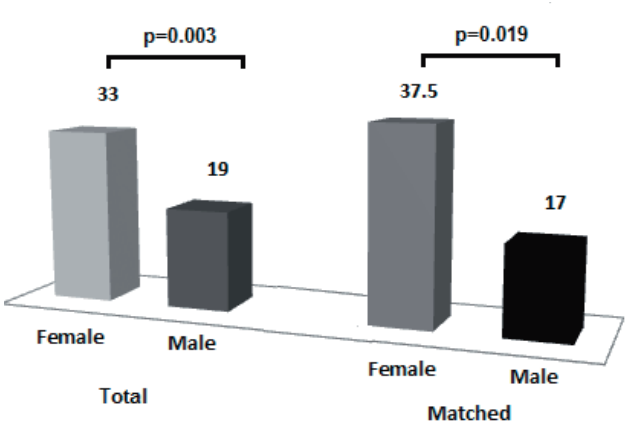


Figure 12. Proportion of disease-related death in total and age matched-groups (percent).

Sex-specific risk-factors for disease-related mortality

At diagnosis age and LVOT-gradient ≥50 mmHg in females and presence of symptoms in males, were significant independent risk factors identified by multivariate Cox hazard regression. Therapy with beta-blockers showed a significant dose-dependent protective effect in the multi-variate model in males, and in univariate analysis in females (Table 3, Paper III).

The cardiac mortality of patients with AF at latest follow-up was non-significantly greater in females in the age-matched group, 44% as compared to 24% in males (p=0.109) (Figure 4, Paper III). The rate-control seemed possibly important for survival, where survivors in the total cohort with AF (n=51) had a heart rate at latest follow-up of 76 (19) beats/min, compared to non-survivors with AF (n=26) with a

heart rate of 87 (39) beats/min, p=0.030. Females with AF who died had heart rate of 90 (23) versus 76 (25) in surviving females. Of those who died in chronic heart failure 32% of females were treated with verapamil/diltiazem compared to 7.7% of males (p=0.0075). HR for chronic heart failure mortality with verapamil/diltiazem therapy was 2.26 [1.15-5.70; p=0.021] in the total cohort which included more young patients with low risk, and 4.20 [1.72-10.23; p=0.002], in the age matched groups. In the age-matched groups in patients ≥50 years at latest follow-up (i.e. post-menopausal), there was an excess female mortality compared to males, but this was not found in patients <50 years of age (Figure 4, Paper III).

Effect of potentially protective pharmacotherapy on disease-related mortality

As beta-blocker treatment showed a significant association with better survival in both sexes in univariate analysis, and in males also in multivariate analysis, we compared the effect of beta-blocker dose on cardiac mortality in both sexes with Kaplan-Meier survival curves. As males have greater body size than females, we compared survival with beta-blocker dose above and below median dose expressed as mg/kg body weight/day (instead of per body surface area (BSA) as there were 15% (females) and 11% (males) missing values caused by missing information of height). The survival of both sexes were significantly better when treated with a beta-blocker dose above or equal with the median of 1.18 mg/kg/day of metoprolol-equivalents compared with <1.18 mg/kg/day in both total group (males p=0.015, females p=0.004; Figure 5A, Paper III), and in age-matched groups (males p=0.007, females p=0.010; Figure 5B, Paper III). The curves did not separate until about seven years after diagnosis. The equivalent HR for disease-related deaths in total cohort with metoprolol therapy ≥1.18 mg/kg/day were 0.32 [0.23-0.84; p=0.020] in males and 0.35 [0.16-0.73; p=0.006] in females. Kaplan-Meier survival analysis in age-matched groups revealed 10- and 20-year freedom from disease-related mortality of 92% and 67% in females, and 94% and 94% in males in the ≥1.18 mg/kg/day groups, as compared to 75% and 51%, in females and 96% and 80% in males, in the <1.18 mg/kg/day groups.

Paper IV

Morbidity and resource usage after myectomy- or pacing-treatment in hypertrophic obstructive cardiomyopathy: a case-control study

This study examines complications and resource usage of pacing and myectomy when compared in patients with same age range and equivalent disease severity. There were no significant differences in baseline features (Table 1, Paper IV) between matched groups. Left atrial diameter was significantly larger in the pacing-group than in the myectomy-group before intervention (but the same at latest follow-up). LVOT-gradient and NYHA class improved equally in both groups. Only the myectomy group showed a significant increase in LVEDD and reduction of hypertrophy at last follow-up. Left atrial size increased significantly in both groups over time, with increasing prevalence of AF. The prevalence of systemic hypertension increased significantly in both groups. Annual hospitalization for heart failure during follow-up was 0.93% in the pacing group compared to 2.3% in the myectomy group (p=0.21).

Peri-procedural complications and re-interventions ≤30 days

Total study population: Peri-procedural complications were significantly common after myectomy than pacing (p<0.001) (Table 2, Paper IV). One peri-operative death occurred among 24 first myectomy procedures performed during 2002 to 2013 (3.5% mortality during study period).

The case-control group: Details of peri-procedural complications are summarized in Table 2, Paper IV, peri-procedural complications were almost 10 times more common in the matched myectomy-group (p=0.001).

