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IMPLANTABLE CARDIOVERTER DEFIBRILLATOR TREATMENT IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

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IMPLANTABLE CARDIOVERTER DEFIBRILLATOR TREATMENT IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

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To my wife Marita and our children Lukas, Melvin, David, and future generations

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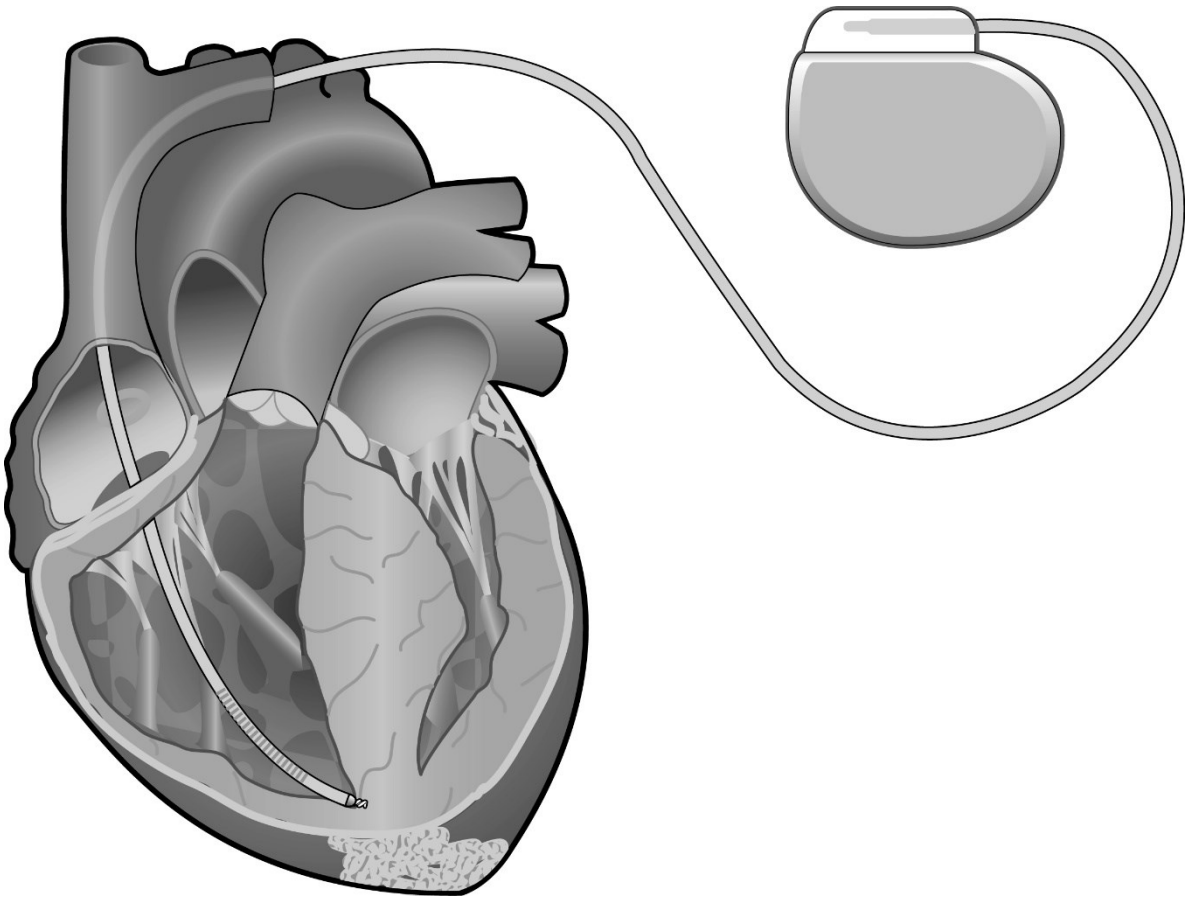


Illustration by Todd Cooper.

1 PROLOGUE

We heard the remote sound of sirens from the ambulance. The characteristic alarm to get the attention in the surroundings. But we were in the emergency department and we were already notified. The ambulance had called to tell us about the young woman who was found unconscious. From the report we knew that there was ongoing cardiopulmonary resuscitation. I caught a glimpse of the medical records and found no known disease of relevance.

She was brought into the emergency room and we took over from the ambulance personnel. We continued longstanding heart compression; we attempted to defibrillate her low-amplitude rhythm, possibly ventricular fibrillation; and we continued pharmacological approaches. In the meantime, we did an echocardiography that showed markedly increased hypertrophy of the septal wall. The team continued cardiopulmonary resuscitation for an extended period even though there were no signs of hemodynamic restoration. In fact, there was no spontaneous circulation at all and the body was getting cold. She was dead. Definitely dead.

I undertook the task of informing the closest relatives. Professionalism is helpful, but some cases affect you more than others. Later, the autopsy confirmed the diagnosis of hypertrophic cardiomyopathy. Since then my mind has been engulfed by a question: how can sudden cardiac death be prevented by implantable cardioverter defibrillators in hypertrophic cardiomyopathy?

2 ABSTRACT

Background. Hypertrophic cardiomyopathy (HCM) is a heterogeneous disease with various clinical manifestations, including sudden cardiac death, which can be prevented by an implantable cardioverter defibrillator (ICD). **Aims.** The general aim of this thesis was to elucidate different aspects of ICD treatment in patients with HCM. This includes the use of ICDs among HCM patients with focus on risk stratification for ventricular arrhythmias, mortality, and cause of death; assessment of health-related quality of life; qualitative aspects of living with an ICD; and characterization using positron emission tomography (PET) to explore risk markers for sudden death. **Methods.** The Swedish Pacemaker and ICD Registry was retrieved to identify eligible patients. Data from the National Patient Registers, the Cause of Death Register, Statistics Sweden, and medical records were used. Health-related quality of life was assessed using SF-36. Interviews were analyzed by hermeneutics and latent content analysis. PET and echocardiography were performed. **Results and Conclusions.** In *Paper I*, the nationwide cohort of unselected HCM patients with ICDs was based on established risk factors for sudden cardiac death at the time. ICDs effectively terminated potentially life-threatening ventricular arrhythmias in HCM. The cumulative incidences of first appropriate ICD therapy at 1 year, 3 years, and 5 years were 8%, 15%, and 21%, respectively. Left ventricular ejection fraction less than 50% and atrial fibrillation were strong predictors of appropriate ICD therapy. In *Paper II,* among HCM patients with ICDs, the main cause of death is deterioration of systolic function leading to end-stage heart failure. The risk of sudden cardiac death was almost eliminated. Still, there was an increased risk of death (standardized mortality ratio 3.4) compared to the Swedish general population matched for age, sex, and calendaric time. In *Paper III*, generic health-related quality of life, both mental and physical components, was lower in HCM patients with ICDs than in Swedish age- and sex-matched population norms. Systolic heart failure and atrial fibrillation are determinants of low health-related quality of life, especially physical functioning. In *Paper IV*, based on qualitative interpretation, HCM patients with ICDs perceive poor health due to limiting dyspnea but accept the change in lifestyle. They feel grateful for their device, which gives them hope during the life course despite necessary restrictions and adaptation, even after experiencing inappropriate shocks. The knowledge about the disease and device therapy varies substantially and the support from the health care providers is generally constrained to technical issues rather than an attempt at a holistic approach. In *Paper V*, HCM patients with ICDs represent advanced disease manifestation determined as decreased myocardial blood flow at stress, altered oxidative metabolism, and sympathetic denervation using the tracers ^{15}O-water, ^{11}C-acetate, and ^{11}C-HED during PET exams. The endocardium/epicardium myocardial blood flow gradient at adenosine stress is lower in HCM patients with nonsustained ventricular tachycardia, which provides a potential marker for risk stratification of sudden cardiac death.

2.1 KEY WORDS

death, hypertrophic cardiomyopathy, implantable cardioverter defibrillator, positron emission tomography, qualitative, quality of life, risk stratification, sudden cardiac death

3 LIST OF SCIENTIFIC PAPERS

This thesis is based on the following publications:

I. Magnusson P, Gadler F, Liv P, Mörner S. Risk Markers and Appropriate Implantable Defibrillator Therapy in Hypertrophic Cardiomyopathy. Pacing Clin Electrophysiology. 2016 March;39(3):291-301.

II. Magnusson P, Gadler F, Liv P, Mörner S. Causes of death and mortality in hypertrophic cardiomyopathy patients with implantable defibrillators in Sweden. J Cardiovascular Med (Hagerstown). 2016 July;17(7):478-484.

III. Magnusson P, Mörner S, Gadler F, Karlsson J. Health-related quality of life in hypertrophic cardiomyopathy patients with implantable defibrillators. Health Qual Life Outcomes. 2016 April 14;14:62.

IV. Magnusson P, Jonsson J, Mörner S, Fredriksson L. Living with hypertrophic cardiomyopathy and an implantable defibrillator. BMC Cardiovascular Disorders. 2017;17:121.

V. Magnusson P, Nordström J, Harms J. H, Lubberink M, Gadler F, Sörensen J, Mörner S. Positron emission tomography (^{15}O-water, ^{11}C-acetate, ^{11}C-HED) risk markers and nonsustained ventricular tachycardia in hypertrophic cardiomyopathy. IJC Heart and Vasculature. 2019 December 20;26:100452.

4 ABBREVIATIONS

ACCF	American College of Cardiology Foundation
AF	atrial fibrillation
AHA	American Heart Association
ASA	alcohol septal ablation
AV	atrioventricular
BPM	beats per minute
^{11}C-HED	^{11}C-*meta*-hydroxyephedrine
CI	confidence interval
CMR	cardiac magnetic resonance
CRT	cardiac resynchronization therapy
CT	computerized tomography
DFT	defibrillation threshold
ECG	electrocardiogram
EF	ejection fraction
ES	effect size
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
HR	hazard ratio
HRQL	health-related quality of life
ICD	implantable cardioverter defibrillator
LGE	late gadolinium enhancement
LV	left ventricular
LVAD	left ventricular assist device
LVOT	left ventricular outflow tract
MCS	mental component summary
MBF	myocardial blood flow
MEE	myocardial external efficiency
MVO_2	myocardial oxygen consumption
NSVT	nonsustained ventricular tachycardia
OR	odds ratio
PCS	physical component summary
PET	positron emission tomography
RI	retention index
RR	relative risk
SCD	sudden cardiac death
SD	standard deviation
S-ICD	subcutaneous implantable cardioverter defibrillator
SMR	standardized mortality rate
TPG	transmural perfusion gradient
US	United States
UK	United Kingdom
VT	ventricular tachycardia
VF	ventricular fibrillation

5 INTRODUCTION

5.1 HISTORY OF HYPERTROPHIC CARDIOMYOPATHY AND SUDDEN DEATH

A case report by Vulpian, published in 1868, on hypertrophic cardiomyopathy (HCM) described findings of septal hypertrophy from an autopsy at Hôpital de la Salpêtrière in Paris.[1] The following year, Liouville and Hallopeau described further morphological findings of HCM.[2,3] Before that, during the 17th century, Bonet wrote in the *Sepulchretum Anatomicum*, a collection of post mortem reports, "*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*." This report was later mentioned by Morgagni (1682-1771) who refined the description of sudden cardiac death (SCD) and its association to heart pathology.[4] During the Renaissance, the physician of Pope Clement XI, Lancrisi evaluated sudden unexpected deaths in Rome in 1705 in *De subitaneis mortibus,* reporting on death associated with left ventricular (LV) myocardial hypertrophy.[5,6] Thus, at that time the gross anatomical findings and the association of sudden death were established, and could be causally linked to the observations of Hippocrates, "*Persons who have had frequent and severe attacks of swooning, without any manifest cause, die suddenly.*"[7,8] Indeed, unexplained syncope, previously called *swooning*, was already recognized as a risk factor for SCD. Lancrisis' contribution also included the documentation of the hereditary component of cardiac disease when a family with disease transmission in four generations was described.[6,9]

Following years of pathology descriptions, the development of heart catheterization and angiography in the 1930s increased our understanding of physiological hemodynamics. In 1957, Brock realized that the LV outflow tract (LVOT) gradient was due to *subvalvular stenosis* in a patient with a normal aortic valve seen at the operation.[10] Bercu further described the familiar disease of unexplained LV hypertrophy as *pseudo-aortic stenosis* that occurred in the absence of valve obstruction or hypertension, which still provides the basis of the definition of HCM.[11] In 1958, Teare published a case series of *asymmetrical hypertrophy* in eight young adults, of whom seven died suddenly; he described symptoms, family history, and myocardial disarray.[12] The same year, in 1958, Cleland resected part of the hypertrophy, considered to be the first myectomy, which relieved the patient from symptoms.[13] This inspired Morrow, who during his career performed 299 cases of myectomy in order to relieve outflow obstruction, to develop a procedure that sometimes bears his name. In 1959, he and Braunwald published a report on three patients with functional aortic stenosis described as malformation characterized by resistance of the LV outflow.[14] In 1964, they described a case series of ten myectomy patients who were assessed postoperatively by left heart catheterization evaluation. The myectomy procedure remains the optimal treatment option for many symptomatic patients, because complications are few and it has excellent long-term results.[15–17] Ironically, Morrow himself was diagnosed with idiopathic hypertrophic subaortic stenosis, the term at the time, by Braunwald in 1961 solely by stethoscope auscultation finding of systolic ejection murmur of the precordium. Despite severe symptoms of exertional shortness of breath, syncope, atrial fibrillation (AF), and stroke, Morrow refused

further evaluation and treatment. He died suddenly at the age of 60 years and the autopsy confirmed the diagnosis of HCM with increased mass (645 gram), septal hypertrophy, thickened anterior mitral leaflet, dilated left atrium, myocyte disarray, scarring, and microvascular abnormalities. Morrow provided evidence of the genetic transmission of the condition as two of his three children were affected; his daughter underwent transplant and his son had the procedure his father had invented.[18]

The development from M-mode echocardiography two-dimensional imaging to cardiac magnetic resonance (CMR) enhanced our morphological and functional understanding of the disease and has gained vast interest as a tool in risk stratification.[19–22] The advanced functional imaging technique of positron emission tomography (PET) is evolving as to understand pathophysiological aspects of the disease using specific tracers and has the potential to refine risk assessment.[23,24]

The molecular linkage of the familiar form of HCM was elucidated in 1989 by the identification of a locus on chromosome 14q1 that accounts for the expression of sarcomeric dysfunction.[25] Since then a rapid evolution of knowledge of the various genetic bases of HCM has established genetic evaluation as an essential part of routine management. Over the past decade, the knowledge of the underlying genetic basis has been proven to be useful in cascade screening by identifying relatives without the phenotype and also relatives who do not need further follow-up. Genetic information can help confirm diagnosis, offer more insight into prognosis, and likely improve individualized management.[26–28] SCD in HCM remained the ultimate, disastrous outcome despite advances in diagnosis and pharmacological and interventional treatments. Together with Mower, Mirowsky realized his vision to terminate ventricular fibrillation (VF) with an implantable cardioverter defibrillator (ICD). In 1978 they published their successful experiment using an implantable defibrillation system in dogs from their self-funded laboratory.[29] Despite major obstacles from authorities in the medical community, they continued their efforts. Finally, they got approval to conduct a study in humans with the inclusion criterion that the patient had to have survived two (!) episodes of cardiac arrest. In 1980, their first case series was published.[30] In fact, two of these three patients had HCM.[31] The defibrillator lead was placed epicardially via thoracotomy until 1992 when the transvenous lead was launched. This spurred the initial trials of ICDs in secondary prevention after cardiac arrest or ventricular tachycardia (VT) and later as primary prevention in patients with heart failure due to ischemic or non-ischemic dilated cardiomyopathy.[32–34] Risk stratification in HCM was different and had to rely on empirical data from smaller observational studies. In 2000, the landmark trial of ICD in HCM was published, which showed high efficacy and appropriate therapy at an annual rate of 11% in secondary prevention and 5% in primary prevention.[15] The experiences from numerous observational trials over the last two decades have shaped current guidelines.[15,16,35] Basically there are two strategies, either risk factor assessment or a prediction model, or possibly a combination. Nevertheless, the consideration of individual patient perspectives along with health care resources is a challenge. There remain controversies in strategies for risk prediction and there is a need for refinement of risk stratification.

This field of science has moved far from the early observations of HCM several decades ago into a field of evidenced-based approaches grounded on more solid, systematic data. This has been made possible through the integration of innovation, development, and implementation of various fields. Promising advancements in medicine and technology in general will likely benefit HCM patients. Indeed, a bright future for HCM patients depends on collaboration, first to conduct meaningful research in the form of ground-breaking trials, but second with systematic organizational efforts to implement evidence-based medicine and bring these findings to clinical practice. Nevertheless, the inherent heterogeneity of HCM expression will always require careful judgement by clinicians and must also consider patient preference.

5.2 DEFINITION AND DIAGNOSTIC PRINCIPLES

A cardiomyopathy is defined by the morphological pathology of the ventricular chamber(s) of the heart that is not due to significant epicardial coronary disease and/or abnormal loading conditions, although concomitant disease sometimes occurs.[15] Therefore, it is important to judge whether a hypertrophied myocardium can be explained by hypertension, aortic stenosis, or any other condition with abnormal loading of the left ventricle.[15,36] A ventricular wall thickness of at least 15 mm in adults is typically required for the diagnosis of HCM. In cases with 13-14 mm in at least one myocardial segment, careful evaluation, including family history, is needed; if a first-degree relative (sibling, parent, and children) is affected HCM is likely.[15,16] In borderline cases, extracardiac signs, electrocardiogram (ECG) pathology, laboratory exams, and findings of CMR imaging in addition to echocardiography may be useful to differentiate between underlying etiologies. It is crucial to be aware of co-existing valvular disease, essential or secondary hypertension, physiological response to intense exercise over extended periods, and isolated mild hypertrophy of the basal part of the septum commonly seen in the elderly.[15,37,38]

The European Society of Cardiology (ESC) guidelines' concise statement of definition is as follows: "HCM is defined by the presence of increased LV wall thickness that is not solely explained by abnormal loading conditions."[15] This statement ratifies a classification system based on morphological and functional criteria, regardless of possible extracardiac disease. Thus, other genetic as well as non-genetic causes are included in the ESC definition of HCM: inborn metabolic errors, neuromuscular diseases, mitochondrial disease, malformation syndromes, drug-induced forms, and amyloidosis. Moreover, this broad approach comprises all ages, including the pediatric population.

Here, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines from 2011 hold another position.[16] They recognize HCM as a clinical entity "…characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systematic disease that itself would be capable of producing the magnitude of hypertrophy…". There are numerous conditions, especially diagnosed during childhood and early adult years, which mimic hypertrophy attributable to sarcomeric protein mutations. The American guidelines emphasize that these conditions, so-called phenocopies, should not be included in the term HCM.

Using the American definition and terminology for HCM, there are other groups of diseases and conditions that present with hypertrophy. These can be categorized based on cellular mechanisms, i.e. neuromuscular, mitochondrial, and metabolic disorders (glycogen storage, carnitine, lysosomal storage). Among the metabolic disorders, glycogen storage diseases such as Danon disease, Pompe disease, and Anderson-Fabry disease are occasionally encountered in adult cardiology.[39] Patients with malformation syndromes are typically diagnosed in pediatric cardiology; LEOPARD (lentiges, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness), Noonan syndrome (facial features, short height, congenital heart disease, bleeding problems, and skeletal malformations), and others.[15] There are complex pathophysiological pathways that are involved in the biological underpinnings of hypertrophy.[40–42] LV hypertrophy can be acquired in different conditions. Patients with diabetes mellitus or renal failure often have myocardial hypertrophy.[43–45] There are endocrine disorders, i.e. hyperparathyroidism, acromegaly, primary aldosteronism, pheochromocytoma, and paraganglioma that can cause hypertrophy.[15,46–49] Hypertrophy also occurs in morbidly obese persons.[50] Myocarditis and other forms of inflammatory/infiltrative disease can cause reversible thickening of the myocardial walls.[51–53] Synthetic anabolic steroids but also long-term pharmacological treatment with chloroquine, corticosteroids, and tacrolimus may cause hypertrophy.[15,54,55]

Cardiac hypertrophy is often seen in amyloidosis which can be divided into different forms with specific therapies in some cases.[56–58] Imaging tools, laboratory markers, and sometimes biopsy are useful to differentiate amyloidosis from HCM.[59–62] LV non-compaction cardiomyopathy can mimic HCM and is difficult to distinguish.[63] Furthermore, it is important to discern athlete's heart from cardiomyopathies.[64]

5.3 EPIDEMIOLOGY

The prevalence of HCM is often reported as 1:500 (0.2%), based on several studies with diverse methodologies, widespread geographical areas and health care systems, and different populations.[65,66,66–71] Recently the prevalence of HCM in Iceland was reported as 1:1,600.[72] In the frequently cited United States (US) cohort (aged ranged from 23 to 35 years), 7 out of 4,111 (0.17%) unrelated individuals had signs of hypertrophy on echocardiography but only 1 reported cardiac symptoms.[65] Both underestimation and overestimation is likely to be common in clinical routine and misclassification seems to be common.[73] HCM is recognized all over the world but prevalence varies, likely due to differences in diagnostic resources.[74] The diagnosis of HCM may be delayed or unrecognized in some patients because they are asymptomatic, have vague or mild symptoms, or are not properly evaluated in family screenings. Interestingly, a remarkably high prevalence (about 1:200) was reported when both phenotypes and genotypes were included based on cohorts from expert centers.[75]

In Sweden, the prevalence of HCM is largely unknown. In general, the Swedish National Patient Register data are considered highly reliable and are used for research purposes in addition to evaluation of health care quality but no nationwide validation, specifically with regard to HCM, has been done.[76]

5.4 NOMENCLATURE

Historically, the descriptions and insights in the field of HCM, often in parallel developments, have led to a diverse nomenclature. In fact, at least 58 different names have been used in the past for the disease known today as HCM.[77] Asymmetrical septal hypertrophy is not a prerequisite, but the term hypertrophic obstructive cardiomyopathy, abbreviated as HOCM, is still frequently used. Nevertheless, obstruction is dynamic due to physiological conditions and may be provoked during physiological or pharmacological challenge. In order to avoid confusion, the term HCM should be used.[15,16] However, one challenge is that hypertrophy is not always present at the time of diagnosis because some patients develop dilatation of the left ventricle and the hypertrophy disappears. The evolution of genetic characterization has led to categorization of patients with the genotype but no phenotype. This group of genopositive-phenonegative mutation carriers is likely to increase due to more widely used cascade screening.

5.5 CLINICAL EVALUATION

5.5.1 Diagnostic work-up

The diagnostic work-up of a definite HCM including underlying etiologies requires an integrated assessment using anamnesis, physical examination, laboratory testing, ECG, and imaging. Besides routine cardiological assessment with extracardiac and molecular approaches, a cardiomyopathy-oriented mindset likely improves diagnostic accuracy.[78] The heterogeneity of morphological expression should be recognized; most typically it manifests as septal hypertrophy but other forms, such as apical, lateral, concentric, and even right ventricular hypertrophy, is seen.[15]

A specific diagnosis is the prerequisite for targeted evidenced-based management of the individual but also for the relatives. Sometimes HCM is diagnosed in a post-mortem analysis of the heart, including molecular diagnosis, which may explain the underlying cause of death. In order to avoid pitfalls, a standardized autopsy protocol in combination with blood samples to ensure possible postmortem molecular testing has been advocated.[79] A definite diagnosis of HCM may be of potential benefit for the biological relatives of victim.

5.5.2 Symptoms

In patients with suspected or established HCM, careful assessment of symptoms is crucial. Dyspnea, especially at exertion, is the predominant symptom of HCM.[80,81] Often the patient has decreased physical stamina and tiredness, causing the diagnostic presentation to be vague. This is caused by the relaxation dysfunction of the left ventricle during diastole and/or LVOT obstruction. This outflow obstruction is dynamic with regard to filling pressure, heart frequency, and body position and may be influenced by pharmaceutical agents that affect both the heart, vessels, and autonomous system.[15,81] Progressive HCM may occasionally imply deterioration of the systolic function of the left ventricle with reduced ejection fraction (EF). If the left ventricle dilates and hypertrophic regions remodel into dilatation, this

indicates a worse prognosis.[82–84] Sometimes the New York Heart Association (NYHA) functional classification is used for estimation of functional capacity in patients with cardiac disease, even though it has not been specifically validated for HCM (Table 1).[85–87]

Table 1. NYHA functional classification.

CLASS	FUNCTIONAL CAPACITY
I	Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.
II	Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III	Comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or angina.
IV	Inability to carry on any physical activity without discomfort and even symptoms at rest.

Modified from: The Criteria Committee of the New York Heart Association.[87]

Chest pain, or probably better reflecting patients' wording, *chest discomfort* or *chest pressure*, is often described in conjunction with physical activities. Often, the coronary angiogram is normal and without significant lumen-narrowing epicardial coronary disease. Cardiac microvascular dysfunction and fibrosis are part of the cardiac disease deterioration; myocardial biopsies often reveal disarray, and modern PET imaging techniques can confirm both structural and functional abnormalities, which may explain reported symptoms.[15,23]

Palpitations of various duration or symptomatic extra beats are often encountered. In some cases, the first symptom of HCM may be a dramatic syncopal episode. The pathophysiological pathways could be either hemodynamic compromise or cardiac arrhythmias or a combination thereof. Pre-syncope, near-syncope or dizziness is a less specific symptom compared to manifest syncope, but the evolution of these symptoms may lead to subsequent diagnosis. Bradycardia can cause syncope, but in HCM, ventricular arrhythmia should be suspected. Atrial arrhythmias, mostly AF, but sometimes atrial flutter or ectopic atrial tachycardia, are common among HCM patients. It seems that AF in HCM is linked to a high risk for ischemic stroke, likely by embolization.[88,89]

Ventricular tachyarrhythmias that lead to SCD are a well-known, dreaded complication of HCM. Unfortunately, death may be the first manifestation. In such cases, the autopsy often confirms HCM even though the microscopy and postmortem genetic evaluation will be beneficial. The definite diagnosis of HCM in such cases is important, as relatives need to be evaluated.

5.5.3 Physical examination

Broad physical examination in patients with HCM and phenocopies may provide clues for further diagnostics.[78] An attempt should be made to provoke a cardiac murmur by the Valsalva maneuver and, if it occurs, its intensity will vary with the patient’s hemodynamic

state. The physician needs to pay attention to other organs and evaluate the patient's function, i.e. deafness, visual impairment, walking difficulties, motoric and sensory loss, paraesthesia, lentigines, angiokeratoma, and hypo- or hyperhidrosis. Notably, carpal tunnel syndrome may be a sign of amyloidosis.[90]

5.5.4 Laboratory testing

Sometimes basic laboratory markers may give clues for further diagnostics. Liver transaminases may be elevated in mitochondrial disorders, Danon disease, and metabolic disturbances of fatty acids. Lactate may be elevated in mitochondrial disorders, which should be part of differential diagnostics in selected cases.[15] Glucose may also be elevated in mitochondrial disorders, but lowered in disorders of fatty acid and carnitine disorders. Creatinine and proteinuria may be elevated in patients in with Anderson-Fabry disease or amyloidosis. In patients with suspected Anderson-Fabry disease, the alpha galactosidase level is typically very low in male patients but normal in females. Immunoglobulin-free light chain and urine electrophoresis are useful in the diagnostic work-up in suspected amyloidosis.[15]

In general, laboratory biomarkers may contribute to the diagnostic and prognostic assessment. Anemia encumbers the cardiovascular system. Elevated levels of NT-pro-brain natriuretic peptide and troponin T reflect cardiac strain and imply worse outcome.[91–94] When the diagnosis of HCM is definite, the main role of laboratory testing is to reveal complicating factors such as comorbidities.

5.5.5 The electrocardiogram

For HCM patients, the 12-lead ECG often shows abnormalities.[95,96] In a tertiary center cohort, only 6% of patients with an echocardiography established HCM diagnosis had a normal ECG.[97] There are no pathognomonic ECG for HCM but some of the patterns are highly suggestive of specific differential diagnoses or morphological phenotypes. P-wave prolongation is a marker of left atrial dilatation and adverse prognosis and is often seen in conjunction with repolarization abnormalities and signs of hypertrophy.[98] Short PQ interval and a delta wave (pre-excitation) is linked to *LAMP2* or *PRKAG2* mutations or Anderson-Fabry disease.[99] Q-waves (duration 40 ms or depth >3 mm or ≥5% of the R-wave) correlates with transmural fibrosis and late gadolinium enhancement (LGE).[100,101] In two studies of HCM, 90% and 96% of patients had an abnormal ECG, but only 2% showed isolated QRS criteria for hypertrophy using the Sokolow-Lyon or Cornell score.[102,103] On the other hand, low amplitudes ≤5 mm in every limb lead is suspicious of amyloidosis. Bundle branch block is often due to septum reduction procedures, such as myectomy or alcohol septal ablation (ASA).[104] Fragmentation (additional R-wave) is a marker of fibrosis. An ST-T segment abnormality is frequently seen in HCM; deep T-wave inversion in lateral leads is typical of apical hypertrophy. QT-prolongation (QT_c exceeding 480 ms) is seen in 13% of HCM patients and 0.5% in control group and has been suggested as a marker for SCD.[105,106] J-waves (J-point elevation >0.1 mV in ≥2 contiguous inferior and/or lateral leads) are seen in approximately a tenth of HCM patients and seem to predict cardiac events.[107]

The T-peak-to-T-end interval has been suggested as marker for ventricular arrhythmia.[108] The ECG also has an important role in screening, and there are clues to differentiate athlete's heart from HCM.[109] T-wave abnormalities are suggestive of apical forms of cardiac hypertrophy.[110] In a study of athletes with T-wave inversion (half of the study population was black, the other half white) and a normal echocardiogram, after comprehensive investigations 21% were diagnosed with a cardiac disease and 91% of these diagnoses were HCM; an inversion in lateral leads was frequently observed.[111] Based on Swedish HCM patients, a risk-score based on ECG amplitudes has been suggested.[112] Thus, the ECG can provide a clue to differentiate between athlete's heart and HCM. The sum of the Q-wave and the S-wave in lead III are higher in HCM compared to athletes (0.71 SD 0.69 mV vs 0.21 SD 0.17 mV; $p<0.001$), which may provide additional sensitivity to international criteria for athletic ECG interpretation.[113]

The presence of fragmented QRS in ≥3 territories (inferior, lateral, septal, and/or anterior) was independently associated with outcome (SCD or appropriate ICD therapy) in HCM patients, which provides incremental value to conventional risk factors.[114]

Holter monitoring, ambulatory ECG for 24-48 hours, is frequently used in follow-up of HCM patients. It provides information about supraventricular tachycardia, VT, extrasystoles, and bradycardia. The presence of nonsustained VT (NSVT) on Holter monitoring is used for risk stratification of SCD. It varies between cohorts. The prevalence of NSVT was 31% in one non-tertiary center and 20% in a tertiary center cohort.[115,116]

The insertable cardiac monitor provides continuous ECG monitoring. Current ESC guidelines consider insertable cardiac monitors a tool for evaluation of HCM patients with recurrent unexplained syncope, who are otherwise deemed as low risk of SCD.[15,117] We prospectively evaluated the burden of arrhythmia among HCM patients with a mean 5-year risk of 2.4%, which yielded 31% AF, 21% NSVT, and 38% sinoatrial block/arrest.[118,119]

5.5.6 Exercise test

Exercise testing, in Sweden almost exclusively the ergometer bicycle test, has been frequently used in cardiac evaluation of diverse patient groups, including HCM, and is considered safe.[120] It may also add information helpful for the differential diagnosis of athlete's heart and metabolic disorders using simultaneous measurement of respiratory gases.[15] The test provides quantitative measurement of physical performance in addition to personal history, which are sometimes ambiguous. This may also be useful in the evaluation of septum reductive procedures.[15] Several studies have shown peak VO_2 as a predictor of heart failure progression and mortality.[121–123]

Preexisting ECG abnormalities may lead to interpretation challenges with false-positive results. However, chest discomfort is common in HCM but often due to microvascular dysfunction, increased oxygen demand of the hypertrophied myocardium, compressive systolic forces on the arterioles, and impaired diastolic function.[124] Indeed, when epicardial disease is present, it implies higher mortality.[125] In intermediate-to-high risk, invasive

angiography may be the preferred option, while computerized tomography (CT) offers a noninvasive alternative in the setting of low-risk patients.[120] Single-photon emission computed tomography lacks specificity in HCM, and false-positive tests have been seen in half of the patients.[126,127]

Stress echocardiography, preferably using physiological exercise, has a role in the evaluation of provocable LVOT gradients. The dynamic nature of gradients can often be reproduced and may explain exercise-related symptoms from personal history, which are amenable to septum reductive treatment. Alternatively, the Valsalva maneuver is used simultaneously with echocardiography assessment, but it has low sensitivity and high specificity regarding LVOT gradients.[128]

A hypotensive or attenuated blood pressure response at exercise testing as an independent risk factor for SCD has shown conflicting results in larger studies.[121,129]

5.5.7 Misclassification

The diagnosis of HCM can sometimes be challenging. In western Sweden, 611 cases (mean age 58.9 years) of cardiomyopathies were validated and categorized into three groups: dilated, hypertrophic, and others (restrictive, arrhythmogenic right ventricular cardiomyopathy, LV non-compaction, takotsubo, peripartum).[130] The diagnostic accuracy of HCM was 88%. We did a regional validation of HCM-related codes 142.1 and 142.2 (International Classification of Diseases) which are used for the Swedish National Patient Register. Approximately one third (31.8%) of the patients had another diagnosis and were thus misclassified as HCM. This implies that registry data on HCM should be interpreted with caution, depending on the purpose.[73]

5.6 CARDIAC IMAGING

Cardiac imaging techniques provides the basis for phenotypic assessment of HCM. Besides echocardiography, CMR has an important role while CT and scintigraphy are occasionally useful. PET has unique properties but are currently limited to research purposes. Imaging is used for diagnostics and follow-up, including risk stratification.

5.6.1 Echocardiography

Echocardiography is a cornerstone in the diagnosis of HCM and valuable for routine follow-up. It is widely available. Nevertheless, it requires careful evaluation, preferably using a standardized protocol. Most often the hypertrophy involves the septal part of the heart, but it may affect any segment, even the right ventricle. Adequate transmission and visualization are crucial, including correct beam alignment without oblique views. An oblique view may lead to overestimation of the wall thickness. For this reason, M-mode measurements in the parasternal long axis can be a pitfall. Visualization and accurate measurements are sometimes difficult, especially in the apical or antero-lateral part of the left ventricle. The linearity of the wall can be enhanced by ultrasound contrast agents. CMR provides high resolution and often resolves these issues. Wall thickness measurement is essential for the diagnosis but also as

part of risk stratification, which makes accurate assessment so important.[131] Recently, body surface area adjustment was shown to impact diagnostic cutoff, especially in women.[132]

Mitral valve abnormalities are often seen in HCM. The mitral leaflets may obstruct the LVOT during systole. This phenomenon, systolic anterior motion, is seen at rest in approximately one-third, whereas another third of patients only exhibit this during increased loading conditions and contractility.[133,134] Some anatomical features of the affected valve apparatus are common: papillary muscle hypertrophy, displacement, and elongation. These abnormalities of the mitral valve, together with the septal hypertrophy, serve as substrate for the LVOT obstruction.

The definition of LVOT obstruction is ≥30 mmHg independent of rest or physiological stress, the Valsalva maneuver, or upright body posture. A higher value, above 50 mmHg, can cause hemodynamic and possibly symptomatic changes.[15]

The left atrium is prone to enlargement in HCM because of increased filling pressures and mitral insufficiency. The size can be quantified using diameter along the parasternal axis and body surface area indexed volume.[135,136] The former is used for calculation of SCD risk assessment.[137]

Echocardiographic assessment of diastolic dysfunction includes several aspects; systolic pulmonary arterial pressure, left atrial size, filling patterns, and strain.[138] Systolic function, expressed as EF, is often above the normal values; indeed, it can be supranormal, i.e. very high values. The radial contractility is often normal or increased, while longitudinal contractility is decreased in the hypertrophied parts.[139] When HCM patients deteriorate into end-stage heart failure, the EF is reduced. Echocardiography also provides valuable morphological and functional information to differentiate among the various etiologies of hypertrophy. Transesophageal echocardiography is recommended in perioperative assessment during myectomy.[15] Echocardiography should be performed for screening purposes in persons at genetic risk every 1-2 years between the ages of 10-20 years and then every 2-5 years during adulthood.[15,140]

5.6.2 Cardiac magnetic resonance

CMR is nowadays often part of the baseline evaluation. In the situation of inadequate visualization of the whole heart by echocardiography, CMR provides diagnostic information as well as maximal wall thickness used for risk stratification. LGE seems to reflect myocardial fibrosis, has been shown to be useful in risk stratification, and is a prognosticator.[141,142] Although the amount of LGE correlates with prognosis, LGE findings are not part of the current ESC guidelines for risk stratification of SCD. LGE analyses can aid in the differentiation among amyloidosis, Anderson-Fabry disease, and sometimes athlete's heart, even though LGE can be absent in patients with mild disease.[143] CMR has an important role in tissue characterization and differentiation of phenocopies.

CMR offers advantages over echocardiography due to its superior spatial resolution and accurate volume assessment. Body habitus, chest wall configuration, and pulmonary tissue disease can sometimes limit echocardiographic assessment. Of note, CMR quality requires gating regarding rhythm and respiratory breath hold for some sequences. Furthermore, its availability, portability, and costs limit its use compared to echocardiography.

Hindieh et al compared maximal wall thickness between echocardiography and CMR in 195 HCM patients (median age 52.8 years) with both investigations performed within a median of 41 days.[144] The echocardiographic measurements were along the parasternal long and short axes and CMR along the short axis. The mean value, using a Bland-Altman plot, was similar (difference 0.5 mm). However, in 49.7% of the patients, the discrepancy between methods was ≥10%. Underestimation in echocardiography was due to focal LV hypertrophy and poor acoustic windows, while overestimation was due to the inclusion of the right ventricular myocardium, LV trabeculations, papillary muscle, and apical-septal bundle, as well as imaging plane obliquity.

Accurate assessment of maximal LV wall thickness in HCM is important in several aspects. It is needed to determine a definite diagnosis, prognosis, and risk stratification. Both imaging techniques are instrumental in HCM evaluation. Echocardiography is portable, easily accessible, and allows superior hemodynamic assessment, including measurement of dynamic obstruction, quantification of mitral regurgitation severity. CMR provides improved spatial resolution, even when limited by acoustic windows. In addition to wall thickness, CMR also allows for additional risk stratification by LGE. However, they are not equal when it comes to LV wall thickness assessment.

Assessment of LV wall thickness may vary depending on the technique used. In a comparative study, 618 HCM patients were evaluated using CMR and echocardiography on the same day.[145] Overall, the median difference between these two measurement techniques was 3 mm. However, for massive hypertrophy with LV wall thickness ≥30 mm, results diverged such that 53% were identified as massive using CMR compared to 17% with echocardiography. Only 30% of this subpopulation (n=63) had a diagnosis of massive hypertrophy in both CMR and echocardiography.

5.6.3 Computerized tomography and scintigraphy

CT is an option in patients if echocardiography is inconclusive and CMR is contraindicated. CT may be useful for high-resolution measurement of wall thickness, chamber volumes, and LV mass.

In differentiation of transthyretin amyloidosis bone scintigraphy ^{99}mTC-DPD is useful.[146] Transthyretin-derived fibrils have an affinity for bone tracers and thus help differentiate HCM caused by sarcomeric protein gene mutations from other forms of HCM. Otherwise, scintigraphy is not useful in microvascular disease with more general disease distribution because scintigraphy shows relative perfusion rather than a quantitative assessment.

5.6.4 Positron emission tomography

PET is a noninvasive imaging modality using radionuclide tracers to quantify pathophysiological phenomena in the heart.[147] Myocardial ischemia without epicardial coronary artery disease is a common feature of HCM and implies worse prognosis.[147] In general, cardiology patients referred for coronary angiography with normal angiograms (HCM were excluded) and subjected to sympathetic stimulation using cold pressor testing showed that impaired myocardial blood flow (MBF) predicted cardiovascular events.[148] Endocardial dysfunction as a predictor of cardiovascular events aligns with several other invasive investigations.[149–151] Notably, myocardial perfusion imaging using PET is a sensitive marker for microvascular dysfunction. As far back as 1991, Camici et al reported impaired MBF using NH_3 in both hypertrophied and non-hypertrophied segments in HCM.[152] The predominant mechanism of microvascular dysfunction is proliferation of smooth muscle collagen in the vessel, which gives rise to luminal narrowing.[153,154] A myocardial disarray, fibrosis, and small vessel disease have been described.[155] MBF at rest is often preserved or slightly decreased, and during stress MBF is often decreased.[156–162] Cecchi et al showed the correlation between MBF impairment and adverse outcome, but there have not been any large-scale outcome studies.[157]

Oxidative metabolism can be evaluated using ^{11}C-acetate PET and one study showed myocardial oxygen consumption (MVO_2) was not significantly different between HCM gene carriers (no phenotype) and controls, whereas myocardial external efficiency (MEE) was significantly lower in carriers.[158] This suggests that myocardial energetics is an early component of the pathophysiological pathways in HCM.

PET also provides insights into other pathophysiological phenomena such as oxidative metabolism and denervation. While it is still used as research tool in HCM, a clinical role has not yet emerged.[23,24,163]

5.7 ATRIAL FIBRILLATION AND HEART FAILURE

5.7.1 Atrial fibrillation

AF is commonly encountered in HCM due to the pathophysiological enlargement of the left atrium caused by increased pressure, diastolic dysfunction, decreased cavity size, outflow obstruction, and mitral insufficiency.[88,89] In fact, if the left atrial diameter is ≥45 mm, 48-hour ambulatory ECG every 6-12 months is recommended.[15]

Stroke is recognized as a leading cause of death, disability, and morbidity, including an association with dementia.[164] AF is a complex condition in interplay with other risk factors and is known to cause stroke and systemic embolization, which can be prevented by anticoagulant therapy.[165] A non-vitamin K antagonist oral anticoagulant is the preferred choice for anticoagulation therapy because of superior efficacy, lower risk of bleeding, and fewer interactions.[166] Both the ACCF/AHA and the ESC guidelines support the prescription of anticoagulation regardless of the patient's CHA_2DS_2-VASc score.[167] More recently, this

approach has been confirmed.[168] Jung et al showed that HCM patients with AF but without any CHA_2DS_2-VASc risk factors had the same risk for stroke as those with a score of 3, which is considered a strong indication for anticoagulation.[169] In a Korean registry, patients with HCM and AF had better outcomes (both efficacy and safety) on non-vitamin K antagonist oral anticoagulants than warfarin (HR 0.47).[170] In the Korean registry, the incidence rate of AF-associated stroke was 2.94 per 100 person-years but 1.49 in patients <45 years and 1.48 if the CHA_2DS_2-VASc score was 0 or 1.[170]

The onset of AF with rapid ventricular response can be highly symptomatic in HCM and should generally be managed by beta-blockers and direct cardioversion.[171] Calcium-channel blockers and amiodarone are sometimes used, but digoxin should be avoided if obstructive disease exists.[15]

In retrospective studies, catheter-based pulmonary vein isolation was associated with favorable outcome in HCM patients with AF.[171]

5.7.2 Heart failure

Patients with HCM may deteriorate into systolic heart failure. When this stage, sometimes called end-stage disease, is reached, the obstruction diminishes and wall thinning occurs when dilatation takes place.[84,172,173] In a tertiary center, end-stage HCM patients comprise 2-3% of cohorts.[174] On an individual level, sarcomeric mutations cannot predict development although genopositive patients, as a group, have higher risk.[175]

The approach to end-stage HCM is usually the same general pharmacological treatment used for heart failure patients with reduced EF, even though no large-scale studies have been conducted specifically in the end-stage HCM population.[33,176] Cardiac resynchronization therapy (CRT) can be used to delay the worsening of heart failure, but transplantation or possibly an LV assist device (LVAD) is considered the definitive treatment in selected patients. In a cohort of transplanted HCM patients the mean age was 42 years, and 8 years elapsed from symptom onset to transplant.[173] The survival after transplant has been reported as 85% at 1 year and 75% at 5 years, which is at least as good as in other underlying cardiac diseases.[177,178] LVAD seems to offer similar results, but experience with HCM patients is limited.[179] In Scandinavia, 2.1% of cardiac transplant procedures were attributable to HCM.[180]

5.8 GENETIC TESTING

In approximately half of the HCM cases, genetic panels can reveal a disease-causing mutation.[181–183] There are numerous mutations, but the vast majority affect myosin protein genes *MYH7* and *MYBPC3*. Occasionally, other genetically determined structures of the actin-myosin coupling filaments (for example troponins or tropomyosin), are found to be the culprit. With some exceptions, the inheritance pattern is autosomal dominant.[184] In younger patients with the classical phenotype, there is a higher probability of finding a disease-causing mutation.

Genetic counselling should be an integral part of the evaluation. A detailed family history should be obtained and assessed, requiring information from multiple sources. The counselling should be performed by trained personnel in a multidisciplinary team. It is important to understand that genetic testing cannot rule out HCM. Moreover, a genetic variant of unknown significance may complicate interpretation.[15]

Typically, the proband is the person in the family who has initially come to medical attention and who takes the first step to inform the relatives. The clinician can facilitate this by providing a letter that can be distributed among the relatives. In families where a disease-causing mutation is identified, it can be used to select patients for further evaluation whereas genotype negative individuals can be discharged from further follow-up.[185] In the case of genotype negative results or if a variant of unknown significance is present in a person with HCM, first-degree adult relatives should still be evaluated by echocardiography and ECG. The penetrance is related to age and repeated assessment is therefore warranted; every 6-12 months is advised in the beginning then less often (every 2-5 years), unless symptoms develop. In children, a pediatric cardiologist should evaluate the findings and inform the patient and family about the potential consequences and timing of genetic testing.