Late complications and re-interventions

Total study population: Late pacemaker-implantations after more than 12 months follow-up occurred in 19.5%, in three cases caused by re-interventions for recurring or residual LVOT-gradients (Table 2, Paper IV). A new procedure for recurring LVOT-gradient was required in 22.0% of patients after myectomy, and 3.4% after pacing-therapy, p=0.001 as reported before.[135]

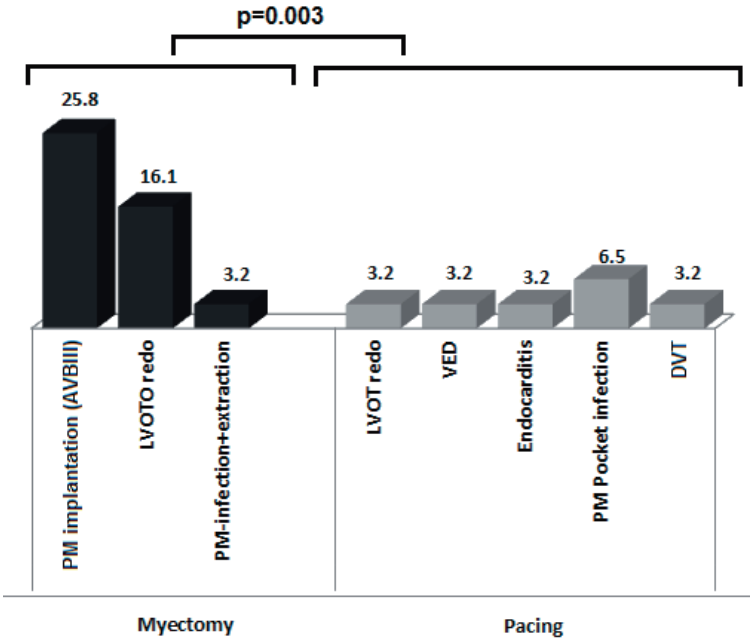


Figure 13. Late complications and re-interventions in case-control groups PM=Pacemaker, AVB=Atrioventricular block, LVOTO=Left ventricle outflow tract obstruction, VED=Ventricle electrode dysfunction, DVT=deep venous thrombosis.

Case-control-group: Pacemaker implantation (including 9.7% perioperatively) was required in 35.5% of myectomy patients during follow-up, 2 patients (6.5%) required mechanical aortic valve due to aortic insufficiency. The need for additional re-do for recurrence of LVOTO was significantly higher after myectomy (16.1%) than after pacing-therapy (3.2%) (Figure 1A, Paper IV log-rank p=0.027). The thresholds for re-do were the same in both groups, Paper II.[135] Total re-intervention rates for all types of re-interventions were also significantly higher in the myectomy-group (38.7% versus 9.7%) (Figure 1B, Paper IV, p=0.003), and are summarized in Figure 13.

Length of stay and costs of hospitalization

Median length of stay (LOS) at specialist centre was 11 [7] days for myectomy patients and 4 [IQR=2] days for pacemaker-therapy patients (p<0.001). Furthermore many myectomy patients had additional in-patient rehabilitation at a local hospital (Figure 2A, Paper IV).

The mean cost of hospitalization (local hospital costs for rehabilitation are not included) was 74 000±16 000 SEK for pacing and 310 000±180 000 SEK for myectomy, p<0.001. One myectomy patient was hospitalised for 81 days because of complications after myectomy with a cost of SEK 3 million (as outlier the cost was excluded from our average patient costs). The average cost per myectomy procedure during study period nationally was SEK 200 000±70 000 (p=0.204 compared to our myectomy costs, and p<0.001 compared to our pacing group costs).

WEAKNESSES IN OUR STUDIES

1. Complete cohort studies are method of choice in order to be able to study risk factors for end-points but not to compare treatment effects

2. The number of myectomy patients was small

3. Possible loss of patients who were not registered in hospital computer systems and were diagnosed and monitored by private healthcare providers

4. The Melior diagnostic patient data base was introduced in 2002. HCM patients who had diagnosis before 2002 and attended follow-up after 2002 became registered in the Melior data base and were included in the study, as well as two patients who died before 2002 but were recorded in other data bases. However, in the subgroup who were diagnosed before 2002 (n=160), we may have missed additional deaths before the study began (survivor bias). For that reason we have also calculated important mortality rates, such as annual risk of SCD, only in the patients diagnosed within the 2002-2013 period. However, the pre-2002 patients are important to keep in the study for the evidence they provide of the effect of pharmacotherapy on long-term morbidity and long-term survival.

5. An inherent uncertainty when determining the LVOT gradient with cw Doppler is the possible influence caused by a mitral regurgitant jet. This is only a problem for those whose outflow-gradients are so large that they cannot be measured with PRF pulsed Doppler, and that is why we have adopted ≥50 mmHg as the cut-off in our risk factor analysis rather than analyzing with the gradient as a continuous function. It also does not affect the diagnosis classification since the diagnosis is based on a LVOT gradient limit value ≥30 mmHg which can easily be measured with pulsed Doppler

6. A moderate amount of missing data on the dose of drug (7% beta-blocker), atrial size (25%) / septum thickness (5.6%) / posterior wall thickness (24%) / systolic anterior movement (SAM) / EF (10%) at diagnosis and in 18.7% of NYHA class at follow-up.

THE STRENGTHS OF OUR STUDIES

1. A total geographic cohort study where all patients in the Västra Götaland region were included regardless of age, gender and comorbidity, and this gives a population representative patient spectrum. This is the method of choice for studying risk factors for adverse outcome without referral bias.

2. Mortality as primary endpoint (hard data)

3. Hundred percent complete follow-up (no patients "lost to follow-up"), and with 100% complete information on the cause of death.

4. Large study-population consisting of 251 HOCM patients, both with the largest pacing group (88 patients), and the longest follow-up, both in comparison with other national and international published studies. It provides many patient years and a large number of end-points, which gives a high statistical power for analysis of risk- and protection factors on multivariate analysis.

5. Long follow-up time allows us to see the effect on mortality, and unusual side effects, of given treatments such as any side effects of prolonged pacing in the HOCM group.

6. Any measurement or documentation errors for septum, LVOT, drug use made by the physicians when establishing the diagnosis ought to be evenly distributed among the different treatment groups without affecting the outcome.