There is a lack of long-term observational data in persons with the genotype but not the phenotype. The risk of SCD in individuals who are phenotype-negative seem to be very low, except for certain troponin mutations. Again, it is important to follow persons who have not yet developed any morphological expression of the disease and provide advice on an individual basis.[15]

A French registry of 1,432 HCM patients from 26 centers (11 expert and 15 non-expert) reported 20% were genopositive and 19% genonegative, while the remaining patients were not tested.[186] In a Finnish HCM cohort, 38% were genopositive.[187] The proportion of genopositive patients varies between centers and up to 60% have a genotype that explains the disease.[15,188,189]

Data from the Sarcomeric Human Cardiomyopathy Registry (SHaRe) showed that compared to genonegative HCM patients, genopositive patients had a doubled risk for adverse outcomes, which was highest for ventricular arrhythmias.[27] Patients with multiple pathogenic mutations have earlier penetrance and more severe disease.[190,191]

5.9 SUDDEN CARDIAC DEATH

SCD is usually defined as the "unexpected witnessed sudden death with or without VF or death within 1 h of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms"[192] There has been much attention on the dramatic events of otherwise healthy athletes who died suddenly from arrhythmia due to underlying HCM.

In 2016, Maron et al published data from the US National Registry of 842 competitive athletes who died of SCD between 1980 and 2011.[193] The most common finding was HCM (36%), which was present more often in males than females (39% vs 11%; $p<0.001$).

HCM was more common in African Americans and other minorities (42%) compared to Caucasians (31%; p<0.001).

From a study in Australia and New Zealand, Bagnall et al reported 490 cases (72% males) of SCD in patients who underwent autopsy and genetic testing.[194] The annual incidence was 1.3 per 100,000 years with 3.2 per 100,000 in the age group 31 to 35 years. Coronary artery disease (24% of cases) was the most common cause, while all inherited cardiomyopathies together accounted for 16%.

Landry et al reported 74 cardiac arrests during sports activities (16 during competitive sports, 58 during non-competitive sports) in Canada, of whom 44% survived to discharge from the hospital.[195] The incidence was 0.76 per 100,000 athlete-years in the age range 12 to 45 years. For competitive sports, 2 deaths (12.5%) were attributed to HCM compared to 6.9% in non-competitive sports. In athletes <35 years of age, structural cardiac disease and primary arrhythmias were the most common causes of cardiac arrest, but at older ages, coronary artery disease was most common of cardiac arrest.

Finocchiaro et al reported United Kingdom (UK) data on 357 SCD cases in athletes (mean age 29 years, 92% males).[196] Sudden arrhythmic death was the most common cause of death, and HCM accounted for 6% of all deaths. There was a strong association of arrhythmogenic right ventricular cardiomyopathy and LV fibrosis with exercise-induced SCD. Notably, 40% of athletes died at rest. A smaller Italian cohort of 54 fatal cases (mean age 27 years; 76% men) revealed HCM in 9.2%.[197]

Lynge et al reported 7% SCD (68% males) among all deaths in persons aged ≤35 years in a nationwide Danish study.[198] The incidence rate was doubled in men compared to women (3.6 vs 1.8 per 100,000 person-years; p<0.01).[199] Between the years 2000 and 2009 there was a decline in SCD from 3.1 per 100,000 person-years to 2.5 per 100,000 person-years. This decline was more pronounced in females. The distribution of the underlying causes remains basically unchanged. Among autopsied individuals (68%), the proportion of the combined group with definite or possible HCM was 9%. In this combined group, 58% could be classified as definite HCM. More than half (55%) reported symptoms before death, and 76% of these patients were evaluated by medical professionals.

Wisten reported Swedish forensic autopsies, drug abuse excluded, in persons 15 to 35 years between 1992 and 1999 (73 males) and the incidence of SCD was 0.9 per 100,000.[200] There was a decline in incidence among females. While no structural heart disease was seen in 21% of the population, dilated cardiomyopathy and HCM were observed in 12.2% and 10.5%, respectively.

Premortal symptoms suggesting possible cardiac disease included chest pain, dizziness, syncope, palpitations, and dyspnea. Notably, in half (50.0%) of all cases, premortal symptoms were reported. In HCM patients, three-quarters (75%) reported symptoms before death.

5.10 RISK STRATIFICATION IN HYPERTROPHIC CARDIOMYOPATHY

SCD remains a disastrous consequence of HCM. The proven efficacy of ICD therapy, documented in diverse HCM cohorts along with the technological advancement, availability, reduced costs, and remote monitoring, have provided a lifesaving tool for patients at risk. However, risk stratification continues to be a major challenge in management of HCM patients. Due to the heterogeneity of the disease, simple risk assessment is not possible. Instead, over the years, guidelines have developed that advise clinicians, but controversies about the weight of each risk factor and potential modifiers are subject to much debate. There are no randomized ICD trials of HCM patients and observational studies do not consistently report outcome and methodologies and risk assessment profiles differ among studies. These issues are further complicated by treatment options, including septum reduction therapies.

In 2003, the ACCF/AHA/ESC guidelines were published, which provided a consensus at the time.[35] In 2011, the ACCF/AHA published updated guidelines.[16] The ESC published its current guidelines in 2014, which endorsed the HCM Risk-SCD calculator.[15] This approach has been both welcomed and criticized. In 2019, a more current, updated, standpoint of ACCF/AHA guidelines was published.[142] In Table 2, the latest three of these documents are summarized.

In the 2011 ACCF guidelines[16] four risk modifiers are used:

- LVOT gradient ≥30 mmHg at rest,
- LGE on CMR,
- LV apical aneurysm,
- Genetic mutations considered as “malignant.”

In the ESC guidelines,[15] the classes of recommendation are used:

- Class I: recommended/indicated,
- Class IIa: should be considered,
- Class IIb: may be considered,
- Class III: not recommended.

The corresponding wording in the ACCF/AHA guidelines are: I: should; IIa: reasonable; IIb: may be considered; and III: no benefit/harm. The level of evidence A is based on solid evidence from randomized trials, B a single randomized trial or observational trials, C from smaller studies and expert opinion.[15,16] In fact, none of the recommendations in the ESC or the ACCF/AHA guidelines for HCM is level A.

Table 2. Summary of guidelines and expert opinion regarding risk factors for SCD.[15,16,142]

Predictor	Model	Key message
Age	ACCF/AHA	NSVT is more important in age <30 years.
	Enhanced ACCF/AHA	Age >60 years implies low risk of SCD. ICD decision on "case-by-case basis only when risk markers are perceived to carry particular weight in the individual patient."
	ESC	Lower age implies increased risk. NSVT, severe LV hypertrophy, and syncope imply higher risk in younger patients. Model used at age >16 years.
NSVT	ACCF/AHA, IIa C	May be a risk factor in the presence of other risk factor/modifier. Some value as a risk factor in long-term ECG when detected on 24-h monitoring.
	Enhanced ACCF/AHA	Risk factor when ≥3 repetitive brief episodes and/or >1 episodes with ≥10 beats at ≥130 BPM, usually over 24 to 48 hours of ambulatory ECG. More important when associated with another risk marker, particularly LGE.
	ESC	Risk factor if ≥120 BPM during <30 s, independent of frequency, rate, and duration.
Maximal wall thickness	ACCF/AHA, IIa C	Risk factor if ≥30 mm cutoff (binary).
	Enhanced ACCF/AHA	Echocardiographic or CMR measurement ≥30 mm, and borderline 28-29 mm in individual patients.
	ESC	Echocardiographic measurement. Continuous variable, non-linear, quadratic term used. Caution is urged for interpretation if ≥35 mm.
Family history of SCD	ACCF/AHA, I B	Family history of SCD or appropriate ICD therapy.
	Enhanced ACCF/AHA	Family history of SCD likely due to HCM in ≥1 first-degree or other close relatives ≤50 years.
	ESC	History of SCD in ≥1 first-degree relatives under 40 years of age or SCD in a first-degree relative with confirmed HCM at any age (antemortem or postmortem diagnosis).
Syncope	ACCF/AHA, I B	Unexplained recent syncope.
	Enhanced ACCF/AHA	Unexplained syncope, generally ≤5 years.
	ESC	Unexplained syncope. Episodes within 6 months are more predictive.
Left atrial size	ACCF/AHA	Not part of guidelines.
	Enhanced ACCF/AHA	Not part of guidelines.
	ESC	Echocardiography, parasternal axis: left atrial diameter.
LVOT obstruction	ACCF/AHA, IIb B	Marked LVOT obstruction if borderline risk, based on other risk factors.
	Enhanced ACCF/AHA	LV outflow obstruction with gradient of 50 mmHg or greater at rest is a modifier in the presence of another risk factor.
	ESC	Maximal LVOT gradient at rest and with the Valsalva maneuver.
Abnormal blood pressure response	ACCF/AHA, IIa C	Possibly when associated with another risk factor or modifier. IIb C without another risk factor/modifier.
	Enhanced ACCF/AHA	Possibly when associated with another risk factor.
	ESC	Not a HCM Risk-SCD variable. Recognized to be associated with SCD in patients ≤40 years.
LGE	ACCF/AHA, IIb B	Risk modifier if borderline risk, based on other risk factors.
	Enhanced ACCF/AHA	Fibrosis ≥15% of LV assessed by CMR, using LGE or estimated by visual inspection to be extensive and diffuse.
	ESC	Not part of guidelines.
EF<50%	ACCF/AHA, IIb C	NYHA II/III, optimal medical therapy, EF≤50%.
	Enhanced ACCF/AHA	End-stage phase, EF<50% by echocardiography or CMR, usually in severely symptomatic patients.
	ESC	Not part of guidelines.
AF	ACCF/AHA	Not part of guidelines.
	Enhanced ACCF/AHA	Not part of guidelines.
	ESC	Not part of guidelines.
Aneurysm	ACCF/AHA	Modifier that may warrant consideration.
	Enhanced ACCF/AHA	Echocardiography or CMR apical aneurysm, independent of size, with discrete, thin-walled, dyskinetic segments with contiguous apical scarring.
	ESC	Not a HCM Risk-SCD risk factor.

The ESC guidelines do not recommend (III B) an ICD in patients with a 5-year risk <4% and no proven risk factors. However, there is a statement "…flexible to account for scenarios not encompassed…" which opens up the possibility of individual judgment in special cases. The HCM Risk-SCD calculator is not validated for those who have undergone or plan to have a myectomy or ASA procedures. Genopositive patients without phenotype should not be considered for ICDs. In the 2011 ACCF/AHA guidelines, double or compound mutations were regarded as a modifier (IIb C), but ESC guidelines do not support this approach. In the 2003 guidelines, "intense (competitive) physical exertion" was listed as a possible risk factor "in individual patients," but the 2011 guidelines stated that an ICD was not to be considered as a reason to allow participation in sports competitions and the HCM Risk-SCD calculator was not appropriate for the subpopulation of competitive athletes. Moreover, electrophysiological studies should not be part of risk stratification.

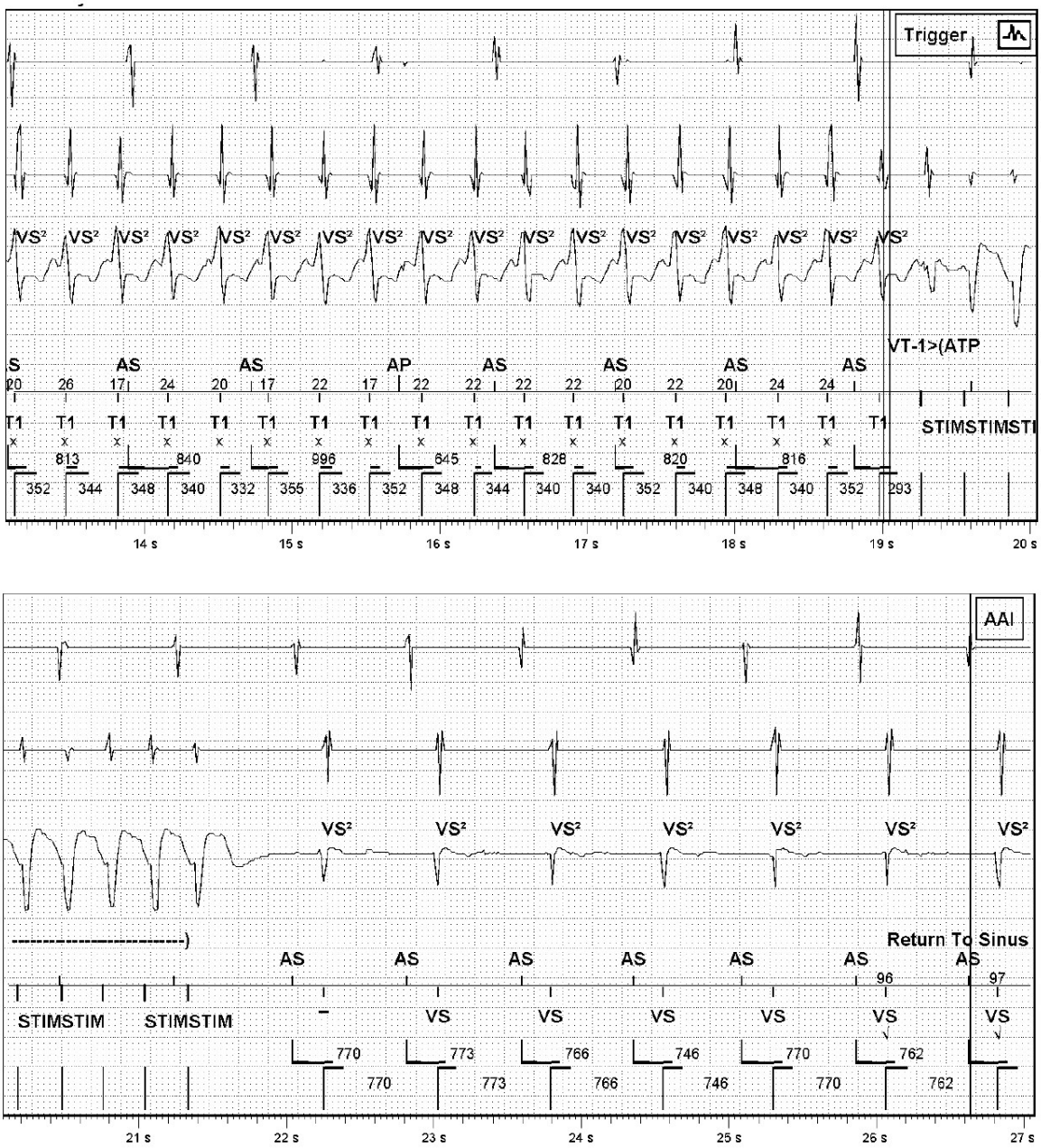
The strongest predictor of SCD is a history of cardiac arrest due to ventricular arrhythmias. Such patients have a 40% risk of another episode of SCD in five years so no further risk stratification is required.[201–203] The low survival rate for cardiac arrest (~10%) makes it appropriate to consider ICDs for primary SCD prevention.[204] The conflicts between guidelines in light of the findings presented in this paper will be extensively elaborated in the Discussion.

5.11 ICD TREATMENT

Although the decision to implant an ICD in HCM patients, especially for primary prevention, requires careful clinical judgement, the implantation itself is often technically feasible.[205] High defibrillation thresholds (DFTs) have been reported, but nowadays perioperative DFT testing is seldom performed in Sweden. Single-coil leads are often used and result in adequate safety margins and make extraction easier.[206] Single-chamber systems can be used unless there is an indication for atrial pacing. The atrial lead will allow for atrial pacing in sinus node dysfunction, AV-synchronous pacing in high degree AV-block and CRT when sinus rhythm is present. Moreover, an atrial lead can detect atrial arrhythmias and allows for possibly better discrimination between atrial and ventricular arrhythmias. The principles guiding ICD programming should be applied.

In a detailed analysis of ventricular arrhythmias in HCM patients with ICDs, monomorphic VT was the most prevalent (86%), followed by VF/ventricular flutter (9%) and polymorphic VT (5%). Ventricular arrhythmias were triggered by premature ventricular complexes in 72% of the cases. The risk was highest during midday and lowest at night.[207] The ICD delivers treatment by either antitachycardia pacing (ATP) or cardioversion. An example of successful ATP treatment is depicted in Figure 1.

Figure 1. Monomorphic VT terminated by ATP (burst) from an ICD.



AS, atrial sensing; VS, ventricular sensing

5.11.1 ICD complications

Perioperative complications with an ICD as well as short and long-term complications, may require intervention. Inappropriate shocks may occur when the ICD cannot effectively discriminate between supraventricular tachycardias and VT/VF or because of T-wave oversensing, lead dysfunction due to insulation defect or lead fracture, and oversensing of external sources.

In a review published in 2012, complications were reported that occurred in HCM patients with ICDs.[208] In the meta-analysis, the summary estimate of annualized inappropriate ICD shocks was 4.8% (95% confidence interval (CI) 2.9-6.7%). Based on 9 studies, 15% of the

patients experienced complications categorized as lead dysfunction (7%), infection (3%), lead dislodgement (3%), and others (2%), with an annual estimate of 3.4% per year. In a later review published in 2017, the annualized inappropriate ICD shock was 4.9%, lead dysfunction 1.4%, lead dislodgement 1.3%, and infection 1.1%, which confirmed previous analyses.[209]

HCM patients with ICDs are generally younger with long life expectancy. Because of the high rate of AF in HCM, thoughtful programming and pharmacological strategies to slow AV-conduction are crucial.[210] In our Swedish national cohort, the annualized event rate was 3.0% and the cumulative first inappropriate ICD shock at 1, 3, and 5 years was 7.0%, 10.8%, and 14.3%, respectively.[211] Notably, 28.2% of the patients experienced recurrent episodes of inappropriate shock. In a multivariable analysis, AF was significantly associated with inappropriate shock (HR 3.5; $p<0.001$) while sex, age, secondary indication, and device type was similar. The most common trigger for inappropriate shock was atrial arrhythmia (56.5%), defined as AF, atrial flutter or ectopic atrial tachycardia. Less common were sinus tachycardia (14.5%), lead dysfunction (14.5%), T-wave oversensing (13.0%), and myopotential oversensing (1.4%). Complications that resulted in surgical revision occurred in 28.2% of the patients during a mean follow-up of 5.4 years. In 31.5% of those patients, at least one more intervention took place, with the maximum number of repeated interventions in one patient being 6. The incidence rate for surgical revision was 8.6 per 100 patient years. The cumulative incidence was 9.1%, 15.4%, 24.3% at 1, 3, and 5 years, respectively. Most reinterventions were classified as lead-related (70.0%), the vast majority involving the ICD leads. Reinterventions were required because of device recalls, a loose setscrew, device removal, or pocket modification to ease discomfort (9.3%). When a new device system had to be implanted (7.3%), the main reason stated was infection. Interestingly, reintervention was associated with female sex (HR 1.6; $p=0.04$). Thus, device-related complications requiring surgical interventions and inappropriate shocks are not negligible in HCM patients with ICDs.

Register-based complication rates may underestimate complications and typically do not report inappropriate shocks. In a Danish nationwide validation of cardiac implantable electronic devices (pacemaker, ICD, CRT), 9.5% of the patients had a complication in the first 6 months (among new implant 9.9%, generator exchange 5.9%, upgrade/revision 14.8%, respectively).[212] Females had significantly higher risk (adjusted relative risk (RR) 1.3) for complications. Dual-chamber ICD was associated with a doubled risk compared with single-chamber devices.

5.11.2 The subcutaneous ICD

In 2009, the subcutaneous ICD (S-ICD) was approved in the European Union and in 2012 in the United States.[213] The S-ICD constitutes an important evolution in device-based rescue therapy, because the entire system is positioned outside the thoracic cavity and does not need vascular access for lead placement.[214] Transvenous leads have procedure-related complications related to vascular access, such as accidental arterial punction, pneumothorax,

and nerve plexus injury. Moreover, the lead itself can damage the tricuspid valve, provoke arrhythmias, and perforate the right ventricle. In addition, the lead may occlude the vein and thrombosis may occur. Leads are prone to insulation breakage and fracture. The system is also at risk for infection – a potentially severe complication.[215,216] This is not trivial, as approximately 20% of ICD leads fail within 10 years.[217–219] From this perspective, S-ICDs are advantageous in HCM patients, who often have long life expectancy. However, an S-ICD does not provide bradycardia pacing or ATP, but there are promising developmental efforts to combine so-called "leadless pacing" using an S-ICD with another device to offer CRT.[220] There has been a concern that QRS and T-wave oversensing may be more common in HCM. In 27 HCM patients eligible for S-ICD, 4 failed the ECG screening due to bundle branch block.[221] In the pooled data of 99 HCM patients with an S-ICD, successful DFT testing was achieved in 98.9% and complication rates of 7.3% (no lead complications) at 12-month follow-up were similar to non-HCM patients with an S-ICD.[222] The National Cardiovascular Database ICD Registry reported on the use of DFT testing and inadequate safety margins with an S-ICD, since these devices require more energy to defibrillate than conventional systems.[223] Inadequate defibrillation energy, defined as an output <65 J, occurred in 6.9% of patients with an initial implant of an S-ICD. This study evaluated S-ICD patients, not all of whom had HCM. Risk markers for high DFT were the need for ventricular pacing, hypertension, greater body surface area, elevated body mass index, and lower EF.[223] Inappropriate shocks remain a problem for both S-ICD and conventional systems with a similar incidence for both types of devices.[224]

5.12 PACEMAKER TREATMENT

According to the general guidelines, HCM patients are indicated for a bradycardia pacemaker if they have sick sinus syndrome, high-degree AV-block, or tachy-brady syndrome.[117] In addition, right-ventricular pacing from the apical region can improve symptoms. AV-sequential pacing seem to exert a negative inotropic effect and reduces hypercontractility, causes dyssynchronous septal-lateral activation, and delays septal thickening, which can reduce LVOT gradient.[225] In elderly patients and those with bradycardia pacing indication, pacing may still be an option.[226] In the early 1990s, observational studies showed promising results.[227–229] However, this could not be confirmed in subsequent randomized studies.[230–232] Perhaps optimized pacing site selection and device programming can improve outcomes. Subsequent observational studies with long-term follow-up should be taken into account for guidance for patients, especially those with ICDs.[226,233,234] In patients with sinus rhythm, this could be a reason to implant an atrial lead, i.e. select a dual-chamber system.

In a recently published paper from the largest center in Sweden, the mean age of HCM patients with bradycardia pacemakers was 71 SD 10 years, while ICD recipients were younger (53 years).[235] Among pacemaker patients, there was an equal distribution between the sexes, but among ICD recipients, the vast majority was men (70%). Of all cardiac implantable electronic devices, ICDs constituted 59%.

5.13 CARDIAC RESYNCHRONIZATION THERAPY

In a subset (5 to 7%) of HCM patients, systolic dysfunction may develop. An EF<50% is considered the onset of end-stage heart failure and some patients rapidly progress toward much lower values.[172]

CRT has been suggested for HCM patients who develop end-stage cardiomyopathy with dilatation of the LV. A small cohort (n=9) of HCM patients did not show prolonged survival with CRT.[177] In another study of HCM patients with left bundle branch block (n=20; mean age 57 years), patients were followed for 13 months, and improvement of one NYHA class was seen in 40% and EF improved (41% to 50%; p=0.009).[236] Reverse remodeling of the left atrium was seen, and the left atrial diameter decreased from 65 mm to 57 mm (p=0.005).[236]

In a US study of end-stage heart failure (defined as EF<50% and NYHA III or IV), 130 patients were included with an EF of 35 SD 14% and a QRS duration of 156 SD 17 ms; 20/130 patients underwent CRT device implant. At 1-year follow-up 14/20 improved at least one NYHA class and echocardiographic parameters showed a decrease in LV end-diastolic diameter from 54 to 51 mm (p=0.02).[237] Five of these responders deteriorated later and two of them received heart transplant.[237]

In a cohort of 61 HCM patients with end-stage heart failure, 13 underwent CRT implant (mean age 49 years).[238] Left bundle branch block was seen in all except one and mean QRS was 173 ms and mean EF was 42%. At one year, there was improvement of one NYHA class in 54% of the patients but during a mean follow-up of 5.2 years, 46% died.[238] The initial improvement was not sustained, and it has been speculated that presence of fibrosis may make CRT less efficient.[239,240]

In summary, CRT may be beneficial in some HCM patient with end-stage heart failure, but results may not be durable, many patients will deteriorate, and LVAD/heart transplant may be the better treatment option for selected cases.

5.14 PHARMACOLOGICAL TREATMENT

The use of pharmacological agents aims to reduce symptoms. Typically, it is targeted to reduce obstruction, because there is no pharmacological treatment that delays or reverses disease progression. Beta-blockade and non-dihydropyridine calcium-channel blockade seem to improve symptomatic burdens, especially exercise tolerance.[241] The negative inotropy and chronotropy reduce obstruction and improve diastolic filling of the LV. A combination of calcium-channel blocker and beta-blocker may cause bradycardia. Less frequently prescribed is disopyramide, the use of which is limited due to its anticholinergic side effects and proarrhythmia.[184,242] Unfortunately, ranolazine does not improve functional capacity in HCM.[243] Angiotensin blocking agents are currently being investigated in sarcomeric HCM. In patients with obstruction, digoxin, diuretics, and vasodilators, including phosphodieserase inhibitors, can worsen symptoms.[244]

5.15 SEPTUM REDUCTIVE TREATMENT

There are two invasive strategies, ASA or myectomy, for reducing septal thickness in order to relieve symptomatic obstruction in HCM. Historically, there have been some controversies about the preferred option, with an American preference for myectomy, but nowadays both methods are considered as safe and effective with some advantages and disadvantages that can be discussed in the individual case.[245–247]

In a systematic review from 2015, a total of 16 myectomy cohorts and 11 ASA cohorts were evaluated.[247] The median age of myectomy (n=2,791) and ASA (n=2,013) patients was 47 and 56 years, respectively. The mean follow-up in myectomy patients was 7.4 years and in ASA patients 6.2 years. Long-term mortality was similar, myectomy 1.4% per year and ASA 1.5% per year (p=0.47). The annualized rate of SCD, or appropriate ICD shock was also similar (myectomy 0.5% per year, ASA 0.4% per year). In ASA patients, a reintervention was more often required (7.7%) compared to myectomy (1.6%). Permanent pacemaker implantation was needed in 4.4% of myectomy patients and 10.0% of ASA patients. Because of improvement in periprocedural care, an analysis of procedures after 2000 showed similar periprocedural mortality; myectomy 1.1%, ASA 1.3%. The risk of stroke was similar at <1% after both ASA and myectomy (p=0.15). Thus, both myectomy and ASA are safe and effective, but there are differences in background characteristics, need for reintervention, and complications.

Septal reduction was recently evaluated in a US cohort from a single center with 10 years experience of ASA (n=99) and myectomy (n=378) patients; ASA patients were older (66 vs 53 years; p<0.001) and had a higher burden of comorbidities.[248] The periprocedural mortality was 0% in ASA and 0.8% in myectomy and permanent pacemaker implant was necessary in 6.1% of ASA patients and 5.0% of myectomy patients. Over a mean follow-up of 4.0 years, mortality was 2.0% for ASA and 2.9% for myectomy, which was not different from the US general population. The efficacy, expressed as NYHA I/II was 96% of myectomy patients and 90% for ASA. ASA is the preferred choice in the elderly and in patients with substantial comorbidity, while myectomy may be preferred in younger patients. Based on several ASA cohorts, the risk of SCD is very low.[249–252] It should be emphasized that a low volume of procedures implies a higher risk of worse outcome and therefore referral to center of excellence should encouraged.[253] In a European study of myectomy (n=347, median age 47 years), with a mean follow-up time of 5.2 years, the mean resting gradient decreased from 72 mmHg to 13 mmHg, 72% of patients improved one NYHA class, there were 5 perioperative deaths, and the 5-year survival was 97% (including perioperative mortality) in those with septal myectomy alone.[254] In total, 6.9% underwent permanent pacemaker implant due to preprocedural AV-block. Patients who underwent concomitant mitral valve procedures had worse outcomes.[254]

A more recent systematic review of myectomy confirmed low 30-day mortality (1.4%) and long-term mortality 0.7% per year in procedures after the year 2000.[255]

In a review by Fitzgerald et al, left bundle branch block was common after septal myectomy (50-100%), while right bundle branch block more often affected patients who underwent ASA (37-70%). A significant AV-block requiring a permanent pacemaker occurred in 2-3% of myectomy patients but 10-15% in ASA patients. The authors concluded that both procedures should be performed in experienced centers.[104]

5.16 LIFESTYLE MODIFICATION

HCM is indeed a heterogeneous disease with varying expression and burden of symptoms. Therefore, individualized counselling is important. Patient education is crucial in order to avoid misunderstanding and promote shared decision-making. HCM patients should refrain from competitive sports participation according to guidelines, which at the same time encourage a healthy lifestyle. Evidence-based approaches to exercise in HCM are lacking. Nevertheless, sports activities seem to be safe in athletes with ICDs and the individual's preferences may be taken into account.[109,256–258] Historical observations about SCD in HCM athletes have been updated to a more currently accepted incidence range of 0.03-0.10%, with most fatal events occurring outside sports activities.[259,260] Sweeting et al evaluated physical activity in HCM patients with and without ICDs using accelerometer data for one week.[261] From the International Physical Activity Questionnaire, mean physical activity was 239 SD 300 min/week with 51% who fulfilled physical activity guidelines and was similar between groups. Interestingly, nearly half of the participants claimed that the ICD made them more confident to exercise.

There are few data specifically on HCM, but moderate-intensity physical activity seems to improve exercise capacity.[262,263] Because obesity confers an adverse prognosis, a healthy lifestyle should be encouraged.[264] Advice on athletic activities should primarily be based on phenotype and rather than genotype only.[265]

Patients with obstructive disease may worsen from large meals, dehydration, sauna, and triggers for sympathetic autonomic nervous system activation.

The disease may influence a patient's occupational activities, life insurance, pregnancy, education, and driving, so a holistic approach is warranted for individual counselling. Fortunately, unhealthful diet, sedentary lifestyle, obesity, sleep-breathing disorder, anxiety, and depression are all amenable to treatment and should be targeted in HCM overall management.[266]

5.17 PROGNOSIS AND SEX DIFFERENCES

Contemporary treatments for HCM are reassuring for a majority of patients with regard to the risk of SCD.[267] The heterogeneous nature of the disease also translates into prognosis. In a recent meta-analysis, the pooled 1, 5, and 10-year survivals are 98%, 82%, and 75%, respectively.[268] Thus, the timely diagnostic evaluation and treatment is warranted in order to recommend interventions to improve survival rates of HCM patients.

A higher proportion of men (55-65%) has been reported in numerous HCM cohorts.[269] Female hearts are generally smaller, even when adjusted for body surface area, which may affect application of diagnostic criteria based on wall thickness. Females are often older at initial evaluation and express more symptomatic burden and possibly worse survival. The reason for this difference is not fully understood and it has been speculated based on animal models that estrogen exerts cardioprotective effects.[270,271] In a large tertiary US cohort of HCM patients (n=2,123), all-cause mortality was higher in women (9% vs 5%, p=0.001) after a mean follow-up of 3.9 years; however, specficially HCM-related mortality rates were similar and after age adjustment, there was no significant difference between the sexes in all-cause mortality.[272] Notably, the age at first appropriate ICD therapy was similar, albeit women presented with HCM 6 years later. At presentation, more women than men had symptomatic HCM categorized as NYHA II-IV (73% of women vs 53% of men), more often developed drug-refractory heart failure, and were diagnosed a mean of 6 years later. In another large US cohort similar findings was seen with worse survival of women in uni- and multivariable analysis (HR 1.17; p<0.001) and using propensity score matching.[273] In a Dutch cohort of 1,007 HCM patients (62% males), females had a higher age at presentation (56 vs 49 years; p<0.001), more LVOT obstruction (37% vs 27%; p<0.001), and more women than men had a low EF (17% vs 11%; p=0.01), but all-cause mortality and cardiovascular mortality were not significantly different at 6.8 years of follow-up.[274] Recently in a study of 4,893 HCM patients from several European tertiary centers (64% males, 49.2 years at first evaluation), the standardized mortality rate (SMR) was 2.0 (95% CI 1.5-2.6), with higher SMR for women than men (2.7 vs 1.7; p<0.001).[275]

6 RATIONALE OF THE THESIS

HCM is a heterogeneous disease with diverse clinical manifestations. Unfortunately, SCD is a well-known outcome of HCM and risk stratification is both challenging and controversial. ICD is an established treatment in the prevention of SCD but the determination of appropriate candidates for device-based treatment among unselected HCM patients is largely unknown. In this regard, the Swedish Pacemaker and ICD Registry provides a valuable resource to identify HCM patients who received an ICD. This nationwide cohort of unselected patients and subsequent validation of medical records from all relevant health care providers constitutes a unique tool for studying the efficacy and association of risk factors without tertiary center bias. The mortality and causes of death of HCM patients with ICD have been largely unknown in unselected patients. Swedish registries and population statistics also provide data for age, sex, and calendaric match compared to the general population. The benefits of ICDs need to be elucidated as part of overall survival rates in long-term studies.

Health-related quality of life (HRQL) is an essential part of patient-related outcome measurements and should be assessed in specific groups, including HCM patients with ICDs, rather than generalized from other patient groups. HCM patients are younger, have different disease manifestations, and have a longer life expectancy than general cardiomyopathy patients. Besides quantitative assessment of HRQL, a holistic view of patients with HCM using a qualitative approach may provide a basis for a deeper understanding from a patient perspective.

Finally, starting with confirmatory analyses of HCM patients with ICDs, an explorative approach using PET technology was performed in order to potentially refine current understanding and risk stratification. Hence, the rationale for this thesis is to elucidate different aspects of ICD treatment in HCM.

7 AIMS

7.1 GENERAL AIM

The general aim of this thesis was to elucidate different aspects of ICD treatment in patients with HCM. This includes: characterization of current ICD use among HCM patients with a focus on risk stratification for ventricular arrhythmias requiring ICD therapy, mortality, and cause of death; assessment of HRQL; qualitative aspects of living with an ICD; and characterization using PET and exploration of risk markers for sudden death.

7.2 SPECIFIC AIMS

The specific aims of each paper were:

I. To describe the characteristics of HCM patients with ICDs in Sweden based on the nationwide cohort and study associations of risk markers and appropriate ICD therapy during long-term follow-up.

II. To assess causes of death, including contributing causes, of HCM patients with ICDs in a nationwide cohort, establish predictors of death, and compare mortality to the matched Swedish general population.

III. To examine generic HRQL among ICD patients with HCM, including comparisons of sub-groups, and compare it to age- and sex-matched general Swedish norms.

IV. To qualitatively explore the individual, patient-reported, experience of living with HCM and an ICD.

V. To describe HCM patients with ICDs using PET parameters that reflect MBF at rest/stress, oxidative metabolism, and innervation, and explore associations of HCM with the presence of NSVT at device interrogation.

8 MATERIALS AND METHODS

This section covers study design, setting, participants, variables, data sources/measurements, bias, study size, statistical methods, including the handling of quantitative variables using the structure of strengthening the reporting of observational studies in epidemiology (STROBE) statement.[276] For the qualitative study, standards for reporting qualitative research (SRQR) applies, which specifically addresses the qualitative approach and research paradigm, researcher characteristics and reflexivity, context, sampling strategy, data collection and processing, data analyses, and trustworthiness.[277]

8.1 STUDY DESIGN

Papers I and II were quantitative longitudinal observational studies using a retrospective approach.

Paper III was a quantitative cross-sectional observational study using a questionnaire.

Paper IV was a qualitative study using a hermeneutic approach and latent content analyses.

Paper V was a quantitative observational study using both a prospective and retrospective approach.

8.2 SETTING

All participants in the studies and comparison groups, i.e. population norms and demographic data, were citizens of Sweden. Their ethnic origins were unknown. Paper I, II, and III were based on the nationwide Swedish Pacemaker and ICD Registry. In Paper IV, the interviews were conducted with patients living in Region Gävleborg and Region Västerbotten. Paper IV, part of the PET-project, recruited patients from four regions: Gävleborg, Dalarna, Västerbotten, and Värmland. A map of Sweden (Figure 2) shows the regions and cities relevant for Paper IV and V.

8.3 PARTICIPANTS

8.3.1 Paper I, II, and III: recruitment and data collection

All patients with an ICD due to HCM were identified by the Swedish Pacemaker and ICD Registry in November 2012. It included every patient with this combination who ever had an ICD, including CRT, with the underlying etiology classified as HCM. Patients who were younger than 18 years at the time for data extraction were removed from the dataset. All patients who were alive were contacted for consent to retrieve data from their medical records for data collection, including validation of the underlying diagnosis. They were contacted by regular mail, including telephone reminders if there was no response by mail. We used the Swedish Tax Authority Census Bureu online, which is frequently updated, for information whether the patient was alive before contact was attempted. Patients were asked to list all relevant outpatient visits and inpatient care at hospitals. The same information was retrieved from the National Inpatient and Outpatient Register, but patients were also asked to cover for

possible delay in registration. The same data collection, including retrieval of medical records, was obtained for deceased patients based on ethical approval. In total, 12 major sites and regional archives were visited for data collection to review medical records, including paper charts, microfilms, and scanned data. The clinics with only a few relevant records were asked to send copies by mail. Patients with an unequivocal diagnosis of HCM were included and phenocopies were excluded. It was sometimes challenging to validate HCM diagnoses, and all patients who were excluded or for whom there was diagnostic uncertainty were discussed in detail by the two cardiologists, Magnusson and Mörner.

The survey was sent by regular mail including a postage-paid envelope for return to the investigators. After three mail reminders, a phone call was made to remind patients who had not returned the survey. When the survey was returned, the patient was contacted if there were missing data in order to obtain complete answers for each item.

Figure 2. Map of Sweden with marked regions relevant for Paper IV and V. Map modified from Statistics Sweden, with permission.[278]

8.3.2 Paper IV: recruitment and data collection

This study was based on interviews of identified HCM patients from the Swedish Pacemaker and ICD Registry who were living in the Region Gävleborg or Region Västerbotten at the time. All patients were adults, >18 years of age, and had an implant of a transvenous ICD at least two years ago to reflect a more chronic state. To explore several aspects of HCM patients with ICDs, a maximum sampling of variables was the objective. This sampling strategy including variables such as age, sex, time since diagnosis, both primary and secondary indications for ICDs, history of appropriate ICD therapy, but also inappropriate shock complications. The candidates were contacted by phone and scheduled for an appointment with the interviewer. The patient could choose if the interview would take place at the research facility, clinic, or as a home visit.

8.3.3 Paper V: recruitment and data collection

Potentially eligible candidates for participation were identified by an updated search in the Swedish Pacemaker and ICD Registry based on their postal address described in the section above. Medical records were scrutinized in order to validate the diagnosis of HCM, but phenocopies were excluded. Patients with a history of decompensated systolic heart failure or CRT were likewise excluded, as they were considered to represent end-stage heart failure at the time of inclusion. Patients who had epicardial coronary artery disease with lumen narrowing of 50% or more at coronary angiography or CT angiography for any clinical evaluation outside the study protocol were excluded. Because PET examinations were part of the study, patients who were pregnant or had a history of claustrophobia were deemed ineligible and thus excluded. As adenosine was part of the exam using ^{15}O-water to achieve physiological stress, a known allergic response or signs of intolerability to adenosine, hypotension (systolic pressure 100 mmHg), increased intracranial pressure, hypovolemia, and concomitant dipyramidole treatment were considered as contraindications.

8.4 VARIABLES

The definitions of the clinical variables are listed below. They agree with widely used definitions in the scientific literature but also reflect areas where there are no commonly agreed standards.

8.4.1 Primary and secondary prevention

Prevention of SCD by ICDs is divided into two categories. Secondary prevention refers to implantation in survivors of cardiac arrest or sustained VT with hemodynamic compromise. Primary prevention, on the other hand, refers to patients without verified sustained VT/VF and is based on evaluation of risk factors. This distinction adheres to the commonly used strategy throughout risk stratification regarding SCD.[32–34]

8.4.2 Risk factors

The risk factors in the Papers are described below.

● Family history of SCD

Our studies used a family history of SCD, or the surrogate appropriate ICD therapy, in a first-degree relative, i.e. parent, child, or sibling, before the age of 55 years and assumed to be due to HCM. This was not prespecified before data collection but turned out to reflect the practice of clinicians who use it as risk factor in the decision-making whether to implant an ICD. The statement in the ESC definition is "...one or more first-degree relatives have died suddenly aged <40 years with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM."[15] The ACCF/AHA guidelines has a definition without any age cut-off: "sudden death presumably caused by HCM in one or more first-degree relatives."[16] Although not a formal guidelines endorsed by an organization, a recent update modified the statement: "Family history of SCD judged to be definitively or likely caused by HCM in one or more first-degree or other close relatives 50 years or younger."[142] See Table 3.

● Unexplained syncope

In Papers I-III, syncope (but not pre-syncope or near-syncope) deemed unexplained by the physician who decided about ICD implantation was considered a risk factor.

● NSVT

A run of ventricular beats, ≥3 in a row at a rate of 150 BPM (400 ms) with a duration of <30 s was considered NSVT in risk stratification in Paper I-III.

● Maximal myocardial wall thickness

The maximal wall thickness of any segment of the entire LV either on echocardiogram or CMR. If there was a discrepancy between imaging methods, typically the higest value was used unless it was deemed invalid from the reasoning in the medical records.

● Abnormal blood pressure response at exercise

Although several definitions of this variable exist, we adhered to the inability to increase blood pressure by ≥20 mmHg or a hypotensive response on exercise test. In Sweden, ergometer bicycle tests are almost always used for this assessment.

● Atrial fibrillation

According to the generally accepted definition of AF, only episodes of ≥30 s was considered.[167] We included all kinds of reliable monitoring devices for AF in addition to the standard 12-lead ECG, i.e., previous pacemaker EGM, insertable cardiac monitor (formerly known as an implantable loop recorder), ambulatory ECG like 24-48 h ECG, or R-test. Thumb-ECG was not used in any case to assess AF.

● Systolic heart failure

Patients often had several echocardiography evaluations. If the EF was <50%, it was deemed a risk marker. This cut-off also harmonizes with current guidelines. CMR was used for EF assessment only if echocardiographic imaging quality was poor.

● Outcome

Appropriate ICD therapy was defined as the combined endpoint of cardioversion, i.e. "shock," and ATP, i.e. burst or ramp. Multiple treatments of different episodes VT/VF within 24 hours were counted as one event. In Paper V, the rate of 160 BPM was used because of uniform assessment of NSVT among ICDs at interrogation. The composite outcome was sustained ventricular arrhythmias consisting of VT with a duration of at least 30 s, cardiac arrest, or appropriate ICD therapy.

● PET-specific variables

In Paper V, several PET variables were used. These PET variables are specified in section 8.5.3.3 along with theoretical background; echocardiographic variables are described in section 8.5.4.

Table 3. Summary of definitions in the largest ICD studies (n >100) of HCM patients.

First author	Year	Size (n)	PP (n)	Family history of SCD	NSVT
Begley[279]	2003	132	85	≥2 sudden death in first-degree relatives <55 years.	NSVT on Holter.
Maron[203]	2007	506	383	SCD judged to be definitively or likely caused by HCM in ≥1 first-degree or other close relatives ≤50 years.	≥3 repetitive brief episodes each consisting of ≥3 or more beats and/or 1 or more prolonged episodes (≥10) at ≥130 BPM, usually over 24 to 48 hours of ambulatory ECG.
Cuoco[250]	2008	123	100	SCD in a first-degree relative.	Not used as risk factor.
Syska[280]	2010	104	78	HCM-related SCD ≥1 first-degree relatives, aged <40 years.	≥3 beats at heart rate of ≥100 BPM on 24-hour Holter.
O'Mahony[281]	2012	334	307	SCD attributed to HCM in ≥1 first-degree relatives.	NSVT on Holter monitoring.
Vriesendorp[282]	2013	134	93	≥1 HCM-related SCD in close relatives.	NSVT on Holter monitoring.
Magnusson[283]	2016	321	237	SCD (or appropriate ICD therapy) of ≥1 first-degree relative assumed to be due to HCM.	≥3 beats at heart rate of ≥150 BPM on any type of ECG.
Thavikulwat[284]	2016	135	125	SCD in a first-degree relative.	≥3 beats ≥100 BPM with a duration ≤30 s.
Wang[285]	2017	160	155	According to ACCF 2011 guidelines.	≥3 consecutive beats at a rate of >120 BPM, 24- or 48-hour ambulatory ECG.

PP, primary prevention

8.5 DATA SOURCES

This thesis is based on studies in which patients with HCM were primarily identified using the Swedish Pacemaker and ICD Registry in conjunction with the National Inpatient and Outpatient Register. To validate registry data, all relevant medical records were scrutinized. In Paper II, demographic data from Statistics Sweden were used.[286] In Paper III, a national Swedish population norm was used for comparisons.

Sweden has a history of registration of personal data, which dates back to 1686 when it became compulsory for the Swedish church to administer parish registers.[287] This facilitated civic planning, including military recruitment. In 1749, Tabellverket was founded to coordinate local parish registers, which was subsequently taken over by Statistics Sweden in 1858.[288] Since 1947, each Swedish citizen has a unique personal code based on date of birth and four more digits. This provides a framework for register research.[289] The Cause of Death Register started in 1961 and the National Patient Register began in 1964 and became mandatory in 1987.[76,290] Today, there are more than 100 national health registries, classified as quality registers, in Sweden.[291] This provides investigators with robust and complete data that few other nations can match.

Many research projects in Sweden are based on registries, often linked to each other either as epidemiological studies or a source to identify patients for recruitment to studies.

8.5.1 Swedish Pacemaker and ICD Registry

The nationwide Swedish Pacemaker and ICD Registry has an almost complete coverage of all implants throughout the country.[292,293] We retrieved data on all patients who had an ICD due to HCM since the start. These data were then merged with data from the National Patient Register to identify all relevant inpatient and outpatient care for each patient.