DISCUSSION

Risk factors for disease-related death

In this unselected geographical cohort of patients with HOCM we found that age, female sex, and an un-relieved LVOT-gradient were significant risk-factors for disease-related mortality as they have been reported to be in studies from specialized centres.[172, 193, 256-258] However, in contrast to tertiary centres who report a SCD rate of 33-56% in HOCM-group with annual SCD-mortality of 0.75-1.26 %,[172, 259] SCD caused a small proportion of disease-related deaths (17%) in our cohort with a low annual SCD-mortality of 0.37% despite of a low rate of ICD-implantation (6.4%). Kofflard et al. 2003, reported 10% SCD during 29 years follow-up in patients with LVOTO, and 8% in non-obstructive group, with an annual SCD rate of 0.6% in a large community based HCM cohort of 225 patients (mean age 41±16 years),[260] similar to our results. This may explain why classical risk-factors for SCD failed to show significant association with total disease-related mortality in our cohort, in contrast to an LVOT-gradient ≥50 mmHg. In contrast to low figures, 32% of heart failure deaths reported from tertiary centres,[172] heart failure constituted 62% of disease-related deaths in our study, similar to findings in a recent study which demonstrated a 4.3 times excess of heart failure, and found that heart failure was more common than SCD and ventricular arrhythmia combined in population-based HCM-patients.[261] This highlights the importance of considering treatments that may reduce non-sudden and heart failure related mortality in HOCM patients, like a good control of significant independent risk-factors for heart failure death in this study such as systemic hypertension and LVOTO.

Effect of pharmacotherapy on risk of death

Effect of beta-blockers

Beta-blocker therapy has hemodynamic benefit in HCM by reducing LVOT-gradient, both at rest and during exercise, and by improving symptoms, diastolic function and exercise capacity.[187, 188, 192, 262-265] In our cohort study, neither univariate nor multivariate Cox hazard analysis could identify that interventional therapy (myectomy or pacing) was associated with a survival-benefit that was independent of other risk-factors for example age. But beta-blocker therapy was the only therapy associated with significant improvement of survival in a dose-related manner on multivariate analysis (Figure 1AB, Paper I). The observation that it takes about five years for survival curves to separate significantly (Figure 1A, Paper I), suggests that the effect may be due to myocardial protection perhaps affecting development of fibrosis, rather than decreasing SCD-mortality as reported with higher paediatric dosages.[167] Frank et al. observed that the time to maximal improvement with medical therapy was 1-6 years (average 2.75), suggesting at least a two years observation time is necessary to see some effect of medical therapy.[187] In one experimental study[266] in rats with diastolic dysfunction due to hypertension and pressure-overload, myocardial fibrosis was observed (mainly in the subendocardium), whereas few fibrotic changes were observed in rats with diastolic dysfunction and metoprolol treatment. The degree of myocardial fibrosis was 4.5 times greater in rats with diastolic dysfunction than in control group ($p<0.001$). Metoprolol stopped not only the progress of LV hypertrophy but also the develop-

ment of diastolic dysfunction, and improved survival (in rats).[266] A meta analysis with 21206 patients of the effect of beta-blockers in patients with heart failure with diastolic dysfunction but preserved ejection fraction (HFpEF), showed that the beta-blocker treatment was associated with a lower risk of all-cause mortality.[267] However, the mechanisms of the benefit of beta-blockers on mortality have not been precisely clarified. Ischemia is considered an important trigger for fibrosis. The rate pressure product is extremely closely correlated with myocardial oxygen-consumption, and beta-blockers reduce cardiac oxygen demand, thereby reducing ischemia during exertion, and maybe, preventing or reducing fibrosis. The significant association of beta-blocker dose to better survival even after successful interventional treatment found in this study is a good argument to not discontinue the treatment in patients with good relief of outflow tract obstruction after interventional procedures (Figure 3, Paper I).

According to US and European Guidelines, beta-blockers or verapamil may be considered in children and asymptomatic adults with resting or provoked LVOTO, in order to reduce left ventricular pressure load.[6, 7] We investigated whether beta-blockers were associated with better survival only in symptomatic patients but we found that the association to better survival was as good in patients without symptom at diagnosis (Figure 7AB).

Could the protective effect of beta-blockers in Paper I be due to a chance association?
That the protective effect of beta-blocker on survival found in Paper I is not a chance finding is supported by the extremely strong significance on Kaplan-Meier survival analysis (p=0.0004-0.0008), and the fact that beta-blocker protection is dose-related, and remains significant on Cox hazard analysis together with all other identified risk factors (Paper I). It is also supported by other reports of survival benefit of beta-blocker therapy in HCM. In childhood HCM beta-blocker therapy is also associated with improved survival,[95] in a dose-related manner,[4, 96, 167] and even reduces risk of SCD.[167] Beta-blocker is associated with better survival in HFpEF patients with other diagnoses causing diastolic dysfunction as well.[267]

There are no randomized long-time beta-blockade studies on mortality in adult HCM-patients. Of the registry studies available, Melacini et al.'s negative study from 2007 is often cited, but in that study, only 26% of patients (77/293; 456 patient years) were treated with beta-blockers, with a median follow-up of 6 years, and the authors only studied effect on sudden cardiac death. The study had only 17 (10%) end-points and lacked statistical power to detect a protective effect of beta-blockers because only about 1/4 of the patients received beta-blockers.[109] In contrast, Lee et al. (2007) found in univariate analysis in a study of 163 patients followed on average 5.3 years, of whom 40% received beta-blockers, that beta-blocker use (dose not stated) had a significant protective effect with a HR of 0.25 [95% CI0.08-0.77], p=0.012; the effect did not remain significant in a seven-parameter multivariate analysis,[193] but their statistical power would be insufficient to test that many parameters in the same multivariate analysis. Recently, in a much larger study focusing on gender differences (3673 patients), Geske JB et al. (2017) has shown in his multivariate analysis that beta-blocking therapy (dose unspecified) was associated with a lower total mortality,[268] but they could not distinguish heart-related mortality from non-cardiac mortality. With

our study with 2613 patient-years on beta-blocker therapy and with 100% follow-up[255] there are now three studies from adult patient cohorts of very different ethnic origin, and several from British and Swedish separate childhood cohorts, that report statistically significant survival benefit from beta-blocker use. The HR for patients with beta-blocker use from diagnosis in our cohort study was 0.49 [95% CI 0.30-0.81] (Paper I). The fact that the association was dose-dependent, (Figure 1AB, Paper I), suggests a pharmacological effect and not a chance association.