8.5.2 SF-36

The 36-item Short Form (SF-36) questionnaire is used to assess general health status and is designed to assess generic health concepts applied in a broad range of age groups, diseases, and interventions across different cultural settings.[294,295] This HRQL instrument, which is often attributed the term “multidimensional”, was developed in the Medical Outcome Study and has been frequently used in studies since the start in the 1990s.[296] The extensive implementation of HRQL questionnaires in research is based on the assumption that they fulfill psychometric prerequisites across a wide range of patient groups and general populations. The researchers set up data quality assurance, properties of test scaling, and measures of internal consistency for all domains in the validation work Medical Outcomes Study. They performed these analyses for thousands of patients, and reproduced them in subgroups with various background with regard to demography, underlying diagnoses, and degree of severity of diseases. It was concluded that the response rate ranged from 88% to 95% for each question; notably a bit lower in the elderly, patients with lower educational levels, and patients with socioeconomic burdens. In 96% of the cases, there was enough data

to calculate a reliable score for each domain. Moreover, 97% of all individual questionnaires passed the test with regard to internal item consistency and item-discrimination validity was 92%. Measurements of reliability coefficients had a median of 0.85, although it varied from 0.65 to 0.94. The floor-ceiling properties were examined. Overall, the floor-ceiling effects were small, but both role disability domains showed floor effects, while ceiling effects were noted in both disability scales and the domain SF. Thus, SF-36 rely on a solid base of validation work, at least for research purposes on a group level. It is notable that SF-36 is a generic instrument for measurement of HRQL, which is not designed for disease-specific research questions. Nevertheless, it constitutes a platform for estimation of generic HRQL.[296]

The standard questionnaire contains 36 questions but there are simpler versions using 8 and 12 questions. In the full version, physical health is divided into Physical functioning (10 items), Role physical (4 items), Bodily pain (2 items), and General health (5 items).[296] The mental health section includes Vitality (4 items), Social functioning (2 items), Role emotional (3 items), and Mental health (5 items). In addition, there is question about general health transition based on the general health today compared to a year ago and another global question about the perception of current health status. McHorney examined discriminant validity, scale homogeneity and reliability using Cronbach´s alpha for internal validity, a kind of intraclass correlation.[296] The precision of the questions is balanced, typically 3-5 of alternatives is enough. Otherwise, it can lead to difficulties distinguishing the different categories of answers from each other. Moreover, a large number of items may lead to unreliability in validation work using repeated testing because answers tend to be inconsistent. If all subjects answer low or high, the test can be said to have floor-ceiling effects. The sensibility across different groups are part of validation work.

The extended applicability of the SF-36 Health Survey into an international context was endorsed by the International Quality of Life Assessment (IQOLA) Project. This adoption by IQOLA incorporated a standardized translation into several languages, including Swedish. The questionnaire was administered through regular mail with a proportion of 68% who responded during 1991-92. The 8,930 respondents, 51.8% females, aged 15-93 years (mean 42.7 years) varied by marital status, education, socio-economic status, and geographical area.[297] The same psychometric methods used in the validation work in the US were applied. More than 90% had complete answers, missing data were more common in the elderly >75 years. Item consistency was excellent and reliability estimates above 0.80 (highest for Bodily pain, above 0.90) and most physical component scales. In summary, this validation work of the Swedish version provided a norm population which allowed age- and sex-matched comparison with our cohort. We decided to use this version rather than version 2 for the purpose of comparison with norm population.[298]

8.5.3 PET technology

PET is a noninvasive imaging modality that depicts the distribution of a radionuclide-labeled tracer that is injected in a vessel.[299] This technology relies on radionuclide decay by the elementary particle positron, an antimatter with opposite charge, but the same mass as an

electron. The positron releases from the nucleus and collides with electrons; kinetic energy is lost and converted to gamma-ray photons. Based on the formula $E=mc^2$, the energy is conserved and the two gamma rays proceed in opposite directions. These rays can be detected and their coordinates refer to the point where the original decay of the positron happened.[300] From these coordinates, geometrical volumes of interest are constructed. The spatial resolution of modern PET technology is 4 mm. The detectors are optimized for the amount of energy generated by the gamma rays (511 keV). The scanner consists of thousands of crystals in a cylindrical form of rings.[301]

Besides high imaging quality, quantitative accuracy is important in cardiac PET to assess distinct anatomical measurements. To achieve accurate measurements, calibrations, attenuation, and scatter corrections are needed for reconstructions. Even though standardized protocols have been developed, the optimal imaging parameters vary among detectors. ECG-gated imaging requires more total counts because of the division of counts over multiple frames; larger doses and longer scan times may be required. PET technology is integrated into CT imaging. Moreover, software application is used to yield final imaging results, including quantification.

8.5.3.1 PET-tracers

PET provides quantitative assessment of MBF in absolute values rather than qualitative, relative findings as in single-photon emission computed tomography imaging.[302] The spatial resolution of modern PET is far better than SPECT, which allows for regional differentiation. This makes this type of imaging advantageous in HCM, because HCM is a heterogeneous disease with regional variations in phenotype. The most widely used tracers for quantification of MBF are ^{15}O-water, ^{13}N-ammonium, and ^{82}Rubidium. ^{15}O-water is an ideal tracer because of free diffusion, metabolic inertness with full complete extraction from the myocardium independent of flow velocity.[303] In the normal heart ^{15}O-water and ^{13}N-ammonium both show high accuracy.[304,305] In the presence of scar tissue and altered metabolism, ^{13}N-ammonium and ^{82}Rubidium are less reliable because of the discrepancy in kinetic modeling due to changes in myocardial tracer uptake.[306] However, many tracers, including those used in our study, require a cyclotron in close proximity to the PET scanner which limits availability.

The tracer ^{11}C-acetate is the most commonly used method for accurate noninvasive assessment of MVO_2. The 2-carbon-chain free fatty acid of acetyl-CoA is metabolized through the tricarboxylic acid cycle. The turnover of ^{11}C-acetate based on the coupling of the tricarboxylic acid cycle and oxidative phosphorylation corresponds to the oxidative metabolism expressed as MVO_2. The bi-exponential curve fitting, or a simplified method from the directly linear portion of the cardiac activity curve over time, is used to measure the kinetics of the tracer in the heart, the rate constant k_1, which represents the myocardial clearance of ^{11}C-activity ($^{11}CO_2$) and correlates closely with MVO_2 under diverse conditions.[147,307–309]

PET also provides an assessment of myocardial autonomic innervation.[310,311] The tracers for presynaptic catecholamine innervation are either biological catecholamines or analogs. The former follow metabolic pathways, while the latter may resist certain pathways, for example in the vesicular storage inside the nerve terminal part or presynaptic uptake transporters. The biological target of ^{11}C-*meta*-hydroxyephedrine (^{11}C-HED) is presynaptic catecholamine uptake.[312,313] This tracer is a norepinephrine analog and is probably the most commonly applied PET tracer for sympathetic neuronal imaging.[311,312] Like norepinephrine, via the uptake-1 mechanisms, plasma HED is transported into the terminal ends in the sympathetic nervous system and is inert to enzyme activity and remains in the myocardium for 30 minutes. Thus, the retention of HED is highly dependent on reuptake by the norepinephrine transporter.[314,315] Autonomic nervous system dysfunction has been elucidated in ischemic cardiomyopathy and dilated cardiomyopathy with marked reduction in retention.[314,316,317]

8.5.3.2 PET-protocol

The PET scans were performed at Uppsala University Hospital, Sweden. The scanners were two GE Discovery MI (GE Healthcare, Waukesha, WI) which made parallel patient exams possible. The procedures started in the morning after fasting overnight and patients refrained from caffeine and tobacco use 24 hours before the first scan. Due to the half-time of the tracers, the scans were conducted in the following order: ^{15}O-water at rest and then at adenosine stress under supervision of a cardiologist, ^{11}C-acetate and finally ^{11}C-HED. The isotopes were produced by a cyclotron. In order to achieve an attenuation correction, a low-dose, respiration-averaged CT was performed before the tracer was injected. A 400 MBq of ^{15}O-water was given intravenously using an automated injector as a fast bolus and a 6-minute emission scan was started. The procedure was repeated at adenosine infusion. The data were reconstructed into 22 frames using a standard protocol. Because of the half-time (2.0 minutes) of ^{15}O-water, the next tracer started approximately 30 minutes after the first tracer was finished. The labelled ^{11}C-acetate (433 SD 84 MBq) was injected by the same technique and a 27 min scan was started. After these exams, the patient left the machine and had a rest while the tracer decayed. In the afternoon, the final exam took place. A second CT was thus required before the ^{11}C-HED scan. Again, after tracer-injection (385 SD 70 MBq) a dynamic list mode emission scan was simultaneously started, this time for 27 minutes. The data were reconstructed using standard protocols including, 22 (^{15}O-water), 31 (^{11}C-acetate), and 31 (^{11}C-HED) frames, respectively.

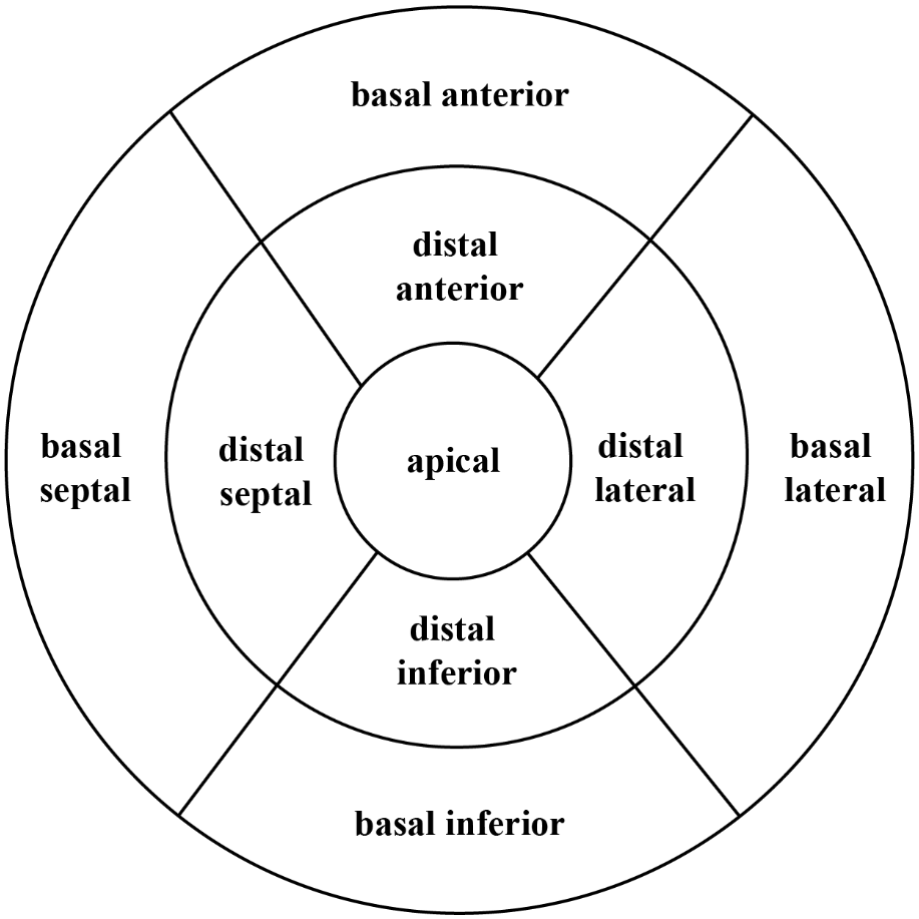
8.5.3.3 Data analyses

All PET scans were analyzed using the aQuant software.[318] The arterial and right-ventricular concentrations were automatically obtained using cluster analysis.[318,319] The standardized myocardial segmentation and nomenclature for tomographic imaging of the LV wall based on the 17-segment model was used (Figure 3).[320]

The 5 regions were categorized as anterior, septal, inferior, lateral, and apex. The analysis and calculation of the PET-variables were performed by two expert physicists who were blinded

to the outcome. Their inter-observer repeatability was excellent, i.e. intraclass correlation was >0.98 for all parameters.

Figure 3. The 17-segment model of the left ventricle.[320]



The tracer ^{15}O-water was quantified using the standard one tissue compartment model.[321] The MBF at rest was adjusted for rate pressure product. Based on a previously published method for heterogeneity index, this was derived by dividing the maximum MBF by the lowest MBF.[322] The transmural perfusion gradient (TPG) was defined as the quotient of the endocardial/epicardial MBF by splitting the 17 segments each in equal halves based on their distance to the LV cavity. To estimate the so-called defect size, the total volume of the LV with MBF × perfusable tissue index below 50% of maximum for rest and MBF <69% of maximum for stress was calculated.

The mathematical modeling of ^{11}C-acetate likewise used a one tissue compartment model, but with corrections for blood volume fraction and spillover from blood.[323] The input functions were calculated by applying the average plasma metabolite correction.[308] The MVO_2 was derived from the clearance rate (k_2) and conversion factors.[308] The MEE is the proportion of MVO_2 that is actually used in cardiac work, thus it was possible to calculate how efficiently the myocardium could handle energy; the calculations for forward cardiac output and LV mass could be derived from PET images.[323] The transmural gradient for

MVO_2 was calculated the same way as MBF. The end-diastolic volume, end-systolic volume, and stroke volume were calculated and adjusted for body surface area using ECG-gated images.[308] The EF of the LV was calculated as stroke volume/end-diastolic volume.

The kinetics of the ^{11}C-HED can be described using a one-tissue-compartment model, corrected for spill-over from both the right and left ventricle, and with average plasma metabolite correction.[324] The basis for this model is the rate of ^{11}C-HED transfer from blood to myocardium and the opposite flow, i.e. the transfer from the myocardium to the blood. The parameter K_1 represents the influx rate, while the k_2 represents transfer from the myocardium to the blood or the clearance rate. The ratio K_1/k_2 (uptake rate/clearance rate) is the volume of distribution (V_T) and represents the net uptake when the equilibrium between tissue and blood has been reached. K_1 is dependent on the extraction fraction of C-HED and can be used as an index of MBF at rest.[325] Retention index (RI) was calculated as the quotient of the late uptake activity and the integral of the non-metabolite corrected arterial input function. The defect size was defined as the total volume of the LV with RI <75% of maximum. Using the principles for calculation transmural gradient mentioned above, RI, V_T, and clearance rate were calculated.

8.5.4 Echocardiography

Echocardiography is a cornerstone in evaluation of HCM patients. Papers I-IV used retrospective data from medical records. These data were used in part for validation of diagnosis, but they were also used for risk assessment. Due to the retrospective nature of data without a standardized protocol for prospective evaluation, several variables were missing or not robust. For example, left atrial size was often not included in the echocardiographic evaluation and the LVOT gradient assessment was often unreliable.

In Paper V, echocardiography was part of the research protocol with predefined variables. Two experienced physicians, blinded to other patient data, independently evaluated all echocardiograms. The objective of this study was to verify the HCM diagnoses of the patients and compare their PET data. In Paper V, it was possible to report the following echocardiography variables: left atrial diameter (mm), left atrial size/body surface area (ml/m^2), LV diameter, diastole (mm), LV diameter, systole (mm), LVOT gradient (mmHg), LV outflow obstruction ≥30 mmHg at rest or with the Valsalva maneuver, EF (%), maximal wall thickness (mm), tricuspid annular plane systolic excursion (mm), and systolic pulmonary artery pressure (mmHg).

8.6 STUDY SIZE

Papers I-III were based on the Swedish Pacemaker and ICD Registry with national coverage. Efforts were made to gather complete data. Compared to many international cohorts, a large database was achieved based on all available data. Nevertheless, subgroup analyses are prone to both type I and type II errors. Paper IV was based on 26 conducted interviews, which is rather large given the qualitative nature of data from patients with long longitudinal narratives of a complex disease. Paper V was based on 25 HCM patients with ICDs; a formal power

calculation was deemed difficult because of uncertainty of outcome estimates in the design phase. Considering the multiple tracers and extensive protocol for selected patients with HCM and ICDs, the number of patients included was comparatively large. PET is also costly and requires considerable resources, which further limited sample size.

8.7 STATISTICAL METHODS

Descriptive statistics is the process of quantitatively describing or summarizing features of a dataset.[326] In inferential statistics, it is assumed that the dataset is sampled from a larger population. The properties of the population are inferred by hypothesis testing and derived estimates.

8.7.1 Descriptive data

Frequencies were described as numbers (n) and ratios (i.e. proportions) as percentages. When a ratio is related to time it was described as a rate. Dichotomized data were used to describe variables with binary outcome but also if a variable had certain cut-offs for definitions or decision-making. The arithmetic mean is the sum of numeric values divided by the total size of sample. The mean uses all the data but outliers may heavily influence this value. If the data were deemed skewed, then the median rather than the mean was chosen for a central measurement. The median was occasionally used, and it reflects the middle value of ordered observations. The median is the 50th percentile but other percentiles could be used to describe the dispersion of the data. Typically, the 25th and the 75th percentile were reported and the interquartile range. The full variability of the dataset was presented as the lowest and highest value, i.e. the range.

The standard deviation and its CI were used to estimate the dispersion of the assumed true parameter within a proposed range. The width of the CI is affected by the data variability, the sample size, and the confidence level. In the analyses, a confidence level of 95% was used by convention.

8.7.2 Statistical models

The distribution of data was categorized as binomial, normal or Poisson. A scatter-plot or histogram was typically used to determine the distribution of the dataset.

8.7.2.1 Comparison of two independent groups

Fisher's exact test, or the chi-square test, was used to compare categorical data based on a contingency table.

The *t*-test was chosen if the data were continuous and normally distributed with similar standard deviations.

In the case of a non-normal data distribution, the Mann-Whitney *U* test was used. It requires the data to be ordinal, i.e. they could be ranked in relation to each other. The null hypothesis

H_0 assumes that both populations are equal, whereas the alternate hypothesis H_1 assumes the distributions are not equal.[327,328]

8.7.2.2 Comparisons using time-related data

A Kaplan-Meier estimate was used to model time to event data, including graphical presentation. The start of time was initial ICD implantation. In Paper I for risk marker analysis, follow-up time was censored when it was no longer possible for the patient to receive appropriate ICD therapy (death, device explant, downgrade to pacemaker, loss to follow-up). In Paper II, data were censored for death. In patients who experienced an appropriate ICD therapy, the time to first event was used. The Kaplan-Meier estimate is non-parametric test based on the survival function using a product-limit function.[328,329]

$$\widehat{S}(t) = \prod_{i:\, t_i \leq t} \left(1 - \frac{d_i}{n_i}\right),$$

In this equation, t_i is the time when at least one event occurred, d_i the number of events (e.g., appropriate ICD therapy or deaths) that happened at time t_i, and the patients known to have not had an event up to time t_i. In the curve, the x-axis denotes time and the y-axis cumulative survival/freedom from event. In the graphical presentation, each horizontal line is the time interval and a vertical line denotes that an event did occur. Below the x-axis, the number of patients at risk was presented. In Paper II, two curves were outlined to represent the 95% CI. When two groups were compared, different lines and dots, in addition to color, was used. The significance between groups was calculated using Mantel-Cox p-values.

The Cox proportional hazard model was used to study the association of covariates with regard to time, expressed as hazard ratios (HRs). It is used for both binary and continuous predictors. In univariable analyses, the predefined predictors were used. The multivariable analyses were based on the rationale for including a predictor rather than backward or forward elimination. There is a general assumption that for every variable included, a minimum of ten events is advisable to ensure regression coefficients with acceptable precision.

Incidence rate was defined as all events that occurred during the total follow-up period. This implied that multiple events were counted several times, in contrast to Kaplan-Meier estimate where only the first event was counted. The annualized rate was calculated as the proportion of patients who experienced at least one event as the numerator and the sum of follow-up time of right censoring as the denominator. Cumulative incidence was the proportion who reached the outcome at a certain time, often expressed as 1, 3, and 5-year incidences.

In Paper II, crude mortality of the whole cohort was calculated with the number of deaths as the numerator and patient-years of follow-up since first ICD implant as the denominator. This study followed patients even if they were downgraded to a pacemaker, underwent heart transplant, or the device was inactivated or explanted for another reason. The SMR was defined as the observed number of deaths in the cohort divided by the expected number of

deaths based on Swedish data from the general population. The population data was controlled for age, calendar period as the mortality changed in the population, and sex. The 95% CI for the SMR was based on the assumption of Poisson distribution.

8.7.3 Significance level

Significance level, denoted by alpha, is the probability of rejecting H_0; when the p-value from a test is less than the significance level it can be concluded that this difference is true.[330] The predetermined alpha level is typically set to 5%. With two-sided distribution, an alpha level of 2.5% for each side was applied.

Type I error is the rejection of a true H_0 which implies a false-positive finding. On the other hand, the non-rejection of a false H_0 leads to false-negative conclusion known as type II error.[328] The probability of type II error is denoted beta. The conventional value beta=0.2 was used.

We used a p-value of 0.05 for confirmatory approaches and 0.10 for explorative approaches. Small cohorts and subgroup analyses are prone to both type I and type II errors, so in these cases p-values in the range of 0.05 to 0.10 were described as tendencies.

8.7.4 Effect size

In Paper III on HRQL, the magnitude of a significant difference between groups was expressed as an effect size (ES). The ES of a difference was estimated by calculating the mean difference, and then dividing it by the pooled standard deviation using Cohen's *d*.[331] We used standard criteria in our descriptions of the ES:

- trivial (<0.20),
- small (0.20-0.49),
- moderate (0.50-0.79), and
- large (≥0.80).[331]

8.7.5 Computer software

The databases were stored as files in Excel 2010 (Microsoft Corporation, Redmond, WA). It was then imported to other statistical software. For statistical analyses and graphical presentations, we used Excel 2010 (Microsoft Corporation, Redmond, WA), SPSS version 22-24 (IBM, Armonk, NY), *R* (R core team, 2014), and SAS version 9.2 (SAS Institute Inc., Cary, NC). Illustrations were done using the software tools Adobe Illustrator 2015.5 (Adobe Inc, San Jose, CA) and PowerPoint 2013 (Microsoft Corporation, Redmond, WA).

8.8 QUALITATIVE METHODS

8.8.1 Practical approach to the interviews

The interview started with information about the study, some initiating background questions followed by open-label questions. The intention was to create an environment that facilitated the patients' freely reflective narratives. The interview guide (Table 4) served as a framework with both open-ended and specific questions to ensure that all relevant areas were covered. This mitigated the risk we might avoid or neglect certain topics and it assured the interviews all had a uniform structure. The order of the questions was not important; instead, participants were encouraged to speak freely and bring up feelings from their own perspectives. At the end of the interviews, the guide was used to check that all areas were covered and sometimes some complementary questions were addressed. Most of the time, active listening by the interviewer allowed most of the topics to be addressed in spontaneous conversation.

Often the patients brought up questions about their disease and management. To separate the roles of the interviewer and the responsible clinician but at the same time provide service to the patient, a contact with the clinician was advised or arranged if requested.

Each interview was audio-recorded digitally and transcribed verbatim. Notably, the interviews ranged from 81-210 minutes and the mean was 135 minutes. In total, this generated about 59 hours of recorded interviews.

Table 4. The interview guide. Reproduced from Paper IV, appendix 1, with permission.[332]

Topic	Questions
Background	• How old are you? • Do you live with anybody? • Do you have children?
Early questions	• What is it like to live with HCM and ICD? • How and when did you get the HCM diagnosis? • When did you get the ICD?
General health	• What do you think about your health? • How do other people consider your health? • In what way does the ICD affect your health? • Has your health changed over time? • What do you think about your future health?
Professional life	• Are you working/studying? • Has your professional life been affected by HCM/ICD? • Do you think your future career will be affected by HCM/ICD?
Leisure time	• In what way has your leisure time been affected? • Do you exercise? How does that work? • Did you get advice on activity levels? Do you follow this advice?
Family & Friends	• Is family life affected by HCM/ICD? • How did your relatives know about your HCM diagnosis and ICD? • What do your family and close friends think about your having an ICD? • What do your family and friends know about your HCM and ICD?
Driving	• Do you have a driver's license? Which certificates? • Are your driver's licenses affected by HCM/ICD? • Did you drive for a living? • What advice did you get about driving?
Insurance	• Did your insurance company act differently based on your HCM/ICD?
Lifestyle	• What kind of food do you eat? Alcohol? Smoking?
Medication	• Which pharmaceutical drugs do you take? • Do you take these drugs as prescribed? • Do think that these drugs relieve symptoms/cause side effects?
Diagnosis of HCM	• What made them suspect HCM? How long did it take to be diagnosed?
ICD	• When and why did they decide about the ICD? • What do you think about the information before ICD implant? • Did you experience ICD shock (appropriate/inappropriate)? • How was the implant procedure? • Did you experience any surgical complications? • Does the ICD give you a sense of security? • Did you ever regret receiving an ICD? • Do you know how to turn the ICD off? • What is the difference between a pacemaker and an ICD?
Health care	• What could be improved in health care in HCM and ICD? • Did you ever contact a patient association? • Do you use internet/social media? For HCM/ICD communication? • What can the society do to improve care for HCM/ICD patients?
Sexuality	• Is your sex life affected by HCM/ICD? • Did you need medication to improve sexual performance?
Reproduction	• What are your concerns about your child getting HCM?
Pregnancy	• Did HCM/ICD affect your pregnancy?
Genetics	• Have they found a mutation causing your HCM? • Did the genetic counselling affect the family?
Sleep	• How is your sleep quality? • Has your sleep been affected by HCM/ICD?

8.8.2 Hermeneutics and content analysis

Qualitative approaches to content analysis allow for a deeper understanding of a text. They aim to analyze a text beyond the sentences to a greater depth, i.e. interpreting the actual underlying meaning. This implies that the analysts acknowledge the usefulness of their own pre-understanding. The pre-understanding is formed by the socially and culturally conditioned background of experiences. Krippendorff refers to this as an interactive-hermeneutic approach.[333] Content analysis is a technique to gain reliable and valid references from texts. It should be highly reliable and thus replicable. Berelson originally stated that content analysis should be an objective and systematic research technique.[334] He argued that a systematic approach was crucial, because humans have the tendency to selectively interpret texts in order to support preexisting thoughts, rather than question the pre-understanding. To improve validity, a systematic approach for handling the texts is needed in order to produce replicability and become part of external validation. In fact, results from content analysis can be measured, but objectivity is inherently difficult because it is interpretation made by humans. However, content analysis can be operationalized as a process toward the meaning of a text within a context. Context is crucial and even when one tries to be objective about context, it still remains a subjective construct.[333] Merten adheres to this thought by claiming that content analysis is a way inquiring into social context and is a tool to infer the nonmanifest message from the manifest message.[335,336] Thus, the analysis needs to handle extra-textual phenomena, that is, the meaning and consequences of what was stated. We set out a framework of areas for exploration by using an interview guide but were also open to the patients leading the interview in specific directions. The empirical grounding of the areas to explore was based on the experiences of clinicians treating these patients along with the methodological expertise of the group. It was inspired by hermeneutics and content analysis.[337–339] The basis for interpretation of a text using a hermeneutic approach is the hermeneutic circle. This circle encompasses "both as a movement between tradition and the movement of the interpreter."[340] The awareness and reflexive approach of the analysts pre-understanding based on contextual experience provided a solid base for meaningful interpretation. The rigor of the study is underpinned by pre-understanding of the area of hermeneutics.[341,342] At the same time, pre-understanding was balanced by a reflective approach and interaction with other in the research group. This was achieved based on a framework of trustworthiness, credibility of the interview technique, and rationale for the interview guide to facilitate richness and in-depth narratives.[343] During the structured analysis and comprehensive understanding, interpretation was approached with critical reflection on pre-understanding.[344] The hermeneutic circle also provided a model for movement between the parts and the whole. While a single interview was dissected into parts, it was also built into the whole of all of the other interviews. The judgement of transferability of text into interpretation used examples of citations and thematization in a stepwise manner. The intertwining of narrative and theoretical themes was discussed among the authors.

The inferences often took an abductive approach from logically distinct domains from one kind to another kind, but also inductive approaches from particulars to generalizations.[345]

The main advantage of unstructured data is the preservation of the data´s sources. Because the text is context sensitive, it is the responsibility of the interpreter to process the data to be meaningful, informative, and representational to the readers.[346] Nevertheless, the unstructured data need to be handled in structured way. The huge quantity of text in this study had to undergo categorization according to a scheme. Importantly, this scheme had to be applied to every text unit in the same way.[347]

8.8.3 Analysis and interpretation of text

The transcription of the interviews was written using the software Microsoft Word. The practical approach to analyze the data was inspired by the concepts and practical procedures proposed by Graneheim and Lundman to organize data and achieve trustworthiness.[348] The first step was a naïve reading of the text. The guiding principle was to read each interview without interruption and to get an overall impression of story from the narrative itself. This was done with of all the interviews and followed by discussions with the researcher of preliminary interpretations of each interview and the cohort as a whole. In the next step, each interview was analyzed using a structured approach in which the text was condensed into meaning units based on the aim of study. In this way, unnecessary parts with less relevance were removed. Then these condensed meaning units were further broken into shorter phrases and labelled with a code. In order to be specific, these codes were diverse. When each interview was analyzed this way, these codes could be decontextualized, i.e. brought out from each interview and put together. Based on further interpretation and interactive discussion among researchers, clear themes emerged based on the narratives. From these narrative themes, more generalized theoretical themes could be developed to characterize the main red threads in the text. Altogether, this was an attempt to concretize the hermeneutic vision of "unfolding the world in front of the text," as stated by Ricoeur.[349] The final determination of themes was preceded by another reading of the interviews from a holistic viewpoint.

8.9 ETHICAL APPROVALS AND LICENSES

The studies were conducted in accordance with good clinical practice based on the principles of the Declaration of Helsinki.[350–352] All patients, who were alive, gave their written informed consent participation including data acquisition. Papers I, II, and III were based on approval by the Ethical Review Board in Stockholm (document number 2012/1301-31/3). The study that resulted in Paper IV was approved by Regional Ethical committee in Uppsala (document number 2015/060). Finally, the PET-study, which also needed approval by the local radiation committee was approved by the Regional Ethical committee in Uppsala (document number 2017/021).

The company Quality Metrics (OptumInsight Life Sciences, Inc., RI) provided the SF-36 (Swedish version) questionnaire with the license number QM015832. The translation into Swedish was validated.

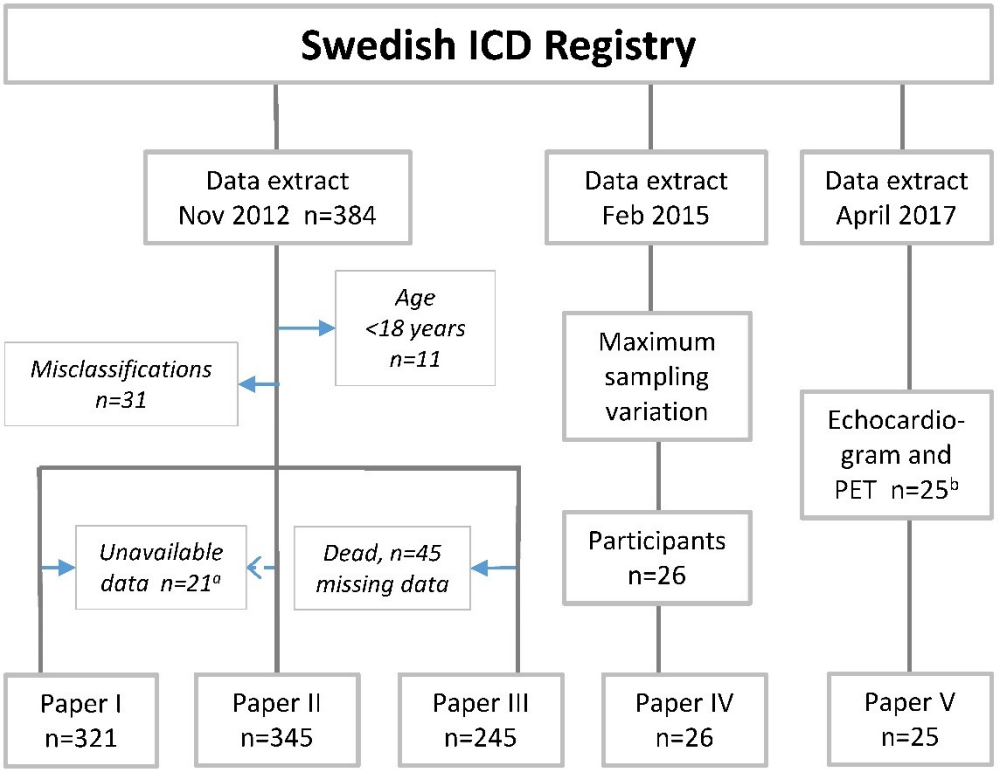
9 RESULTS

This section summarizes the key findings from the scientific projects, upon which Papers I-V were based.

9.1 VALIDATION OF DIAGNOSIS AND DATA EXTRACTION

In all papers, the diagnosis of HCM was validated using medical records followed by a thorough discussion between the cardiologists Magnusson and Mörner. The extract from the Swedish Pacemaker and ICD Registry based on HCM as the underlying etiology yielded misclassification in 31 patients (8.3%). In these cases, there was never actually a diagnosis of HCM. Instead, other forms of cardiomyopathies, valvular heart disease, malignant hypertension and ion-channelopathies were diagnosed. A flow-chart summarizes patient extraction and recruitment into each study (Figure 4).

Figure 4. Flow-chart of patient extraction in each study.



[a] 21 missing for prediction analyses in Paper II
[b] 1 missing for ^{15}O-water at stress

9.2 PAPER I

9.2.1 Patient characteristics

Patients with an unequivocal HCM diagnosis and available medical records with all relevant variables were analyzed. The final sample consisted of 321 patients, of whom 225 were men (70.1%). The mean age at the time of ICD implant was 52.1 years SD 15.4 with a mean follow-up of 5.4 years, which corresponds to a total of 1,733 patient-years. The vast majority (n=237; 73.8%) had ICD due to primary prevention and the remaining due to secondary prevention. Most patients underwent dual-chamber ICD implantation (n=225; 70.1%), i.e. a right atrial lead and a right ventricular lead. In 66 patients (20.6%), a single-lead ICD was implanted either because of permanent AF or no need for atrioventricular (AV) synchrony based of absence of sinus node dysfunction. A total of 30 patients (9.3%) underwent implantation with a LV lead, i.e. CRTD.

Notably, 42 patients were upgraded from a pacemaker to an ICD/CRTD. Among these 42 patients, 22 (52.4%) had the first implantation of the pacemaker to alleviate symptoms due to LVOT obstruction. The decision to implant an ICD/CRTD was based on risk stratification at the time (the five conventional risk factors and EF≤35%) in all except two patients (0.6%). One of these patients experienced VF during the implantation of a bradycardia pacemaker when the right ventricular lead encountered the apical wall. This induced VF caused the implanting physician to switch to an ICD system. It was deemed as primary prevention, as it was not a spontaneous VF but rather was induced by catheter manipulation in the right ventricular chamber. The other patient who lacked an established risk factor was physically active and whose uncle (second-degree relative) suffered from HCM with subsequent lethal VF without successful resuscitation.

The five risk factors were NSVT, unexplained syncope, abnormal blood pressure response at exercise test, wall thickness ≥30 mm, and a family history of SCD. In primary prevention, these risk factors are typically addressed in the clinical evaluation. In contrast, systematic assessment was deemed unnecessary by the clinician in secondary-prevention patients, i.e. survivors of cardiac arrest or sustained VT, as the decision to implant an ICD did not require such evaluation. In addition to the conventional risk factors, we added a history of AF and EF<50%. The clinical characteristics of the whole cohort are reported in Paper I. The summary of the risk markers among primary and secondary prevention patients is presented in Table 5.

Table 5. Risk markers among HCM patients with primary and secondary prevention indication for ICD. Modified from Magnusson et al.[283]

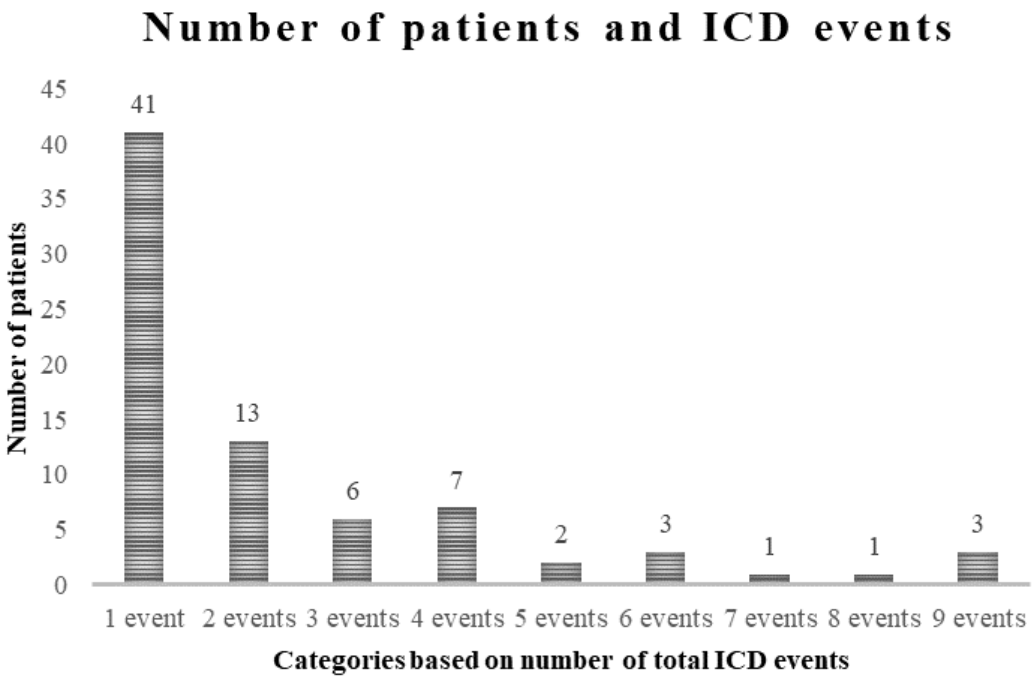
Variable	Primary prevention n=237 (73.8%)	Secondary prevention n=84 (26.2%)	All patients n=321 (100%)
Age at implant, year	51.6 SD 15.6	53.5 SD 15.2	52.1 SD 15.5
Men	165 (69.6%)	60 (71.4%)	225 (70.1%)
Risk markers†			
Atrial fibrillation	66 (27.8%)	25 (29.8%)	91 (28.3%)
Ejection fraction <50%	50 (21.1%)	15 (17.9%)	65 (20.2%)
NSVT	138 (58.2%)		
Syncope	84 (35.4%)		
Exercise BP response	17 (7.2%)		
Wall thickness ≥30 mm	58 (24.5%)		
Family history of SCD	62 (26.2%)		

BP, blood pressure; †Atrial fibrillation and ejection fraction <50% were risk markers evaluated for all patients, whereas the others were solely for primary-prevention patients.

9.2.2 Outcome

A total of 45 patients died. The primary outcome, appropriate ICD therapy, occurred in 77 patients (24%). Using the definition described in the Method section, i.e. that multiple treatment of different episodes of VT/VF within 24 hours were counted as one event, the total number was 183 appropriate ICD therapies. The distribution is shown in Figure 5.

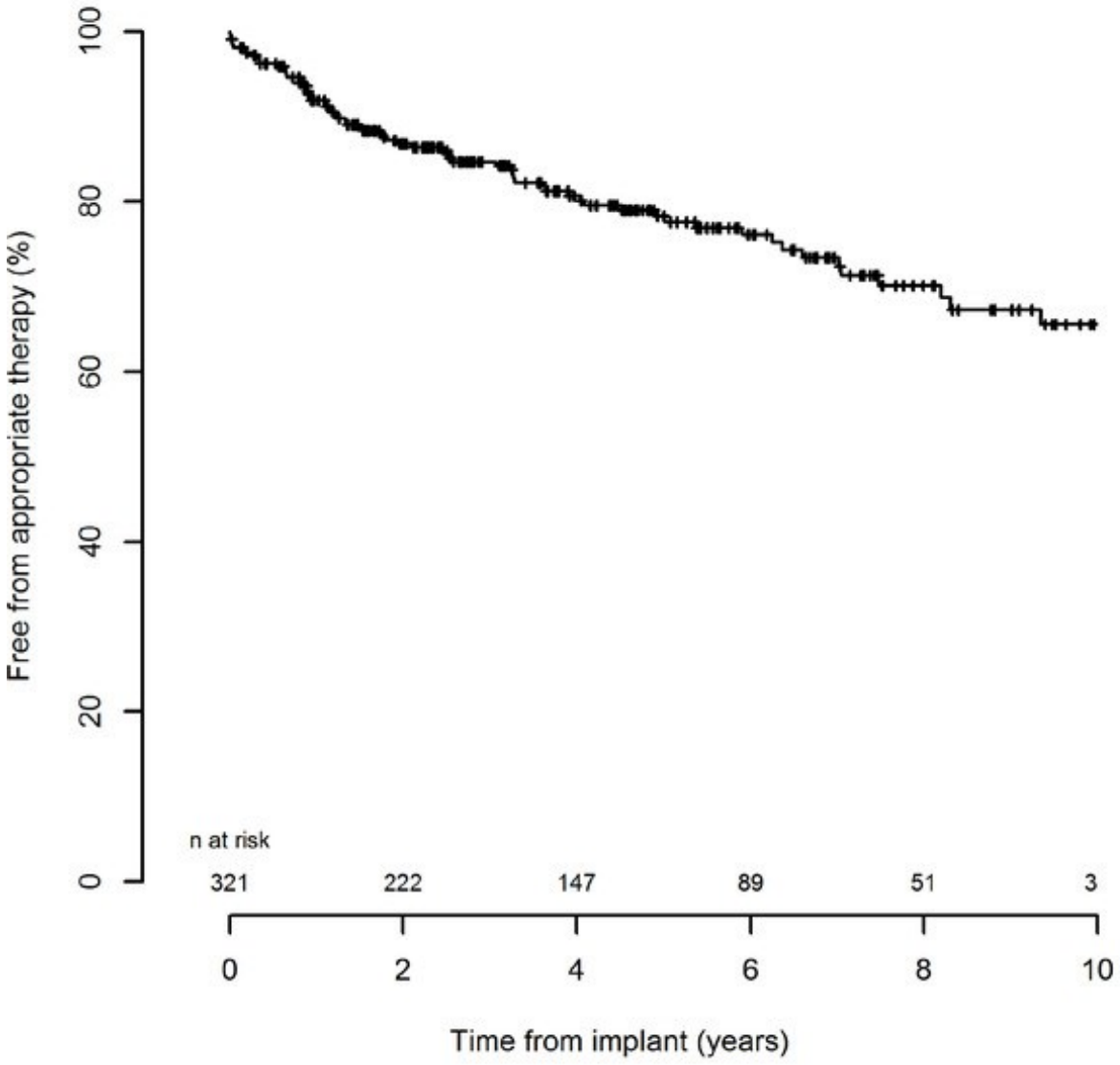
Figure 5. Number of appropriate ICD therapy events during follow-up per patient.



Among the first episodes in the 77 different patients who experienced an appropriate ICD therapy, 40 (52%) required cardioversion while in the remaining 37 (48%), ATP was enough to terminate the VT. The overall efficacy of terminating potentially life-threatening ventricular arrhythmias was excellent. All VT/VFs were terminated by the ICD, but in one case a VT below the programmed detection zone recurred, which resulted in prolonged circulatory collapse and subsequent multiorgan damage and finally death.

The cumulative 1, 3, and 5-year incidences of appropriate ICD therapy were 8.1%, 15.3%, and 21.3%, respectively. The time-to-event analysis is graphically shown as Kaplan-Meier estimates (Figure 6). Thus, the risk of VT/VF requiring appropriate ICD therapy persists over the years.

Figure 6. Kaplan-Meier event-free appropriate ICD therapy for the whole HCM cohort. Reproduced from Magnusson et al, with permission.[283]



In patients with a secondary-prevention indication, the time-dependent Kaplan-Meier estimate of appropriate ICD therapy was higher than for primary prevention (p=0.044). The difference was mainly due to a higher risk in the first year in secondary prevention compared to primary prevention (Figure 7). There was a trend toward a higher risk among males than females (p=0.073) as shown in Figure 8.

Figure 7. Kaplan-Meier event-free appropriate ICD therapy for primary and secondary prevention in HCM. Reproduced from Magnusson et al, with permission.[283]

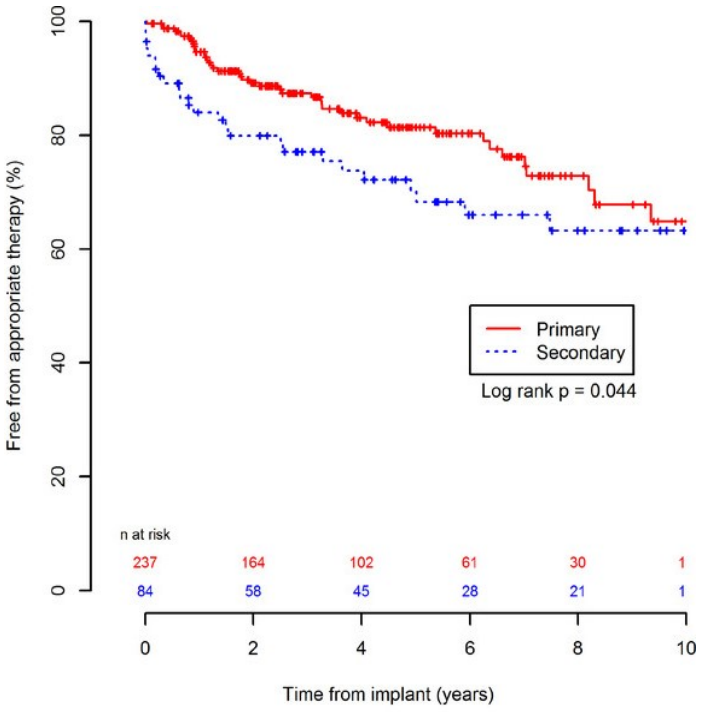
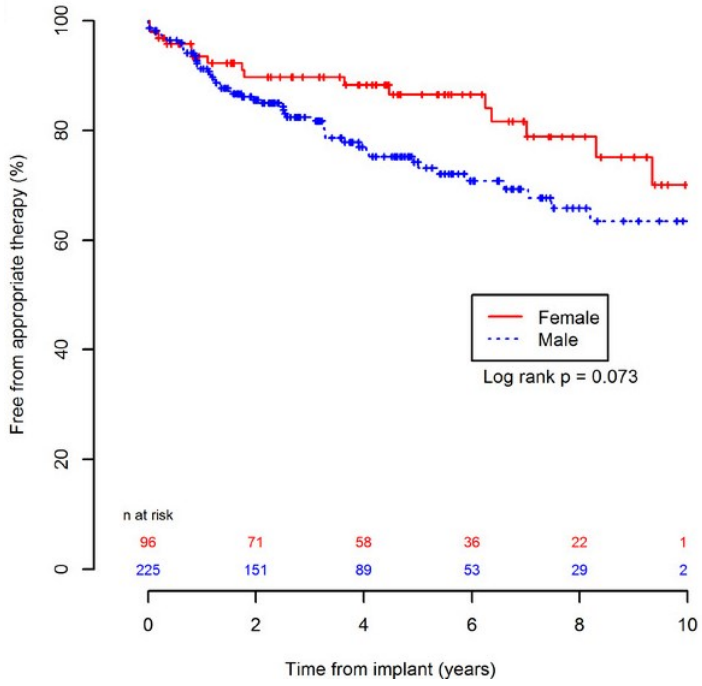


Figure 8. Kaplan-Meier event-free appropriate ICD therapy for men and women with HCM. Reproduced from Magnusson et al, with permission.[283]



9.2.2.1 Risk markers for appropriate ICD therapy in the whole cohort

In secondary prevention, the decision to implant an ICD was based on a history of a spontaneous, life-threatening VT/VF. Thus, a systematic collection of risk markers was not considered necessary by the clinicians. Instead, AF, EF<50%, male sex, and age at implant were analyzed in a univariable followed by a multivariable analysis in a Cox proportional hazard regression model. The result is summarized in Table 6.