Could the protective effect of beta-blockers in Paper I be a result of bias in treatment selection?

We have included all patients in the complete geographical cohort and have a long follow-up time (14.4±8.9) years, with no patients lost to follow-up, and no selection or referral bias. There are no significant differences in co-morbidity that could be confounders between the various treatment groups. There is a slight gender bias for women being given lower beta-blocker doses than men (Paper III), but the protective effect of beta-blocker therapy is significant both in men and women (Paper III), and remains significant on multi-variate Cox hazard analysis including both age and sex as co-factors in the analysis (Paper I). Thus we cannot find evidence of the result being affected by bias in any known risk factor.

Hypothetical mechanisms for benefit of beta-blockers on pathogenesis of hypertrophy in HCM

There is animal experimental evidence that increased cardiac sympathetic activity is an important trigger of compensatory both generalized and localized cardiac hypertrophy.[49] Generalized cardiac hypertrophy results from physical exercise[269, 270] and from beta-agonist administration (isoprenaline).[271, 272] The compensatory left ventricular hypertrophy due to experimental coarctation of the aorta[273] and right ventricular hypertrophy due to hypoxia,[274] can both be reduced or prevented with non-selective and $beta_1$-selective beta-adrenoceptor blockade.[73, 74]

Beta-adreno-receptor blocking drugs have been reported to decrease cardiac hypertrophy, e.g. in experimental renal hypertension,[275] in spontaneously hypertensive rats,[276, 277] and in systemic hypertension in man.[278, 279] Conversely, vasodilator therapy that normalizes the systemic blood pressure and at the same time increases cardiac sympathetic nervous activity, is not associated with regression, but often with progression, of cardiac hypertrophy in the spontaneously hypertensive rat.[280, 281] As detailed in introduction there are many studies reporting pathologically increased cardiac sympathetic nervous activity in HCM-patients,[91-94] and it is a reasonable hypothesis that modifying this pathophysiology may be of benefit. For example, regarding HCM in children and adolescents, retrospective well-matched cohort studies showed that untreated HCM patients had a 24-26% increase in left ventricular hypertrophy over follow-up, whereas patients who had been on high-dose beta-blocker therapy because of symptoms (>4.5 mg propranolol/kg BW) instead showed a reduction in cardiac hypertrophy by 20-28%.[282] As maximal wall thickness is an important risk factor for SCD,[6, 7] a beneficial effect on disease-progression may partly explain the dose-related reduction in the risk of sudden arrhythmia observed in childhood HCM.[4, 96, 167] However, a reduced

progression of hypertrophy may also hypothetically reduce the risk of progressive fibrosis and deteriorating function.

Calcium blocker therapy

Harmful acute effects of verapamil have been reported before and it has to be used with caution.[194, 283, 284] The observed long-term excess mortality in heart failure in HOCM-patients getting verapamil/diltiazem in our studies (Paper I and Paper III) is concerning but should be interpreted with caution due to the small numbers receiving calcium-channel blockers. This underlines that more studies in HCM-populations with greater use of calcium-channel blockers than in our study are needed.

Effect of invasive treatment on clinical outcome and mortality in HOCM patients

Short AV-delay pacing

In Paper II, which is the biggest one hitherto with longest follow-up time, we showed that pacing improved NYHA class and reduced LVOT gradient significantly (Table 2, Paper II). Pacing was not inferior to myectomy on disease-related mortality on Kaplan-Meier curves (Figure I, Paper II, p=0.71, Figure 11 <65 years age pacing vs myectomy), and had the same result on LVOT gradients in patient <65 years-old compared to ≥65-years-old (Figure 2, Paper II). Pacing had a significantly lower risk for re-intervention and peri-procedure complications than myectomy (Table 2, Paper IV). Even in matched groups the cumulative hazard for re-intervention for LVOTO or any other re-intervention during follow-up was significantly lower than after myectomy (Paper IV, Table 2 and Figure 1AB). Pacing patients had significantly shorter stay in hospital and substantially lower costs compared to myectomy (Paper IV, Figure 2AB). Myectomy patients received significantly higher disopyramide use (24%) compared to pacing (7%) (p=0.016), and some cases needed a second intervention to achieve the same LVOT gradient at latest follow-up.

In DDD pacing with short AV-delay for pre-excitation of the left ventricle the placement of pacing electrode to stimulate the right ventricular apex for achieving complete ventricular capture is important for the treatment result.[218-221, 223, 235-237] Observational short-term studies with short AV-delay pacing from the USA and Europe showed good symptom improvement and LVOT gradient reduction with pacing.[235, 237, 241] Significant benefit was confirmed in a European multi-centre randomized cross-over study with 83 patients.[222, 240, 285] Some of the symptom benefit may be a placebo-effect,[286] but active short AV-delay pacing reduced gradient significantly more than sham-pacing.[222] The improvement of symptoms and reduction of LVOTO is not persistent after cessation of pacing, re-initialization of pacing promptly reduces the LVOTO and improves symptoms to a preexisting extent.[287] In two small American randomized crossover studies (patients n=21-48), with short follow-up time (6-36 months) compared DDD versus AAI pacing. The outcomes measured were the size of LVOT gradient, quality of life, exercise tolerance and Peak $V0_2$. The result showed that active pacing was associated with improvement of LVOTO within 3 months with progressive improvement over the next 9 months, accompanied with improvements in quality of life and