Table 6. Association of clinical variables and first appropriate ICD therapy for the whole HCM cohort (77 events in 321 patients). Reproduced from Magnusson et al.[283]

Predictor	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at implant, year	1.016	1.000-1.032	0.043	1.009	0.99-1.03	0.273
Men	1.63	0.96-2.76	0.073	1.54	0.90-2.64	0.113
Atrial fibrillation	1.83	1.14-2.93	0.012	1.39	0.83-2.14	0.214
Ejection fraction <50%	3.05	1.89-4.92	<0.001	2.63	1.60-4.33	<0.001

Notably, age was significant in the univariable analysis (p=0.043) but after adjustment of other risk markers, it was not significant in the multivariable analysis (p=0.273). Similarly, the risk marker AF showed significant difference in the univariable (p=0.012) but not in the multivariable analysis (p=0.214). The risk factor EF<50% was strongly associated with appropriate ICD therapy in univariable analysis with a three-fold increase and remained highly significant in the multivariable analysis.

9.2.2.2 Risk markers for appropriate ICD therapy in primary prevention

In primary prevention, the conventional risk markers were analyzed with regard to the outcome appropriate ICD therapy. The risk marker abnormal blood pressure response/ exercise blood pressure response was not systematically addressed in some cases, because the clinician had enough information to recommend an ICD; the absence of this risk marker was assumed when an exercise test was not part of the clinical evaluation. The uni- and multivariable variable analyses are summarized in Table 7.

Table 7. Association of clinical variables and first appropriate ICD therapy in primary prevention (47 events in 237 patients). Reproduced from Magnusson et al.[283]

Predictor	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at implant, year	1.025	1.004-1.046	0.017	1.001	0.98-1.02	0.915
Men	1.20	0.64-2.27	0.572	0.93	0.48-1.80	0.833
Atrial fibrillation	3.60	1.95-6.65	<0.001	2.54	1.25-5.17	0.010
Ejection fraction <50%	3.70	2.00-6.87	<0.001	2.78	1.39-5.56	0.004
Nonsustained VT	1.97	1.05-3.69	0.034	1.80	0.88-3.68	0.109
Syncope	1.13	0.63-2.03	0.688	1.11	0.59-2.10	0.746
Exercise BP response	1.62	0.64-4.12	0.312	1.40	0.50-3.92	0.520
Wall thickness ≥30 mm	0.99	0.50-1.95	0.936	1.42	0.69-2.92	0.342
Family history of SCD	0.60	0.28-1.29	0.190	0.77	0.34-1.75	0.532

BP, blood pressure.

Again, age at implant turned out to be significant in the univariable analysis but not in the subsequent multivariable analysis. Both AF and EF<50% were significant in univariable and multivariable analyses. Among the conventional risk markers, NSVT had the strongest association; it was significant in the univariable (p=0.034) analysis but had a borderline tendency in multivariable analysis (p=0.109).

In patients with any of the five conventional risk markers alone, appropriate therapy occurred in 15 out of 52 patients with NSVT; 3 out of 23 with unexplained syncope as a risk marker; exercise blood pressure response 0 of 2; wall thickness ≥30 mm 1 of 15; and family history of SCD 2 of 26. When patients without a history of AF or EF<50% were excluded, no patient with the single risk marker of unexplained syncope (0/15) and family history of SCD (0/15) experienced appropriate ICD therapy. In this subset of patients, no one had solely abnormal blood pressure response as a single risk marker.

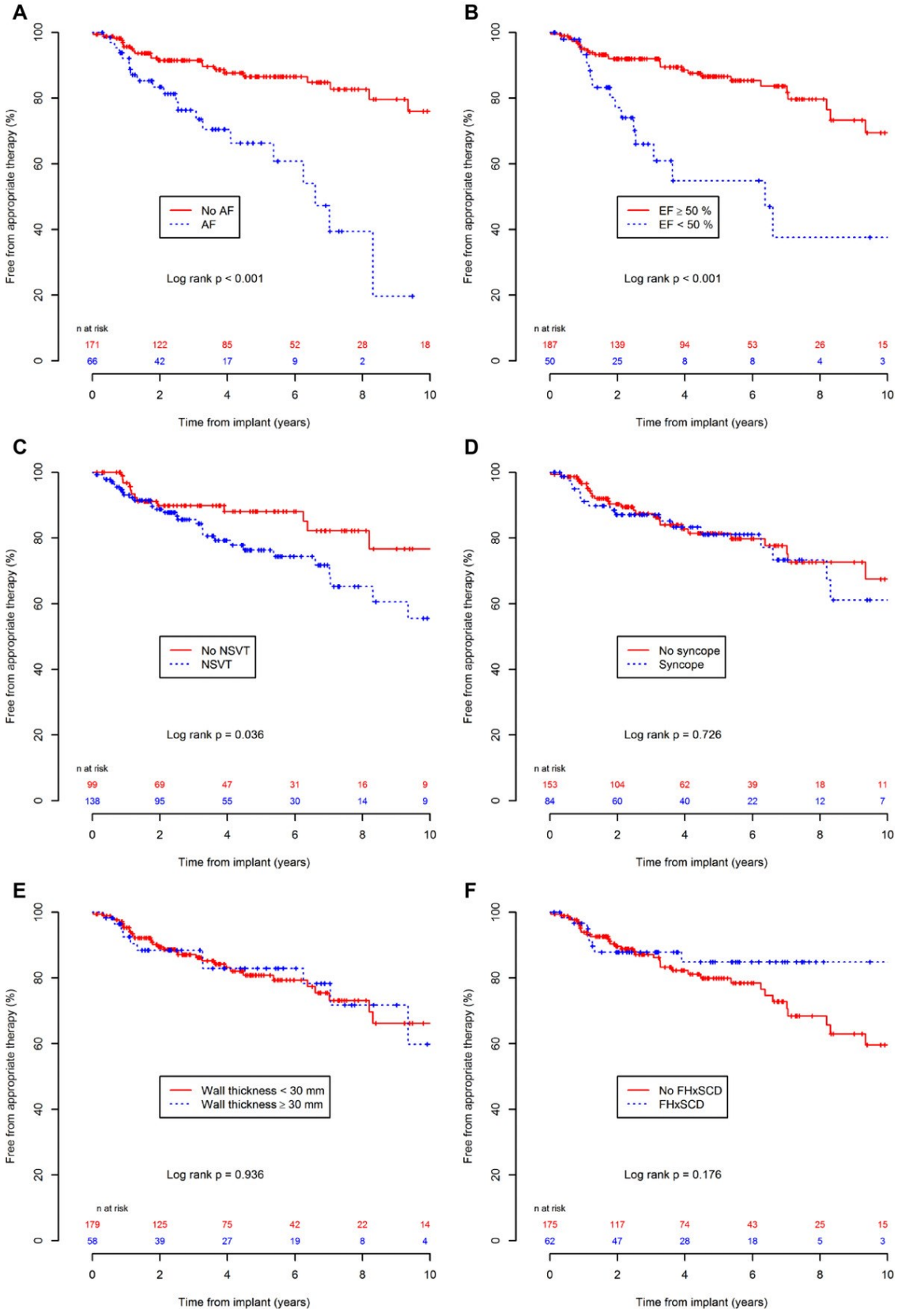
In another multivariable analysis of the four risk markers NSVT, unexplained syncope, wall thickness ≥30mm, and a family history of SCD, but not abnormal blood pressure response at exercise, the risk marker NSVT was the strongest (Table 8).

Table 8. Association of four established risk factors and first appropriate ICD therapy in primary prevention. Based on the study by Magnusson et al.[283]

Predictor	**Multivariable**		
	HR	**95% CI**	**p-value**
NSVT	1.97	1.00-3.88	0.050
Syncope	1.25	0.68-2.32	0.475
Wall thickness ≥30 mm	1.08	0.53-2.18	0.837
Family history of SCD	0.78	0.34-1.78	0.557

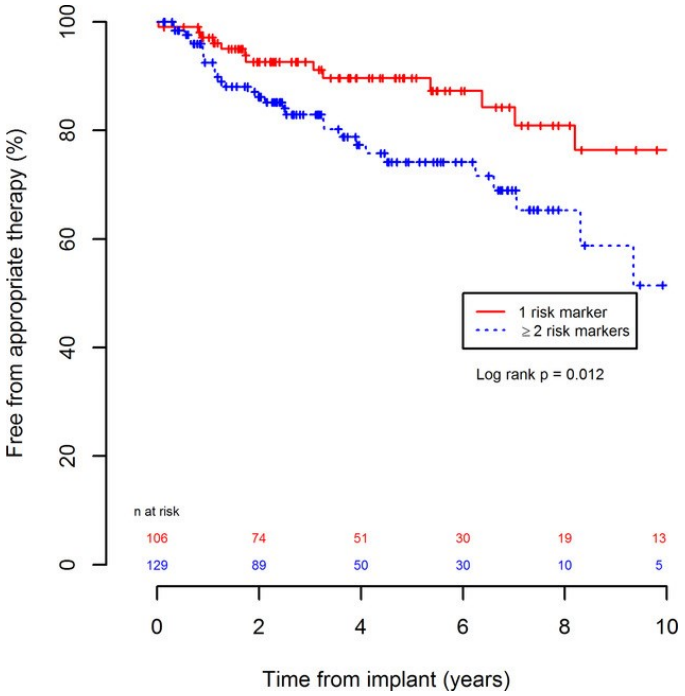
The corresponding Kaplan-Meier estimate of these four risk markers plus AF, and EF<50% is shown in Figure 9. The Mantel-Cox p-values differ slightly compared to Table 8 due to methodological difference in Cox regression between the softwares.

Figure 9. Kaplan-Meier event-free appropriate ICD therapy for primary prevention patients with HCM and risk markers: A) atrial fibrillation, B) ejection fraction ≤50%, C) nonsustained ventricular tachycardia, D) syncope, E) wall thickness ≥30 mm, and F) family history of SCD (FHxSCD). Reproduced from Magnusson et al, with permission.[283]



Clearly, for patients with 2 or more risk markers, compared to a single marker, the time to first appropriate ICD therapy was significantly shorter (p=0.012), as depicted in Figure 10.

Figure 10. Kaplan-Meier event-free appropriate ICD therapy for HCM patients with primary-prevention indication based on number of risk markers at implant. Risk markers: NSVT, syncope, exercise blood pressure response, maximal wall thickness ≥30 mm, family history of SCD, EF at implant ≤35%. Reproduced from Magnusson et al, with permission.[283]



9.3 PAPER II

9.3.1 Patient characteristics

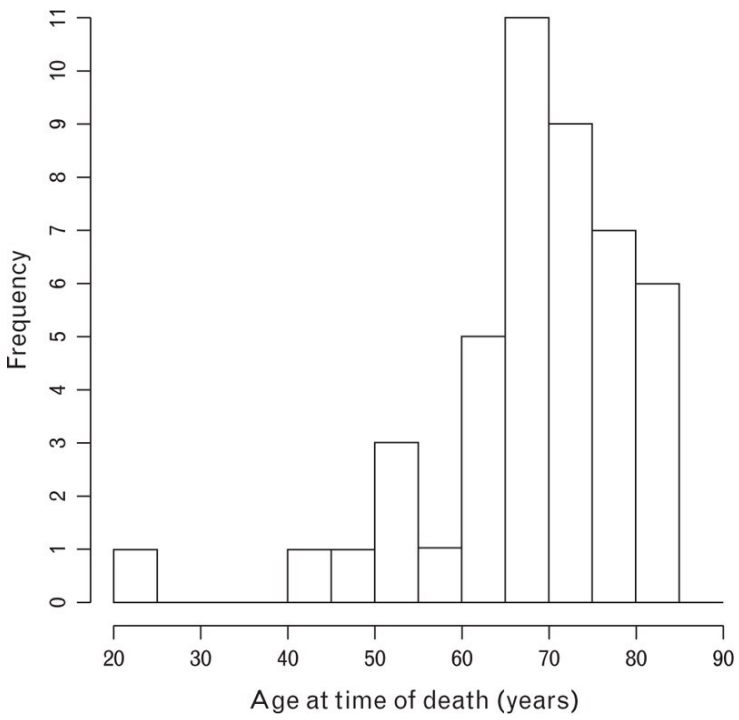
This paper was based on the same extract of the Swedish Pacemaker and ICD Registry used in Paper I with an additional 21 patients, for whom additional data were available, specifically age at implant and date of death if appropriate for mortality calculations. However, there was paucity of detailed data on clinical characteristics for risk prediction for these 21 patients.

As explained in the Method section, the follow-up time was from primary ICD implant until last follow-up (death or alive). The mean age at ICD implant was 51.8 SD 15.5 years and 70.8% were men. The 25th, 50th, and 75th percentile age at implant was 41.6 years, 53.4 years, and 63.9 years, respectively. The age distribution between men and women at ICD implant were similar; the mean age was similar overall (p=0.63), and in the oldest quartile (p=0.77).

9.3.2 Outcome

In total, 45 out of 342 patients (13.2%) died during a mean follow-up of 5.4 SD 4.2 years. Among the 45 deceased patients, the mean age at death was 68.2 years. The 25th, 50th, and 75th percentile ages at death were 63.6 years, 69.8 years, and 76.8 years, respectively. The age at the time of death is depicted as a bar chart (Figure 11).

Figure 11. Age at death among 45 patients with a history of hypertrophic cardiomyopathy and implantable defibrillator. Reproduced from Magnusson et al, with permission.[353]



During follow-up, 15 patients underwent explant of the ICD at the time of heart transplant or LVAD and 2 of them died. One of these patients died postoperatively due to circulatory collapse caused by a cardiac tamponade. The other patient died from progressive heart failure of the transplant. In addition, 5 other patients had their ICDs explanted. The reasons were downgrade at advanced age (n=2), extraction after infection without replacement (n=2), and recurrent inappropriate shocks (n=1). In the latter patient, despite several attempts and strategies to avoid inappropriate therapy delivery, he requested that the ICD device to be turned off. Unfortunately, he died from subsequent VF a few years later.

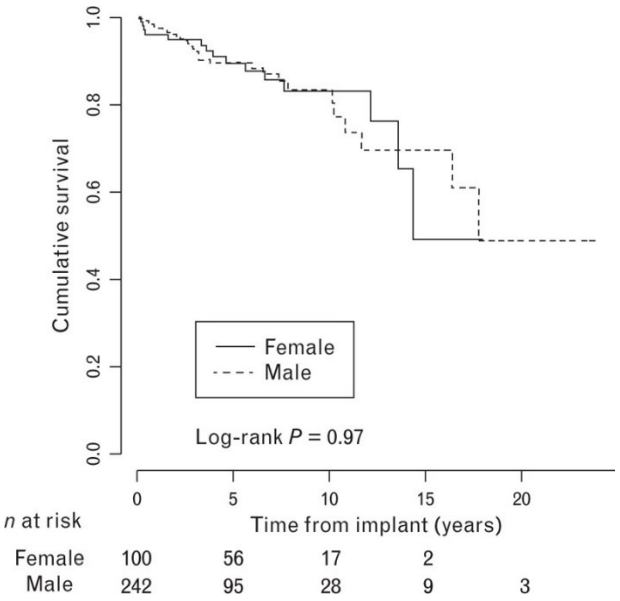
The cumulative 1, 3 and 5-year survivals were 97.0%, 93.4%, and 89.4%, respectively. The estimated mean survival of the whole cohort was 17.3 years.

9.3.2.1 Mortality

The crude mortality was 2.44 per 100 patient-years for the whole cohort. Among the 45 decedents, 30 were men (13.3%) and 15 women (15.6%). In the time-dependent analysis,

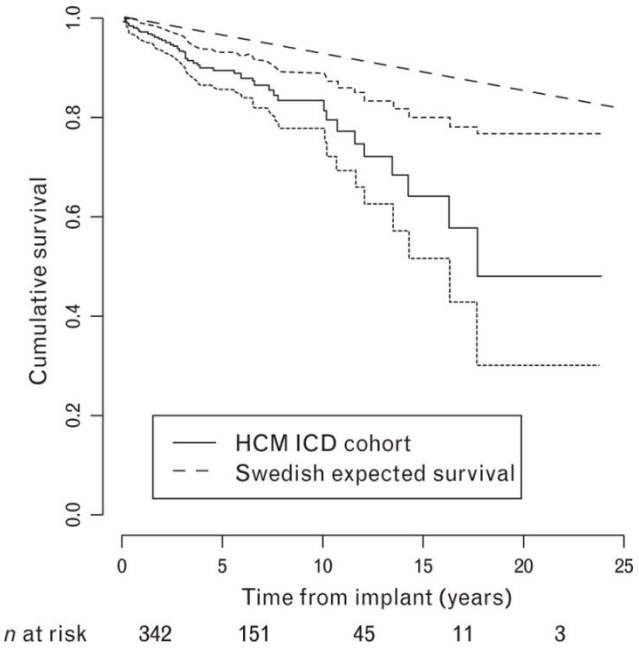
using Kaplan-Meier survival, the crude mortality was almost identical (p=0.97) between sexes as seen in Figure 12.

Figure 12. Kaplan-Meier survival of 342 hypertrophic cardiomyopathy (HCM) patients with implantable defibrillator (ICDs) with regard to sex. Reproduced from Magnusson et al, with permission.[353]



The SMR, i.e. matched for age, sex, and calendar period in relation to the national general population in Sweden, increased (3.35 [95% CI 1.5-4.8]; p <0.0001). The Kaplan-Meier survival plot including 95% CI and expected survival in the general Swedish population as a reference is seen as Figure 10.

Figure 13. Kaplan-Meier survival of 342 HCM patients with ICDs compared with Swedish general population (age- and sex-matched). The log-rank p-value is <0.0001. The dotted gray lines represent 95% CI. Reproduced from Magnusson et al, with permission.[353]



Again, there was a similar SMR between men (3.15; 95% CI 2.12-4.49) and women (3.85; 95% CI 2.15-6.30). Moreover, 12% of the primary-prevention patients died, while 19% of the secondary-prevention patients did, which implied similar death rates (p=0.77).

9.3.2.2 Causes of death

In three quarters (75.6%) of the patients, the main cause of death was related to the underlying HCM. The vast majority died from progressive systolic heart failure (60.0%). The other HCM-related causes of death were VT/VF (4.4%) and embolic stroke (11.1%). The main causes of death are summarized in Table 9. Notably, in 45.5% of the cases with a non-HCM-related main cause of death, HCM was deemed a contributing cause of death.

Table 9. Main cause of death among 45 patients with a history of HCM and ICD. Reproduced from Magnusson et al.[353]

Main cause of death	Frequency	%
HCM-related	**34**	**75.6**
Heart failure	27	60.0
Stroke	5	11.1
Ventricular arrhythmia	2	4.4
Non-HCM-related	**11**	**24.4**
Cancer	3	5.4
Myocardial infarction	2	4.4
Sepsis	2	4.4
Pneumonia	1	2.2
Alzheimers disease	1	2.2
Diabetes mellitus	1	2.2
Ileus	1	2.2
All deaths	**45**	**100**

9.3.3 Prediction of death

We performed a Cox regression univariable analysis of age at implant, male sex, AF, EF<50%, secondary indication, and a history of appropriate ICD therapy, followed by a multivariable analysis of all these variables included in the model (Table 10). Age at implant, calculated in 1-year increments was significantly associated with death in both the univariable and multivariable analyses. AF was strongly associated with death in the univariable analysis (HR 3.36; p<0.0001) but less so in the multivariable analysis (HR 1.81; p=0.214). EF<50% was strongly associated both in the univariable analysis (HR 5.02; p<0.0001) and multivariable analyses (HR 5.00; p<0.0001).

Table 10. Association of clinical variables and death in HCM patients with ICDs. Reproduced from Magnusson et al.[353]

Predictor	Univariable			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at implant, year	1.101	1.068-1.135	<0.001	1.086	1.05-1.12	<0.001
Men	1.00	0.54-1.86	1.00	1.04	0.53-2.02	0.113
Atrial fibrillation	3.36	1.79-6.30	<0.001	1.81	0.93-3.56	0.214
Ejection fraction <50%	5.02	2.80-9.04	<0.001	5.00	2.57-9.73	<0.001
Secondary indication	1.10	0.59-2.04	0.77	1.26	0.64-2.48	0.50
Appropriate ICD therapy	1.04	0.55-2.00	0.89	0.55	0.28-1.10	0.09

9.4 PAPER III

9.4.1 Patient characteristics

In total, 245 adult HCM patients with transvenous ICD systems returned a complete SF-36, which was 82.5% of those eligible. The mean age was 55.9 SD 14.7 years and ranged from 19 to 88 years. The distribution between age strata were as follow: 18-39 years (15.5%), 40-65 years (37.6%), and ≥65 years (46.9%). A majority was male (70.2%) and primary prevention (73.5%) was more common than secondary prevention. There was a history of AF in 35.7% and systolic heart failure in 19.6%. At least one appropriate ICD therapy occurred in 22.9% and inappropriate ICD shock in 13.5%. Complications that required an invasive intervention occurred in 29.4% during the follow-up since first ICD implant.

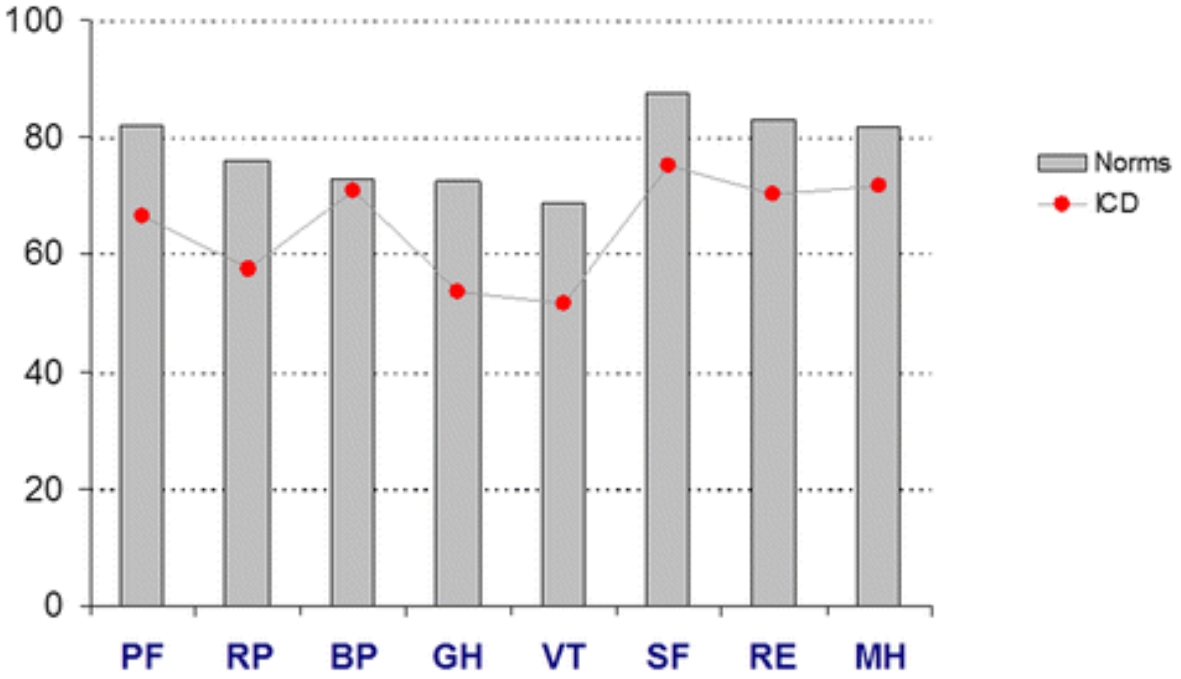
9.4.2 SF-36 score compared to norm population

The HCM patients with ICD were compared to age- and sex-matched Swedish population norms. All domains, except for bodily pain, had a lower score than the norms, which is summarized in Table 11. Both component score, physical component summary (PCS) and mental component summary (MCS), were likewise significantly lower than norms. In Figure 14 the score of eight domains are visualized using bar charts. The effect sizes varied from small to moderate and even large in one domain (General health). A higher age was associated with lower scores on Physical functioning, Role physical, and PCS. On the contrary, the domains Mental health and MCS showed higher scores with increasing age within the cohort.

Table 11. SF-36 score in HCM with ICDs compared to general Swedish population norms. Reproduced from Magnusson et al.[354]

SF-36 domains	Cohort mean	SD	95% CI	Effect size	Norm mean	SD	95% CI	p-value
Physical functioning	66.6	27.6	63.1-70.0	0.62	82.1	22.4	80.5-83.8	<0.0001
Role physical	57.4	43.6	52.0-62.9	0.46	76.0	37.1	73.2-78.7	<0.0001
Bodily pain	70.7	29.4	67.0-74.4	0.08	72.9	27.3	70.9-74.9	0.550
General health	53.7	25.5	50.5-56.9	0.77	72.4	23.1	70.7-74.1	<0.0001
Vitality	51.8	26.2	48.5-55.1	0.67	68.7	24.4	66.9-70.5	<0.0001
Social functioning	75.1	26.9	71.7-78.5	0.52	87.7	21.3	86.2-89.3	<0.0001
Role emotional	70.1	40.8	64.9-75.2	0.35	82.9	32.0	80.5-85.3	<0.0001
Mental health	71.8	22.9	69.0-74.7	0.47	81.7	18.8	80.3-83.1	<0.0001
Physical Component Summary	40.8	12.4	39.3-42.4	0.62	47.9	10.5	47.1-48.7	<0.0001
Mental Component Summary	45.5	12.9	43.9-47.1	0.46	50.8	10.2	50.0-51.6	<0.0001

Figure 14. Bar chart SF-36 score in 245 HCM patients with ICDs compared to Swedish age- and sex-matched population norms (n=735). Reproduced from Magnusson et al, with permission.[354]



PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

9.4.3 SF-36 score in subgroups

Subgroups analyses within the cohort are shown in Table 12. Thus, patients with a history of AF reported significantly lower score in the domains of Physical functioning, Role physical, General health, Social functioning, and borderline value for Bodily pain. As a consequence,

the component summary score PCS was significantly lower in those with a history of AF than those without. Notably, patients with AF were older (mean difference 7.4 years; p<0.001). The differences expressed in effect sizes were typically small. Similarly, a history of systolic heart failure implied a lower score on physical domains and its component score (Physical functioning, Role physical, General health, and PCS). Heart failure patients were older, with borderline significance, with a mean difference of 4.6 years (p=0.053).

The fact that patients had experienced appropriate ICD therapy resulted in significantly higher Mental health and a tendency toward better MCS. Inappropriate shock, on the contrary was associated with lower score on Role emotional and a tendency toward lower score regarding Vitality, Social functioning, and MCS.

There were no significant differences in any domain or component score with regard to primary and secondary prevention. A tendency of better Vitality (p=0.07; ES 0.28) was seen among secondary-prevention patients.

Table 12. Subgroup analyses of hypertrophic cardiomyopathy patients with implantable defibrillators. Reproduced from Magnusson et al.[354]

SF-36 domains	Atrial fibrillation		Heart failure		Appropriate therapy		Inappropriate shock	
	p-value	ES	p-value	ES	p-value	ES	p-value	ES
Physical functioning	**<0.001**	0.47	**<0.001**	0.68	0.812		0.119	
Role physical	**0.002**	0.38	**0.003**	0.48	0.211		0.382	
Bodily pain	**0.051**	0.26	0.260		0.229		0.188	
General health	**0.004**	0.38	**0.023**	0.33	0.864		0.118	
Vitality	0.234		**0.075**	0.30	0.166		**0.080**	0.31
Social functioning	**0.004**	0.42	**0.069**	0.36	0.180		**0.058**	0.37
Role emotional	0.234		0.195		0.209		**0.028**	0.42
Mental health	0.288		0.681		**0.033**	0.30[a]	0.242	
Physical Component Summary	**<0.001**	0.48	**<0.001**	0.63	0.735		0.252	
Mental Component Summary	0.495		0.884		**0.076**	0.27[a]	**0.060**	0.38

[a] Higher mental health and mental health summary scores (all other effect sizes were lower).

9.5 PAPER IV

9.5.1 Patient characteristics

All 26 patients who were asked to participate consented and were interviewed. At the time of interview, the youngest patient was 27 years, the oldest 76 years, and the mean age was 58 years. The time since diagnosis of HCM varied from 4 to 45 years with a mean of 16 years. The mean time since first ICD implant was 6.7 years. All patients had an ICD at the time of interview except one whose ICD was removed during heart transplant. The vast majority (76.9%; n=20) had ICD as primary prevention and the remaining due to survived cardiac arrest or life-threatening VT/VF requiring external electrical conversion/defibrillation. In 3 patients, a history of appropriate ICD therapy was reported while 8 experienced at least one inappropriate ICD shock. In Table 13 the characteristics of participants are further reported.

Table 13. Characteristics of 26 interviewed HCM patients with history of ICD. Reproduced from Magnusson et al.[332]

Sex	Age	Civic status	Child	Indication	ICD duration	ICD shock	Diagnosis	NYHA
M	27	Cohabitate	0	primary	4.9	no	9	I
F	32	Cohabitate	2	primary	2.4	no	17	II
F	33	Cohabitate	2	secondary	6.3	no	14	I
M	37	Divorced	1	primary	3.0	no	8	II
M	42	Married	2	secondary	8.4	inappropriate	9	I
M	48	Divorced	2	primary	4.8	no	30	I
M	49	Cohabitate	0	secondary	6.9	appropriate	7	II
F	54	Cohabitate	1	primary	10.9	inappropriate	20	II
M	55	Single	0	secondary	8.0	appropriate	37	IIIB
M	59	Married	2	primary	3.8	inappropriate	4	I
M	59	Cohabitate	2	primary	1.0	no	32	IV/I[a]
F	60	Married	3	secondary	10.9	inappropriate	20	I
M	61	Married	2	primary	8.9	no	18	I
M	61	Divorced	5	primary	11.3	inappropriate	45	IIIB
M	63	Married	2	primary	16.6	appropriate	17	I
M	64	Cohabitate	2	primary	3.0	no	4	I
F	65	Single	1	primary	5.3	inappropriate	8	I
M	65	Married	1	primary	5.1	no	42	I
M	65	Married	2	primary	7.6	no	9	I
M	67	Married	2	primary	3.2	no	4	II
F	68	Married	4	primary	7.8	no	7	I
M	69	Married	1	primary	4.5	no	5	I
M	72	Divorced	7	secondary	3.5	no	20	II
F	75	Divorced	0	primary	11.2	inappropriate	15	I
F	75	Married	1	primary	9.8	inappropriate	14	IIIA
F	76	Single	2	primary	5.2	no	7	I

M, male; F, female. ICD duration refers to time (years) with an ICD and Diagnosis time (years) since first known diagnosis of HCM. [a] Heart transplant due to NYHA IV, at the time of interview NYHA I.

9.5.2 Key findings

The main findings from the interviews are summarized below in each section. This is further elaborated in the Discussion in relation to other studies and clinical implications.

9.5.2.1 Diagnostic considerations

There was a variety of diagnostic pathways. Diagnosis was sometimes based on family screening, detection of a cardiac murmur, abnormal ECG, symptom evaluation, but in many other cases diagnosis was made as a part of clinical work-up for another medical reason, for example: infection, surgery, stroke or cardiac arrest. In several cases, the diagnosis of HCM was considerably delayed and initial misclassification was common. When patients reported the name of their diagnosis, they often used terms other than the established nomenclature. Instead of HCM, they said "*enlarged heart"*, "*heart trouble"*, and "*heart thickness"*. They also claimed that their health care provider used several descriptions of the disease, which led to confusion. This made it difficult for them to search for information on their own.

9.5.2.2 Pharmacological compliance

The interview situation created a trustful relation, and patients were asked about their compliance with pharmacological treatment. In fact, they told the interviewer that they adhered to the prescription regarding the HCM-related regimen, typically beta-blockers and calcium-channels blockers.

9.5.2.3 Inheritance

Genetic screening was widely accepted and appreciated among the patients. However, the cascade screening was sometimes challenging or even impossible due to broken relationships.

Patients who withheld information exhibited ambivalence but rationalized their decisions for several reasons, including protecting their offspring. Parents of very young children pondered the consequences of genetic testing for their children. But in several cases the parents talked openly to their child about HCM. Even when the inheritance pattern was obvious, no one in the study blamed their parents for their HCM.

9.5.2.4 The patient perspective of the ICD

The decision to implant an ICD was clear-cut to the patients with a secondary-prevention indication. Among those with a primary-prevention indication, the risk factors upon which the decision was based were seldom known by the patients, except for SCD in a first-degree relative.

Many patients felt there was a lack of information about the procedure before it took place and would have appreciated better communication and a more personalized approach. In a few cases, the feeling of isolation was strong before the operation: "*When I was waiting for surgery, I felt like a chicken going into the slaughterhouse.*" Complications were diverse and generally accepted, but extraction procedures and long hospitalization resulted in

disappointment. Typically, patients recalled the implant procedure as fast and convenient, even though it was not completely painless. They had swelling, pain, and discomfort in the days following surgery.

Patients thought of the device as part of their own body, although there were sometimes situations where it was evident, they had a device. Being at a public swimming hall or beach could be embarrassing, especially in the younger patients who disliked people staring at them. Among close family members, it was not an issue and regarded as a reminder of security. Children and grandchildren often expressed fascination about the device. The gratitude and trust made both the patient and, according to them, also their relatives feel secure. However, some patients reported the device as bulky, which could cause localized discomfort when lying in bed or carrying a backpack.

Undoubtedly, the ICD provides reassurance. All patients were grateful to receive an ICD and none regretted the decision to get an ICD. It was considered as a true "*life insurance*" and the phrase "*my life-saver*" was repeatedly said by different patients.

9.5.2.5 Knowledge about HCM and ICD

Knowledge about HCM and ICD varied substantially among the patients. Generally, patients with a higher educational level knew more, but still lacked basic knowledge. Moreover, many patients were concerned about the level of knowledge among health care professionals in different settings, i.e. prehospital care, emergency rooms, anesthesia, gynecology, and other specialized care outside of cardiology units. For example, one patient received multiple shocks that could have been avoided by magnet application to inhibit shock therapy. Even among cardiologists, patients noticed that some were not familiar with disease management. For that reason, when such patients find knowledgeable health care professionals for ongoing care, they put a lot of trust in these clinicians and appreciate them. Simple information, such as basic information about the ICD and its function, was considered helpful in several situations. The patients who were interviewed were aware of the difference between a pacemaker for bradycardia and an ICD, but they did not think this was common knowledge in the general population.

Some patients expressed concerns about the possibility of terminal illness and the risk of repeated unnecessary shocks as they neared end of life. Some worried how health care providers would manage their ICD and whether or not the ICD shock function would be deactivated.

9.5.2.6 Experience of ICD shocks

In the event of appropriate shocks, patients had symptoms or even became unconscious. It could be a dramatic event for bystanders, but patients somehow were prepared for this to occur. One patient explained as, "*It was fantastic…I was sitting in a dark room and everything turned bright white.*" Sometimes they did not seek urgent medical care because they felt fine afterward.

Patients who experienced inappropriate shocks often had multiple shocks and were fully conscious at the events. The unpredictable nature of these shocks and their inability to stop it made them feel scared. They remembered these situations as "*ghastly*", "*painful*", and "*terrible*". It was described in their own words as "*being hit by a stone,*" "*being shot by a revolver*", and "*I jumped a foot, and I was like a jumping Jack.*" Despite this initial experience, they felt reassured, typically after a couple of weeks. They accepted the shocks as a side effect of the ICD that nevertheless is a life-saver. Some patients who wondered if the device would work in the case of a life-threatening arrhythmia stopped questioning it and actually felt more comfortable. Again, bystanders were sometimes profoundly affected by the dramatic event. A four-year old child whose father was shocked in her presence avoided physical contact with him for a while after the event.

The ICD as two-edged sword was described by an elderly woman who had several complications, including infections, multiple inappropriate, but also appropriate shocks. It took her considerable time to come to terms with ICD therapy, but she eventually came to accept her need for the device.

9.5.2.7 Overall health experience

The patients often considered themselves as healthy, at least in the beginning of the interview. They refused to see themselves as victims of a disease. Their core personal identity remained the same, although they in fact had made several adaptions over the course of their lives. They did not see themselves as being sick but indeed admitted constraints, "*My husband has energy but I have almost no energy",* and "*I learned to live with it"*, and "*I listen more to my body…"* They sometimes stopped certain activities and survivors of cardiac arrest often needed considerable time before they reoriented themselves. In primary-prevention patients who not yet experienced an appropriate ICD therapy, there were various viewpoints on the necessity of the device, for example, "*Maybe I do not need a device. I feel healthy".* Even those who thought that way regarded the ICD as an insurance policy that they would probably never need. The manifestation of the underlying HCM varied in the cohort. In patients with systolic heart failure, AF, and comorbidities, patients recognized that the underlying disease, not the ICD, accounted for their symptoms and associated physical functional deficits. In professional life, the disease affected their career opportunities and sometimes made them dependent on help from others.

Secondary-prevention patients often had long rehabilitation periods after cardiac arrest. Still, they enjoyed life and returned to their former activities. Interestingly, the close relatives of SCD survivors kept expressing anxiety for a very long time. Partners could become overprotective and there were certain overshadowing worries in families with young children. Moreover, younger patients felt more worried and limited than older patients. The older patients remembered situations from their youth that caused them to feel like they were different. A woman said, "*My teenage years were difficult".* Over time, these patients came to terms with having HCM, adapted to managing a chronic condition, and accepted their situation.

The physical constraints of the disease, rather than the ICD itself, restricted leisure time activities. Patients sometimes had to quit activities like ice-hockey, badminton, and soccer. But more often they continued but adapted the intensity, for example in swimming, dancing, and hiking. Many patients were unsure about individualized recommendations. Driving was sometimes restricted by authorities, but these restrictions were not always followed. In some cases, a spouse reinforced regulations about driving beyond what was required by authorities. The restrictions on driving had consequences for both leisure time activities and professional life. Physical intimacy was sometimes affected by the underlying disease state, but not the device. No patient expressed fear of shocks during sex.

Professional life was affected by the burden of symptoms, mainly shortness of breath. Young and middle-aged patients had to reorient themselves. In the elderly, there was already adaptation and acceptance in place. In some specific occupations, the ICD imposed restrictions, for example, a welder had to change his main working tasks.

9.5.2.8 Relationships

Among cardiac arrest survivors, their relationships somewhat changed. For example: "*The event has made us better connected but also creates problems…these worries can be really tiresome…on the other hand, we have a shared experience that somehow bonds us."* Patients were offered support more or less, but the relatives did not receive the same support. Some patients claimed that they coped better with the situation than their relatives. Indeed, these feelings were shared among relatives and close friends. Nobody attended patient support-group meetings because they felt it was irrelevant for them with their disease. Some patients found a Swedish homepage and web group for ICD patients in general, which they thought was beneficial. One patient was member of the specific American HCM patient organization.[367] In general, the younger patients often went to internet sources for information about HCM and ICDs.

A recurring complaint about the absence of information from health care providers was addressed. When they had contact with HCM specialists, they appreciated it very much. Many patients were aware of media reporting on athletes who died of HCM, and this worried them. For example, a young skier said: "*The fact that athletes drop dead…it is not advantageous for me."* Occasionally, the media interest in SCD was deemed troublesome. "*The less you know, the less ill you are*" as a young patient said. Patients' reaction toward extensive talks about the disease varied and could be contradictory, depending on the situation. A young single said talking about HCM was a matter of distress in new relationships and conflicted with the patient's self-image of being an ordinary normal person.

In two cases, patients were convinced that the disease had contributed to divorce. Having a relative with HCM can affect a patient's self-perception. For example, a young man developed increasing anxiety with age and it culminated when he was about the same age as his father was when he died suddenly due to HCM. This was the trigger for the young man to request an ICD.

9.6 PAPER V

9.6.1 Patient characteristics

The participants in the study had a mean age of 56.8 SD 12.9 years and a majority were males (n=19; 76.0%). An echocardiogram was assessed in all patients. About half of the patients were genopositive (n=13; 52%). Most participants had an ICD as primary prevention (n=22; 88%). A detailed summary of the clinical characteristics was provided in Paper I.

9.6.2 Adherence to PET protocol

The full PET-protocol, including four PET scans (^{15}O-water at rest/stress, ^{11}C-acetate, and ^{11}C-HED) was performed in 24/25 patients. In one young woman, ^{15}O-water at stress was not possible due to emotional stress. In one ^{11}C-HED scan there were motion artifacts, such that analyses beyond RI were not possible.

9.6.3 ICD interrogation

The ICDs were interrogated at 12 months for evidence of NSVT. In total, 10 patients (40%) reached the endpoint of documented NSVT. Another composite endpoint based on a history of appropriate ICD therapy and secondary indication was present in 8 patients (32%).

9.6.4 PET results

The PET data were derived and analyzed. Mean MBF at rest after adjustment of the rate pressure product was 0.91 ml/g/min and severely decreased at stress 1.59 ml/g/min. The mean gradient expressed as the ratio of endocardium to epicardium at rest was 1.14 SD 0.09 but inversed at stress to 0.92 SD 0.16. The MVO_2 mean was 0.088 ml/g/min and the MEE 18.5%. The mean RI was 0.11 /min.

The distributions were typically skewed, which is why percentiles are also presented. The summary of the results is presented in Table 14. Using polar plots, it was possible to visualize individual patients with regard to anatomical distribution. The anatomical view and polar plots are depicted in Figures 15, 16, 17, and 18.

Figure 15. Anatomical visualization of the myocardium using ^{15}O-water exams.

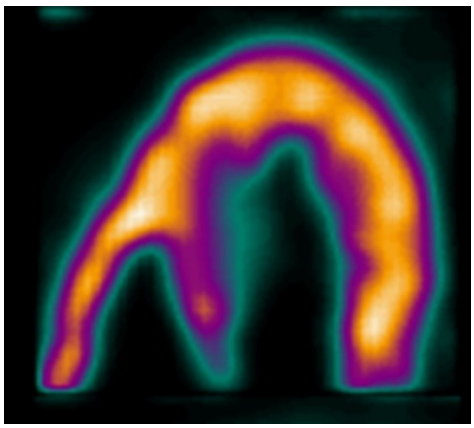


Figure 16. Example of polar plots of MBF at rest and stress of two patients from ^{15}O-water exams.

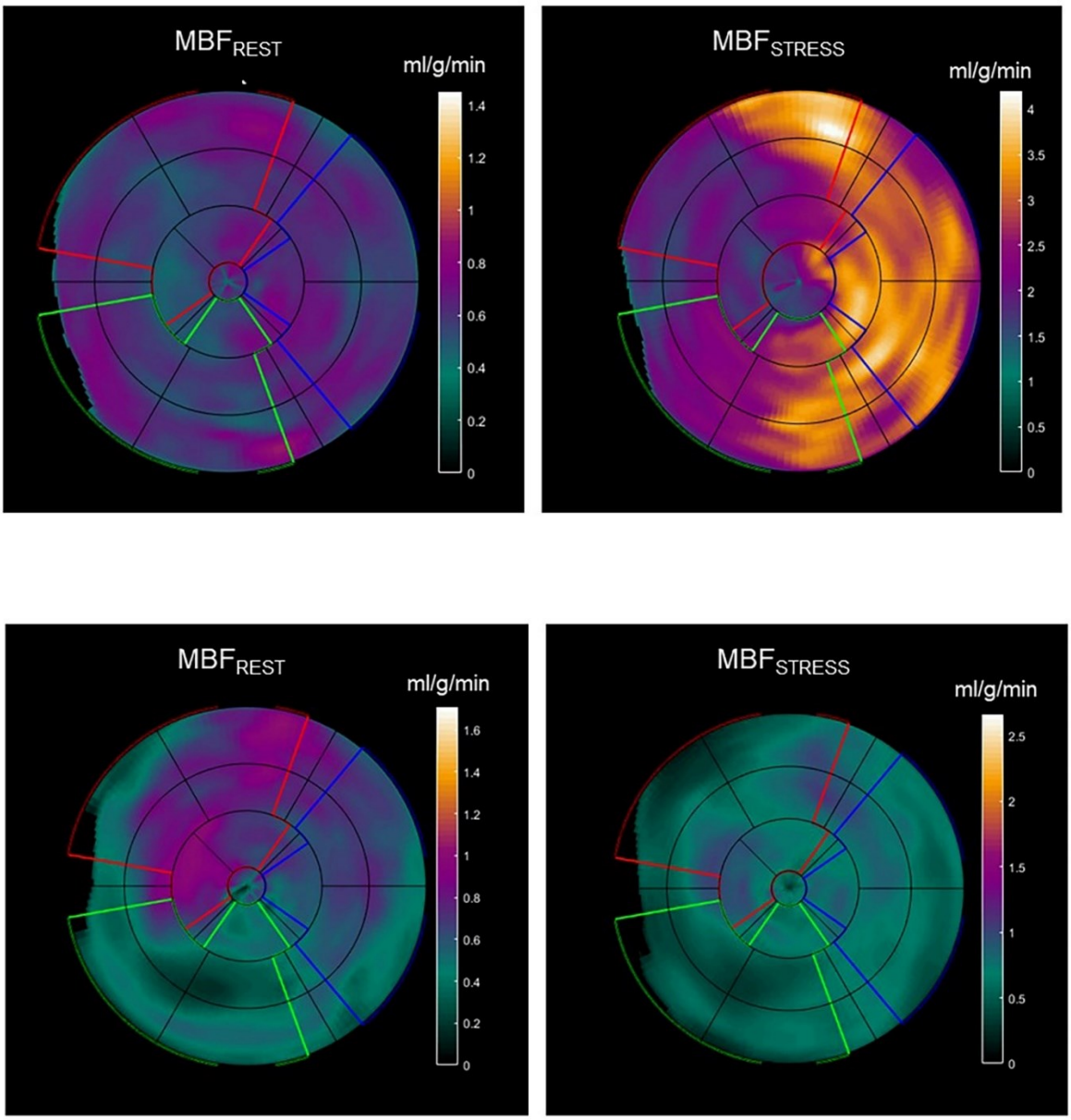


Figure 17. Example of polar plot of MVO_2 of one patient from an exam with ^{11}C-acetate.