or NYHA class in majority of patients. The larger American randomized double-blind cross-over study (Multicenter Study of Pacing Therapy for Hypertrophic Cardiomyopathy (MPATHY) of 48 patients confirmed significant benefit of pacing treatment to outflow gradient and quality of life, but found no significant improvement in exercise ability.[3] This study had 16 (33%) of patients lost to follow-up, and medication was reduced during the study in a non-standard manner. In the end, 3/32 (9.4%) of the remaining patients were without cardio-protective medications, and it is not clear from the study how much of the drug doses had been reduced in the remaining patients. In addition the MPATHY authors in retrospect defined a responder as the combination of improvement >1 NYHA class, >10% exercise time and >10 points in the Minnesota Living with heart failure score. By this strict and also limiting definition only 6 of 48 randomized patients were responders to active pacing. In this study responders were significantly older (mean age 69±4 years) than non-responders (mean age 51±16 years) and had a lower initial exercise time (9.7±3.4 min) and Peak VO_2 (12.4 mL/kg/min) than non-responders (17.1±5.5 mL/kg/min), $p<0.0005$. Based on those small numbers the authors therefore suggested that DDD pacing could be an option for patients >65 years of age if they reject other treatment options[244] but the result of our study showed that pacing is equally effective for patients <65 years old (n=44) as for patients ≥65 years old (n=44) (Paper II, Table 3).

Another small non-randomized study compared 20 patients treated with myectomy, based on patient preference, with 19 patients treated by short AV-delay pacing.[243] In this study, significantly better gradient reduction and greater improvement in exercise capacity were reported in the myectomy group than in the pacing group. The follow-up time in the study, however, was longer for myectomy than patients with pacing therapy, myectomy patients were on average 17 years younger, many sick patients undergoing myectomy were not included in the study (selection bias), and in addition patients who underwent DDD pacing under study time (1995-1997) were part of a multicenter randomized trial as mentioned above (M-PATHY) with a LVOT gradient reduction by 40% in M-PATHY study.[244] However, the same cohort of patients as in M-PATHY in this study had a LVOT gradient reduction by 29%, thus a 25% smaller reduction than in M-PATHY (also suggesting selection bias), all this may be relevant for their ability to increase exercise capacity and the result of this study. These two studies[243, 244] were probably influential in that short AV-delay pacing was removed from considerations as a first choice in the American Heart Association (AHA) guidelines for HOCM treatment.

More recently positive long-term results have been reported from non-randomized retrospective studies of pacing.[245, 246] Our results are in concordance with results from these studies regarding the improvement of symptoms and reduction of LVOT gradient. Lucon et al.[246] reported on 51 patients treated with pacing at an average age of 59 years, with follow-up of 11.5 years, with survival rates at 5 and 10 years of 90% and 65%, respectively. Thus, our total pacing cohort of 88 patients is by far the largest till now reported in the literature with very long-term results after pacing treatment. Similar to Lucon et al.[246] the total survival, including non-cardiac mortality, in our pacing group was 91%, and 70% for survival at 5 and 10 years. In addition to mortality we report also the morbidity, and cost of procedure with length of stay in hospital which is not reported in a systematic way before. The European Guidelines from the

European Society of Cardiology 2014 recommends pacing to patients who are elderly, at high risk when undergoing septal reduction, patients who do not want to undergo surgery and those who have a mild hypertrophy.[7] However there is a now new interest in pacing.[238, 288] In a recent meta-analysis of 34 studies comprising 1135 patients with short AV-delay pacing Arnold et al. reported that pacing reduced gradient by 35% ($p<0.0001$) in 4 short blinded randomized controlled trials (RCTs), but there was only a trend towards improved NYHA class ($p=0.066$). The un-blinded observational studies reported a 54.3% ($p<0.0001$) reduction in gradient and significant improvement in NYHA class ($p<0.0001$). Since those studies had much longer follow-up the results could well be due to progressive gradient reduction over time with beneficial remodeling. Through all studies, the LVOT gradient gradually decreased at longer follow-up durations, by 5.2% per month.[288] In these times of increasing financial pressures on health services we feel that the comparatively very low cost, good success rate and very low morbidity of short AV-delay pacing could justify it being adopted as a first-line therapy for drug resistant obstructive HCM.

Myectomy

Surgical myectomy at tertiary centers has been the gold standard treatment for most patients with severe drug-refractory symptoms since 1964 with a reduction of LVOT gradient in 90% of patients when performed in expert centres.[6, 21, 225-227]

The long-term result of myectomy in our cohort study showed a significant clinical improvement and LVOT gradient reduction at follow-up (Paper II). To achieve this reduction of LVOT gradient a significant larger proportion (24%) of myectomy patients had disopyramide compared to pacing-group (7%), $p=0.016$, following a strategy for advanced treatment of HOCM patients as advocated by Sherrid et al.,[190] and a significant proportion underwent a second re-intervention and myectomy group had significantly longer stay at hospital and much higher costs compared to our pacing group (Paper IV).

The total pooled peri-procedural complication-rate after myectomy in our total myectomy group (31%), and in matched myectomy-group (35.5%), Table 2, Paper IV, was comparable to other reports (28%-30.2%).[232, 233] One peri-operative death occurred among 24 first myectomy procedures performed during study period 2002-2013 (3.5% annual mortality) in line with audited operative mortality of 3.8% reported by Kim et al.[233] from highest volume tertile myectomy centres in the USA (four hospitals with 126 myectomy during nine years of study period), but substantially higher than the self-reported figures of 0.3-1.1% from the same centers.[228, 289]