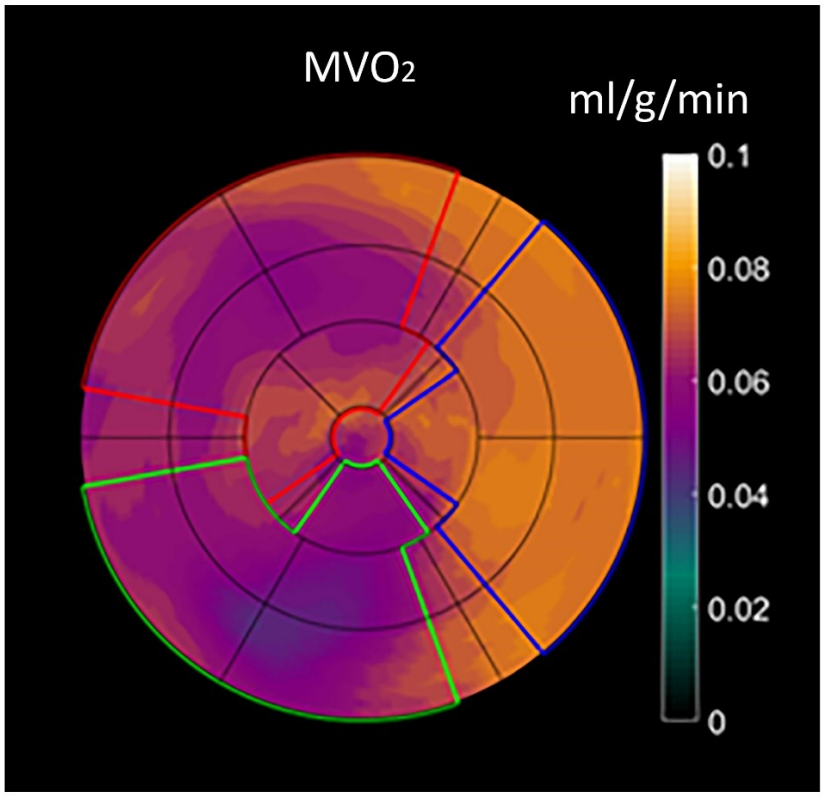


Figure 18. Example of polar plots of retention index of one patient from an exam with ^{11}C-HED.

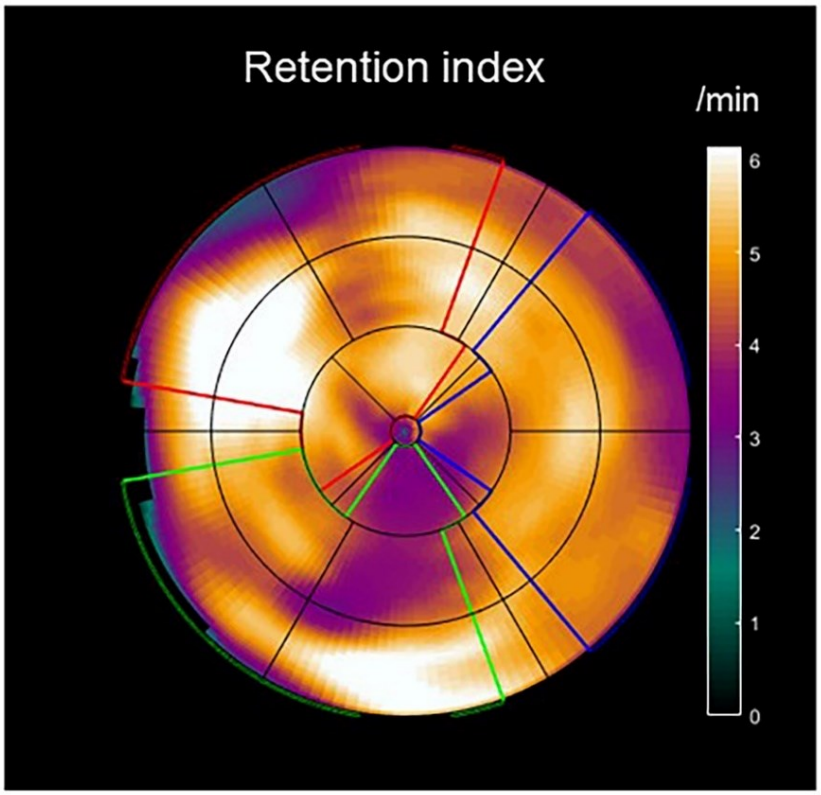


Table 14. PET results from ^{15}O-water, ^{11}C-acetate, and ^{11}C-HED. Modified from Magnusson et al.[355]

	Mean	25th percentile	Median	75th percentile
^{15}O-water				
MBF_{REST} (ml/g/min)ǂ	0.91	0.77	0.90	1.00
MBF_{STRESS} (ml/g/min)	1.59	0.94	1.36	2.29
Heterogenity $index_{REST}$	1.34	1.91	1.26	1.41
Heterogenity $index_{STRESS}$	1.58	1.31	1.55	1.79
Coronary flow reserve	1.78	1.28	1.60	2.32
Defect $size_{REST}$ (%)	1.97	0.09	0.27	3.32
Defect $size_{STRESS}$ (%)	29.51	7.07	30.46	50.80
TPG_{REST}	1.14	1.07	1.13	1.22
TPG_{STRESS}	0.92	0.77	0.91	1.05
^{11}C-acetate				
MVO_2 (ml/g/min)	0.088	0.070	0.085	0.10
MEE (%)	18.5	13.3	16.3	20.9
LV-mass (g/m^2)	109	77	102	129
EDV (ml/m^2)	94	80	96	106
ESV (ml/m^2)	36	22	31	53
SV (ml/m^2)	58	47	56	66
EF (%)	63.3	49.7	64.4	75.1
TG_{MVO2}	0.99	0.94	0.99	1.05
^{11}C-HED				
RI (min^{-1})	0.11	0.090	0.117	0.0126
Defect $size_{RI}$ (%)	14.92	7.19	13.60	20.04
Heterogenity $index_{RI}$	1.73	1.38	1.58	1.75
TG_{RI}	1.06	1.03	1.06	1.09
VT	17.43	15.83	17.76	22.35
Clearance rate	0.019	0.014	0.018	0.020
TG_{VT}	0.960	0.88	0.99	1.03
$TG_{clearance\ rate}$	1.21	1.06	1.12	1.29
^{11}C-HED - ^{15}O-water				
Defect $size_{RI}$ - Defect $size_{REST}$ (%)	12.95	3.88	11.86	17.94
Defect $size_{RI}$ - Defect $size_{STRESS}$ (%)	14.53	−41.60	−13.39	10.39

ǂ Corrected for rate pressure product; heterogenity index=MBF_{MAX}/MBF_{MIN}; TPG=$MBF_{ENDOCARDIUM}$/$MBF_{EPICARDIUM}$; MVO_2, myocardial oxygen consumption; MEE, myocardial external efficiency; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; TG, transmural gradient; RI, retention index; heterogenity $index_{RI}$=RI_{MAX}/RI_{MIN}; VT, volume of distribution.

9.6.5 Hypothesis test

We explored the variables with regard to the binary outcome of NSVT. The most striking result was that the MBF gradient at stress was significantly lower (p=0.022) with NSVT and was borderline significant at rest (p=0.059). The results of the Mann-Whitney *U* test appear

in Table 15. The regional differences were analyzed and are shown in Table 16. Of note is that myectomy was non-significant between those with and without NSVT. The same holds true for genopositivity compared to genonegativity. The composite outcome of appropriate ICD therapy and a secondary-prevention indication defines those with a history of sustained ventricular arrhythmias and was non-significant for all parameters.

Table 15. PET results from ^{15}O-water, ^{11}C-acetate, and ^{11}C-HED with regard to presence of NSVT. Reproduced from Magnusson et al.[355]

	NSVT (p-value)
^{15}O-water	
MBF_{REST} (ml/g/min)[ǂ]	0.405
MBF_{STRESS} (ml/g/min)	0.114
Heterogenity $index_{REST}$	0.134
Heterogenity $index_{STRESS}$	1.000
Coronary flow reserve	0.320
Defect $size_{REST}$ (%)	0.824
Defect $size_{STRESS}$ (%)	0.725
TPG_{REST}	**0.059**[a]
TPG_{STRESS}	**0.022**[a]
^{11}C-acetate	
MVO_2 (ml/g/min)	**0.023**[b]
MEE (%)	0.405
LV-mass (g/m^2)	0.579
EF (%)	0.120
TG_{MVO2}	0.542
^{11}C-HED	
RI (min^{-1})	1.000
Defect $size_{RI\_75\%}$ (%)	0.202
Heterogenity $index_{RI}$	0.120
TG_{RI}	0.698
VT	**0.089**[a]
Clearance rate	**0.061**[b]
TG_{VT}	0.380
$TG_{clearance\ rate}$	**0.052**[a]
^{11}C-HED - ^{15}O-water	
Defect $size_{RI}$ - Defect $size_{REST}$ (%)	0.267
Defect $size_{RI}$ - Defect $size_{STRESS}$ (%)	0.380

ǂ Corrected for rate pressure product; heterogenity index=MBF_{MAX}/MBF_{MIN}; TPG=$MBF_{ENDOCARDIUM}$/EF, ejection fraction; $MBF_{EPICARDIUM}$; MVO_2, myocardial oxygen consumption; MEE, myocardial external efficiency; LV, left ventricle; NSVT, nonsustained ventricular tachycardia; TG, transmural gradient; RI, retention index; Heterogenity $index_{RI}$=RI_{MAX}/RI_{MIN}; VT, volume of distribution. Comparisons performed using Mann-Whitney *U* test. [a] Lower rank in NSVT; [b] higher rank in NSVT.

Table 16. PET results from ^{15}O-water, ^{11}C-acetate, and ^{11}C-HED at regional level with regard to presence of NSVT (p-values). Reproduced from Magnusson et al.[355]

	Anterior	**Septal**	**Inferior**	**Lateral**
^{15}O-water				
TPG_{REST}	0.134	0.244	**0.017**	**0.040**
TPG_{STRESS}	0.178	**0.019**[a]	**0.005**[a]	0.101
^{11}C-Acetate				
MVO_2 (ml/g/min)	**0.052**[b]	**0.086**[b]	**0.046**[b]	**0.027**[b]
TG_{MVO2}	0.222	0.956	**0.059**	0.542
^{11}C-HED				
TG_{RI}	0.292	0.824	0.782	0.698
VT	0.222	**0.027**[a]	0.267	**0.076**[a]
Clearance rate	**0.007**[b]	**0.023**[b]	0.183	**0.035**[b]

[a] Lower rank in NSVT. [b] Higher rank in NSVT.

10 GENERAL DISCUSSION

10.1 PAPER I

In Paper I we validated and analyzed the characteristics of Swedish HCM patients with ICDs, and the efficacy and risk profile with regard to appropriate ICD therapy in a nationwide cohort. The data collection was done before the HCM Risk-SCD prediction model was part of ESC guidelines. Therefore, an extended discussion of the knowledge of risk stratification to date, including its controversies, is integrated into this discussion.

10.1.1 Efficacy of ICD

In Swedish HCM patients, treatment with ICDs was able to terminate all ventricular arrhythmias within the programmed zones. In about half of the cases, ATP was enough, while in the remaining cardioversion was required, sometimes after multiple attempts. The programming of the ICD should be tailored for the individual.

Our study confirmed the efficacy of appropriate ICD therapy in unselected HCM patients, which is reassuring. This is in line with vast experience from international studies, mostly from tertiary/expert centers.[208,209] In fact, there was no single case of ICD failure to convert an episode of VA, even though ATP was often ineffective and several cardioversions sometimes were needed before sinus rhythm was restored. It should be remembered that the extended study period included devices spanning several generations of ICD technology. In the beginning, there were also a few epicardial systems until transvenous system became available. In our cohort there were no S-ICD systems, and implementation thereof has been slow in Sweden.[292,356]

Nowadays, high-voltage ICDs are standard and sophisticated waveform optimization is advantageous. Based on findings from general ICD patients, the tendency in the last decade has been to avoid DFT testing. In Sweden, DFT testing is rarely performed and it has become much less frequent in Europe and even in the United States.[357] The current ICD systems are known to be highly efficacious, testing does not provide a clearly relevant clinical scenario, and the best available systems are used as standard care. Moreover, induction of VF is not without risk and the tolerance for devastating complications is very low, especially in primary prevention. Thus, the potential benefit of DFT testing does not justify the risk.

Historically, because of the increased LV mass in some HCM patients, there has been a concern about the efficacy of cardioversion.[358] High DFTs have been reported to the same extent in HCM and general ICD patients. In a study by Quin et al, 89 HCM and 600 general heart failure patients had similar mean DFTs (10.4 SD 5.8 J vs 11.2 SD 5.6 J) and 3.4% of HCM patients had a DFT above 20 J.[359] In a smaller study of 23 HCM patients compared to general ICD patients, the DFT was higher in HCM patients (13.9 J vs 9.8 J; $p<0.001$) and could be correlated to increased LV mass. A DFT of 20 J or more was noted in 22% of the HCM patients.[359] In another study, prolonged QRS duration was a predictor of higher DFT in HCM.[360] A recently published substudy of SIMPLE found a similar DFT safety margin in 52

HCM patients compared with 1,047 ischemic or nonischemic cardiomyopathy patients (p=0.63).[361]

The fatal case of the young man who suffered from anoxic brain injury after an arrhythmic event and eventually multi-organ failure, described in the Results section, highlights the importance of programming. In this physically active patient, a relatively high detection zone for ventricular arrhythmias was programmed in order to avoid inappropriate shocks. The recurrence of a VT below the detection zone after the vulnerable period of hemodynamic collapse due to VT/VF was catastrophic. The patient was taking two antiarrhythmic agents, which are known to slow reentry circuits and may have contributed to the VT recurrence.[362] This underlines the importance of an individualized approach to programming. The principles of allowing an extended number of intervals, including redetection, will reduce the frequency of unnecessary treatments, because VT may be self-terminating. When therapy is delivered, ATP attempts should be used first, preferably in the form of bursts.[32,34] In the Swedish cohort, programmed bursts were standard, but in the early era, ramp was also a common ATP strategy. While ICDs effectively terminate VT/VF, they do not prevent the occurrence of arrhythmias. The ICD solely rescues the patient from the potentially fatal consequences of dangerous arrhythmias. For most patients, an ICD shock is a dramatic event. From reports from general ICD patients, it seems that a history ICD shock is a marker for decreased HRQL and even mortality.[363] Thus, it is important to utilize strategies to prevent arrhythmias and avoid therapy as much as possible. In patients with recurrent VT episodes, radiofrequency ablation may be considered according to HCM guidelines.[15] This is in line with previous knowledge from general ICD patients. Antiarrhythmic agents or catheter ablation can indeed prevent the recurrence of VT as can shock therapy, even though it has not been proven to improve overall mortality on a group level.[32,34,364]

In our cohort, among the first episode VT/VF, about half (52%) required cardioversion for termination. In the largest ICD study of HCM patients (n=506), 103 patients received appropriate therapy (47.6% defined as VF).[203] Interestingly, 94 of the 103 first episodes were treated by cardioversion and ATP only was used in the remaining 9 episodes. This is considerably higher than in the prospective PainFREE trial (ischemic and nonischemic cardiomyopathy) that aimed to reduce the numbers of cardioversion by using ATP (80.6% of episodes were terminated by ATP) with a zone 188-250 BPM and defining rates above 250 BPM as VF.[365] It should be noted that HCM patients with ICDs are probably more heterogeneous than general ICD recipients. Often HCM patients are younger, have longer life expectancy, less comorbidity, and different and more active lifestyles. This necessitates tailored programming on an individual level.

In addition to preventing SCD as a consequence of ventricular arrhythmia, pacing may also protect the patient from potentially life-threatening bradycardia. Not to forget, bradycardia is often present in HCM because of beta-blockade and other antiarrhythmic therapy. In patients with substantial LVOT obstruction, right ventricular apical pacing may be considered to alleviate gradient and its related symptoms. This should be borne in mind when

programming, including the activation and optimization of the rate-adaptive sensor. My impression from reading numerous device reports based on interrogations from the cohort is that Swedish HCM patient with ICDs are managed by cardiologists with expertise in ICD programming and electrophysiology. As a rule, ICDs were programmed using the most appropriate strategies at the time. It should be stressed that close collaboration among different branches of cardiology is important not only for decision-making regarding ICD implant, but also during follow-up, especially for the optimal management of inappropriate ICD therapy.[366]

10.1.2 Appropriate ICD therapy

Approximately a quarter of the patients in our cohort experienced appropriate ICD therapy over a mean of five years. The annualized rate of appropriate ICD therapy in secondary prevention was 7.0% and in primary prevention 4.5%, which is in line with international experiences. The risk for a dangerous arrhythmia during the first months after secondary-prevention ICD implant is pronounced. In primary prevention, the risk is linear and continues throughout the study period, which is why device exchange should be standard even after years without the need for therapy.

In our cohort, appropriate ICD therapy occurred in 26% of the patients during a mean follow-up of 5.3 years. The proportion and rate of appropriate ICD therapy was higher among patients with an ICD for secondary rather than primary prevention. In secondary-prevention patients, the risk for a dangerous arrhythmia was higher in the first year after implant than later on. This is expected because after a cardiac arrest or sustained VT, there is vulnerable period in the early months. This is well-known from other ICD patients and can be generalized to HCM patients. On the other hand, primary prevention, i.e. prophylactic ICD implant, shows a linear event rate over the years. From a clinical perspective, after a life-threatening arrhythmia, the patient should be continuously monitored by ECG in the hospital and, when appropriate, an ICD should be implanted before they are released from the hospital. In special cases, a wearable cardioverter defibrillator could be an alternative if the implant of a transvenous or S-ICD is not possible before discharge. In primary-prevention patients, there is a continuous risk even after several years with no events and no need for therapy delivery. This is an important point, because sometimes the question arise that device replacement is not necessarily due to the absence of any life-threatening arrhythmias for many years. There may sometimes be legitimate reasons not to exchange a depleted ICD, especially in the elderly with severe comorbidities and very short life expectancy. However, the fact that there has not yet been an arrhythmic event requiring therapy cannot justify removing an ICD and not replacing it.

In our cohort, the annualized rate of appropriate ICD therapy in secondary-prevention patients corresponds to 7.0% and in primary prevention it is 4.5%. The rate will depend on the underlying risk of the patients. It will also be affected if the rate is not linear over the time period. Various follow-up periods within the cohort with patients based on different risk

profiles make an analysis even more complicated. For this reason, interpretation can become quite complex when several studies are compared.

10.1.3 Comparison of implantation rates, temporal trends, and selection

General ICD implantation rates have been modest in Sweden but have increased and are similar to other Nordic countries, higher than the UK, lower than Germany and the United States. The proportion of primary-prevention ICDs in HCM is higher than stated in a review (74% vs 83%). The rate of appropriate ICD therapy is comparable to international experience, although slightly higher rates are observed. The burden of established risk factors is higher in Swedish patients than in many international studies and age is older, which indicates a more conservative approach toward prophylactic ICDs in HCM. The unselected nature of the Swedish cohort may account for discrepancies.

The risk profile and other baseline characteristics may change in clinical practice over the years. One must bear in mind the historical context; ICDs have been more frequently used in recent years, which was also seen in our cohort. It is likely that less bulky and cheaper devices, improved implantation techniques without DFT testing, streamlined follow-up including home monitoring, and overall available resources for diagnostics and follow-up have led to more implants. Evidenced-based expansion from other indications and the availability of surgical facilities have increased implantation rates in general.[32–34] Awareness of HCM disease and risk stratification may also influence implants. The guidelines and their implementation are of course likely to impact the volume of implants. Notably, the general ICD implant rate has historically been modest in Sweden although it is increasing. It is less than in the United States but comparable to many other European countries. In 2013, the median European ICD implantation rate was 82 per million inhabitants. Sweden had 198 per million, comparable to other Nordic countries (Denmark 231, Norway 214, Finland 194, and Iceland 171), lower than Germany (336) but higher than the UK (92).[367–369]

In the largest tertiary center in Sweden, two-thirds (66%) of ICDs in HCM during 2005-2016 were implanted for primary prevention, and it should be noted that this may indicate a more conservative approach toward primary prevention than in published international cohorts.[235] The structure of care may differ among countries but can also vary within countries from region to region and even among hospitals, and finally among the prescribing clinicians.

Since the first case series of HCM patients with ICD, several studies have reported outcome with regard to appropriate ICD therapy. Sometimes these cohorts are merged with other cohorts or there are multiple reports after extended follow-up and inclusion of more patients. There are also cohorts with a mix of HCM patients with and without ICDs. An extract of publication from these cohorts reporting annual rate is summarized in Table 17. Cohorts based on less than 10 patients or pediatric patients were excluded.

Table 17. Studies on HCM patients with ICDs with regard to appropriate ICD therapy.

First author	Year	Size, (n)	Geographic area	Follow-up, mean (years)	Age, (years)	Male, (%)	PP, (n)	ICD therapy, PP and SP	ICD therapy, PP	Annual rate
Primo[370]	1998	13	Belgium, Spain	2.2	48	62	2	2	NR	SP & PP: 7.0%
Begley[279]	2003	132	USA	4.8	34	61	85	27	13	SP: 11% PP: 4.5%
Almquist[371]	2005	75	USA	3.6	36	65	71	NR	NR	SP & PP: 1.9%
Lawrenz[372]	2005	3.4	Germany		53	53	6	4	1	SP: 10% PP: 5%
Marin[373]	2006	45	Spain	2.7[c]	43	62	27	10	1	SP:11.1% PP: 1.6%
Medeiros[374]	2006	26	Brazil	1.7	43	46	16	4	1	SP & PP: 11.1%
Maron[203]	2007	506	USA, Europe, Australia	3.7	42	64	383	103	55	SP: 10.6% PP: 3.6%
Woo[375]	2007	61	Canada	3.3	46	66	50	8	NR	SP & PP: 4%
Cuoco[250]	2008	123[b]	USA	2.9	48	66	100	9	9	PP: 2.8%
Syska[280]	2010	104	Poland	4.6	36	45	78	27	13	SP: 7.9% PP: 4.0%
O'Mahony[281]	2012	334	UK	2.2	40	62	307	28	21	SP: 4.3% PP: 2.0%
Prinz[376]	2013	87	Germany	3.5	50	60	85	15	NR	SP & PP: 16.4%
Shiozaki[377]	2013	26	Brazil	3.2	39	46	21	13	NR	SP & PP: 15.6%
Vriesendorp[282]	2013	134	Netherland, Belgium	4.2	44	66	93	38	20	SP & PP: 6.8% PP: 5.1%
Debonnaire[378]	2014	92	Netherlands	4.7[c]	50	69	70	21	16	SP & PP: 4.9%
Frommeyer[379]	2016	18[a]	Germany	2.6	35	83	14	1	1	SP & PP: 2.1%
Konstantinou[380]	2016	37	USA	3.1[c]	49	76	37	NR	10	PP: 7.2%
Lambiase[222]	2016	99[a]	USA, New Zealand, Netherland, UK	1.8	42	75	87	3	NR	SP & PP: 1.8%
Magnusson[283]	2016	321	Sweden	5.4	52	70	237	77	47	SP: 7.0% PP: 4.5%
Rigopoulos[381]	2016	32[b]	Germany	5.3[c]	50	53	31	4	4	SP & PP: 2.5%
Ruiz-Salas[382]	2016	48	Spain	4.1	44	67	48	NR	8	PP: 4.2%
Thavikulwat[284]	2016	135	USA	5.2	48	85	125	25	20	SP: 9.8% PP: 2.6%
Viswanathan[383]	2016	60	Canada	5.1	44	73	60	9	9	PP: 2.5%
Weinstock[221]	2016	16[a]	USA	1.5	40	NR	13	0	0	SP & PP: 0%
Francia[384]	2017	66	Italy	4.4	45	62	65	14	NR	SP & PP: 4.8%
Wang[285]	2017	160	USA	4.0	47	61	155	24	NR	SP & PP: 3.8%

Follow-up was reported as mean if not specifically noted as median. [a] S-ICD cohort; [b] ASA cohort; [c] median. NR, not reported; PP, primary prevention; SP, secondary prevention.

Schinkel et al published a systematic review in 2012 based on 2,190 patients with HCM and ICDs with a mean follow-up of 3.7 years.[208] The mean age was 42 years and a majority was men (62%). The percentage of primary-prevention ICDs was 83%. The risk factors included LV wall thickness ≥30 mm (20%), family history of SCD (43%), NSVT (46%), syncope (41%), and abnormal blood pressure response (25%). The average number of risk factors was 1.8 per patient. The authors pinpoint that in only 7 of the 16 studies there was sufficient information about the risk factor profile for further meta-analyses. The annualized rate of appropriate ICD therapy was 3.3%.

A subsequent systematic review of HCM patients with ICDs was published in the beginning of 2017.[209] It included 3,797 patients with a mean age of 44.5 years and a majority was men (63%). Most patients had ICDs for primary prevention, 83% (compared to 74% in our cohort). The risk profile was as follows: LV thickness ≥30 mm (10%), family history of SCD (26%), NSVT (25%), syncope (7%), and abnormal blood pressure response (22%). This burden of risk factors, except for abnormal blood pressure response, is less than in primary-prevention patients in our cohort. This could be interpreted that it is harder to qualify for an ICD in Sweden compared to other geographical areas. If so, it may be in line with the more conservative approach in Sweden reflected in the general implantation rate of ICDs overall. It could be speculated that this approach implies less sensitivity, which could result in SCD that could have been prevented. However, the number of SCD events in HCM patients who did not receive an ICD remains unknown. Moreover, the diagnostic pathways of HCM are often complicated and many patients may be undiagnosed. In the pooled meta-analysis by Wang, the annualized rate of appropriate ICD therapy was 4.8% (95% CI 3.9-5.9).[209] It should be noted that there was significant heterogeneity between studies I^2=84%, reflecting the diversity of the cohorts. In our nationwide Swedish cohort of unselected patients without tertiary center bias, the corresponding annualized rate of appropriate therapy was 5.3%. This is a bit higher than in the meta-analysis, but still falls within the 95% CI. The mean age in our cohort was 52.1 years, which is higher than in the meta-analyses. It likely reflects the unselected nature of the cohort based on nationwide inclusion, which may be different from tertiary centers.

10.1.4 Appropriate ICD therapy in primary and secondary prevention

Survival after cardiac arrest or sustained VT in HCM warrants ICD treatment if life expectancy and related quality of life is reasonable. The scientific controversies are mainly about assessment and judgment of risk factors to decide the eligibility for primary prevention. Most studies are from the Western world and the majority of patients are male, as in our study. The mean follow-up time of our study was in the upper range compared to other ICD cohorts. The baseline characteristics and outcome regarding appropriate therapy from our study can be generalized to the findings from tertiary center cohorts of general HCM patients with ICDs. The annual rate and 5-year cumulative incidence in our cohort was comparable to international tertiary-center data.

Secondary prevention is often a straightforward decision when it comes to risk evaluation, but challenges arise when it comes to overall risk assessment, because life expectancy and estimated HRQL deserve careful clinical judgement. Secondary-prevention patients are at elevated risk right after they get an ICD, but this risk subsides over time, which could have impacted the total rates found in our cohort, which followed patients for 5.4 years. Furthermore, the eligibility criteria for secondary prevention may differ along with ICD programming, but these details remain unknown.

The controversies of risk stratification focus on primary prevention. From this perspective, it is interesting to review data on primary prevention and appropriate ICD therapy. Maron et al merged data from 506 HCM patients with primary-prevention ICDs from the United States, Europe, and Australia.[203] This is by far the largest study of this population and patients were followed for a mean of 3.7 years. Three-quarters of the total study population (75.7%) was men. The annualized appropriate ICD therapy was 3.6% and 10.6%, for primary and secondary prevention, respectively. This differed slightly from our study, with higher rates for secondary prevention (7.0% vs 10.6%, respectively) and lower rates for primary prevention (4.5% vs 3.6%, respectively). At 5 years we reported a cumulative incidence of 21% for the whole cohort, while Maron reported 23%.

In primary prevention, the eligibility criteria may differ even more than in secondary prevention, as it is based on clinical judgement of risk factors. ICDs are more widely used in the United States for general heart failure, which makes a European comparison more relevant. Vriesendorp et al reported 134 Dutch HCM patients from two tertiary centers (66% males) with ICD with a mean age of 44 SD 17 years over a mean follow-up of 4.2 SD 4.8 years.[282] They reported 6.8% annualized rate of appropriate ICD therapy in the whole cohort and 5.1% for primary-prevention patients, which is similar to our results and is also from the same period. In a Polish single-center study 104 HCM patients with ICD, who had a mean age of 36 years was followed for 4.6 years.[280] Notably, a minority of these patients was male (45%). Their annualized appropriate ICD therapy rate was similar to our cohort: the whole cohort (5.6%), secondary prevention (7.9%), and primary prevention (4.0%). However, the differences between the underlying patient characteristics are striking with regard to age, sex, and selection. Finally, a large British study on HCM and ICD by O'Mahony et al analyzed 334 patients (62% men, 92% primary prevention) with a mean age of 40 years from a tertiary center during a median follow-up of 3.6 years.[281] The outcome measurement was appropriate shock, not ATP, and the annual rate was 4.3% for secondary prevention and 2.0% for primary prevention. Because of the difference in outcome measurement, comparisons are difficult to draw. The ratio between secondary and primary prevention is similar. The lower incidence reflects the definition of the endpoint and raises the matter of differentiation between shock and ATP. From one perspective, cardioversion and ATP might be considered identical because they both terminate life-threatening VT/VF. However, sometimes therapy delivery is unnecessary, because the arrhythmia would have self-terminated. The proportion of self-terminating arrhythmias is likely higher among ATP-treated episodes compared to cardioverted episodes. This issue is complicated as programming decisions may come into

play that affect when each therapy modality is used: ATP is often programmed for lower rates and more intervals than shocks, which, in turn, may be programmed for higher rates and only after ATP has failed. In the highest detection zones, some ICDs do not offer an ATP programming option, although it is increasingly becoming more standard. Furthermore, ATP is only moderately effective for the treatment of monomorphic VTs in HCM patients (69% were converted by ATP).[385]

10.1.5 Evidenced-based approach to risk stratification

The evidence for risk stratification relies on observational studies of diverse cohorts and expert opinions. Typically, appropriate ICD therapy and potential risk markers are evaluated at baseline. In the connection, it is important to note that the evaluation of risk factors is prone to measurement errors and misinterpretation of patient history. Every patient with an ICD has already been deemed at elevated risk based on known underlying risk factors. In both univariable and multivariable analyses, these risk markers compete with each other and this confounding effect should be taken into account when considering HRs.

The decision to offer an ICD for primary prevention is based on the evaluation of established risk factors and sometimes markers regarded as modifiers of SCD risk. This task of risk stratification is of utmost complexity on an individual level. There are no randomized controlled trials, as in many other fields of medicine, including ICDs in heart failure.[33] Instead, the relevant guidelines are based on observational studies and expert opinions. Many of these studies are limited by small sample size, methodological inconsistencies regarding definitions, and even study design flaws. These cohorts are based on widespread geographical areas with different resources and traditions. In Sweden, the health care system provides an insurance coverage for the whole population, and by law socioeconomic factors should not bias health care decisions for the individual. Because our study was national, it may offer a more generalized approach to risk assessment. In addition, we included all patients and we are not at risk for the selection bias that may occur at tertiary centers.

Before comparing our results to other cohorts, the interrelationship of risk factors should be highlighted. Risk factors may compete with each other. Thus, an HR >1 means that this particular factor is stronger with respect to the other factors. In the same study, an HR <1 still represents risk, even though it is not as strong compared to the other risk factors. In theory, all patients who receive an ICD are selected because the clinician considered the patient and their increased risk for SCD. In reality, risk assessment is not always so straightforward. The judgement of some risk factors and markers may be arbitrary and imaging can be imperfect with imprecise measurements. The interpretation of an anamnesis can be quite complex, for example, determining the cause of a syncopal spell. Typically, studies of outcome measurements, for example appropriate ICD therapy, and their association with the risk profile relies on baseline values. In such cases, the time of ICD implant is considered as baseline. During follow-up or even since evaluation of previous risk factors, things may have changed. Although most HCM patients remain stable over a few years, there can be measurable disease progression as well as less apparent changes of possible arrhythmogenic

substrates, modifying factors of the disease, comorbidities, lifestyle changes, and interventions. The concept of *long-term follow-up* is rather arbitrary and is far from a lifetime analysis. This is especially true in HCM patients, who often are younger and have a long life expectancy. The occurrence of an arrhythmia can be based on a complex interplay of factors, in which each risk factor/marker and possible triggers are largely unknown in the individual case.

We adhered to the statistical methods commonly used in this scientific field. It should be noted that multivariable analyses may produce different results than other forms of statistical analysis and the associations reported were not always clear-cut and could vary among cohorts. The interaction among risk factors can be analyzed, but still requires careful judgement. Moreover, there are several approaches as to whether to include a risk factor in a multivariable analysis; it may be based on results from earlier studies, backward/forward stepwise elimination, or a combination thereof. The predictive power of risk factors depends on two things: sample size for one, and for the other, the number of events, which is indirectly linked to follow-up time. To increase sample size and follow-up time, data can be merged but this approach may increase heterogeneity and make generalization more difficult. This is even more pronounced in meta-analyses, where a reduction of information takes place when data are pooled. The estimates of such analyses may seem more precise but some skepticism is warranted and should not replace clinical judgment.

10.1.6 Adherence to guidelines

In our Swedish nationwide cohort, almost all patients had an established risk factor at baseline.

Our study was performed before the HCM Risk-SCD calculator was implemented. Instead, clinicians based their decision on the guidelines at that time, possibly with some modifications based on their own clinical judgement and interpretation. Only two (0.8%) of the primary-prevention patients in our study were considered not to fulfill established risk assessment, but they were deemed as high risk by the clinician. From a specificity perspective, the Swedish cohort reflects a strong adherence to the established risk stratification strategy. There was basically no off-label use. The two exceptions were well motivated based on the knowledge at the time. In comparison, a Dutch study reported 15% of the recipients did not meet established criteria (notably AV block due to septum reductive procedures) and the largest of merged cohorts had 3.5% who did not fulfill these criteria.[203,282] It is understandable, although not scientifically sound, to prescribe an ICD in borderline cases if there is already an indication for permanent pacemaker system.

10.1.7 Sudden cardiac death outcome measurement

Appropriate ICD therapy is often used as surrogate for SCD. This leads to an overestimation of the benefit of ICDs, as not all ventricular arrhythmias are lethal. This issue is complex as ICDs also protect patients from life-threatening bradycardia. In HCM cohorts without ICD, SCD is categorized based on anamnesis when ECG is not available. Our cohort adhered to

the most widely used definition of appropriate ICD therapy, but awareness of differences in outcome measurement is warranted.

In primary prevention, risk stratification is based on an evaluation of risk factors/markers and is related to outcome. The outcome in ICD cohorts is essentially appropriate ICD therapy based on the definition described in the Materials and Methods section. The time to first endpoint is used. However, there are studies that solely use cardioversion, i.e. ICD shock or discharge, and not ATP as an outcome. It can be argued that ICD shock is more likely to indicate life-threatening arrhythmias than ATP, but this is not necessarily true and certainly not always the case. The use of shock also depends on programming, including detection zones and numbers of intervals before therapy delivery is launched. For example, an episode detected in the VF zone is often programmed to be treated quickly, usually after only a few intervals. While noncommitted systems will abort a shock if the arrhythmia resolves on its own during charging, a shock for VF may be delivered so quickly that it cannot be cancelled even if the rhythm might have converted spontaneously on its own a few seconds later. With ATP, at least one attempt is often used in VF-zones and may be effective. Slower VTs may degenerate into VF and result in shock therapy if ATP was not attempted. The tendency to avoid shock by programming several ATP sequences in different zones after an extended number of intervals has evolved over the years, and this evolution can create a bias when comparing studies from different time periods. Since there is no standard ICD programming, comparisons of studies are not possible, Furthermore, ICD programming may change, even more than once, over the follow-up period. Using appropriate ICD therapy of both ATP and cardioversion will lead to a non-differential bias within studies, because all markers are evaluated the same way. Comparison with other studies using the same approach is possible, but if a study limits outcome to shock therapy only, then this will result in differential bias.

In HCM cohorts without ICD, SCD or aborted SCD after resuscitation is often used as the outcome. This is appealing because it may reflect the actual proportion of SCD. By contrast, using ICD therapy delivery as the outcome will overestimate the number of life-threatening arrhythmias, as some are self-terminating. Nevertheless, in reality, the definite cause of SCD is a matter of judgement and the definition described above is not always easily applicable. In retrospective analyses, it can be difficult to access reliable and detailed data to determine cause of death. The distinction between SCD and deterioration of heart failure can sometimes be challenging to determine. The HCM populations often constitute a mixture of outcome measurements, as some patients have an ICD. Thus, the composite endpoint includes appropriate ICD therapy. The outcome is typically SCD, survived cardiac arrest, or appropriate ICD therapy used as an equivalent. Clearly, this can make comparisons difficult. Instead, the relative strength of risk markers within a study or among studies with similar design should be interpreted in its context. ICD outcome has the advantage in that it correlates with a definite ventricular arrhythmia, even though it will overestimate the benefit of an ICD if all therapies are regarded as life-saving. On the other hand, the simultaneous protection from bradycardia death offered by an ICD cannot be determined and is therefore underestimated.

10.1.8 Risk factor evaluation

We confirmed the usefulness of established risk factors as predictors of appropriate ICD therapy. Among these risk factors, NSVT was the strongest while family history of SCD was the weakest. There was an increased risk with increased age but this association disappeared after adjustment for other factors. Neither was sex related to outcome. AF and EF<50% emerged as risk markers, especially in primary prevention.

The established risk factors for SCD in HCM have been NSVT, family history of SCD, maximal wall thickness >30 mm, and unexplained syncope. Abnormal blood pressure response at exercise test has been a matter of debate and was missing in some evaluations in our cohort. These risk factors were analyzed using Kaplan-Meier estimate and Cox proportional hazards in uni- and multivariable analysis. We added AF and EF<50% in both the analyses of primary and secondary prevention. In secondary prevention, there was no uniform assessment of the established risk factors, because the decision-making physician did not deem it necessary, since survivors of cardiac arrest or VT with hemodynamic compromise were already eligible for an ICD, regardless of other risk factors.

In secondary prevention, AF (HR 1.8) and EF<50% (HR 3.1) were highly significant in univariable analysis. Increasing age was associated with increased risk of outcome, but with a borderline p-value of 0.043. Male sex showed a tendency toward higher risk (p=0.073). In the multivariable analysis, EF<50% (HR 2.6) remained significant but age, sex, and AF were not.

In primary prevention, increasing age was significantly associated with outcome but after adjustment in multivariable analyses it turned out to be not significant at all. It seems that both low EF and AF increase with age and long-term follow-up, which may explain these findings. In univariable analysis, both EF<50% (HR 3.7) and AF (HR 3.6) were strongly associated with outcome and remained significant in the multivariable analysis. In fact, these risk factors were actually stronger than the established risk factors. Only NSVT was significant in univariable analysis (HR 1.97) but weakened in the multivariable analysis. Again, it is important to realize the relativity of HR as a measurement, since risk factors compete with each other in the analysis. These findings underscore the importance of NSVT as a risk marker, even in this population of patients with a higher mean age than many cohorts. In an analysis based on only the five established risk factors, the magnitude of risk was in the following order: NSVT, syncope, abnormal blood pressure response, maximal wall thickness, and lastly family history of SCD. In a subgroup study where all patients with AF and EF were excluded, none of the patients with syncope or family history of SCD had received any appropriate therapy. While there were only 15 patients in each of these subgroups, it nevertheless suggests less of an independent predictive value than expected for AF and EF. Based on our findings, we suggest increased attention to further evaluation of these risk markers in patients eligible for ICDs.

10.1.8.1 NSVT

NSVT was the most common risk factor in our cohort and its importance, based on several studies from diverse populations, is unequivocal. The predictive power seems stronger in younger patients. The role of duration, frequency, and rate of the NSVT has not yet been completely elucidated.

NSVT was highly prevalent in the risk profile (58.2%) and emerged in our cohort as the strongest single risk factor in primary prevention, which intensifies its strength with respect to the other risk factors. While the role of NSVT as a risk factor in elderly patients has been questioned even in the guidelines, it seems to make sense to use it in this context as many patients in our cohort had multiple risk factors.

The presence of NSVT is considered an established risk marker for SCD in HCM, even though its predictive value seems to differ between age groups. The definition of NSVT also may vary, as described in the Materials and Methods section. Typically, a Holter monitor for 24-48 hours represents the standard evaluation in routine follow-up of HCM patients. Nevertheless, telemetry in the hospital ward, exercise ECG, thumb-ECG and other hand-held devices, insertable cardiac monitors, and the availability of smart-watches and fitness monitors are additional sources for rhythm monitoring. It should be remembered that most scientific studies use 24-Holter monitoring at baseline, i.e. before ICD implant, for the assessment of this risk factor. The characteristics of patients may vary among cohorts and over time, for example, half of the patients in an early study by Fananapazir et al of 230 consecutive HCM patients (mean age 39 years) had NSVT on Holter.[386] In a study using 14-day Holter monitoring in 77 HCM patients (mean age 53 years), NSVT occurred in 75%; 23% and 45% during the first 24 and 48 hours, respectively.[387]

Prior to the ICD era, a study by Maron et al (99 HCM patients, mean age 38 years) found that NSVT on 24-hour Holter was shown to predict SCD (24% vs 3%; $p<0.05$).[388] Spirito et al analyzed 151 asymptomatic HCM patients, of whom 27.8% had NSVT and the RR of SCD (n=6) was 2.4 compared to those without NSVT (p=0.24) during a mean follow-up of 4.8 years.[389] In a study by Elliott of 368 HCM patients (mean follow-up 3.6 years, 22 SCD), the HR for NSVT was 1.8 (p=0.21), which remained unchanged in the multivariable analysis (HR 1.9).[192] In a later report by Elliott et al of 917 HCM patients (mean age 37 years), 18.8% had NSVT and it was the strongest risk factor in multivariable analysis (RR 3.8; $p<0.001$).[133]

Monserrat et al reported that among 531 HCM patients (5.8 years follow-up) who underwent a mean of 41 hours Holter monitoring, 19.6% had NSVT, and the proportion increased with age. In patients younger than 30 years, freedom from 5-year SCD was lower in those with NSVT (77.6% vs 94.1%; p=0.003). The NSVT odds ratio (OR) with regard to SCD was 4.4 (p=0.006) in the group age ≤30 years and 2.2 (p=0.1) in those >30 years. NSVT increased significantly with age (p=0.008), maximal wall thickness, and left atrial size. There was no relation between duration, frequency, and rate of NSVT and outcome at any age group.[116]

Wang et al studied 160 HCM patients with ICDs. About half (54%) had had NSVT at baseline or at device interrogation. NSVT was significantly associated with appropriate ICD therapy (HR 4.0; p=0.009). Notably, NSVT runs at a rate >200 BPM (HR, 15.6; p<0.0001) and >7 beats (HR 6.2; p=0.002), and repetitive runs of NSVT (HR 9.2; p=0.001) but not slower, shorter or single episodes were associated with outcome.[285] This contrasts with the previously mentioned study by Monserrat.[116]

Dimitrow et al reported on 1,306 HCM patients, of whom 27.0% had NSVT and although the study confirmed the significance of NSVT, it did not report HR.[390] Their study design was different than other studies, because they use time since birth instead of first evaluation of HCM.

Gimeno et al showed that exercise-induced NSVT (mean 221 BPM) was associated with SCD/appropriate ICD therapy in a large cohort of 1,380 HCM patients, of whom 24 had exercise-induced NSVT (n=24) and exercise-induced VF (n=3).[391] Patients with exercise-induced NSVT/VF had more severe hypertrophy (22.6 vs 19.5 mm, p=0.009) and larger left atrial diameter (47.3 vs 43.7 mm, p=0.03). The HR for the combined endpoint of NSVT and VF was 3.7 (p=0.002) and the HR for solely NSVT 2.8 (p=0.049) for SCD/ICD discharge.

Francia et al reported on 51 HCM patients (mean age 48 years) with ICDs, of whom 66% had NSVT as a preimplant risk factor.[384] During a mean of 3.2 years follow-up, 11 experienced appropriate ICD therapy. NSVT length in beats (HR 1.05; p=0.02) but not heart rate (HR: 1.00; p=0.86) was associated with outcome.

In the study by Syska et al of 104 HCM patients (mean age 36 years) with ICDs, the HR of NSVT was 10.3, which was the only predictor for an appropriate ICD therapy (positive predictive value 22%, negative predictive value 96%).[280]

In the HCM Risk-SCD cohort (n=3,675), 17.3% had NSVT at baseline and its HR regarding SCD was 2.5 (p<0.001).

The relative impact of NSVT compared to other risk factors is strong based on most studies. In the largest study (n=506), Maron et al did not state HR, but appropriate ICD therapy per 100 person-years was 4.2 for NSVT, which was the strongest of all four established risk factors. In an analysis of patients with only NSVT as a risk factor, it remained strong with 4.0 events per 100 person-years.

10.1.8.2 Family history of SCD

The definition of family history of SCD varies, and in our real-life setting we found a discrepancy from guidelines. Based on numerous studies, family history of SCD is an established risk factor even though its strength independent of other risk factors has been questioned.

In ACCF/AHA guidelines, a family history of SCD is a risk factor that justifies ICD implant but in the ESC guidelines, family history is one part of the risk model. Even though it is used

as a binary variable, the interpretation of family history is not always straightforward, and may depend on the age of the SCD victim, whether a first- or second-degree relative is involved, the likelihood of HCM in the fatal case, the surrogate appropriate ICD therapy, the number of relatives/proportion and the age of the patients who are to be risk stratified. Other potential risk factors and modifiers are also taken into account, either based on the risk model or by clinical judgment.