Among postoperative cardiac complications (<30 days) after myectomy 7.2% of our patients in the total myectomy-group were implanted with a pacemaker for total AV-block after first myectomy. This rate was greater than reports from dedicated American HCM-centres (1%)[227] or from Mayo clinic of 2%,[234] but in line with reports from a national US registry data that showed the audited incidence of pacemaker-implantation was actually 8.9% for this high-volume tertile, as compared to 10% in the tertile with lowest volume of myectomies.[233] In total 26.7% of the total myectomy-group in our total cohort needed a pacemaker during follow-up, almost equal to the 25.8% in

the case-control group. This high need for pacemaker implantation after myectomy during late follow-up has not been reported before. There was only a 4.1% need for pacing on long-term follow-up even in much older patients treated only medically, comparable to the rate of 4.4% reported in literature.[290] Thus our 100% complete and significantly longer follow-up, and recording also all types of late re-intervention not only surgical ones, can partly explain why we find a relatively high need for pacemaker-implantation and also of re-do, after myectomy, compared to previous reports from tertiary centres. In our total myctomy group 22% required re-do for recurrence of LVOT gradient during 12.9 years of follow-up, but re-do rates was slightly lower in non-growing patients, being 15.6%, in patients ≥18 years at myectomy. However, all but one re-intervention occurred more than 1 year after the first myectomy. Surgical re-intervention for LVOTO after myectomy at Cleveland Clinic, excluding patients <18 years of age, and >65 years at surgery, was 3.4% over an 8.7 year follow-up[289] as in our pacing group but less than in our myectomy patients, however non-surgical re-interventions were not reported. Our result presented as freedom from cardiac deaths at 10 years follow-up of 93%, and total survival at 10 years of 88%, are comparable to the high volume tertiary centers with patients of comparable age at myectomy like Mayo clinic (96% survival),[291] the Stanford clinic (81% survival),[5] and a Swiss group (80% survival)[292] at 10 years. In contrast to our study with 100% follow-up and report on re-intervention (Paper IV, Table 2 and Figure 1AB) those studies had 11-14% of patients lost to follow-up with unknown survival status and did not report re-intervention rates.

The LOS in hospital for myectomy in our study was a median of 11 days similar to that reported by others,[231, 232] with a mean costs of 310 000±180 000 SEK for each myectomy comparable to American reported costs.[232] The similar cost was 74 000± 16 000 SEK in our pacing-group. In this regards pacing has significantly shorter duration of stay and significantly lower cost compared to myectomy for drug refractory HOCM patients (Paper IV, Figure 2AB).

Short AV-delay pacing continued to be widely used in Europe, at least until the increasing acceptance of ASA as an alternative treatment option for symptomatic LVOTO.[224, 293] ASA has recently been used to a greater extent in Europe as it is alleged that it has an effect as good as myectomy,[7] but there are no randomized studies. ASA has a higher frequency of complications in the form of atrio-ventricular blocks requiring permanent pacemaker following the procedure (7-20%)[7] compared to myectomy (4%).[249] ASA has 10% re-do rate for LVOTO[250, 259] and in this study re-do after pacing is 3.5%. Quintana et al. reported that patients who are referred to myectomy after ASA with insufficient relief of LVOTO have poorer diastolic function and higher frequency of arrhythmias, a higher frequency of postoperative complete heart block and a higher perioperative mortality rate of 6.2%.[251] In our study pacing, with no mortality, few complications, cost effective, a smaller need for redo (3.5%) and not inferior to myectomy regarding re-intervention and survival, might be considered as first option for drug refractory HOCM patients. We believe that it is not justified to virtually abandon it as a first-line therapy option as has been done in the 2011 AHA guidelines.[6]

The best way to settle the rightful place of short AV-delay pacing among the treatment options would be a prospective-randomzed study comparing pacing with ASA, and of sufficiently long duration that the continued fall of gradient over the first two years that has been amply documented in pacing patients is allowed to register.

Gender

Is it a "risk factor" to be a woman, or is the risk for disease-related death underestimated in women?

In this total geographical cohort study females had excess HCM-related mortality compared to men (Paper I),[255] (Paper III, Figure 1), also reported from tertiary centres.[118, 257, 258, 268] However, the factors causing the increased mortality in females have not been established. In all published sex-comparisons of mortality HCM females are significantly older than males at diagnosis[118, 255, 257, 258, 268] making comparisons of mortality uncertain because of significant differences in non-cardiac mortality between, females and males (non-age matched), shown in our study (Paper III, Figure 2). Delay in establishing diagnosis has been speculated on as cause of the excess mortality.[258, 268] The excess female mortality in groups matched for age at diagnosis and other clinical features showed in this study, suggests that referral-bias or age differences at diagnosis is not the probable cause of the reported excess female death in HCM patients.

The main criterion for making the diagnosis of HCM in both AHA and ESC guidelines is a maximal wall thickness ≥15 mm (or ≥13 mm in the presence of an affected first-degree relative).[6, 7] This immediately presents a sex-bias, since the upper limit of LV wall thickness is normally 1 mm lower in adult females than in males at all ages.[294, 295] Accordingly, to meet the requirements for the HCM diagnosis a woman has to show up to 17% larger increase in cardiac wall thickness in relation to normal values than men. This can postpone the diagnosis to somewhat later in the disease development, and might be a factor in the reported age-related gender-difference in disease penetrance.[296, 297] This could be avoided by implementing sex-independent hypertrophy criteria by using M-mode echocardiographic wall-to-cavity ratios, for making the diagnosis. This method is sex-independent with the same normal range in males and females, and was originally studied to simplify the diagnosis of HCM, or following development of hypertrophy, in the growing child/adolescent.[298, 299] Another possibility is to measure LV remodeling index by using CMR, dividing LV mass by end-diastolic volume,[300] or by the use of CMR wall-to-cavity ratios.[301]

Sex-differences in LV-remodeling and fibrosis between age-matched HCM-patients, with a higher LV-remodeling index and greater extent of late gadolinium enhancement (LGE) in women compared to men, are proposed to be a cause for severity of disease-expression in females.[300, 302] In our study patients had no difference in NYHA class at the time of diagnosis, but whereas a majority improved NYHA class with treatment, twice as many women as men showed the opposite and worsened to NYHA class ≥III, also in age-matched group (Paper III, Tables 1 and 2), similar to two tertiary center results.[257, 268] Regarding hormonal influence, our data (Paper III, Figure 4) from

an unselected geographical cohort, agrees with findings by Olivotto et al.[257] that the excess mortality occurs in post-menopausal age, in contrast to a study from a Chinese tertiary centre.[258]