While a family history of SCD in HCM is well recognized, its role and weight as a risk factor is actually more controversial. In Table 18, established risk factors and their HRs are depicted, but it should be noted that univariable and multivariable associations may differ due to interaction between factors. In high-risk cohorts, for example ICD cohorts in which all patients are deemed at high risk, the risk factors then compete with each other. Thus, the relative strength of the factors becomes apparent. In most of these studies (Table 18) a family history of SCD had an HR >1.0. To achieve absolute incidence, the rate can be used but this strategy does not resolve the interaction among variables and modifiers.

Table 18. HCM studies on risk markers of SCD.

Author	Year	Size (n) (% ICD)	HR/RR, uni-/multivariable	NSVT	Unexplained Syncope	Family history of SCD	LV hypertrophy
Monserrat[116]	2003	531 (4.0%)	HR multivariable	4.0	1.3	1.4	3.5
Elliott[133]	2006	917 (5.9%)	RR multivariable	3.8	2.3	1.9	1.7
Gimeno[391]	2009	1,380 (unknown)	HR multivariable	2.6	2.1	1.8	0.9
Efthimiadis[392]	2009	166 (unknown)	RR univariable	3.5	13.7	1.8	10.1
Rubinshtein[393]	2010	424 (9.7%)	HR univariable	6.9	0.7	2.4	6.4
Syska[280]	2010	104 (100%)	HR univariable	10.3	0.9	3.6	1.0
O´Mahony[137]	2014	3,675 (15.2%)	HR univariable	2.5	2.3	1.8	Not reported
Ismail[394]	2014	711 (unknown)	HR univariable	1.7	0.8	0.8	1.6
Debonnaire[378]	2015	195 (29.7%)	HR univariable	2.5	5.6	1.4	3.6
Magnusson[283]	2016	237 (100%)	HR multivariable	1.8	1.1	0.8	1.4
Klopotowsky[395]	2016	328 (30.5%)	HR multivariable	3.3	1.8	2.1	3.7
Todiere[396]	2019	354 (unknown)	HR univariable	1.2	Not reported	0.9	6.3

In the largest study, a compelling analysis was made among patients with only family history of SCD as a risk factor: the HR was 2.7 (95% CI 1.1-5.1) as seen in Table 19.[203]

Table 19. In the study by Maron et al, based on 506 HCM patients of pooled cohorts, the four risk factors were established and expressed as appropriate ICD therapy per 100 person-years.[203]

	Appropriate ICD therapy per 100 person-years (95% CI)	
Risk factor	**All 4 risk factors (n=383)**	**Only 1 risk factor (n=173)**
Family history of SCD	2.9 (1.7-4.7)	2.7 (1.1-5.1)
Syncope	3.6 (2.2-5.6)	5.2 (2.5-9.6)
Massive LV hypertrophy	4.0 (1.9-7.3)	2.1 (0.04-11.4)
NSVT	4.2 (2.7-6.2)	4.0 (1.5-8.7)

In another, smaller study by Bos et al, those with a family history of SCD as a single risk factor had appropriate ICD therapy at a rate of 2.2 per 100 person-years.[397] In patients where all four established risk factors were analyzed, family history of SCD had HR 2.9 (95% CI 1.7-4.7). Several studies (Table 18) and meta-analyses have confirmed family history of SCD as a risk factor.[398] The argumentation regarding family history of SCD as a primary indication has been emphasized.[399] Other experts oppose this view and advocate an overall risk stratification using the HCM Risk-SCD calculator.[400] They highlight that ICD cohorts by definition are high-risk patients and are not necessarily representive of general HCM patients when risk stratification has be applied. Based on their algorithm from 3,675 HCM patients (558 ICDs), family history had an HR of 1.8 (95% CI 1.2-2.4; p<0.001) as summarized in Table 20.[137]

Table 20. The HCM Risk-SCD calculator was based on merged cohorts of 3,673 HCM patients. In univariable analysis risk markers were evaluated using HR with regard to SCD or its equivalent.[140]

Risk factor	**HR (95% CI)**	**p-value**
Age (year)	0.988 (0.979-0.997)	0.007
Maximal wall thickness (mm)	1.048 (1.025-1.071)	<0.001
Fractional shortening (%)	0.992 (0.977-1.008)	0.334
Left atrial diameter (mm)	1.035 (1.018-1.052)	<0.001
LVOT gradient (mmHg)	1.005 (1.001-1.008)	0.005
Family history of SCD	1.76 (1.32-2.35)	<0.001
NSVT	2.5 (1.85-3.47)	<0.001
Unexplained syncope	2.3 (1.69-3.20)	<0.001

Of course, the definition of family history of SCD varies across studies, which increases complexity. Often it is limited to first-degree relatives and excludes more distant relatives. Moreover, the number of affected and nonaffected family members are not taken into account. The position is that family history of SCD should be used along with other risk

factors and weighted by the use of the risk model. From a perspective of the practicing cardiologist, the family history of SCD risk factor gets special attention, because it is part of the patient history and it may carry special emotional importance for the patient and their family. In real-world clinical practice, the emotional weight of family history is likely to affect the decision-making process.

Family history of SCD has prognostic implications with a delay to the fifth decade of the life span according to Dimitrow et al who also showed that multiple cases of SCD in the family imply additional risk.[390] Dimitrow et al used a different approach and estimated a lifetime risk and all 4 established risk factors were confirmed.

10.1.8.3 Maximal wall thickness

Maximal wall thickness can be used either as a dichotomous variable with cutoff or as a continuous variable. It is an established risk factor based several studies, but careful measurement is important in each individual case. Many patients with extreme LV wall thickness are likely to be highly symptomatic and will undergo septum reductive treatment, which seems to decrease risk of SCD.

In the early era, Spirito et al evaluated 480 patients over a mean follow-up of 6.5 years. The risk of SCD was increased with maximal wall thickness (p=0.001).[401] The incidence per 1,000 person-years (stated in parentheses) with regard to maximal wall thickness divided into 5 groups was as follows: <15 mm (0), 16-19 mm (2.6), 20-24 mm (7.4), 25-29 (11.0), and >30 mm (18.2). Elliott et al identified maximal wall thickness (cutoff 30 mm) as a risk factor in multivariable analysis of 368 HCM patients with a follow-up of 3.6 years: the HR was 4.1 (p=0.001) in univariable analysis and 2.9 (p=0.03) in multivariable analysis.[192]

Elliott confirmed this association in a cohort of 630 patients (mean age 37 years, mean follow-up 4.9 years), in which 39 patients had an ICD discharge or SCD. For every 5 mm increase in maximal wall thickness, the RR was 1.31 (p=0.029).[402]

Efthimiadis et al studied 166 HCM patients (mean age 47.9 years, mean follow-up 2.7 years) did a multivariable analysis of syncope (HR 10.4; p<0.001), maximal wall thickness 30 mm (HR 7.5; p=0.005), and NSVT (HR 1.4; p=0.64).[392]

Monserrat et al specifically analyzed patients younger than 30 years and found a significant association between maximal wall thickness ≥30 mm and SCD (HR 3.5; p=0.03), which was the strongest predictor next to NSVT.[116]

The relationship of maximal wall thickness and SCD was non-linear, rather U-shaped, in the analysis by O'Mahony et al of 3,673 HCM patients.[403] They reported HRs with respect to strata: 15-19 mm (HR 0.93), 20-24 mm (HR 1.09), and 25-29 mm (HR 1.21; p=0.02), 30-34 mm (HR 2.1), and ≥35 mm (HR 0.22).

Maximal wall thickness is modifiable risk factor. Many of the patients with high wall thickness undergo septum reductive treatment. Overall, the prognosis and risk of SCD are

low after myectomy and ASA. The current risk calculator is not adapted for risk assessment in these subgroups. Discrepancy between CMR and echocardiography may occur in individual cases.

10.1.8.4 Syncope

Although categorizing syncope as unexplained is based on judgment after careful evaluation, it is an established risk factor. In our study, about a third of patients had syncope as risk factor at baseline evaluation. Based on guidelines, syncope can be considered a risk factor regardless of when it occurred, but recent episodes constitute higher risk of SCD.

Unexplained syncope is an established risk factor for SCD in HCM that occurred in 35.4% of our patients. However, there are several pathophysiological pathways and complex mechanism of syncope in general.[15] Besides ventricular arrhythmias, atrial arrhythmias, complete AV block or sinus node dysfunction can cause syncope. Primary hemodynamic mechanisms are attributed to LVOT obstruction, abnormal vascular response, and impaired filling due of abnormal relaxation of the myocardium and diminished LV cavity.[404] Mostly, the cause of syncope is determined from the anamnesis. A careful evaluation is therefore warranted. Since an insertable cardiac monitor is indicated for unexplained syncope, it has a limited place in studies of HCM patients. From a safety point of view, it should be noted that an insertable cardiac monitor is a diagnostic tool and does not offer treatment. Despite the somewhat arbitrary judgement of this risk factor, it has been established as a risk factor based on several cohorts.

Spirito et al evaluated 1,511 HCM patients (mean age 70 years; 70% male) and syncope occurred in 14% (10% unexplained, 4% deemed as neurally mediated).[405] During a mean follow-up of 5.6 years, the RR was 1.8 for unexplained and 0.91 for neurally mediated syncope. Interestingly, a syncope within the last 6 months had RR of 4.9 compared to those without syncope. Remote syncope (more than 5 years earlier) in persons older than 40 years had very low risk.

In fact, in the largest HCM-ICD cohort, unexplained syncope was a significant risk factor (3.6 events per 100 patient-years; $p<0.001$) and the strongest single risk factor among those with only one risk factor (5.2 events per 100 patient-years: $p<0.001$).[203] In the HCM-risk cohort, unexplained syncope had an HR of 1.76 and was significant ($p<0.001$) in univariable analysis. Dimitrow et al confirmed syncope as a risk factor (28% of the cohort) in the lifetime analysis.[390] In an early study, Kofflard et al evaluated 225 HCM patients (mean age 41 years) of whom 19% had a history of syncope) and in a multivariable analysis only syncope was a significant risk factor (RR 4.3; $p<0.05$).[406] In another study by Efthimiadis et al of 166 HCM patients (mean age 51.8 years), syncope emerged as the strongest risk factor (RR 13.1; $p<0.001$).[393]

Even though syncope is based on the somewhat subjective practices of history taking and clinical judgement, it seems valid to use it as a risk factor. The time between when the syncope occurred and the patient is evaluated is recognized as a key factor, but guidelines

differ in how they interpret this window of time. In the HCM Risk-SCD calculator "history of unexplained syncope at or prior to evaluation" is stated, but the ESC guidelines state that episodes within 6 months are considered more predictive than earlier episodes.[15,137] If a syncopal episode was caused by bradycardia (or more rarely by AF) it is likely to recur within a shorter period than VT, which carries a higher risk for SCD but occurs far more infrequently. Thus, a remote episode of syncope caused by VT may still represent a risk to the patient. Syncope from hemodynamic causes without arrhythmia will likely recur within a shorter period of time; if it does not, then the history should be reviewed to suggest what triggers these episodes. In most cases, "unexplained" syncope describes the risk factor, although the definition of the term "unexplained" is admittedly broad and Spirito et al use it to describe the majority of syncopal epsiodes.[405] Because recent episodes are more predictive of SCD than remote episodes, patients should be made aware to seek prompt medical attention when syncope occurs.

10.1.9 Overview of analyses of established risk factors

The HCM Risk-SCD showed significant SCD outcome for the binary variables NSVT, family history of SCD, and unexplained syncope. In addition, the continuous variables maximal wall thickness, left atrial diameter, and age reached significance. Several studies report the relative impact of these established variables, and the largest study of HCM patients confirms their importance when calculated as risk per year.

In HCM-ICD cohorts, the established risk factors are generally reported even though methodologies vary. Some of these studies are summarized below. The relative strength within a study is a key to understanding the weight of each factor. However, this was complicated by different approaches about what to include in multivariable analysis. To overcome the relativity inherent in the reporting of HRs, the outcome per person-years is preferable, especially in patients with only a single risk factor at baseline. This approach is appealing but requires a large cohort and it does not account for addition of risk factors during the follow-up period.

10.1.9.1 Low EF

Systolic dysfunction, expressed as EF, is a cornerstone in general risk assessment of heart failure patients. In HCM, an EF<50% should be regarded as severe impairment. Thus, we included this risk marker in our analyses. Indeed, it turned out to be the strongest risk factor for the whole cohort. This hold true in primary prevention and implied an almost threefold risk based on multivariable adjusted for age, sex, AF, and the established risk factors. Thus, in addition to conventional risk factors, EF<50% should be considered in risk stratification.

In risk stratification of general cardiomyopathy patients with ischemic or nonischemic dilated cardiomyopathy, low EF is a strong predictor of SCD. Current guidelines use a cutoff value of 35-40% in these patients for a class I recommendation for an ICD.[32–34] In patients with bundle branch block, especially left bundle branch block, concomitant CRT is a cornerstone in heart failure management even though the necessity of ICD in nonischemic

cardiomyopathy in the elderly is subject to debate.[407,408] While EF is used to guide the management of general heart failure patients with ischemic heart disease and nonischemic dilated cardiomyopathy, LV systolic dysfunction is not emphasized in for the risk stratification of HCM.[15,16,33]

The vast majority of HCM patients have normal or even supranormal EF, but there is nevertheless a risk of deterioration into end-stage heart failure. This clinical spectrum has been extensively described.[84,174,409,410] The risk of SCD in this subgroup has long been recognized.[411]

In the enhanced ACCF/AHA strategy, low EF, using the cutoff <50%, was considered one of the major risk markers to justify prophylactic ICD implant.[142] This guidance referenced one single study of HCM patients undergoing evaluation for heart transplant. In this cohort, 27 patients had end-stage heart failure with EF<50% and all of them received an ICD and 8 of them experienced appropriate ICD therapy while waiting for transplant.[409] In the ACCF/AHA guidelines from 2011, the indication for primary prevention ICD in end-stage HCM patients was defined by EF≤50% and NYHA III/IV despite optimal pharmacological therapy (IIb, C). In ESC guidelines, ICD therapy is not specifically mentioned, but CRT may be considered (IIb, C) in nonobstructive HCM patients, drug refractory NYHA II-IV, EF<50%, and left bundle branch block >120 ms.

Begley et al had previously observed that patients with systolic dysfunction are are elevated risk for arrhythmias and SCD; 3 out of 11 patients in their study had appropriate ICD interventions.[279]

Rubinshtein et al studied 424 HCM patients (mean age 55 years, mean follow-up 3.6 years) who underwent CMR/LGE with regard to SCD/appropriate ICD therapy.[393] In this study, the mean EF was 67% and 20 patients had EF<50%, of whom 17 had LGE. In univariate analysis, EF<50% had an OR of 3 but was not significant.

Minami et al followed 346 HCM patients during a mean of 8.4 years. Elevation of brain natriuretic peptide levels with a cutoff 312 pg/mL predicts the combined endpoint of SCD and appropriate ICD therapy ($p<0.001$) and also in multivariable analysis with established risk factors (HR 5.7; $p<0.001$). This supports the finding that systolic dysfunction is a significant risk factor.[412]

O'Mahony et al used fractional shortening (percentage change in LV diameter during systole using M-mode in parasternal long axis view).[281] When ventricular geometry is normal and there are no regional wall abnormalities, there is good correlation with EF. Fractional shortening was the only independent predictive marker for an appropriate ICD shock in the multivariable analysis (10% decrease in fractional shortening was associated with a 34% increase in risk for shock after adjustment).

Ismail et al reported 711 HCM patients (median age 56.3 years) who were followed for a median of 3.5 years.[394] They all underwent CMR including assessment of LGE; LV dysfunction (CMR EF≤55%) was present in 23 patients (3.2%). Of these 23 patients, 9

(39.1%) had SCD or aborted SCD. When cardiovascular mortality was added to this outcome, a total of 9 patients (39.1%) reached the composite outcome. In total, 21 of 23 patients with LV dysfunction had LGE-defined fibrosis. The extent, but not the presence of myocardial fibrosis, was a significant univariable predictor of the primary endpoint (HR per 5% LGE: 1.24, 95% CI 1.06 to 1.45; p=0.007 and HR for LGE: 2.69, 95% CI 0.91 to 7.97; p=0.073). Interestingly, on multivariable analysis, only EF reached significance (HR: 0.92, 95% CI 0.89 to 0.95; p<0.001).[394] For the secondary endpoint cardiovascular mortality/aborted SCD, the presence and the total amount of fibrosis were significant predictors on univariable, but not multivariable, analysis after adjusting for EF and NSVT.[394] They concluded that the predicted value of EF is greater than that of fibrosis and that EF should be emphasized in guidelines. CMR signs of fibrosis were seen in two-thirds of patients, and the amount of fibrotic tissue turned out to be a predictor of SCD or aborted death, however not independently and it did not offer any incremental beneficial information in addition to EF.

Harris reported on 1,259 HCM patients, of whom 44 (3.5%) had LV systolic dysfunction defined by echocardiography as EF<50%.[84] In total, 29 patients (66%) died of progression of heart failure, had SCD events, or underwent heart transplantation. The mortality rate was 11% per year. Appropriate ICD therapy occurred at a rate of 10% per year in patients awaiting transplant.

It is of utmost importance to recognize and treat HCM patients whose systolic function deteriorates. Of course, this is more likely to be observed in long-term follow-up and not risk assessment based on baseline characteristics. From vast evidence from other indications, low EF is a strong predictor. Perhaps EF<50% in HCM can be regarded as equivalent to EF of 35-40% in the general heart failure population, which would warrant ICD recommendation. Most HCM studies are limited by a low proportion or even outright exclusion of this subgroup. As a result, their predictive power is limited. Even though low EF is mentioned in the guidelines, it could be highlighted even more in future updates. In addition, merged large cohorts specifically addressing low EF and SCD are welcomed.

10.1.9.2 LGE

In our cohort, LGE was not systematically assessed and was not routine at the time for evaluation before ICD implant. Recent findings suggest LGE with a cutoff of 15-20% to be at least a modifying risk marker in risk stratification. The incremental value of LGE has to be further evaluated.

Myocardial fibrosis is pathophysiological substrate for re-entrant ventricular arrhythmia and progression to systolic heart failure. There is an association between LGE and NSVT on Holter monitoring.[413,414] Because patients at risk for SCD may lack the established risk factors, CMR has emerged as a tool for risk stratification.[415] The early studies provided promising results but were not powered to determine the role of LGE as a risk factor.[376,393,416]

In an early pooled analysis, LGE trended specifically toward the adverse outcome of SCD.[417]

In a meta-analysis (5 studies, n=2,992 patients, mean age 54.6 years, mean follow-up 37 months) by Weng et al, the presence of LGE was associated with SCD (OR 3.4; p<0.001) and cardiovascular mortality (OR 2.9; p<0.001).[418] There was a linear relationship between LGE and SCD (HR 1.6 per 10% LGE; p<0.001) and cardiovascular mortality (HR 1.6; p<0.001). Based on these findings, LGE should be looked on as a continuous risk marker rather than a binary one. The majority of HCM patients, up to 70%, have LGE on CMR which would imply a very low positive predictive value, because the prevalence of LGE is high. It is not known whether LGE provides incremental value in addition to established risk factors and its place in risk assessment of HCM patients in clinical decision-making remains controversial.

Doesch et al suggested LGE as an additional tool for risk stratification. In the group with an ESC risk score (<6%) and LGE ≥20%, the sensitivity for predicting a life-threatening arrhythmic event was 84.6%.[419] A Kaplan-Meier estimate using this cutoff was significant (p<0.0001). Notably, for 11 events in this low-intermediate risk group (n=26), an annual rate of 10.5%, was seen. Moreover, among those with a high ESC risk score ≥6%, none of the patients with an extent LGE <20% suffered from an event (negative predictive value 100%). Based on their findings, the authors argue that the absence of extent LGE (cutoff 20%) may corroborate the decision against ICD implantation in selected high-risk patients.

Mentias et al evaluated 1,423 HCM patients (mean age 66 years) with preserved EF (≥50%) and an ESC risk score <6% with LGE at CMR.[143] Notably, 686 underwent myectomy and ASA patients (n=42) were excluded. The endpoint was reached by 60 patients (40 SCD and 20 appropriate ICD therapy) after a mean follow-up of 4.7 years. The authors suggested an LGE 15% cutoff for patients with either non-obstructive or obstructive cardiomyopathy, but a 25% cutoff for patients who underwent myectomy.

Ismail et al evaluated 711 HCM patients (mean age 56.3 years) with CMR and found LGE fibrosis in 66.2% (median 5.9% of the LV mass).[394] Few patients (3.1%) reached the composite endpoint of SCD or aborted SCD over a median time period of 3.5 years. The extent of LGE fibrosis (per 5%) was significant in univariable analysis (HR 1.24; p=0.007) but not in multivariable analysis. Interestingly, EF remained significant (HR 0.92; p<0.001). Regarding the composite endpoint of cardiovascular mortality/aborted SCD, both the presence and the amount of fibrosis were significant predictors in a univariable analysis. However, this changed after adjustment for EF and NSVT.[394]

Chan et al reported 1,293 HCM patients (mean age 46 years) who underwent LGE evaluation after a median follow-up of 3.3 years and 37 patients (3%) reached the endpoint of SCD/appropriate ICD therapy.[141] There was continuous relationship between LGE percentage and SCD risk (p=0.001). For every 10% increase of LGE, the HR increased by 1.46 (p<0.002) for the endpoint, and this also occurred in multivariable analyses. Using the cutoff value of LGE 15%, there was doubled risk in patients with ESC risk <6%. Patients without LGE had less than half the risk (HR 0.39; p=0.02). Notably, the extent of LGE of 10% significantly increased the risk of end-stage heart failure (HR 1.8).

The discrepancy between these two studies may be due to power, difference in adjustment, and the presence of low EF according to Weng et al.[418] The incremental value of LGE has been described, but its definite role remains to be elucidated in coming guidelines.[22,420]

Todiere et al reported LGE in 354 HCM patients (73% males) with a 5-year risk SCD score <6%. LGE was seen in 92% of those who experienced the composite outcome of appropriate ICD therapy, cardiac arrest, or sustained VT. The receiver operating characteristic cutoff was 10% LGE extent (area under the curve 0.74). The Kaplan-Meier estimate showed that LGE ≥10% had a worse prognosis (p<0.0001). Thus, LGE ≥10% represents increased risk for individuals with low-to-intermediate ESC SCD risk score.[396]

Hen et al reported on 102 HCM patients with ICDs (median age 63 years; 62% males) who had undergone CMR. During a median follow-up of 2.8 years, the annual rate of appropriate ICD therapy was 10.3% for secondary prevention and 7.4% for primary prevention. In primary prevention about half of patients (47%) was LGE positive in ≥4 of 17 LV segments (receiver operating characteristic curve cutoff). The annualized rate of appropriate ICD therapy was higher above that cutoff (11.1% vs 4.6%; log-rank p=0.038).[421]

In a systematic review of risk markers for SCD in HCM, including both ICD cohorts and other cohorts, confirmed the classic four risk markers: family history of SCD (RR 1.8), severe LV hypertrophy (RR 1.9), syncope (RR 2.3), NSVT (RR 2.8), and abnormal blood pressure response (RR 1.5).[398] Using myocardial fibrosis as a binary variable, an association between the presence of LGE-detected fibrosis and SCD outcome was found in 4 studies, of which one study had all of the risk markers present.[141,394,395,414] The RR from the effect model was 3.4.

10.1.9.3 Age

In our cohort outcome was independent of age after adjustment for other variables. This is in line with many studies, including the largest merged ICD cohort. Nevertheless, HCM Risk-SCD has introduced age into the algorithm, but otherwise it is probably integrated as part of the clinical judgment in the selection of eligible patients.

Many studies have not found age to be an independent risk factor for SCD, including the largest ICD cohort (p=0.64).[203] In the ESC HCM Risk-SCD calculator, younger age implies a higher risk score based on the cohort. Here, age is an integral part of the algorithm, while in cohorts based on judgment of risk factors and modifiers, age may also come into play. In individual cases, it is likely that clinicians integrate age with other findings to assess risk. As described, some risk factors seem to be highly important, i.e. the presence of NSVT, unexplained syncope, and severe LV hypertrophy in younger patients.[15]

10.1.9.4 Left ventricular apical aneurysm

In the rare case of an aneurysmatic left ventricle there is an increased risk of SCD.

A few patients, approximately 2-5% of HCM patients will develop LV apical aneurysm, which indicates worse prognosis and has been associated with SCD.[399] Rowin et al reported on 93 patients with LV aneurysm from a cohort of 1,940 HCM patients (mean age 56 years, 69% male). The composite endpoint of SCD or appropriate ICD therapy rate was 4.7% per year and HCM-related death/aborted death was threefold higher than in other HCM patients.[422]

10.1.9.5 Genotype

The genotype itself was never used as a risk marker in our cohort, which is in line with guidelines.

Although SCD can occur in clusters in relatives with HCM, the genotype itself has not been clearly demonstrated as a risk factor in sarcomeric HCM. Currently genotype information is not used for routine risk stratification of SCD. There may be indirect associations, as Lee et al reported AF in a cohort of 1,040 HCM patients with genotype; *MYH7* had a higher incidence of AF after adjusting for age, sex, left atrial size, and maximal wall thickness (HR 1.7; p=0.009) after a mean follow-up of 7.2 years.[423]

10.1.9.6 LVOT gradient

The LVOT gradient is based on various clinical conditions and attributable to treatment. It was not systematically assessed in our cohort, nor was it evaluated as a risk predictor.

The LVOT gradient was rarely assessed systematically in our cohort. Often the quality of gradient measurement was poor and it varied substantially from time to time. Medication and invasive procedures can influence the gradients. It must be considered a modifiable risk factor.

Elliott et al reported a prevalence of LVOT gradient >30 mmHg at rest in 31% of 917 HCM patients. During a median follow-up of 5.1 years, the 5-year survival (or heart transplant) was lower (86.5% vs 90.1%) in those with obstruction. The risk was 2.4 times higher for SCD or ICD discharge in those with obstruction. The incremental RR for every 20 mmHg was 1.4.[133] However, there are also reports where survival in those with an LVOT gradient ≥30 mmHg was the same.[392]

Maron et al reported on LVOT obstruction, defined as rest peak instantaneous gradient of ≥30 mmHg as a risk marker (RR=1.9; p=0.014).[424] This risk marker was also linked to all-cause mortality (RR=1.6; p=0.02) and the composite of progression to NYHA III/IV, death from heart failure, or stroke (RR=2.7; p<0.001).

In the validation work of HCM Risk-SCD, this risk factor has been re-established and is included as a continuous variable.[137] Notably, the measured value of gradient from either rest or the Valsalva maneuver can be used in this model.

10.1.9.7 Abnormal blood pressure response

Abnormal blood pressure response at exercise test was analyzed in our cohort, but it was not performed systematically in all patients. The definitions vary among studies and the interest in this risk marker has diminished.

This risk factor has been controversial. The definition varies among studies. Sadoul et al evaluated 161 HCM patients <40 years and 37% had abnormal blood pressure response and 15% in the group with this risk factor had SCD compared to 3% SCD in the group with normal blood pressure response.[425] Since this early study, this risk marker has been diminished in importance and is no longer part of ESC guidelines. In the ACCF/AHA guidelines it can be taken into account when associated with another risk factor or modifier.

10.1.9.8 Left atrial diameter and atrial fibrillation

AF was a significant univariable risk marker for appropriate ICD therapy in our cohort. In primary prevention, AF was significant in both uni- and multivariable analysis. AF was a stronger risk marker than any of the established risk factors. It may be suggested to include AF as part of risk stratification. AF is closely linked to left atrial size. In fact, left atrial diameter has been included in HCM Risk-SCD.

In our cohort, AF was associated with appropriate ICD therapy in the univariable analysis of the whole cohort, but in multivariable analysis it was no longer significant. In primary-prevention patients, AF was associated with an HR 3.6 ($p<0.001$) in univariable analysis and remained significant in the multivariable analysis (HR 2.5; $p=0.010$). In fact, it was more strongly associated with appropriate ICD therapy than the established risk factors. We did not collect data on left atrial diameter, since the numerical value was not always stated in the reports.

AF is associated with increased mortality based on a meta-analysis of 104 studies with a total of almost 10 million persons.[426] A history of AF was associated with all-cause mortality (RR 1.46), cardiovascular mortality (RR 2.03), stroke (RR 2.42), and SCD (RR 1.88).

An early study by Robinson et al could not demonstrate a mortality difference between HCM with and without AF, but SCD was not specifically addressed.[427] AF was associated with the risk of heart failure and stroke.[125]

In a systematic review (n=27 studies) including meta-analyses by Rattanawong et al, AF in the general population was associated with SCD (pooled risk ratio 2.04; $p<0.01$).[428] They reviewed 4 studies of HCM and the pooled risk ratio for AF was 2.05 (95% CI 1.2-3.4; $p=0.01$). Except for the study by Kofflard, the other three studies showed a significantly higher risk of SCD in HCM patients with AF.[125,406,429,430]

Minami et al analyzed the left atrial diameter in 564 HCM patients over 10.8 years.[429] SCD was higher in those with left atrial diameter ≥48 mm (19.8% vs 8.2%; $p=0.002$). Enlarged left atrium was an independent determinant of SCD (HR 5.2; $p<0.001$), but there was no

difference regarding those with known AF or not (p=0.567).[429] In another publication of an overlapping cohort, paroxysmal AF (but not other forms of AF) was associated with SCD (HR 4.7; p=0.002).[430] Sorajja et al showed that among 433 HCM patients with epicardial coronary disease and normal EF, AF increased risk of SCD.[125]

Woo et al identified age <30 years at the time of implant (HR 3.0; p=0.03) and AF (HR 3.1; p=0.02) as risk markers of appropriate ICD therapy.[375]

Siontis et al evaluated 3,673 HCM patients (55% men) between 1975 and 2012 with a median follow-up of 4.1 years and 18% had AF.[431] AF was associated with left atrial enlargement and also increased risk of death (annual mortality 6.9% vs 4.4%; HR 1.48; p <0.001), which remained unchanged after adjustment for age and sex. The mortality was increased compared to a US age- and sex-matched population. Specifically regarding SCD, AF trended for increased risk (HR 1.73; 95% CI 0.96-2.92) and was similar after age- and sex adjustment.

Spirito et al identified left atrial size, measured as diameter, as a significant variable for SCD in a multivariable model (RR 1.03 per mm). In another study by Spirito of 653 HCM patients (mean age 46 years) with mean follow-up of 5.3 years without known risk factors and with low symptomatic burden, annualized SCD was 0.6% per year (heart failure 0.2% per year, stroke 0.1% per year).[432] The annual rate of SCD in patients with an left atrial diameter <40 mm was 0.3% per year, but increased to 3.1% with an left atrial diameter of 41-50 mm and above 50 mm it was 8.0% per year.

In the HCM Risk-SCD model, the association was similar (HR 1.035) and established the use of left atrial size as a continuous variable.[137] It was decided to use left atrial size instead of AF due to less missing data.

Since the guidelines were published, another study added more evidence in support of left atrial size, but used the left atrial volume index as assessed by two-dimensional echocardiography as a marker in 427 HCM patients (66% men mean age 52 years) with a mean follow-up of 6.7 years. In multivariable analysis the left atrial volume index but also global longitudinal strain were associated with the composite endpoint of death, transplant, SCD, or appropriate ICD therapy. They suggested 34 ml/m^2 for the left atrial volume index and -15% for the global longitudinal strain for incremental value to standard risk evaluation (C-index increased from 0.68 to 0.73).[433]

Left atrial enlargement is common among HCM patients as a result of the dysfunctional relaxation of the LV, LVOT obstruction, mitral insufficiency, and atrial myopathy.[434] The left atrial volume index is superior to diameter for estimating left atrial size.[435] In a small study of 81 HCM patients, left atrial volume index was an independent risk marker for cardiovascular events, which was also seen in another study of 140 HCM patients.[134,436]

Debonnaire et al reported that left atrial volume index, using the cutoff 34 ml/m^2,was associated with appropriate ICD therapy in 92 HCM patents (69% men, mean age 50 years)

during 4.7 years follow-up.[378] A total of 21 patients experienced ICD therapy, but none with both left atrial volume index <34 ml/m^2 and global longitudinal strain <-14%.

The link between left atrial diameter and AF in HCM was recently further reinforced by Klopotowsky et al, who evaluated 546 HCM patients, aged <65 years, with regard to a history of AF.[437] In addition to age, NSVT (HR 2.7; p<0.001), left atrial diameter at baseline (HR 1.065; p=0.001), and left atrial diameter at the last assessment before AF occurrence (HR 1.10; p<0.001) were identified as risk factors for AF.

Even though the association between AF and SCD has been demonstrated, the mechanisms are not completely elucidated. There is anecdotal evidence of a direct causal link between AF and VF; Favale et al reported a case of rapidly conducted AF as a trigger of recurrent VF.[438] But, in general, the causal pathways are complex. The underlying pathology of heart failure and ischemic heart disease may play a role and the irregular, often rapid cardiac conduction through the AV node may cause unfavorable changes in action potential, leading to proarrhythmic propensity.[439–441]

10.1.10 Hypertrophic cardiomyopathy risk calculation

In 2014, the ESC endorsed a novel risk evaluation based on an algorithm which intregrates several risk factors. It uses age, maximal wall thickness, left atrial diameter, LVOT gradient, family history of SCD, NSVT, and unexplained syncope. It was developed to improve discrimination between high, middle, and low risk.

To improve risk stratification in primary prevention, a new risk assessment tool was developed and endorsed by the 2014 ESC guidelines.[15,137] It was claimed that previous guidelines overestimated risk and resulted in ICD implants in patients with low risk.[442]

This new prognostic tool was based on retrospective analyses of six European centers.[137] In total, 3,675 HCM patients (mean age 48 SD 17 years; 64% males) were evaluated during a median of 5.7 years. The outcome was reached by 198 patients (5%) with a 5-year cumulative incidence of 3.8% (annual rate 0.81%). The outcome consisted of 118 cases of SCD (60%), 53 appropriate ICD shocks (27%), and 27 aborted SCD events (14%). At baseline, 1% had an ICD but during the study period, a total of 15% underwent ICD implant.

The continuous variables were checked for linear correlation with outcome using a univariable Cox regression model. If a correlation was deemed non-linear, a quadratic term was used instead in the multivariable model. In addition, a 15% significance level was used in a backward elimination before the final risk model was chosen.[442] The HRs for the selected variables in the univariable model were as follows: Age in years (HR 0.988), maximal wall thickness in mm (HR 1.048), left atrial diameter in mm (HR 1.035), LVOT gradient mmHg (HR 1.005), family history of SCD (HR 1.760), NSVT (HR 2.533), and unexplained syncope (HR 2.326).[137] Based on calculations from this validation cohort, the number needed to treat (ICD implant) was 16 for every life that could be potentially saved during the 5-year period in patients with ≥4% 5-year SCD risk. Patients who did not reach the 5-year SCD endpoint

(n=2,982) had a mean predicted 5-year SCD risk score of 3.7%, while those who fulfilled the SCD endpoint (n=84) had a risk score of 7.3%.[137]

The previous guidelines provide a rough estimate.[16] The new guidelines incorporate the relative weight of each risk factor using a multivariable analysis.[15] Risk factors that are continuous variables were handled to reflect the actual proportional risk rather than being dichotomized. In addition, age was part of the model. Compared to using four conventional risk factors, the new model has a C-index of 0.54, which was deemed superior as discrimination. Even though the formula is complex, there is a calculator on the web that may be used by clinicians as a part of the evaluation.[443]

Although an improvement, the current risk calculator is imperfect. In fact, around one-third of the cases of SCD in HCM patients have no known risk factor. The risk calculator will identify some of them, but the authors admit "…the performance of the model in this patient subgroup is not optimal." Moreover, patients with extreme LV thickness (≥35 mm) or septum reductive interventions (ASA or myectomy) require special attention and the calculator is not fully applicable according to guidelines.[15,137,443] However in a recent study of 844 ASA patients of whom 46 experienced SCD during a mean of 6.5 SD 4.2 years (another 20 patients who had SCD during the 30-day post-procedure period were excluded), the C-index for the use of the HCM Risk-SCD model was 0.61 (p=0.02), the 2003 ACCF/ESC guidelines was 0.59 (p=0.051), and the 2011 ACCF/AHA guidelines was 0.58 (p=0.054).[444] Importantly, the analyses excluded 20 SCD cases during the first months.

Notably, EF and abnormal blood pressure response to exercise were not prespecified. The reason for this was that these factors were not clearly associated with SCD in multivariable analyses in previous studies.[116,133,192,392,445]

Left atrial size was chosen as predictor instead of AF because of less missing data regarding left atrial measurement. Indeed, both left atrial size and AF are considered risk factors.[125,405] AF was used as minor risk factor in US guidelines from 2003.[35] The pathophysiological rationale and association between left atrial size and AF is well established.[446,447]

10.1.10.1 External validation of the HCM Risk-SCD model

The validation and usefulness of the HCM Risk-SCD model has been established in several studies. However, severe criticism regarding its sensitivity in the identification of patients at risk of SCD must be addressed.

The HCM Risk-SCD model has been validated in several studies. This validation work was conducted in several ways, from simple descriptive data on sensitivity/specificity, to positive/negative predictive values, to measurements like area under curve, C-index, and D-statistics. Indeed, an effective sample size is needed for external validation.[448]

The C-index is a measure of discrimination between high and low risk in a mathematical model. An ideal situation would be a C-index of 1.0, meaning there is perfect discrimination,

while 0.5 is poor discrimination.[449,450] The D-statistics quantify the observed discrimination based on log HR for the outcome and a score of 0 means no separation at all while higher values are improved results.

The usefulness of the HCM Risk-SCD has been further established by EVIDENCE-HCM collaboration.[451] In this study, 3,703 HCM patients from different continents were evaluated and the 5-year incidence of SCD (or equivalent outcome) was 2.4%. The C-index was 0.70 and D-statistics 1.17. This study supported that when the 5-year risk ≥6%, an ICD should be offered and <4% did not merit an ICD, while the range of 4-6% should be regularly assessed. With the 6% cut-off, the number of ICDs needed to prevent one case of SCD over 5 years was 13.

Despite the solid evidence for the HCM Risk-SCD as a helpful tool in risk stratification in adult HCM, severe criticism has been expressed by Maron et al.[452,453] They point out the lack of sensitivity of the algorithm.

Wang et al did a meta-analysis of 9,651 patients followed for a mean of 5 years. The discriminatory model showed a C-index of 0.75. The sensitivity ranged from 41% to 71% to predict SCD over the time period.[209] The Tufts experience showed inadequate sensitivity when the ESC model was adopted according to the Maron et al.[142] Instead, they advocate for the 2011 ACCF/AHA guidelines based on the risk marker profile and incorporating additional risk markers based on more recent findings in an individualized strategy.[16,142] In 2019, they published data on 527 ICD patients from among their HCM population of patients without a history of SCD at baseline (n=2,094).[142] Of this ICD population, 15.6% had appropriate ICD therapy and the cumulative 5-year probability of appropriate ICD therapy was 10.5% (95% CI 8.0-13.5). They argued that when retrospectively applied to study patients, the ESC risk score was much less sensitive than the ACCF/AHA criteria (34% [95% CI 22-44] vs 95% [95% CI 89-99]).

Wang et al recently published a systematic review of 13 studies (mean age 52 SD 6.3 years, mean follow-up 5.4 SD 2.2 years). The global C-index was 0.75 (95% CI 0.67-0.83). Using the cutoff 4%, area under curve was 0.69 (95% CI 0.62-0.75), while using 6% cutoff area under curve was 0.65 (95% CI 0.59-0.72). This study confirmed high specificity but the authors regarded sensitivity as poor and discrimination as moderate. Notably, the predictive power was slightly lower in US publications.[454] There was no heterogeneity regarding age, sex, follow-up period, and publication year.

The validation of the model by O'Mahony et al, based on 3,703 HCM patients from different countries, confirmed the accuracy of the model.[451] In patients with a risk <4%, the 5-year risk was 1.4%, while 8.9% of patients had a risk ≥6%. Using the cutoff ≥6% would yield 13 ICD per life potentially saved. The C-index was 0.70 and D-statistics 1.17. In cohorts from Europe, China, and South America, the ESC model performed better than previous approaches.[455–457] However, in the US cohorts, the model seems less robust, but differences in comparison measurements deserve greater scrutiny.[452,458] It seems that regional difference is a

key factor to explain this heterogeneity. There may be several explanations for this discrepancy. Firstly, there are underlying differences in the HCM cohorts regarding baseline characteristics and management during follow-up; for example, the proportion of myectomy. The risk calculator already recognized the potential limits in this subgroup of patients. Secondly, ICDs are more frequently used in the United States in general compared to Europe and this also holds true in these HCM cohorts. Maron reported 28% ICDs in the population. In the validation study, 3.3% had ICD at baseline and 10.7% received ICDs during follow-up.[451] In the independent validation by Maron of 1,629 HCM patients, 460 had ICDs (28.3%) and 10% of ICD patients experienced appropriate ICD therapy. The majority (59%) of appropriate ICD therapy occurred in low risk, i.e. <4% per year based on the HCM Risk-SCD score. The higher proportion of ICDs in a cohort will imply a higher sensitivity of detecting VTs that would be self-terminating. This, in turn, will overestimate the actual benefit of ICD. The proportion of patients who reached the outcome SCD may be partly a result of how SCD was defined.

In a recently published study on Korean HCM patients (n=730), 7/11 (64%) of endpoint SCD or appropriate ICD shock had a low ESC risk score (<4%), but specificity was high (C-index 0.72).[459] This may be added to the previous criticism addressed by Maron et al, who advocates a strategy based on enhanced ACCF/AHA guidelines.[142] They claim that extensive LGE, systolic dysfunction (EF<50%), and LV apical aneurysms should be considered as they constitute one quarter of appropriate ICD therapies.[459,460] Lui et al compared the enhanced ACCF/AHA strategy, 2011 ACCF/AHA strategy, and ESC Risk SCD cutoff of 6% in 1,369 Chinese HCM patients (mean age 50 years) of whom 39 reached SCD endpoint, with a yield of 67%, 51%, and 13%, respectively for each guideline.[461]

Recently, a systematic review by O'Mahony et al of 7,291 HCM patients based on 6 publications reported the 5-year risk for primary-prevention patients.[129,137,451,455,457,462,463] In their pooled analysis, the SCD endpoint at 5 years from baseline evaluation in low (<4%), middle (4-<6%), and high risk (≥6%) patients was 1.0%, 2.4%, and 8.4%, respectively, which was interpreted as accurate risk estimation.[462] About half (51%) of SCD endpoints occurred in high-risk patients, and 68% in middle-high risk patients which comprised 30% of the merged cohort. C-index ranged from 0.69 to 0.92. Notably, ATP was excluded from the SCD endpoint. Some smaller studies which lacked 5-year data, included ATP, or constituted pure ASA cohorts were excluded from the meta-analysis.[284,381,382,444,464] Moreover, the systematic analysis did not include the data from Maron et al.[452] The authors of the systematic review recognized LGE as a predictor for future endeavours to further improve the risk model.[419,465]

In addition to the systematic analysis, Nakagawa et al reported on 289 HCM patients with ≥50% and 81 patients with EF<50% during a mean follow-up of 5.2 years.[466] In patients with EF≥50%, Risk-SCD score was higher in those with outcome, 6.8% vs 1.8% 5-year risk, and 60% of those with outcome were classified as high risk. In the group EF<50%, 16 out of 81 (19.8%) experienced SCD outcome. There was not a significant HCM Risk-SCD score in patients with EF<50% and the authors suggested insufficient accuracy in this subgroup.

Ommen et al has proposed using the principles established by Maron et al as a highly sensitive screening, but also integrate the 5-year score from the HCM Risk-SCD calculator.[366] Rather than using cutoffs for strict decision-making, these values can be looked on as pieces of evidence. This could provide a basis for shared decision-making with the patient. They describe this challenge as not for the "cognitive miser" but for the "domain of healers."[366]

The decision to implant an ICD is a turning point in the management of the HCM patient.[467] After careful evaluation of risk factor/markers and potential modifiers by a qualified physician, preferably after discussions with colleagues, the recommendation needs to be shared with the patient in trustful communication.[468] Patients, and often also relatives, need to be extensively informed about complications of ICDs and consequences for lifestyle. Even though inappropriate shocks and device-related infections can be devastating, they should not be a reason to refrain from the obvious benefits of preventing SCD. Like any other ICD indication, there will always be individuals who will not benefit from device implantation. From a health economy perspective, ICDs in general based on the indications established by current guidelines are advantageous. For a long time, there has been limited health economy analysis regarding other forms of cardiomyopathy.[469] Recently, a health economy analysis using a Markov model showed excellent cost-effectiveness from both a health care sector viewpoint and a societal viewpoint based on our published Swedish data.[470,471] No risk stratification model can ever be perfect, and SCD is inherently unpredictable.[472] Thus, the decision to implant an ICD should be based on an overall assessment, with a holistic approach, but always with the guiding principle to avoid SCD, after shared decision-making with the patient.

10.1.11 Single vs multiple risk factors

Our study confirmed that multiple risk factors imply higher risk than single risk factors.

There has been an ongoing debate whether multiple risk factors imply higher risk than a single risk factor. The question could also be turned to ask if a single risk factor is enough for a patient to be eligible for an ICD. Already in 2001, Elliott et al noticed that a higher number of risk factors (one, two, or three) was superior to predict SCD or ICD shock compared to maximal wall thickness (RR per additional risk factor 2.00; p=0.058) based on 630 HCM patients.[402] However, many early studies were not powered to detect a difference between the numbers of risk factors. ESC guidelines have overcome the problematic binary approach of regarding risk factors and the ACCF stress the use of a more refined judgement of multiple risk factors in conjunction with modifiers and elaborate on the interpretation of each factors, although ACCF does not quantify risk assessment. In our comparatively large study, we were able to confirm that multiple risk factors do indeed imply higher risk. This does not address the related question as to whether a single risk factor is enough to justify ICD, because that is a matter of acceptable sensitivity and specificity. However, in borderline situations it could sometimes be useful to take more risk factors into account.

10.1.12 Special situations in risk stratification

Long-term results, including SCD, after septum reductive procedures have showed low risk of unfavorable outcome. Genetic profile does not yet play a role in risk stratification.

The HCM Risk-SCD states precautions in patients who have undergone septum reductive procedures. Desai et al studied 1,809 HCM patients with obstruction. In 65% of the patients, there was no risk factor, 1 risk factor in 26%, and ≥2 in 8%. The HCM Risk calculator categorized 65% of the patients as low risk (<4%), 18% as intermediate risk (4-6%), and 17% as high risk (>6%). A total of 64% underwent myectomy.[458] On multivariable competing-risk analysis, myectomy (HR 0.69; p<0.01) was associated with lower risk of SCD events while ESC SCD risk score was not (HR, 1.31; p=0.36). Thus, myectomy seem to mitigate risk of SCD.

Liebregts et al evaluated 844 ASA patients (mean age 56 years, 54% men) without a secondary indication for an ICD. Periprocedural 30-day mortality, occurred in 20 patients. Another 46 patients reached the composite endpoint of SCD or appropriate ICD therapy during a mean follow-up of 6.5 years.[444] The C-index for HCM Risk-SCD was 0.61 (p=0.02), and using the 2011 ACCF/AHA guidelines was 0.58 (p=0.054). They concluded that the ESC model was applicable for ASA patients.

In the systematic review from 2015 (16 myectomy cohorts and 11 ASA cohorts) long-term mortality was similar, myectomy 1.4% per year, and ASA 1.5% per year (p=0.47). SCD, or appropriate ICD shock, was also similar (myectomy 0.5% per year, ASA 0.4% per year).[247]

Genetic profile should not be used for risk stratification. The clinical expression is relevant and not the specific gene mutation. However, from the Portuguese HCM Registry (only 51% underwent testing, 28% genopositive, 9% had variants of unknown significance) the *MYH7* gene was associated with a risk of LV systolic deterioration. This indirectly warrants attention to clinical deterioration and subsequent risk of SCD, but not the genotype per se.

10.1.13 Limitations

Often data are presented as crude annual event rates which does not imply completely accurate representation of the incidence data. Instead, the time to event analysis is beneficial, but often not reported.[209]

Risk stratification in HCM is inherently limited by the unpredictable nature of ventricular arrhythmias. A high sensitivity can be achieved at a cost of lower specificity and vice versa. Many studies are hampered by limited power and there are difficulties in adjusting for known and unknown risk markers. Moreover, modifiers and changes in risk since baseline prove difficult to take into account. Typically, long-term risk is relative and does not always align with life expectancy. Most studies use both ATP and cardioversion in their outcomes, but some studies omit ATP, which can underestimate the benefit of device therapy. At the same time, an unknown proportion of ventricular arrhythmias are self-terminating, with the result that the benefits of device therapy are overestimated. Cohorts may contain different

proportions of ICD patients which will affect outcome, typically defined as the composite of SCD, aborted SCD, and appropriate ICD therapy. Moreover, the generalizability of studies may be influenced by setting, tertiary center bias, and changes in risk stratification over time.

10.1.14 Summary

In the Swedish nationwide cohort of HCM patients an excellent efficacy of appropriate ICD therapy was confirmed. In other words, in a clinical setting the device was able to convert potentially life-threatening ventricular arrhythmias. An individualized approach to programming is important to assure efficacy in addition to avoiding inappropriate shocks. A quarter of the patients in our cohort experienced appropriate therapy, and there is continued risk over the years. This underlines the unpredictable nature of VT/VF in HCM. Therefore, device exchange should be advised even if the patient received no appropriate therapy for several years. The burden of risk factors in the Swedish cohort was comparatively high compared to other cohorts. Sweden has a conservative approach to ICD therapy compared to many other high-income countries which was evidenced here with a lower proportion of primary-prevention patients and older age at implant, resulting in a higher annualized rate of appropriate ICD therapy. There was a majority of male patients who had ICD due to HCM as seen in other studies but outcome with regard to appropriate ICD therapy is similar between sexes. There is a strong adherence to risk factors in the decision-making. AF and EF<50% emerged as risk markers, especially in primary prevention. Age is not an independent risk factor in this unselected cohort. NSVT is the strongest conventional risk factor. Our study was performed before the implementation of the HCM Risk-SCD calculator and which makes comparisons impossible. Several studies have confirmed the benefit of this new algorithm, but controversies remain regarding its sensitivity. Complementary risk factors like LGE are promising for improving risk stratification. Left atrial size enlargement is part of current ESC guidelines and our findings about AF likely reflect such risk. Importantly, our data suggest that EF<50% implies an increased risk and should be taken into account to improve risk assessment. In individuals with deteriorating systolic function, there is a substantial risk for SCD.

10.2 PAPER II

10.2.1 Mortality among general hypertrophic cardiomyopathy patients

Mortality in general HCM patients depends on the underlying characteristics of the cohort. Merged cohorts from tertiary centers show a doubled SMR while unselected cohorts of middle-aged patients seem to have mortality comparable to the general population, but this has been questioned. NYHA III/IV, AF, possibly female sex, but not necessarily obstruction, seem to be associated with an increased risk of death. Over extended periods of follow-up, heart failure seems to be the main culprit, but there may be advanced treatment options available.

Over the decades diagnosis and treatment have improved within the field of HCM. Kofflard reported an annual mortality of 1.3% in 225 HCM patients between 1970 and 1999 with a

mean age 41 years at first evaluation.[406] By 2006, Elliott et al showed historical trends toward improved survival.[473] With the contemporary treatments, the HCM-related death rate is low and many patients are believed to have a normal or near-normal life expectancy without major adverse events.[80] Maron et al reported low cardiovascular mortality among middle-aged HCM patients (range 30-59 years, mean 45 years) over 7.2 years follow-up with 5 and 10 years freedom from HCM-related death estimated to be 98% and 94%, respectively.[80] Surprisingly, this was comparable to the general US population, which included all deaths (p=0.25). In a later comparison, they stated superior 5-year survival rates for HCM patients in relation to myocardial infarction, heart failure, and many forms of cancer.[474] Even though this is somewhat reassuring, at least for middle-aged patients, and, indeed, the treatment of HCM patients has improved, it does not unequivocally answer the question of differences in survival compared to the normal population, because populations should also be matched with regard to age, sex, and calendar time.

In 2017 Liu et al published a meta-analysis regarding HCM and survival.[268] Their search yielded 19 studies and a total of 12,146 patients (62.5% males) but many studies did not report data for all analyses. The pooled 1, 3, and 5-year cumulative survivals were 98.0% (95% CI 97.4-98.6%), 94.3% (95% CI 93.1-95.6%) and 82.2% (95% CI 75.2-89.2%), respectively.[268] Few studies reported 10-year data, but based on 4 studies it was 75.5% (95% CI 71.1-78.9%). It should be pointed out that there was substantial heterogeneity, which may involve age, comorbidity, treatment, and time period for the cohort. The natural course of the disease and follow-up interventions may likewise differ among cohorts. In a heterogeneity analysis, publication year (cutoff 2005), sample size (cutoff 1,000), and geographical area were not statistically significant. NYHA III/IV was the strongest risk factor for cardiovascular death (HR 2.5) and all-cause death (HR 2.0). Regarding cardiovascular death, the average age, NYHA functional class, NSVT, family history of SCD, syncope, AF, maximal LV wall thickness, and obstruction were significant prognostic factors. Family history of SCD showed strong predictive power for cardiovascular death (HR 2.4), but no significant correlation with all-cause death was observed. NSVT, LVOT obstruction, and syncope were risk predictors for cardiovascular death (HR 2.5; HR 1.5; HR 2.4, respectively). Syncope was also associated with all-cause death (HR 1.4). Left atrial diameter and EF were not determined to be significant prognosticators based on the limited data in their analyses. In regression analyses, age at first evaluation of HCM is often used rather than actual calendar age. Meta-analyses in a heterogeneous disease like HCM must be regarded with some degree of caution.[475]

Notably, Autore et al found that AF was the strongest predictor of cardiovascular mortality (HR 4.3; $p<0.001$) both in uni- and multivariable analysis.[476] There has been a debate whether obstruction implies worse prognosis. This was also addressed in another meta-analysis (n=20 studies) of 7,731 HCM patients comparing annualized mortality with and without LVOT obstruction (1.8% vs 1.6%; p=0.40).[477] Spirito et al also evaluated death from any cause with regard to maximal wall thickness: the incidence per 1,000 person-years with

regard to maximal wall thickness divided into 5 groups was as follows: <15 mm (11.7), 16-19 mm (15.9), 20-24 mm (21.4), 25-29 mm (27.5), and >30 mm (28.6).[401]

Late November 2019, Lorenzini et al from the HCM Outcome Investigators reported mortality data from a dataset of 4,893 patients (63.9% males, mean age at first evaluation 49.2 years) with a median follow-up of 6.2 years.[275] Of note, the data were confined to tertiary centers and covered the time period of 1980-2013. A composite endpoint of all-cause mortality, aborted SCD, and heart transplant (but not appropriate ICD therapy) was used in the main survival analysis. They used strata of time intervals for calculation of SMR. Patient age at the end of the follow-up period was used for comparison of expected mortality, based on yearly mortality rates by age in the general population. Indeed, HCM patients had excessive mortality (SMR 2.0, 95% CI, 1.5-2.6) compared to the general population. The SMR was significantly higher among women than men (2.6; 95% CI 2.4-3.0 vs 1.7; 95% CI 1.5-1.9; p<0.001). The categories of outcome were: SCD or ICD shock (not ATP) 3.4%, heart failure 2.6%, transplant 1.7%, other cardiovascular causes 2.2%, and unknown causes 0.5%. As the authors admitted, Eurostat data do not contain specific causes of death. The study highlighted the high mortality among women, whereas men aged 65 years or more had mortality rates similar to general population. The authors suggested higher prevalence of heart failure and advanced disease due to tertiary center bias. At the same time, patients with much comorbidity, especially the elderly, are probably not referred to tertiary centers. In another study, registry data from HCM patients compared to the general population showed an excessive amount of SCD, heart failure, and AF.[478]

Also, in November 2019, Rowin et al reported the US experience of 2,123 patients (38% women) with HCM from a tertiary center.[272] Women were diagnosed at an older age than men (55 SD 18 vs 44 SD 16 years; p<0.001) and more often developed NYHA III/IV symptoms. EF<50% was similar between both sexes (5% among men and 4% among women p=0.33) but heart failure with preserved EF was three times more common in women (p=0.001). Appropriate ICD therapy was similar in women and men (0.9 vs 1.0% per year; HR 0.92; p=0.73). HCM mortality was infrequent, 0.3% per year in both sexes, p=0.25. The age-adjusted all-cause mortality rate also did not differ between women and men (1.7% vs 1.3% per year; HR 1.32; p=0.13).

In the SHaRe study, 4,591 HCM patients (2,763 genotyped) with a mean age of 45.8 years at diagnosis were followed for a mean of 5.4 years.[27] The composite outcome was SCD, appropriate ICD therapy, heart transplant, all cause death, AF, stroke, NYHA III/IV, or EF<35%. Patients aged <40 years at the time of diagnosis had a 77% cumulative incidence of achieving the endpoint before the age of 60 years. Patients with a positive genotype had a doubled risk. Patients 20-29 years of age had a fourfold mortality rate compared to the normal population and more than a threefold higher rate of HCM patients who were 50-69 years of age at evaluation, but this study did not adjust for sex and time period. In a merged cohort of Italian and British patients with HCM including phenocopies, the prevalence of rare

phenocopies was associated with a nine-fold prevalence of LV dysfunction. Amyloidosis is often associated with low EF and poor prognosis.[478]

The vast majority of patients with HCM due to sarcomeric mutations have normal or above-normal EF values due to their small LV cavity. Using the echocardiographic definition <50%, the prevalence is about 2-5% and the annual incidence less than 1%.[83,84,479] The transition to end-stage HCM can occur at any age but typically occurs at least 10-15 years after symptoms.[83] Traditionally, the risk of death in HCM has largely focused on SCD. Due to the efficacy of ICDs, there is now improved long-term survival, with new concerns arising over disease progression into heart failure. US data for 1, 5, and 10-year survival after transplant due to HCM are 85%, 75%, and 61%, respectively, which compares to other underlying diseases.[178] Transplant or LVADs should be considered in HCM patients with end-stage disease.[409] CRT may be considered but should not delay transplant/LVAD.[237] Recently, Songsirisuk et al evaluated 161 HCM patients (mean age 66 years, 42% males), of whom 25 (16%) died of HCM-related causes during a mean follow-up of 6.8 years.[480] These deaths could be attributed to heart failure (52%), SCD (44%), and stroke (4%). Geske et al reported sex differences in a tertiary center cohort of 3,673 HCM patients.[273] Females were the minority (45.2%). The age at first evaluation was higher in females than males (59 vs 52 years; p<0.001) and females were more symptomatic based on NYHA III/IV class (45.0% vs 35.3%; p<0.001). A Kaplan-Meier estimate showed lower survival in females than males (p<0.001). In a multivariable analysis, female sex was associated with a higher risk of death adjusted for age, NYHA class, and cardiovascular comorbidities.

Age-matched data from Iceland showed similar all-cause mortality rates for patients with HCM and those of the general population (HR 0.98; p=0.9).[72] The HCM-related mortality was 0.78% per year with a mean age of 68 years compared with 81 years for non-HCM-related mortality (p=0.02). Importantly, they did not include individuals who died before a clinical diagnosis of HCM. Genetic evaluations of patients found pathogenic mutations in 67% of subjects, of which *MYBPC3* mutations were most prevalent, but seemed to be associated with a relatively benign course of HCM.

A British population-based cohort of 3.3 million people found 0.035% with HCM (median age 57 years, 59% men). During a median follow-up of 4.0 years, the risk of cardiac arrest/SCD was higher than in the matched general population (incidence rate ratio 23.5; p<0.001). This was also seen with regard to AF (HR 3.8; p<0.001). Using Kaplan-Meier estimates, at 3 years, the risk of cardiovascular death or heart failure was 8.8%. This underscores the increased risk and unmet need for the implementation of evidenced-based medicine in HCM.[481]

10.2.2 Mortality and cause of death among HCM patients with ICDs

In our nationwide study of HCM patients with ICDs, the SMR was 3.4 which was significantly higher (p<0.0001) than the normal population, even adjusted for age, sex, and calendar time. Risk of death increases with age. Patients with EF<50% had five-fold risk of

death in both uni- and multivariable analysis with regard to death. AF is also associated with death, but is weaker in multivariable analysis. Death from SCD do occur in end-stage heart failure. This warrants careful attention to deterioration of systolic function in patients with HCM.

In 2018, in a study of 486 HCM patients with ICD (mean age 51 SD 16 years) from 8 tertiary centers in the United States, Europe, and Australia, 94 experienced appropriate ICD therapy with a mean follow-up of 6.4 SD 4.7 years.[482] Among these 94 patients, one died suddenly because of device malfunction and 3 died of end-stage heart failure. In the meta-analysis by Schinkel et al, mortality based on 13 studies was reported. Cardiac death was 0.6% per year and non-cardiac death 0.4% per year.[208] Only 5 studies reported heart transplantation as an outcome, which occurred in 2.3% with an annualized rate of 0.5%. In this meta-analysis, the largest ICD cohort was included and reported more details on cause of death. Out of 507 HCM patients with ICDs, 39 died (7.7%) during the mean follow-up of 3.7 years.[203] About half (n=20) died from HCM-related causes: end-stage heart failure (n=12), embolic stroke (n=7) and SCD (n=1). The single SCD event occurred in a young man whose ICD device malfunctioned.[483] The remaining causes of death in the other 20 patients were due to cancer, renal failure, coronary artery disease, and trauma. Wang et al, who analyzed 16 studies, found an all-cause mortality of 1.3% (95% CI 0.9-1.9) divided into cardiac 0.9% and non-cardiac 0.8% per year.[209] Table 21 summarizes mortality in HCM patients with ICDs.

Table 21. Mortality in HCM patients with ICDs.

First author	Year	Size (n)	Follow-up, mean (years)	Age (years)	HCM-related mortality (%)	Non-HCM-related mortality (%)
Primo[370]	1998	13	2.2	48	0	0
Begley[279]	2003	132	4.8	34	3.0	1.5
Almquist[371]	2005	75	3.6	36	2.7	0
Lawrenz[372]	2005	15	3.4	53	6.7	13.3
Marin[373]	2006	45	2.7[a]	43	4.4	0
Medeiros[374]	2006	26	3.7	43	3.8	0
Maron[203]	2007	506	3.7	42	4.0	3.8
Woo[375]	2007	61	3.3	46	1.6	0
Syska[280]	2010	104	4.6	36	3.8	0
O'Mahony[b,281]	2012	334	2.2	40	2.7	1.2
Vriesendorp[282]	2013	134	4.2	44	8.2	2.2
Lambiase[222]	2016	99	1.8	42	0	0
Magnusson[353]	2015	342	5.4	52	9.9	3.2
Rigopoulos[381]	2016	32	5.3[a]	50	0	3.1
Ruiz-Salas[382]	2016	48	4.1	44	0	0
Thavikulwat[284]	2016	135	5.2	48	Not reported	7.4
Viswanathan[383]	2016	60	5.1	44	0	Not reported
Francia[384]	2017	66	4.4	45	1.5	0
Wang[285]	2017	160	4.0	47	6.9	3.8

[a] median. [b] additional 0.9% mortality of unknown cause. Stroke was not clearly discernable among non-cardiac deaths in a few cases, which implies some uncertainty regarding HCM-related mortality.

Our cohort of HCM patients with ICDs represents patients with a high proportion having an EF<50%. The crude mortality was 2.44 per 100 patient-years. In the meta-analysis by Schinkel et al the annualized mortality was 1.0% per year (0.6% cardiac, 0.4% noncardiac). In the meta-analysis, the mean age at implant was 10 years younger, follow-up was shorter (3.7 years), and patients were selected from highly specialized centers.

The SMR in our cohort was 3.4 which was significantly higher ($p<0.0001$) than the normal population adjusted for age, sex, and calendar time. There is no other comparable study with this measurement in a nationwide cohort. In older, general HCM patients, but not necessarily ICD patients, Maron found an SMR of 1.5 compared to general US population.[484] The cumulative survival in our cohort was 97.0% at 1 year, which supports a highly selected cohort based on the guidelines of offering ICDs in patients with at least one year of life expectancy. The 5-year survival rate of 89.4% indicates a substantial proportion of death with longer follow-up. There was no significant survival difference between men and women in our cohort. Neither was there a sex difference in the cohort with respect to age or calendar-matched data. From this perspective, there seems to be no selection bias in candidates for ICD, as survival rates are similar. Interestingly, primary and secondary prevention patients had similar survival. This also reflects the selection of patients with acceptable long-term prognosis after cardiac arrest and sustained VT.

The excess mortality in our cohort was due to HCM-related causes. In fact, three-fourths of all deaths could be attributed to HCM. Interestingly, this is higher than the largest HCM-ICD study, in which 51% of deaths were HCM related. In that study, investigators attributed 31% of all deaths to heart failure. The likely explanation for this discrepancy is the higher proportion of low EF in our cohort, including patients with CRT. Our data support EF<50% to be the critical level that marks a transition toward end-stage heart failure. The unfavorable prognosis of low EF in HCM is well-known.[83,172] Patients with EF<50% have a five-fold risk of death in both uni- and multivariable analysis.

The detailed interpretation of main and contributing causes of death confirms that underlying systolic deterioration is the culprit. This underscores the importance of attention to end-stage heart failure in HCM. It requires a multidisciplinary effort to provide optimal treatment in the individual case.

Not surprisingly, AF was likewise a predictor of death in our study. There was a three-fold increase in univariable analysis, which diminished to a doubled risk with borderline significance after adjustment of other variables. There is an association with embolic stroke, but this can effectively be prevented by anticoagulation. Of note, ICDs can monitor AF episodes and most patient also have remote monitoring systems, which can be helpful when prompt anticoagulation is deemed indicated. AF is also a consequence to heart failure and may lead to or worsen heart failure, which may explain the difference in HRs in uni- and multivariable analyses.

The efficacy of ICDs in terminating ventricular arrhythmias has been demonstrated in Paper I. This is in line with massive evidence from diverse cohorts. In a survival analysis, the potential life-saving benefits of bradycardia pacing should also be taken into account. The exact benefits of bradycardia treatment cannot be quantified.

Paper II also offers insights with respect to the risk of the consequences if the ICD is removed. In Paper I, the analysis was performed based on time until right censoring, for example, removal of the device. Here we analyzed the overall survival and not just appropriate ICD therapy, which acts as a surrogate for SCD. As reported in the Results section, there can be catastrophic results when an ICD is inactivated, as occurred in the patient who had the device disabled after several inappropriate shocks. This highlights how important it can be to avoid inappropriate therapy delivery so that the patient is motivated to keep the device activated.

From other studies, it is obvious that a holistic view of patient management is of utmost importance to improve survival. It should include alertness of signs of developing heart failure, prompt evidenced-based pharmacological treatment, and LVAD or transplant in selected cases.[485] CRT may be beneficial, but long-term survival benefits from CRT seem modest.[173,177] ICDs are indeed beneficial due to high efficacy, but there can arise certain complications, including inappropriate shocks that may undermine device acceptance among both patients and health care providers. Therefore, it is crucial to take action against the risk of complications and carefully handle them from several perspectives, including the patient's emotional response. Based on Papers I and II it should be stressed that the risk of life-threatening arrhythmias persists over the years and ICDs offer excellent protection from SCD. Indeed, ICDs almost eliminate SCD, which can occur suddenly in heart failure. This is reassuring, and should be emphasized in the long-term management of HCM patients.

10.2.3 Limitations

Many cohorts of HCM patients with ICD are from tertiary centers of selected patients, while our nationwide study is without referral bias. We also reported relatively long-term follow-up periods compared to other studies, but still far from the estimated life expectancy. The challenge with long-term data is that treatment changes over time with improvements in disease management, with the patient's underlying condition and disease progression, and with comorbidities. Home monitoring of the device and anticoagulation may be of benefit in ICD patients and further reduce mortality. More available options for advanced heart failure therapy are likely to emerge in this disease, due to the fact that many patients have otherwise long life expectancy.

10.2.4 Summary

The natural history of HCM varies enormously. It covers asymptomatic disease, mild expression, disease of moderate severity, but also end-stage heart failure or SCD. Even though there has been a decline in death rate, efforts are still needed to reduce adverse disease manifestations and offer effective treatment. Given the clinical heterogeneity of the disease,

individuals need to be stratified for risk of SCD, heart failure, and embolic stroke. The contemporary treatment options have led to a paradigm shift in the natural history of the disease. Nowadays, many patients can expect a near-normal life expectancy, but each individual needs to be carefully managed, including risk stratification for SCD. Complete reassurance can never be applied since each individual must be treated holistically with evidence-based management strategies. ICD patients with HCM constitute a group who is at increased risk of adverse outcome with a more than threefold SMR. Our nationwide cohort of HCM patients with ICDs show that SCD can occur quickly in heart failure, making monitoring of any deterioration in systolic function of crucial importance.

10.3 PAPER III

Our paper was the first one specifically addressing HRQL in HCM patients with ICD.

This was the first paper on HRQL specifically in HCM patients with ICD. It is essential to address this patient group, because they are younger than typical ICD patients and thus there is less burden of age-related comorbidity. The underlying disease is also different than other ICD patients, including risk factor profile. We decided to use the widely recognized SF-36 questionnaire, which has been used in tens of thousands of publications throughout different medical fields. The importance of HRQL assessment in heart failure patients in general is widely recognized, as poor HRQL predicts adverse outcomes, including death.[486]

10.3.1 The concept of HRQL

Patient-reported outcome measurements reflect subjective well-being. Generic questionnaires reflect general HRQL from a holistic perspective and cover multiple aspects.

In addition to the traditional evaluation of outcome in both observational and randomized controlled studies, patient-reported outcome measurements are often used to reflect subjective well-being. Quality of life in its broadest sense is often used interchangeably with other terminology, but we prefer the term HRQL, which is widely used to stress the health aspects.[295] Still, HRQL has resisted strict definition. Instead, its meaning may vary from study to study, but it is generally agreed that it includes general health, physical functioning, emotional functioning, symptoms, cognitive functioning, social functioning, and well-being. It may reflect spiritual issues, coping strategies, and satisfaction with life.[295] Because HRQL covers multidimensional constructs, a single, global question is likely going to be ambiguous, unreliable and unspecific. Thus, multi-item measurements scales are used for each part of the overall concept. Generic HRQL includes both health status and domains reflecting quality of life and is thus more general, i.e. holistic, but are not as sensitive as questionnaires developed for a certain, specific diseases.

10.3.2 Choice of HRQL questionnaire

SF-36 is a highly validated, widely accepted instrument for general health status in many patient groups and there is a Swedish population norm for comparison.

The SF-36 determines the general health status and is designed to assess generic health concepts applied in a broad range of age groups, diseases, and interventions across different cultural settings.[296,487] This broad HRQL assessment tool was developed in the Medical Outcome Study and is frequently used in studies since the early 1990s.[296]

The major advantage of these questionnaires is that its generic measures may allow for comparisons with the general population, which was possible in our study where we used the 36-item SF-36 Health Survey. Therefore, we decided to use version 1 based on its solid psychometric foundation, Swedish contextualization, and the availability of a norm population for comparison purposes.[297,488,489] Despite extensive and robust validation work carried out to make this questionnaire suitable for use in Swedish populations, the Swedish SF-36 pioneers have brought up issues relating to the PCS and the MCS scores. They performed simulations to pinpoint the impact of the scoring model to discrepancies between subscale profiles and summary component scores. Notably, significant correlations were found between PCS and MCS scores at their upper scoring intervals, which should be interpreted to mean that they are not highly independent. Moreover, regression analyses showed that within these ranges, PCS mainly measures of mental health (57% of variance) and MCS measures physical health (65% of variance).[297,488,489] Nevertheless, PCS and MCS are widely accepted as summary scores, but it should be emphasized that all 8 domains constitute the basics of interpretation.

When we used the SF-36 version 1, the norm population was collected more than 20 years ago.[297] It is unknown whether this influenced the score. Most other validation studies are from respondents of the same age and without renewed follow-up of the general population. Differences could be interpreted as reflecting improvements in the general population's HRQL due to improvements in their overall welfare.

Even though SF-36 was validated as a single questionnaire when posted by regular mail, it is often used in conjunction with other questionnaires and metrics. We followed the practical approach of distribution by mail in our study. In addition, we had phone reminders to improve response rates and eliminate missing data. We dispensed with the use of multiple questionnaires as they risked a reduced response rate plus there can be carry-over effects in the questionnaires as patients get tired of the tedious work involved in completing the many forms. In our national cohort, we had actual clinical contact with only a few of the included patients and we anticipated the risk of low response rate. Fortunately, the response rate was 82.5%. We believe these patients with chronic disease and ICDs were grateful toward the health care sector in general and willing to contribute to research by answering questions. Often patients wrote additional sentences of the paper sheets or included an extra sheet with personal reflections about their HRQL. This could not be addressed quantitatively in this study but became a motivating factor to conduct the study that resulted in Paper IV.

There is no HRQL questionnaire specifically for HCM. We could have included a more general heart failure questionnaire like the Kansas City Cardiomyopathy Questionnaire (KCCQ) and possibly the Hospital Anxiety and Depression Scale (HADS).[490,491]

There are device-specific questionnaires, but they are not widely used. Instead, we had validated clinical data from medical records that could be used for comparisons of subgroups using the SF-36 and its norm population. The age- and sex-matched sample was randomly selected from the normative data base (n=8,930). The sample of 735 persons (516 males) had the same mean age and was used for comparisons.

10.3.3 HRQL in relation to population norms

Swedish HCM patients with ICDs reported a poor HRQL compared to population norms.

Our study demonstrated a poor HRQL in patients with ICDs. Compared to Swedish age- and sex-matched population norms, 7 of 8 domains showed significantly lower SF-36 scores. The only non-significant domain was Bodily pain, otherwise the differences were highly significant ($p<0.001$). A graphical presentation using bar charts is shown as Figure 14. Effect sizes (ES) varied from small to moderate. General health had the highest effect size (0.77), followed by Vitality (0.67) and Physical functioning (0.62). The PCS score (0.62) was more affected than the mental component score (0.46). The moderate effect size of physical domains contrasted with the smaller effect size of mental domains.

10.3.4 HRQL in relation to other studies

A British tertiary center study of younger HCM patients before the ICD era showed poor HRQL. In a small Norwegian study on HCM patients, SF-36 score was lower than in the population norm. An Australian cohort of HCM patients reported a lower PCS but similar MCS score compared to population norms. A recent international study of HCM patients with ICD, without population norms, showed similar scores between patients with and without ICD therapy using the SF-12.

In a study by Cox et al published in 1994, a total of 137 HCM patients returned completed SF-36 data (response rate 80.1%).[492] Similarly, scores were coded and transformed to a scale between 0 and 100, where 100 indicates the best possible health. All 8 domains scored significantly lower than the UK norms, but no ESs were reported. The comparison group comprised of 144 patients with serious cardiac conditions included in the Medical Outcomes Study. Interestingly, these results are similar to the findings in our cohort, but there are three important differences between our study and the British study. First, the British study was performed in the early 1990s, before the era of efficient therapy options. Secondly, patients were recruited from a tertiary center, likely representing patients with advanced HCM. Thirdly, the British patients were comparatively young, with a mean age of 43 years, i.e. more than 10 years younger than our cohort and 54% were males (in our cohort 70%). The results we obtained in terms of similarities in comparison with a group of seriously ill cardiac patients and significantly lower scores than norms in all domains imply that HCM patients have poor HRQL (Table 22).

Table 22. SF-36 score of UK patients, norm and serious cardiac conditions. Modified from Cox et al.[492]

Domain	HCM	Serious cardiac conditions[294]	UK norm[493]
Physical functioning	60.9 SD 25.3	57.4 SD 28.1	88.4 SD 18.0
Role physical	55.9 SD 42.9	43.9 SD 39.7	85.8 SD 29.9
Bodily pain	66.1 SD 27.2	65.1 SD 24.7	81.5 SD 21.7
General health	47.2 SD 24.4	49.1 SD 21.6	73.5 SD 19.9
Vitality	43.6 SD 24.2	47.8 SD 21.8	61.1 SD 19.7
Social functioning	70.2 SD 26.3	80.0 SD 24.4	88.0 SD 19.6
Role emotional	64.2 SD 40.7	76.2 SD 37.3	82.9 SD 31.8
Mental health	65.6 SD 21.1	77.6 SD 15.8	73.8 SD 17.2

A Norwegian study published in 2010 compared HCM patients (n=19) referred for genetic counselling to the general population using the SF-36 (Table 23).[494] The eight domains were significantly ($p<0.05$) lower for HCM patients or had a tendency ($p<0.10$) to lower scores in all domains except for bodily pain and mental health.

Table 23. SF-36 score of Norwegian patients UK patients compared to norm. Modified from Hamang et al.[494]

Domain	HCM	Norwegian population norm	p-value
Physical functioning	73.2 SD 19.5	84.9	0.021
Role physical	50.0 SD 43.3	73.3	0.024
Bodily pain	62.0 SD 30.8	72.9	0.127
General health	54.1 SD 23.9	73.2	0.004
Vitality	44.5 SD 19.5	61.9	0.001
Social functioning	61.4 SD 43.4	74.1	0.068
Role emotional	61.4 SD 43.4	81.5	0.054
Mental health	76.3 SD 14.0	79.9	0.245

In an Australian study on cardiogenetic studies and HRQL (response rate 55%), 208 patients with the HCM phenotype (mean age 54 SD 15 years, 62% males) were evaluated by SF-36 version 2 (Table 24).[495] The evaluation took place between 2007 and 2010. A majority had no shortness of breath (NYHA I), and the remaining were in NYHA II (36%) and NYHA III (3%). A quarter (25%) had an ICD. Predictors of worse HRQL on physical domains were female sex, presence of comorbidities, and lower NYHA functional class. The PCS score was significantly lower in HCM while the MCS score was indistinguishable from the general Australian population.

Table 24. SF-36 score of Australian patients compared to norm. Modified from Ingles et al.[495]

Domain	HCM	Australian population norm	p-value
Physical functioning	70.1 SD 25.9	83.3	<0.001
Role physical	72.3 SD 27.9	81.8	<0.001
Bodily pain	72.3 SD 25.3	76.2	0.037
General health	55.4 SD 23.0	71,8	<0.001
Vitality	53.3 SD 21.7	74.9	<0.001
Social functioning	79.5 SD 24.2	86.4	<0.001
Role emotional	83.7 SD 22.3	84.7	NS
Mental health	74.5 SD 16.9	76.2	NS

NS, non-significant

In 2018, a study on 486 HCM patients with ICD (mean age 51 SD 16 years) at 8 tertiary centers in the United States, Europe, and Australia addressed HRQL as part of the research question.[482] They used three questionnaires. The Florida Shock Anxiety Scale (10 items, 5-point Likert scale; higher score implies more anxiety) is a validated ICD shock-related anxiety questionnaire, especially relevant with regard to the fear of triggering a shock and the consequences of a device discharge, including cognitive, behavioral, emotional, and social impact.[496–498] Patients who experienced appropriate ICD therapy (cardioversion n=64; ATP n=30) or inappropriate shock reported slightly higher levels, with borderline significance of anxiety than did patients who were free of ICD therapy (17.4 SD 6.7 vs 15.9 SD 6.2; p=0.05). There was no difference in the level of anxiety experienced when patients with appropriate ICD therapy (n=94) were compared with patients who experienced inappropriate shocks or major device complications. Hospital Anxiety and Depression Scale (HADS) is frequently used across diverse populations.[491,499] There were no significant differences in HADS scores among the ICD patient subgroups. Patients with ICD therapy (either appropriate or inappropriate) had similar scores (5.2 SD 3.7 vs 5.5 SD 3.9; p=0.51). Only 20.6% of patients with appropriate shocks (13/63) had HADS scores with an abnormal psychological profile (≥8). The SF-12 version 2 showed similar scores among patients who had experienced either any ICD therapy compared to no ICD therapy (50.5 SD 10.2 vs 52.0 SD 8.4; p=0.52).[500] There were no comparisons with population norms.

10.3.5 Septum reductive treatment and HRQL

ASA and myectomy relieve symptoms, and smaller studies suggest they can improve HRQL.

ASA is known to relieve symptoms in obstructive HCM and this seems to translate into better HRQL. In a study by Serber et al, 22 HCM patients were assessed before and at 3 months follow-up after ASA. They used 6 HRQL questionnaires, including the SF-12. The overall interpretation was that ASA reduces psychological distress and improves well-being. The short time period implies the risk of cognitive dissonance, a psychological theory that patients choosing to undergo a procedure will perceive their post-procedure health status favorably so

that it is congruent with all that they have experienced (i.e., disease severity and procedure).[501]

Myectomy effectively reduces symptoms and may be the preferred choice over ASA, especially in younger and middle-age patients. A preference for myectomy has been advocated.[245,502] Still, formal analyses of HRQL would be beneficial, in addition to the evidence of improvement of physiological parameters.

In HCM, pacing can alleviate obstruction and improve outcomes.[225] Studies have shown patient-reported improvement in both physical and mental SF-36 domains during the first year of pacing treatment.[230,503,504] The long-term effects of pacing with regard to HRQL are less known, even though a study of 50 patients (mean age 62 SD 11 years) with a mean follow-up of 5.0 SD 2.9 years, indicates long-term benefits.[234]

In our study, only 3% of the patients had their ICD implanted in the last year. Thus, these patient reports likely reflect a chronic state rather than temporary changes at the time of ICD implant. Because HCM patients have comparatively long life expectancy, this seem relevant.

10.3.6 Hypertrophic cardiomyopathy-related comorbidities and HRQL

10.3.6.1 Heart failure

Heart failure is associated with worse HRQL in HCM. This is consistent with findings from other cardiomyopathies.

Our HCM patients with ICDs and a history of heart failure scored lower in HRQL than those without heart failure. The score was lower in the following domains: Physical functioning (ES 0.68), Role physical (ES 0.48), General health (ES 0.33), Vitality (ES 0.30), Social functioning (ES 0.36), which resulted in a low PCS score (ES 0.63). Heart failure patients were older (mean 4.6 years), but the *t*-test p=0.053 value indicates that age has only a minor influence. Heart failure-related symptoms, mainly shortness of breath, are a key feature of HCM. Symptoms are due to LVOT obstruction, mitral regurgitation, diastolic dysfunction, AF, and comorbidities. The limited physical capacity, especially at exertion, is likely to affect younger patients and their lifestyle. Even though these causes can be attributed to poor HRQL, a history of heart failure (defined as EF<50%) is detrimental. This finding is consistent with patients who receive an ICD due to dilated or ischemic cardiomyopathy.[505–507]

10.3.6.2 Atrial fibrillation

AF is associated with worse HRQL in HCM.

AF is common in HCM, and in our cohort 36% had a history of AF. This included paroxysmal, persistent, and permanent forms of AF. Patients with HCM often suffer from highly symptomatic AF. Heart failure can be caused by LV systolic dysfunction, but AF can cause a further decrease in EF due to rapid AV conduction and the lack of the atrial contribution to ventricular filling. AF may also reflect an underlying comorbidity. The

association of AF to stroke is well-known and HCM patients seem particularly vulnerable to embolization stroke, which warrants anticoagulation even without a single CHA_2DS_2-VASc risk factor.[15] In HCM patients with ICD, AF is the most common cause of inappropriate shocks.[211] In our study, patients with a history of AF were older (mean 7.4 years) than those without AF. In a subgroup comparison, the presence of AF affected mainly the physical domains: Physical functioning (ES 0.47), Role physical (ES 0.38), Bodily pain (ES 0.26), General health (ES 0.38), Social functioning (ES 0.42), and the PCS (ES 0.48). AF is main culprit in worsened HRQL, which is in line with findings from other patient groups.[508] Indeed, this is a challenge, because the burden of AF is common during the clinical course of HCM. Interestingly, patients with ICDs have continuous cardiac monitoring and device home-monitoring systems make early detection and intervention possible. For AF patients in general, there is ongoing debate about the cut-off for clinically relevant AF that warrants anticoagulation.[509] The fact that HCM patients are prone to embolization may be taken into account in reaching anticoagulation decisions in individual cases.

10.3.6.3 Appropriate therapy

Appropriate therapy is not associated with more unfavorable HRQL in HCM, which is reassuring.

Patients with at least one episode of appropriate ICD therapy reported significantly better mental health (p=0.033; ES 0.27) when compared to the subgroup who did not receive any appropriate therapy. All other domains showed no significant difference. The MCS was borderline significant (p=0.076; ES 0.27) driven by the domain Mental health. This is somewhat reassuring. An arrhythmic event which leads to appropriate ICD therapy can result in anxiety, may impose restrictions on the patient, such as driving, and can interfere with lifestyle. Despite these concerns, the negative ramifications of appropriate therapy may be outweighed by a psychological impact of feeling secure, and even a relief that the ICD system is reliable. In paper IV, using qualitative assessment, this was further elaborated. The impression is that patients with appropriate therapy are grateful to be alive and get a more pronounced feeling of the life-saving capability of the ICD.

10.3.6.4 Inappropriate shock

Mental health is worse among HCM patients with inappropriate shocks, which warrants careful attention.

Inappropriate ICD shocks often come unexpectedly, may be multiple, and typically lead to emergency actions. If appropriate therapy is a confirmation of the benefit of the ICD system, the opposite is the case with inappropriate shocks. This distress is likely difficult for patients, but the small effect sizes indicate that they do eventually cope with it. Mental health was significantly lower (p=0.028; ES 0.42), and Vitality (p=0.080; ES 0.31) and Social functioning (p=0.058; ES 0.37) showed a tendency toward worse score. The MCS was borderline (p=0.060; ES 0.38). Our cohort had a similar rate of inappropriate shocks as other

studies, which suggests that these findings have external validity, i.e. can be generalized to other cohorts, even though none of these studies addressed HRQL.[208,211]

10.3.6.5 Other subgroup analyses

In our study HRQL scores were similar in both primary- and secondary-prevention ICD treatment. Other ICD cohorts without cardiomyopathy have HRQL scores similar to the normal population, which leads to our speculation that it is the disease of cardiomyopathy rather than the ICD device, which accounts for poor HRQL. Symptoms and risk perception seem to be major determinants of HRQL in HCM.

HCM patients who received an ICD due to cardiac arrest or sustained VT had scores similar to those of primary-prevention patients (tendency toward better vitality in secondary prevention). In another study of general ICD patients, primary-prevention patients had lower scores in all domains except Bodily pain).[510] The typical primary-prevention patients in cohorts of ischemic or nonischemic cardiomyopathy are based on EF<35-40%, and these patients are typically in NYHA II/III. The worse HRQL likely reflects underlying heart failure and comorbidities. Nevertheless, primary-prevention patients, including HCM patients, express low HRQL which should be addressed with a holistic view of disease management.

It is interesting to compare patients with and without structural heart disease. A French study of Brugada patients with and without ICDs reported better physical performance than the norm population, Bodily pain and Social functioning were similar to the general population, but Role physical, General health, Vitality, Role emotional, and Mental health were all lower compared with the general population.[511] The SF-36 scores were non-significantly different between Brugada syndrome patients with and without ICDs.

A Dutch study of HCM mutation carriers (response rate 87%) confirmed that symptoms and risk perception are major determinants of HRQL (Table 25).[512] In patients with the phenotype and symptoms, HRQL was worse than those who were genopositive-phenonegative. Patients with manifest HCM scored significantly worse than the general population in 4 of 8 domains and PCS. This supports the assumption that symptoms are the main determinant of poor HRQL in HCM.

Table 25. SF-36 score of Dutch patients compared to norm. Modified from Verkerk et al.[512]

Domain	HCM-genotype	Dutch population norm	p-value
Physical functioning	74.0 SD 25.1	83.2 SD 22.6	<0.05
Role physical	69.1 SD 34.8	76.6 SD 36.1	NS
Bodily pain	77.5 SD 25.8	75.0 SD 23.3	NS
General health	58.5 SD 22.6	70.9 SD 20.6	<0.05
Vitality	59.6 SD 21.5	68.6 SD 19.3	<0.05
Social functioning	78.7 SD 25.4	84.2 SD 22.3	<0.05
Role emotional	79.7 SD 34.8	82.5 SD 32.8	NS
Mental health	76.4 SD 16.1	76.9 SD 17.4	NS
Physical component score	47.0 SD 10.5	50.0 SD 10.0	<0.05
Mental component score	48.9 SD 9.7	50.0 SD 10.0	NS

NS, non-significant

Patients who experienced complications requiring a surgical intervention had similar scores as those without such complications. This is reassuring, in that at least on a group level, patients cope well with complications in the long-term. Further analyses did not reveal significant differences in ICD patients with a risk factor of SCD in a first-degree family member.

In a study of general ICD patients in the INTRINSIC RV trial, HRQL, using SF-36, revealed improvements from baseline until 1-year follow-up in all domains.[513] That confirmed the previous findings from the ENHANCED-ICD trial, using EQ-5D, which showed that the level of distress and perceived health status were lowest at the time of implant and gradually became better at 2, 6, and 12 months follow-up.[513]

Moreover, in a Swedish survey study (n=3,067, response rate 55%) of general ICD indications, it was concluded that ICD-related problems exert a larger impact on psychological distress than the experience of an actual shock. This underlines the importance of handling ICD-related concerns as an integrated part of follow-up. The concerns should be addressed in all ICD patients, not just in patients who received ICD shocks.[514]

In our study, there was no difference with regard to sex except for PF, which showed a tendency to slightly lower values in women. In a large study of general ICD patients, a lower score on PF and VT were seen among females, while sex-related differences in the other domains were non-significant. It should be recognized that comorbidities, rather than sex, is the determinant of poor HRQL. Importantly, the decision to implant an ICD should be reached because of the individual risk profile and not sex.

HCM patients with ICDs are a heterogeneous group with a complex pattern of comorbidities and risks of complications. In addition to specific pharmacological regimens surgical interventions, and device programming strategies, a holistic view is crucial, including targeted information and individualized socially relevant approaches in order to achieve patient satisfaction and possibly improve HRQL.[515–519]

10.3.7 Limitations

At the time this paper was published, it was the largest study on generic HRQL in HCM patients with ICDs. SF-36 was used and the sample was compared with an age- and sex-matched Swedish norm population. Patient data were validated using medical records. However, the assessment of the norm population was older, and it cannot be ruled out some aspects expressed in the SF-36 score might have changed over the years. It should be remembered that HRQL was assessed in a cross-sectional design and does not take the natural course of disease progression into account. The benefit of a generic instrument like SF-36 is its inherent lack of sensitivity to disease-specific concerns for the patients. Moreover, the use of SF-36 in a group is not the same as an individual assessment, especially in a condition with such high heterogeneity. Finally, associations of variables should be interpreted with caution, as causal relationships cannot be assumed.

10.3.8 Summary

Our study of HCM patients with ICD represents a nationwide cohort, without tertiary center bias, and a high proportion of responders. It demonstrated poor HRQL compared to the Swedish norm population, despite advanced treatment, including pharmacological and interventional options, and also treatment of diverse comorbidities. In all SF-36 domains, except Bodily pain, there were significantly lower scores than in the norm population. The physical components are even more severely affected. It seems that HCM, especially when heart failure or AF complicates its natural course, are the main determinants of HRQL. Both primary- and secondary-prevention patients score similarly. Complications requiring surgery do not affect HRQL. HRQL results are similar in men and women. A history of appropriate ICD therapy is not associated with poor outcome, but inappropriate shocks implies worse mental health. In order to improve HRQL in HCM patients with ICDs, several approaches are needed both regarding disease management and device optimization.

10.4 PAPER IV

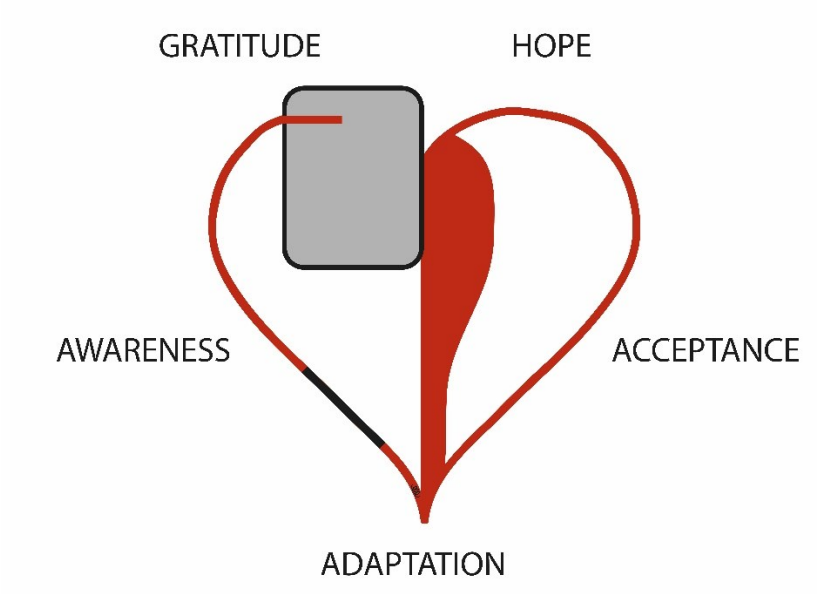
10.4.1 Narrative and theoretical themes

In our cohort, the following themes emerged: awareness, adaptation, acceptance, gratitude, and hope. The awareness of the disease and ICD varied among patients and their interaction with other people, including health care professionals. Both the HCM and the ICD required some adaptation by patients. They were grateful toward their cardiologist contacts and device, which gave them hope for the future. Despite restrictions and limitations to their lives, acceptance was generally high.