Possible causes of excess female mortality

A larger LVOT-gradient increases the risk for death and clinical deterioration.[303] Neither in our total geographical cohort nor in age-matched group were there any significant differences in resting LVOT-gradients between males and females at diagnosis (Paper III, Tables 1 and 2) despite contrary reports from several tertiary centre studies.[258, 268]

The reason for the contrasting results one can only speculate. Is there a higher threshold for referral to a tertiary centre for women, particularly in China? The findings in our geographical cohort however shows that the observed impaired prognosis among females could not be explained by differences in resting LVOT-gradients at diagnosis between men and women. It is notable however, that among our patients with an initial LVOT-gradient ≥50 mmHg females had 37% and males 22% mortality during later follow-up (p=0.004). According to this finding one has to reflect if the differences in pharmacological treatment between the sexes found could be relevant for the poorer outcome in women. Significantly fewer females were given beta-blocker therapy initially, 66% versus 80% among age-matched patients, and the initial dose used was smaller even adjusting for body size.

It is notable that a lower proportion of women were given beta-blockers, with a median dose of only 50 mg/day in metoprolol-equivalents after diagnosis, despite women being more symptomatic (76%), and 44% versus 34% in men complained about chest pain. This observation is in line with another study in Australia (ischemic study) reporting more active treatment in men, as angiography was around 25% higher among men, and PCI/CABG in men were around 150% higher than in women.[304] Similar reports with less active treatment of women for acute coronary syndrome are reported from the USA[305] and Sweden.[306] Our findings suggesting a protective effect of beta-blockers have been discussed in section above. Beta-blocker therapy has been reported to reduce risk of death in both children and adult patients with HCM [95, 167, 255, 268] but it is worth to re-emphasize that the protective effect is dose-dependent in multi-variate analysis[167, 255] including sex as a variable (Paper I).[255] The protective effect of higher than median doses of beta-blockers (≥1.18 mg/kg/day in metoprolol-equivalents) was present in both sexes (Paper III, Figure 5AB), and we observed that in the age-matched groups, female 10-year survival was much closer to that of males in the ≥1.18 mg/kg/day group (92% versus 94%). The survival with doses of ≥150 mg metoprolol-equivalents/day was even better (97% 10-year freedom from disease-related death when both sexes combined, log-rank for trend p=0.00008 (Paper I, Figure 1B).[255]

In this study females with AF had a tendency to a poorer prognosis than males with AF at last follow-up, with disease-related death of 44% compared to 24% (Paper III, Figure 4, p=0.109). A theoretical explanation is that the females, perhaps with impaired diastolic function, had not as good rate-control of their AF during physical ac-

tivity as males, because of lower prescribed beta-blocker doses. Beta-blocker therapy has been shown to reduce compensatory cardiac hypertrophy in animal models,[49] and to reduce cardiac fibrosis and myofibre degeneration by 67-91% in spontaneously hypertensive rats,[307] so it is not unreasonable to hypothesize that beta-blocker therapy could influence disease development positively and reduce progress of fibrosis also in human HOCM, mainly in patients with sub-optimal control of outflow-gradients leading to subendocardial ischaemia on activity. Disopyramide therapy is also significantly underused in females, 7% versus 16% in males (p=0.027). A significant additional disease-related mortality in the age-matched group occurred specifically in myocardial infarctions among women (Paper III, Figure 2), also reported by others.[305] That calcium-channel blocker therapy was significantly more common in the female group might be a potential factor in the excess mortality, especially in chronic heart failure seen in females, and multi-variate analysis in the total cohort revealed that verapamil/diltiazem therapy was a significant risk factor for heart failure deaths (Paper I).[255] Our group of calcium-blocker treated patients is quite small, so the harmful effect of verapamil/diltiazem on heart failure related mortality showed in this study has to be interpreted with caution.

Reducing the delay in diagnosis in females, using effective beta-blocker and disopyramide therapy early to control LVOT-gradients adequately even in asymptomatic patients, and increasing physician awareness that women have a higher propensity for diastolic dysfunction than men might be associated with improvement of prognosis in women. Furthermore, early recognition and management of atherosclerosis and other co-morbidities might be helpful in reducing mortality in females with HCM.

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.

Short AV-delay pacing as a simple, cost-effective procedure was not inferior to myectomy in the relief of LVOTO. Furthermore, pacing therapy was associated with a low need for perioperative complications and later re-interventions. Our data support the view that short AV-delay pacing should be considered a valid option to treat patients with HOCM, and the comparatively low costs suggests that, while we await results of randomized prospective comparisons with alcohol septal ablation, it merits consideration as first choice option on cost-benefit criteria, particularly in countries with a population size that mean that surgical volumes for myectomy will remain low even if centralized to one centre.

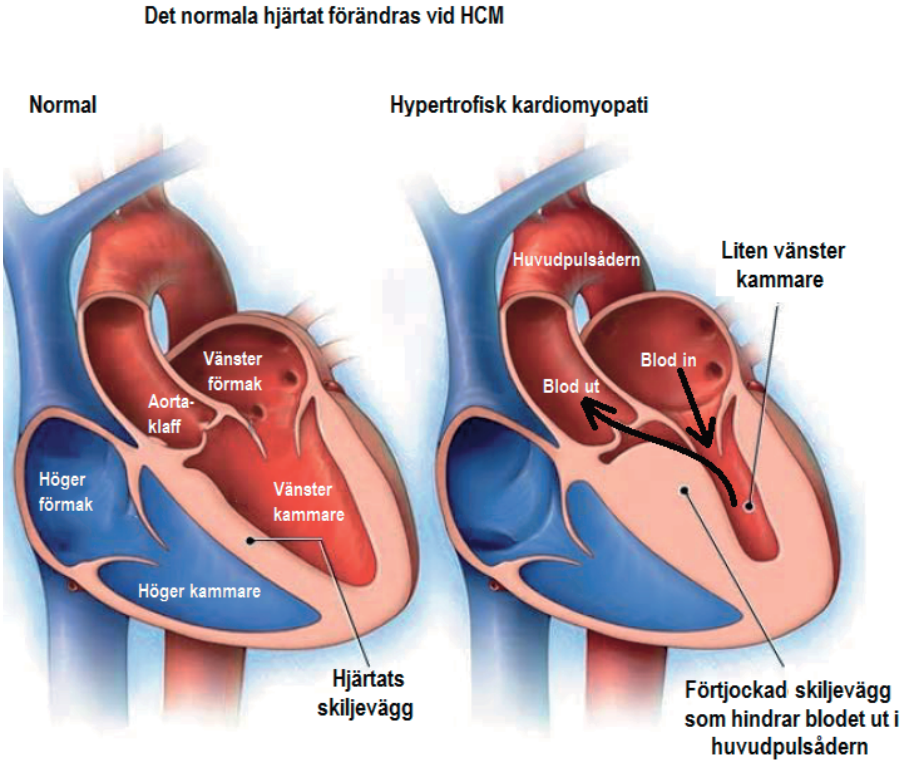
Greater efforts at early diagnosis in females, and a more liberal, and earlier, use of beta-blocker therapy and disopyramide to optimize gradient-control and diastolic function, might improve outcome in females with HCM.

Generally it can be commented that a significant proportion of HOCM patients do not receive appropriate escalation of therapy according to international guidelines even when substantial outflow gradients remain. Despite their worse prognosis female were especially likely to receive inadequate treatment.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund

Hypertrofisk kardiomyopati (HCM) är en ärftlig hjärtmuskelsjukdom som drabbar 0,2% av befolkningen. Hjärtmuskeln är förtjockad, vanligtvis i vänster hjärtkammare. Av dessa har ca en fjärdedel en extra förtjockning belägen i vänster hjärtkammares utflödesdel som ger upphov till en förträngning (”obstruktion”). Man talar om hypertrof obstruktiv kardiomyopati (HOCM). Utflödeshindret innebär att hjärtat blir mer ansträngt när det skall pumpa ut blodet i kroppspulsådern. Det uppstår en skillnad i blodtrycket mellan hjärtkammaren och kroppspulsådern (”utflödesgradient”). En minsta tryckskillnad om 30 mmHg krävs för HOCM-diagnos men det kan bli mer än 100 mmHg.



Symptomen kan antingen vara obetydliga eller uttalade med andfåddhet och bensvullnad, bröstsmärta, blodpropp i hjärnan eller till och med dödliga rytmrubbningar. HOCM anses ligga bakom stor proportion av dödsfall hos unga idrottsutövare.

Prognosen vid HOCM som handlagts i rutinsjukvård är ofullständigt känd. De flesta undersökningarna kommer från högspecialiserade centra som tar hand om de sjukaste patienterna.

Behandlingen syftar till att minska utflödesgradienten. Många patienter blir förbättrade av mediciner, men en stor grupp kräver ytterligare behandling för att må bra. Man kan då med viss pacemakerbehandling åstadkomma god lindring. Om man med en pacemakerimpuls startar kontraktionen långt nere i kammaren vänder man på förloppet och kammaren kan till stor del tömma sig innan ringmuskeln blivit fullständigt sammandragen. Goda resultat kan man också få med en hjärtoperation där man tar bort en del av den muskel som bildar ett hinder för hjärtkammaren att tömma sig. Detta ingrepp ”myektomi” är förstahandsrekommendation i alla internationella riktlinjer. Pacemakerbehandling är accepterad i de europeiska riktlinjerna, men förbigås i de amerikanska. Orsaken härtill torde vara att det endast finns ett fåtal uppföljande studier av pacemakerbehandling vid HOCM och att de har få patienter med kort uppföljningstid.

Ett litet antal patienter blir så svårt sjuka att de måste genomgå hjärttransplantation.

Avhandlingens syfte har varit att via långtidsuppföljning kunna jämföra effekterna av de olika behandlingsmetoderna i en oselekterad kohort som handlagts i svensk allmänsjukvård.

Via diagnosregistren vid samtliga västsvenska sjukhus under tiden 2002-2013 identifierade vi 251 patienter med HOCM: av dessa behövde 121 enbart mediciner, 88 erhöll pacemakerbehandling och 42 genomgick hjärtoperation med myektomi.

Under en uppföljningstid om 14 år avled 65 patienter vilka analyserats närmare. Klart ökad risk för död förelåg om höggradigt utflödeshinder kvarstod. Trots att kvinnorna erhöll pacemaker eller hjärtoperation i samma omfattning som männen var risken för död fyra gånger högre och berodde på hjärtsvikt och hjärtinfarkter. Den samlade risken för att avlida var densamma oavsett om patienten fick pacemaker eller hjärtoperation.

Ungefär var tredje opererad patient drabbades av komplikationer vid ingreppet eller under uppföljningen jämfört med 3.2% vid pacemakerbehandling.

Mest uppmuntrande är resultaten av tablettbehandling med betablockare. En dos metoprolol om minst 100 mg/dag minskar risken för död, lägre dos har tveksam effekt och kan delförklara den ökade dödligheten för kvinnor eftersom kvinnor fick betablockerarbehandling i lägre dos än män även korrigerat för kroppsstorlek. Positivt var också att majoriteten av patienterna fick bättre ork av alla behandlingsformer.

Huvudbudskapet blir att hjärtsvikt var huvudorsaken till dödsfallen. Risken för att avlida skilde sig inte åt mellan de olika behandlingarna, men risken är starkt avhängig av en tillräckligt hög dos betablockare. Här finns en klar förbättringspotential vad gäller medicinsk behandling av kvinnor. Pacemakerbehandlingen är effektiv och skonsam och medför betydligt lägre kostnader än myektomi. Den borde kunna komma till ökad användning som första alternativ för de som inte svarar på medicinsk behandling.

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