From the narratives, the condensed meaning units could be categorized as themes. These themes could be used to label the codes from diverse areas of the narratives. On a more abstract, theoretical level, the meaning of content of these narrative themes could be summarized as red threads through the intertwined expressions from the texts. Even though individual aspects cannot be reduced without losing details and there were some extreme

views and anecdotes, five common themes emerged: awareness, adaptation, acceptance, gratitude, and hope. These main themes are depicted in Figure 19. It should be noted that these themes appear to be influenced by the respondent's personal traits; their knowledge of their condition and therapeutic response; the degree of support they receive from family, friends and colleagues; and their perceived limitations based on their personal life situation and measured against their expectatations.

Figure 19. Theoretical themes emerging from narratives of HCM patients with ICD. Reproduced from Magnusson et al, with permission.[332]



The awareness of HCM seems to vary among patients. The nomenclature of HCM has historically been a hodgepodge and it is still confusing to the patients. Because of diffuse descriptions, many patients could not communicate effectively about the disease, and few of them searched for information about the disease. They were not prepared for visits with health care providers. Even though HCM is the most common cardiogenetic disease, there is no specific HCM patient organization in Sweden. Indeed, there are internet groups for ICD patients and these are considered helpful. Often patients were ambivalent about discussing their disease. Instead, they were often left alone with their thoughts. The genetic transmission of the disease was well-known to some of the patients, while others claimed they were never told about it. Indeed, there was missing genetic testing for some patients, but even in the case of genetic counselling, patients did not recall much. From a clinical perspective, there seems to be a demand for repeated, individualized information. Outside of cardiology care, patients often felt misunderstood and reported that they thought that many health care providers had limited knowledge of HCM and were unable to meet their needs.

At the same time, patients who often felt misunderstood expressed gratitude for contact with their cardiologist. Often, they had long-term relationships with their cardiologist, based on trust and support. Because these patients have a long history of disease, they appreciated the continuous, long-lasting relationship with their cardiologist and associated professionals.

However, patients also said that clinicians would focus mainly on device function and medical evaluation, leaving only limited time for other concerns. Patients often lacked information about their prognosis and did not receive much guidance on lifestyle matters. The ICD was genuinely appreciated, and patients said they felt grateful to have been selected for this potentially life-saving treatment. Nevertheless, the pre-implant information these patients received was sometimes scanty. Remote monitoring was appreciated for its technical safety, but it could not replace information about the ICD in the form of a dialog with the physician. Beyond the information from health care professionals, patients were often left on their own to manage their emotional and existential issues. They turned to their closest relatives with these inner feelings, which could be complicated and confusing. It was reported that family members were often helpful when the symptomatic burden prevented patients from doing ordinary or household tasks.

The burden of the disease also meant patients had to adapt, including dealing with restrictions. They reduced workload or changed employment. They had to limit social activities and contend with worse economic situations and status. Younger patients in particular sometimes felt isolated. On the other hand, fewer working hours meant more time for relationships with family members and friends. Over the years, patients adapted and accepted their situation. Their inner identity remained the same, and they navigated the path through their new life course. The symptomatic burden of the underlying HCM was the limiting factor over time, not the ICD. The device could lead to restrictions and younger patients often suffered frustration in certain situations, but it faded away over time.

The ICD sometimes required some adaptation, but it actually gave them hope. They felt relief. They trusted the device as a life-saver. In fact, many patients thought bystanders were more concerned about arrhythmia episodes than they were, at least in secondary prevention. In primary prevention, patients were likewise grateful and highly motivated, especially if SCD ran in the family. Patients who received appropriate ICD therapy were particularly grateful, as expected. Surprisingly, even with a history of inappropriate shocks, patients were grateful. They admitted fear and concern during the immediate period after inappropriate shocks. Indeed, inappropriate therapy delivery was a scary and painful experience, but they were able to cope with the situation. Complications, even inappropriate shocks, were accepted as a side effect of the treatment. Here the pre-understanding based on our clinical experience had to be changed. From the perspective of the device physician, who is involved in the care and possible reprogramming or intervention immediately after an inappropriate shock, it was reassuring that patients are able to cope with the situation. Typically, soon after such an event, patients returned to their normal state and continued their ordinary life. This long-term perspective is valuable and must be recognized in contrast to the emergency situation when patients experience pain, fear, and anxiety.

Overall, despite chronic disease, patients in our cohort reported satisfaction. Although adaptation and acceptance were needed to handle many obstacles in life, the overall

interpretation was that patients with HCM and ICDs had a strong spirit and a robust will to live. Their joy, appetite for life, and hope was a lodestar for their future expectations.

10.4.2 Findings in relation to other studies

HCM patients with ICDs likely represent more advanced disease manifestation than HCM patients without an ICD. The physical constraints seem to be the limiting factor and require adaptation of professional and leisure activities, which have been seen in other HCM studies. Recent studies confirm that, perceived from a patient perspective, there are important knowledge gaps among health care professionals. Educational efforts regarding both ICD and HCM are crucial and should include health care professionals, patients and their relatives, friends, and colleagues. Individualized information about ICDs before and during follow-up should be part of care. Knowledge of genetic aspects of HCM have often been identified as weak.

HCM is a heterogeneous disease and ICD patients generally represent more severe manifestations of HCM. Our study is the only qualitative study to date that focuses on the subset of adult HCM patients with an ICD. There is one other qualitative study with 15 HCM patients (interview length 35-180 minutes), but the number of ICD patients in this population was not reported.[520] They recruited from a patient organization by word of mouth using a convenience sampling method. This may create a bias compared to our selection of participants. Subasic described three themes that arose; “it is in the family,” “finding a new normal”, and “HCM and relationships.” HCM affected not only the individual patient, but also family members, and created worries at home. Indeed, we recognized this situation among our patients. There were concerns for disease transmission, especially for parents in relation to their children. Concerns were typically shared among family members, but were communicated much more selectively outside the family, for example to their employer. Again, our impression was the same, namely that patients, especially younger patients, carefully selected who they trusted when sharing information. In this regard, the alteration of identity and finding a new normal were necessary. Here our interpretation was somewhat different, possibly due to varying views on the concept of personal identity; among our patients, their notion of identity remained the same, even though they had to adjust their lifestyle. Patients in this other study also reported having to adapt to physical limitations, which were caused by the underlying HCM rather than the device. These adaptations sometimes required support and adjustments from others. As in our study, the misdiagnosis of HCM and its latency were commonly encountered. In the other study, patients with ICDs reported being concerned about inappropriate shocks, but gratitude outweighed this; we made this same striking finding in our study, too. In the US cohort, patients reported struggles with insurance companies to get rehabilitation after cardiac arrest. While this was different from national health care insurance in Sweden, Swedish patients with private insurances also had to argue with companies to get coverage. The different insurance system in the US created stress, while in our Swedish cohort this was less of a concern. However, in both studies, it appeared that career opportunities were hampered. Relationships were changed in the

families. Often it caused overprotection, and while some families became closer to each other, it could also cause tension, anger, and weakened relationships. There was often frustration of not being able to participate in sports or other activities. Our data adhered to their findings, but the general impression in our study was things became better over time due to coping strategies. During the younger years, patients seem to be more affected by not "being normal", but later in life, they found a way to move forward, feel joy, and have hope despite their limitations.

Subasic claimed that "the possibility of death and dying moved to the forefront, igniting added fear and concern."[520] This was not the case in our study. Their patients were afraid that physical activity would trigger ICD shock therapy, while our patients typically felt reassured and conducted physical tasks with more confidence, even though they were limited by the disease. Like our study, HCM patients had to accept modified plans when it came to travel, work life, and hobbies. In our study, patients with a family history of SCD described fear before they got the ICD, but a sense of calm afterwards. This contrasted somewhat to the Subasic conclusion that HCM stayed in the foreground. In our study, the ICD contributed to less anxiety and facilitated a reorientation of life, giving these patients new hope.

The poor knowledge about HCM and inheritance pattern has been described previously by Fitzgerald-Butt et al.[521] In the study by Subasic, only 47% of the patients were aware of the possibility of genetic testing for HCM. We also noticed poor understanding of disease transmission, but this may be complicated by the fact that genotype is not required for diagnosis and information from health care professionals is likely to be individualized.

Burns et al qualitatively investigated attitudes and knowledge of genetic findings in HCM.[522] They found that results of testing varied and were sometimes poor. The reason for undergoing genetic testing was altruistic, and these patients often did not recognize the implications for the cascade screenings in their family. This pinpointed the importance of individualized communication about the need for and ramification of genetic counselling.

A disease may change the life experience of a person, who has to make adaptations in lifestyle and future plans. Disease can alter body perception, identity, relationships, and life course. Indeed, everyday life situations, cultural patterns, social norms, and practical abilities may require change and adaptions.[523] There is inherent uncertainty in genetic disease with regard to prognosis and how it will affect life.[524] This is certainly true in patients at risk for SCD, which has been described in HCM and long QT syndrome.[525] Smart conducted interviews on HCM genetic counselling and found that most patients welcomed more knowledge, which alleviated uncertainty, but there was also resistance to share information, which could have social, psychological and other lifestyle effects. In fact, the genetic test for HCM does not predict the course of the disease, and there remains uncertainty. Fortunately, these concerns seemed to fade away with time, and the disease was no longer the primary focus for the individuals and their relatives. For these reasons, Geelen et al advocated an individual approach to genetic counselling in HCM and the involvement of the families.[526]

In a survey study by Baskar et al of 538 HCM association members (54% males; mean age 58 years; 59% response rate), the vast majority of patients perceived the ICD in a favorable way.[518] In about 5% of respondents, there were concerns that questioned the value of ICD therapy, i.e. that patients perceived the drawbacks outweighed the benefits. Importantly, patients reported dissatisfaction with the explanation about their indication for ICD therapy and never had a thorough discussion about ICD with their physician. In another study based on focus groups, 33 of 41 patients (80%) did not recall any discussion of either periprocedural or long-term device complications.[527] In a review of patient perspectives on ICD decision-making, investigators pinpointed the influence of a shared decision-making paradigm as a key for satisfaction.[528] Baskar et al showed that lead dislodgement was associated with poor satisfaction, which suggests that more extensive pre-implant information is welcomed. This approach is endorsed by AHA.[529] To improve this counselling, tools have been developed to aid the patient and facilitate this discussion with the clinical team.[530]

The awareness of the ICD as a protection from SCD is widely recognized in general ICD patients.[531–533] This leads to a sense of gratitude for the technology and health care professionals involved in its management. Patients feel secure and the ICD gives them hope for a longer life according to other qualitative studies.[531–533] This powerful message was particularly strong in our cohort, and it may reflect that many HCM patients are younger and have a better life expectancy than other ICD groups.

Physicians' knowledge of ICDs in general has been tested in a large Swedish survey with 432 respondents working in internal medicine, geriatrics, and in cardiology clinics.[534] Because ICD patients are encountered throughout the health care system, this poor knowledge of ICD therapy is worrisome. Many patients reported situations in their own health care in which poor knowledge translated into worse care and a loss of trust.

10.4.3 Limitations

This qualitative study shares the inherent characteristics of an explorative approach. Still, despite maximal sampling variation and relatively large sample size, all combinations and shades of the lived experienced cannot be covered. Moreover, condensation implies reduction of information; interpretation is subjective. So, despite the action taken to structure data objectively and promote reflexivity and trustworthiness, our study could not encompass all experiences. A patient's self-reported view may differ from the view of other persons; relatives, friends, employees may have markedly different perspectives than those reported by the patient. Even though the narrative design of our study allowed participants to reflect on their experiences, it is not the same as longitudinal follow-up with several interviews. This is not necessarily a limitation, but should be borne in mind. Our sample was recruited from two Swedish regions and all who were asked to participate consented, which avoided selection bias. Nevertheless, the external validity should be addressed with respect to other settings of geographical, cultural, and different health care systems.

10.4.4 Summary

HCM patients with ICDs express health complaints due to their underlying cardiomyopathy, mainly physical limitations and functional deficits. HCM affects their professional life, leisure time activities, family dynamics, and sometimes restricts their activities or make them dependent on others. Nevertheless, they accepted their condition, adapted, and felt renewed hope. At a younger age, being different seemed to be more problematic and often had consequences for lifestyle, but over the years, patients coped with their situation. There was a reorientation with respect to professional and competitive activities toward supportive relatives. Patients showed a wide spectrum of knowledge of the disease and considered the knowledge and skills of health care providers to be quite varied, depending of the setting. The ICD was deemed as a life-saving device and, after implant, they gradually considered it as an integral part of their body. It facilitated a forward-looking attitude and created a hope for the future. Complications, including inappropriate shocks were generally well tolerated, but emotional response varied, although after a short time period, life returned to normal. Appropriate ICD therapy increased the awareness of SCD and reinforced the feeling of reliance on the device and thus gratitude. Improvement of health care should be based on a holistic view of the patient's underlying HCM and not limited to just the technical aspects of the ICD. Health care providers need to anticipate the emotional concerns of the HCM patient in particular, but also consider the concerns of their relatives. The knowledge about HCM and ICD need to be improved both within and outside the cardiology community. Continued relationships with health care providers specialized in the field were appreciated by the patients and provided a solid basis of care, but several other specialties are likely to be engaged during the course of the disease. There needs to be an individualized approach as patients have different prerequisites and perspectives. The optimal communications model would encourage patients to share their inner thoughts and may improve their awareness of their limitations and possibilities, help them adapt to lifestyle changes, encourage an acceptance of their new situation, and promote hope for the future.

10.5 PAPER V

In our PET study of HCM, patients with ICDs were selected because of the uniform assessment of arrhythmia outcome. All patients had the same timeframe during which the outcome could occur. The period of 12 months was deemed appropriate, because it was long enough to assess the outcome but not too long so that the underlying myocardial substrate would not change substantially. The ICD provides continuous monitoring of arrhythmias that can be retrieved by interrogation of the device electrograms. Studies with various follow-up periods and temporary ECG monitoring lack this standardized outcome evaluation.

The selected sample likely represents typical ICD patients due to HCM in terms of age, sex, time since first ICD implant, and proportion of primary prevention. This subset of HCM patients likely constitutes more advanced disease than HCM patients without ICDs.

The PET exams, using triple tracers, were performed during the same day for all patients, starting in the morning and in the same sequence. First ^{15}O-water at rest followed by adenosine stress, then ^{11}C-acetate, and finally ^{11}C-HED. This approach is beneficial because other physiological variables basically remain constant. All tracers were used under resting conditions and ^{15}O-water was also used at stress induced by adenosine.

The main findings are discussed in relation to the respective tracer in following discussion. The PET characteristics of our cohort are compared with those from other studies. One should bear in mind that most PET studies have a small sample size, differ in methodological approach, lack standardized reference values, and have composite outcomes. Moreover, the occurrence of an arrhythmia is end product of a intricate interaction of many factors. The PET technology we used was probably the most advanced to date and provided highly detailed quantitative information about the cardiac substrate and its propensity to act as an arrhythmogenic prerequisite vulnerable to one or more triggers, which remain unknown in the individual case.

Despite the shortcomings of PET studies and constraints due to statistical power, PET technology provides an opportunity to explore pathophysiological features and elucidate potential pathways for ventricular arrhythmias. Indeed, PET technology has contributed to the understanding of HCM and translated knowledge from other diseases. HCM is known as a heterogeneous disease with various expression and prognosis. In our study, we explored HCM patients with ICDs using the established ^{15}O-water at rest and stress to assess MBF, oxidative metabolism using ^{11}C-acetate, and, for the first time in HCM, the ^{11}C-HED that reflects sympathetic innervation.

The potential value of our study has been recognized by Schindler et al, who recently stated, “Magnusson et al provide unique information of some association between a stress-related endocardium/epicardium flow gradient and the prevalence of NSVT in HCM that may suggest such flow gradient as potential novel risk biomarker.”[163]

10.5.1 Global ^{15}O-water at rest and stress

In our cohort, the mean MBF at rest was 0.91 SD 0.23 ml/g/min and ranged from 0.47 to 1.70 ml/g/min. At adenosine-induced stress the mean MBF was 1.59 SD 0.77 ml/g/min and varied from 0.64 to 3.50 ml/g/min between the patients. Thus, even though the sample represents HCM patients with advanced disease, it shows a considerable spread of MBF values and implies heterogeneity.

Most previous studies on MBF, based on other groups than HCM, used ^{13}N-ammonia and in a review (23 studies) of 363 healthy controls, the weighted mean was 0.71 ml/g/min at rest and 2.58 ml/g/min at stress.[535] Notably, both rest and stress values differ due to methodological differences in protocol, tracer kinetic models, software usage, and adjustment for cardiac workload (rate-pressure product).[535–541] There is an obvious need for standardization in order to facilitate comparison between studies.[542] Typically, MBF values reported in women have been slightly higher.[536,543,544] In a pioneering work of the tracer ^{15}O-

water from 1989, normal subjects had homogenous flow through the myocardium and the mean value was 0.90 SD 0.22 ml/g/min at rest and 3.55 SD 1.15 ml/g/min at stress induced by dipyramidole.[545] In a validation work of 330 patients (not HCM) published 2014, using ^{15}O-water and invasive coronary angiography in conjunction with fractional flow reserve, the cutoff value of 2.3 ml/g/min at adenosine stress for hemodynamically significant coronary stenosis was advocated.[546,547] It was deemed superior to CT-angiography and single-photon emission computed tomography in ischemic heart disease. This is in line with a previous study but offers somewhat higher values than in another study.[548,549]

The PET technology has been applied in HCM.[550] A few PET-studies of HCM, reporting MBF at rest and stress, have been conducted and are summarized in Table 26. As can be seen from these results, HCM patients have slightly lower MBF at rest but considerably lower values at stress compared to healthy controls.

Table 26. Myocardial blood flow at rest and stress in HCM patients in PET studies.

First author	Year	Tracer/stressor	Sample size	Rest MBF ml/g/min	Stress MBF ml/g/min
Choudhury[156]	1999	^{15}O-water Dipyramidole	15 HCM No controls	1.02 SD 0.28	1.39 SD 0.31
Cecchi[157]	2003	^{13}N-ammonia Dipyramidole	51 HCM 12 Controls	0.84 SD 0.31 1.0 SD 0.23	1.50 SD 0.69 2.71 SD 0.94
Knaapen[159]	2008	^{15}O-water Adenosine	18 HCM 10 Controls	0.92 SD 0.25 1.30 SD 0.38	2.26 SD 0.97 2.93 SD 0.64
Timmer[158]	2011	^{15}O-water Adenosine	15 Phenonegative 11 Controls	1.19 SD 0.34 1.18 SD 0.32	3.87 SD 0.75 3.96 SD 0.86
Timmer[160]	2011	^{15}O-water Adenosine	15 HCM pre-ASA 15 HCM post-ASA	0.94 SD 0.23 0.98 SD 0.15	2.25 SD 0.91 2.94 SD 1.18
Bravo[161]	2011	^{13}N-ammonia Dipyramidole	33 HCM No controls	1.04 SD 0.33	1.58 SD 0.49
Sciagrà[162]	2017	^{13}N-ammonia Dipyramidole	18 HCM, normal EF reserve 16 HCM, abnormal EF reserve[a]	0.86 SD 0.20 0.89 SD 0.18	1.86 SD 0.41 1.93 SD 0.56
Magnusson[355]	2019	^{15}O-water Adenosine	25 HCM No controls	0.91 SD 0.23	1.59 SD 0.77

[a] Abnormal EF reserve was defined as reduction of more than 5 percentage units at dipyramidole stress.

10.5.2 Transmural global ^{15}O-water at rest and stress

The global TPG, defined as MBF endocardium/epicardium ratio with each part as a half of the wall thickness throughout the entire LV, was 1.14 at rest and 0.92 at stress. The positive ratio, i.e. >1, during rest implies a higher MBF of the endocardial than the epicardial layer. Analogously, a negative ratio, i.e. <1, is the consequence of lower MBF in the endocardial rather than the epicardial layer. Knaapen et al and Choudhury et al reported a similar mean TPG at stress as in our cohort.[156,159] Sciagrà et al reported a higher TPG at stress but a subgroup in their cohort had a negative ratio as well; following dipyramidole, both groups (normal vs abnormal EF reserve) reached a similar level of subendocardial MBF, while the epicardial MBF remained significantly higher in the group with abnormal EF reserve.[162] The

number of segments per patient with TPG <1 was 3 in those with normal EF reserve compared to 6 in the abnormal EF reserve group.[162]

Subendocardial ischemia seems to reflect functional impairment in HCM patients during maximal coronary vasodilatation. Previous findings using single-photon emission computed tomography suggest involvement of the subendocardial layers, but the lower resolution and lack of detailed quantitative assessment needed confirmation by modern imaging techniques.[551,552] CMR with perfusion assessment and LGE has confirmed this phenomenon in HCM.[553,554] Finally, this was assessed using modern PET technology.[159,555]

Knaapen et al compared 18 HCM patients with 10 age-matched controls using ^{15}O-water at rest and stress using adenosine. As summarized in Table 26, MBF at stress was blunted in HCM compared to healthy controls. The endocardial-epicardial gradient was unchanged among controls (1.38 SD 0.15 vs 1.25 SD 0.19; p=not significant) at rest and stress, respectively. On the contrary, in HCM patients the gradient decreased significantly (1.20 SD 0.11 vs 0.88 SD 0.18; p <0.01). This was seen in both the hypertrophied septum and the non-hypertrophied lateral wall. Hyperemic MBF is more severely affected at the subendocardial level in HCM patients. The impairment correlated with increased LV loading conditions and LV mass. In this study, CMR was used for the assessment of LV mass and heart catheterization for invasive measurement of LVOT gradients. From these findings, it can be suggested that extravascular forces, in addition to reduced capillary density, explain microvascular dysfunction.[159] We used the same measurement of endocardial-epicardial gradient by diving ROIs with a central line and reported very similar ratios.

10.5.2.1 Mechanisms of transmural perfusion gradients

Consistent with Laplace's law, wall stress decreases from the subendocardial to the subepicardial layer, which is why an opposite transmural gradient can be observed.[159] Interestingly, MBF at stress in the epicardial layer did not differ between the control group and HCM patients. The absence of impairment in the epicardial layers, which are at least influenced by wall tension, strongly suggests that extravascular compressive forces contribute as a factor in the elevated vascular resistance of the subendocardial layers in HCM patients.

10.5.2.2 Pharmacological interaction of microvascular function

Beta-blockers or calcium-channel blockers act on diastolic functions and do not relieve microvascular dysfunction.[156,556] These drugs were not discontinued for ethical reasons and because we wanted to have clinical representative situation.

10.5.3 Microvascular dysfunction and outcome

As early as the 1990s, Dilsizian et al showed an association between myocardial ischemia and the composite of cardiac arrest, syncope, and NSVT on Holter monitoring in a retrospective analysis of 23 HCM patients aged 6-23 years, using thallium scintigraphy.[557]

A decade later, Cecchi et al published a landmark trial of 51 HCM patients (NYHA I or II at baseline) who underwent PET with ^{13}N-ammonium at rest and dipyridamole-induced stress.[157] The composite outcome (cardiovascular death [n=9], progression to NYHA III/IV [n=6], sustained VT/VF requiring ICD [n=3]) was reached by 16 patients during a mean follow-up of 8.1 SD 2.1 years. MBF at stress was categorized into three groups: low (n=18; 0.59-1.11 ml/g/min), middle (n=16; 1.13-1.57 ml/g/min), and high (n=17; 1.62-3.77 ml/g/min). Patients in the lowest group had an HR of 20.1 (p=0.003) after multivariate analysis, compared to the other groups combined. Notably, all 4 patients who died from progressive heart failure were in the low-flow group and 3/5 of those with SCD were in the low-flow group. Another striking fact is that no single event happened the first two years, and the mean time to first event was ≥5 years. This underlines the fact that PET markers are sensitive and early signs of adverse outcome.

Another decade later, Castagnoli et al reassessed the association of microvascular dysfunction in HCM.[558] Dipyramidole was used to induce stress MBF in 100 HCM patients (follow-up 4.0 SD 2.2 years), who were then categorized into three groups: low (0.73-1.53 ml/g/min), middle (1.54-2.13 ml/g/min), and high (2.14-5.89 ml/g/min). In a similar analysis, the RR was 7.1 for the low-flow group compared to the other groups. The authors, partly the same as in the previous paper, concluded that previous cutoffs were extreme and 1.53 ml/g/min was a better threshold. This was also seen by Lu et al. Interestingly, MBF stress in the lateral wall (but not the septal wall) predicted adverse outcome.[322] This may be interpreted that when the disease is in the lateral wall, it represents a more widespread, severe disease state. In our study of TPG at stress, septal and inferior segments were associated with positive NSVT outcome, while the lateral wall showed a p-value of 0.101.

Olivotto et al showed that 42 genopositive HCM patients had significantly lower MBF at stress (dipyramidole) than genonegative patients (1.7 SD 0.6 ml/g/min vs 2.4 SD 1.2 ml/g/min; p=0.02) despite similar clinical profiles. Patients with sarcomere myofilament mutations display more severe impairment of microvascular function compared with genotype-negative individuals, which suggests a link between mutations and adverse remodeling.[586]

10.5.3.1 Global ^{15}O-water at rest/stress and outcome

The main finding of the PET-study involves TPG at stress and its association with NSVT. The fact that a borderline significance of TPG (p=0.059) turned into significance (p=0.022) during MBF at stress is striking and is explained by a more pronounced microvascular dysfunction in the endocardial layers in HCM. The association of a pure arrhythmia outcome measurement, even though a surrogate for life-threatening VT/VF, may emerge in further studies.

10.5.3.2 Regional ^{15}O-water at rest/stress and outcome

The segments for the heart, grouped as regions, showed that septal and inferior parts were most strongly associated with outcome with regard to TPG at stress while the inferior and

lateral regions were significantly associated with MBF at rest. The mechanistic explanation for this is unclear but lateral involvement likely represents patients with more advanced disease. The fact that 8 patients had undergone myectomy may affect results, but this group did not have a significantly different risk of outcome. The sample was too small to build a multivariable model where several factors could be taken into account.

In HCM, MBF at rest is typically within normal mean values for the entire LV, even though regional values may be lower, especially in hypertrophied segments.[550] At induced vasodilation, MBF at stress is often reduced.[152] In HCM, the arterioles of the coronary vessel, rather than epicardial coronary vessel, are the level of disease, which is supported by histological findings.[152,154,157] This microvascular dysfunction explains the reduced MBF at stress both globally in the LV but also in segments without hypertrophy.[152]

10.5.3.3 Defect size and outcome

The concept of defect size has been used in other quantitative assessments using PET in ischemic cardiomyopathy.[325,559] The heterogenic scar zone may contain vital myocytes and fibrosis adjacent to each other. In fact, CMR has shown scar-related features in ischemic cardiomyopathy associated with SCD.[560–562] The size of the scar seems to be correlated to the risk of ventricular arrhythmias.[560–563] The defect size increased markedly between rest and stress. However, in our sample, neither defect size at rest nor stress was associated with outcome.

10.5.3.4 Heterogeneity index and outcome

Regional ischemia can lead to action potential shortening of the myocyte, dispersion of ventricular repolarization, and subsequent conduction from the substrate to reentry circuits. It could be speculated that marked disparities in the regional perfusion might promote ventricular arrhythmias.[564] This pathophysiological pathway provided a rationale for the heterogeneity index used by Lu et al in 133 HCM patients (23 with ICD).[322] The heterogeneity index was defined as dividing the highest regional MBF by the lowest regional MBF value at rest and stress in every individual patient. A high heterogeneity index using the cutoff ≥1.85 derived from the receiver operating characteristic curve (area under curve 0.64) implied a sensitivity of 35% and specificity of 94%. The outcome in that study was the composite of ventricular arrhythmia (appropriate ICD therapy, NSVT at Holter monitoring or ICD interrogation) during a mean follow-up of 3.3 SD 1.6 years. This outcome was reached by 53% of those with a high heterogeneity index and 13% of those with a low index. Based on this predictive potential, we did the same calculation using our outcome with uniform assessment. Neither MBF at rest nor MBF at stress in our sample were associated with outcome. The two studies differ in methodological approach and patients in our sample likely represent HCM patients with more advanced disease.

10.5.3.5 Arrhythmia substrate mechanisms

In an autopsy study by Tanaka et al, the external diamater of the intramyocardial small arteries were similar in HCM specimens than in normal hearts, whereas the lumen was significantly reduced in HCM specimens.[153] In another necropsy study, the wall thickening was due to proliferation of medial and/or intimal components, especially smooth muscle and collagen.[154]

The arrhythmogenic substrate for ventricular arrhythmias is highly complex with both fixed and dynamic properties. Sarcomeric dysfunction may lead to hypertrophy, disarray, fibrosis, altered ion channel expression, and abnormal gap junctions. Altogether this may slow down conduction velocity heterogeneously, and it creates pathways for reentry mechanisms and promotes triggered activity that can cause arrhythmias.[83] The architectural and electrophysiological remodeling is affected by reduced arteriolar density and the structural wall of vessels, at the arteriolar level.[565] The microvascular dysfunction becomes more apparent at vasodilator stress. During stress, the reduction of oxygen delivery leads to adenosine triphosphate depletion, activation of adenosine triphosphate sensitive K^+ channels, action potential shortening, and makes these vulnerable as reentry circuits.[564]

10.5.3.6 Treatment principles to reduce gradients

Microvascular dysfunction in HCM, which causes decreased MBF at stress, is expressed in both hypertrophied and non-hypertrophied segments.[553,566] Thus, this pathophysiological phenomenon is widespread over the entire left ventricle. Histological findings of intramural vessel remodeling throughout the myocardium provide a basis of explanation.[154] Hypertrophy in itself seems to play a role, as myocardial hypertrophy due to hypertension or aortic stenosis also shows decreased MBF at stress, presumably due to lower capillary density.[567,568] Moreover, the microvascular resistance may be elevated due to compression exerted by the increased pressure within the cavity due to LVOT obstruction.[159,569]

It has been demonstrated that reduced MBF at stress may appear in segments without delayed contrast enhancement using CMR. This has been interpreted as microvascular dysfunction, which precedes ischemic injury and chronic tissue responses.[570] Indeed, replacement and interstitial fibrosis are characteristic features of end-stage HCM.[154] Myocardial fibrosis is thus believed to play a role in the deterioration of systolic function, likely by interfering with myocardial shortening.[571,571–573] Altogether this may imply that in HCM with severely decreased perfusion there is an increased risk of systolic heart failure and life-threatening arrhythmias.[553]

This provides a rationale for beta-blocker therapy.[574] For the same reasons, septum reductive procedures, ASA, or surgical myectomy seem to be effective and grounded in this treatment principle.[566] From this perspective, calcium-channel antagonists are not equally beneficial regarding MBF.[156]

In patients with LVOT obstruction and impaired diastolic relaxation, this microvasculature dysfunction may be more pronounced.[159] Based on Laplace's law, the wall tension increases from subepicardial to subendocardial layer, which leads to an inverse TPG.[159] This may be more pronounced if the LV loading conditions are elevated.

In 15 patients with HCM who underwent ASA, MBF at rest was unchanged (0.94 SD 0.23 ml/g/min vs 0.98 SD 0.15 ml/g/min; p=0.45) but coronary vascular reserve increased (2.55 SD 1.23 ml/g/min vs 3.05 SD 1.24 ml/g/min; p=0.05).[160,575,576] Before ASA, the endocardium/epicardium MBF ratio was lower during stress than at rest (0.80 SD 0.18 vs 1.18 SD 0.15; p<0.001). After ASA, MBF at stress increased to 1.03 SD 0.26; p=0.02. The MEE using acetate increased from 15 SD 6 to 20 SD 9%; p=0.04. Thus, ASA alleviates the LVOT gradient which, in turn, affects loading conditions and, in so doing, improves microvascular function and myocardial energetics.

10.5.4 ^{11}C-acetate

The myocardium relies on the oxidation of metabolic substrates in the Krebs cycle. Therefore, the early clearance rate of ^{11}C-acetate correlates with myocardial oxygen consumption (MVO_2) under various conditions.[159,308,577] In HCM, MVO_2 per gram of myocardial tissue was found to be within normal range in two studies or slightly reduced. In hypertrophic segments where the MVO_2 per gram seems to be reduced compared to non-hypertrophic segments, i.e. the lateral wall; this differs from the results obtained from healthy controls.[575,578–580] In hypertrophied segments, hypokinesia, decreased systolic wall thickening, increased diffusion distance, and lower capillary density may reduce oxygen uptake.[154,566,572,581]

Myocardial energy efficiency, expressed as myocardial external efficiency (MEE), is based on the proportion of energy produced by the LV in relation to the energy consumed, both expressed in Joules. Thus, the MEE is the ratio of conversion of MVO_2 into actual cardiac work.

The study by Ishiwata et al from 1997 claimed lower oxygen consumption in hypertrophic and non-hypertrophic segments, but this was not adjusted for per gram tissue and the spatial resolution was poor (about 7.5 mm).[575] Tadamura et al found lower K mono values in HCM compared to controls, but these studies share methodological shortcomings with the previously mentioned study.[580] In HCM, MVO_2 is relatively robust and is similar to control values, at least at rest. In contrast, MEE is substantially affected. Some studies using ^{11}C-acetate are summarized in Table 27.

Table 27. Oxidative metabolism in HCM and miscellaneous diseases in PET studies.

First author	Year	Tracer/ stressor	Sample size	MVO_2 ml/g/min	MEE %
Timmer[578]	2010	^{11}C-acetate	20 HCM 11 Control	0.13 SD 0.05 0.12 SD 0.04	21 SD 10 35 SD 8
Timmer[160]	2011	^{11}C-acetate	7 HCM pre-ASA 7 HCM post-ASA	0.12 SD 0.03 0.13 SD 0.03	15 SD 6 20 SD 9
Timmer[158]	2011	^{11}C-acetate	15 HCM genotype (no phenotype) 11 Controls	0.14 SD 0.06 0.13 SD 0.04	27 SD 10 36 SD 8
Harms[323]	2018	^{11}C-acetate	33 Aortic stenosis 20 Mitral regurgitation 10 Control	0.12 SD 0.04 0.11 SD 0.03 0.10 SD 0.02	17 SD 4 18 SD 5 24 SD 4
Clemmensen[582]	2018	^{11}C-acetate	25 Amyloidosis 15 Control	0.09 SD 0.02 0.10 SD 0.02	13 SD 5 24 SD 5
Magnusson[355]	2019	^{11}C-acetate	25 HCM No control	0.088 SD 0.025	18.5 SD 8

Our results are comparable with the Dutch studies of HCM with a phenotype. Notably, even in carriers without phenotype, MEE is decreased, and this variable seems to be a sensitive marker of early signs of disease.

The LV mass correlated with reduced MEE in HCM in the study by Timmer et al.[578] In a study by Crilley et al, using magnetic resonance spectroscopy, a lower (around 30%) PCr/adenosine triphosphate ratio was shown in patients with HCM-associated mutations (n=31) than controls (n=24).[583] Notably, these parameters of deteriorated energy metabolism were similar, irrespective of degree of hypertrophy and including those without hypertrophy. This adds to the evidence that cardiac energy handling is impaired in the disease expression. The resting energy abnormalities are a primary sign, rather than secondary to hypertrophy. Functional studies of HCM with sarcomeric mutations have shown inefficient adenosine triphosphate utilization, which increases the cost of contractility.[584–586]

Microvascular dysfunction is also likely to play a role in reduced MEE. Carriers of the *MYBPC3* mutation exhibit reduced MEE in the absence of perfusion defects.[158] The hypertrophy, fibrosis, disarray, and microvascular dysfunction limit oxygen delivery in a viscous circle.

There is a pathophysiological pathway in myocardial fatty acid metabolism and LV hypertrophy. Early observations in children with genetic defects were later confirmed regarding abnormalities in regulatory subunits of adenosine monophosphate-activate protein kinase, a key part of the beta-oxidation cascade known to cause HCM.[587,588] This is supported by animal models of hypertrophy.[589] In patients with hypertension alone, MVO_2 per gram is elevated, but when hypertrophy develops, there is a normalization in MVO_2 per gram of

tissue. However, this adaptation comes at the expense of reduced myocardial efficiency, which possibly makes the heart prone to systolic heart failure.[590]

In the paper by Timmer et al 15 carriers of the *MYBPC3* mutation without phenotype underwent ^{15}O-water and ^{11}C-acetate evaluations and were compared to 11 healthy controls. LV mass was similar (93 SD 25 gram vs 99 SD 21 gram; p=0.85). Mean MBF at rest was also similar, and at stress, MVO_2 was similar but MEE was significantly lower (27 SD 10% vs 36 SD 8% in controls p=0.02). Thus, MEE seems to be an early component of HCM pathology before hypertrophy occurs.[158] Increased energy expenditure, i.e. mechanical work inefficiency, is a characteristic feature of HCM. This is clearly displayed already as an early feature in the clinical course.[575,578,579,591]

10.5.4.1 The benefit of myectomy and ASA

Septum reductive procedures, myectomy, or ASA can alleviate symptoms. In a small study of 7 patients who underwent ASA, the procedure did not affect mean MVO_2, but after 6 months the amount work per gram of tissue increased the MEE significantly from 15 to 20%.[160] This confirms early findings, using invasive catheters, that showed improvement of coronary flow and metabolism (lactate) after myectomy.[590]

10.5.5 ^{11}C-HED

Abnormalities in the autonomic nervous system have been associated with VT/VF.[592,593] Our study is the first study of sympathetic innervation using the tracer ^{11}C-HED in HCM. The mean RI was 0.11 /min in our cohort. Because there are no standardized reference values, our results can be compared to the largest study using ^{11}C-HED, the PAREPET study.[594] In the PAREPET study, 204 patients eligible for a primary-prevention ICD due to ischemic cardiomyopathy with EF≤35% were enrolled. The RI defined as the segment with maximal uptake was 0.136 SD 0.037 in PAREPET compared to 0.11 SD 0.042 in our study. The outcome in the PAREPET study was SCD or appropriate ICD therapy due to VT/VF at a rate of 240 BPM or more over a mean period of 4.1 years. The amount of denervated left ventricle, i.e. the defect size in the group (n=33) that reached the outcome, was significantly higher (33 SD 10% vs 26 SD 11%; p=0.001). In comparison, the overall mean defect size in our sample was 15 SD 10%. Thus, our sample comprised a cohort with a smaller sample size and defect size was similar in those with and without NSVT (p=1.00).

The PAREPET study has a more SCD-specific outcome, although it is measured very conservatively, in contrast to other studies of innervation that use composite endpoints. In another study (n=116) also eligible for ICDs, those with a high ^{123}I-*m*IBG myocardial imaging-derived defect score significantly more frequently met the composite endpoint death and appropriate ICD therapy.[595]

In a study by Pietilä et al, 46 patients with ischemic or nonischemic cardiomyopathy, NYHA II/III (mean EF 35 SD 8%) were followed for a mean of 55 SD 19 months.[312] Using the median retention of 0.184 SD 0.061, significantly more patients reached the endpoint (death

due to SCD or heart failure) in the group below the cut-off (3 vs 8; p<0.02). Notably, 9 of 11 deaths were considered as sudden.

Autonomic nervous system dysfunction has been elucidated in ischemic cardiomyopathy and dilated cardiomyopathy. The absolute retention was approximately reduced by 40% compared to healthy controls.[316,317,538]

In ADMIRE-HF, 961 patients in NYHA II/III with EF≤35% either due to ischemic cardiomyopathy or nonischemic cardiomyopathy with a mean follow-up of 17 months were studied using ^{123}I-*m*IBG myocardial imaging. Measurements of denervation were strongly associated with the composite outcome of cardiac death, NYHA class progression, and sustained VT/appropriate ICD therapy.[596]

Other smaller studies have shown an association between ^{123}I-*m*IBG myocardial imaging parameters and VT/VF.[592,596–598] Moreover, the defect size may indicate the risk of VT/VF.[623] We explored this in our sample, but defect size, heterogeneity index, and transmural gradients were non-significantly associated with NSVT as outcome.

Furthermore, clearance rate in the model can be used as a surrogate of denervation. Here, an interesting finding, with borderline significance for the NSVT group was noticed. Based on the idea of the relevance of transmural gradients in HCM, the clearance rate of the endocardium/epicardium was analyzed. Again, it was borderline significant. The transmural gradient, with a higher degree denervation of the endocardium compared to the epicardium, turned out to be a sensitive marker of NSVT with a borderline significance. Using the concept of mismatch, defect size difference derived from RI and MBF at rest/stress was calculated but did not show a significant association with NSVT.[599]

10.5.6 Limitation

This first triple-tracer PET study of HCM patients with ICDs with a uniform assessment of the outcome of NSVT was a novel approach to characterization and risk marker evaluation. However, there are several limitations. First, although NSVT is an established risk factor in HCM, it is a surrogate of SCD. Secondly, an episode of arrhythmia is the endpoint of a complex interplay of cardiac substrate and potential triggers that are unknown in the individual case. Thirdly, PET studies often have small sample size and analyses are prone to both type I and type II errors in statistical hypothesis testing. It should be highlighted that this study has an explorative design and confirmatory studies are needed before risk stratification can be improved. Nevertheless, novel approaches are needed to refine risk stratification in HCM, which remains a challenge.

10.5.7 Summary

In this study, HCM patients with ICD underwent PET with three tracers (^{15}O-water, ^{11}C-acetate, and ^{11}C-HED) for evaluation of MBF, oxidative metabolism, and sympathetic innervation. MBF at rest was 0.91 ml/g/min at rest (slightly decreased) and decreased at

adenosine stress 1.59 ml/g/min which is reduced compared to normal hearts. The mean TPG (endocardium/epicardium ratio) was 1.14 SD 0.09 at rest and inversed at stress, 0.92 SD 0.16. The main finding was that patients with NSVT had significantly lower gradients at stress (p=0.022) and borderline at rest (p=0.059). Global MBF at rest and stress were not significantly different with regard to NSVT. Mean MVO_2 was 0.088 ml/g/min and the MEE was hampered, 18.5%. Sympathetic denervation was present, RI 0.11 /min; a higher volume of distribution (p=0.089), transmural gradient of clearance rate (p=0.061) and lower clearance rate (p=0.052) showed tendency of association with the outcome NSVT. Based on pathophysiologically plausible mechanisms of the TPG at stress and arrhythmia in this explorative study, a potentially novel risk marker of SCD in HCM has been elucidated.

11 FUTURE PERSPECTIVES

HCM continues to fascinate clinicians and researchers. The heterogeneity and unpredictable nature of the disease expression requires careful evaluation over the life course. Despite efforts in risk stratification, there will always be limited sensitivity and specificity with regard to SCD prediction. In addition to current guidelines on risk assessment, further incorporation of additional risk markers will hopefully improve outcomes. Such novel risk markers should ideally be simple, easily available, and have incremental value if applied in routine care. Nevertheless, more sophisticated imaging tools may be useful in HCM research and should be welcomed, even if they are not part of clinical routine in the near future. While PET is currently costly, requires considerable resources, and is not yet widely available, it provides a valuable insights into pathophysiological mechanisms and explores the potential predictors of clinically relevant outcome measurements.[23,24] PET accurately quantifies pathophysiological parameters and the high sensitivity is beneficial, because most HCM patients have slow disease progression, which would be valuable in evaluation of therapies. However, the lack of standardization of methodology in PET, including reference values, needs to be addressed and global collaborations are warranted.

Larger studies based on our initial findings of risk markers would provide necessary information. MBF at stress, especially TPF using ^{15}O-water but also findings from ^{11}C-HED, are promising candidates for further studies. Ideally, such studies should be prospective, have long-term follow-up, be powered for detection of different outcomes, such as SCD (or a surrogate) and disease progression, including systolic heart failure. Moreover, PET could provide accurate and sensitive outcome assessment in intervention studies, such as septum reductive procedures (ASA or myectomy) or pharmacological trials. Patients without ICDs would likewise be interesting and relevant to study. It can be suggested that patients with estimated intermediate risk of SCD should be a prioritized targeted subgroup.

Studies should be designed so that confounding can be addressed by a randomized controlled trial or, more realistically, observational trials with robust assessment of predictors and outcomes and the possibility to adjust for multiple interactions among variables. The unpredictable nature of arrhythmia and definite assessment of outcome need to be addressed. It is important to distinguish outcome measurements, as they may have different predictors. SCD and heart failure are often combined rather than separated, even though there are clear differences in their respective clinical management. In order to overcome the unknown burden of arrhythmia without an ICD, the insertable cardiac monitor could be an alternative. Indeed, it is crucial to improve sensitivity and specificity in SCD risk assessment, albeit difficult. Imaging tools, including PET have the potential to refine the risk stratification in HCM. Further standardized prospective multicenter studies are warranted to explore and confirm additional tools for risk assessment with clearly defined outcome measurements.

As overall management of HCM continue to improve, it is important to revise guidelines and risk stratification algorithms. Because many patients have a low annual event rate of life-threatening arrhythmias, large studies are needed to accurately predict outcomes and validate

stratification systems, especially in specific subgroups and diverse settings. Therefore, joint collaborations across borders are welcome. In this connection, it is important to include unselected patients throughout the cardiology community outside centers of excellence. A close cooperation between clinicians with diverse expertise will hopefully be spurred by digitalization of health care. Furthermore, educational efforts among health care professionals, patients, and relatives will be crucial to improve the quality of care and implement guidelines. Future perspectives may include machine learning to identify risk factors and assist physicians in decision-making, which already has shown promising yield.[600] The diagnostic challenges in HCM remain problematic and need to be addressed in future endeavors involving health care digitalization and networking among experts and general health care providers.

ICD technology has improved and the use of S-ICD systems in HCM can be expected to increase. Because HCM patients are often younger, have long life expectancy, and are prone to lead-related complications, S-ICD technology should be embraced. The possibility to combine S-ICD with leadless pacing may further enhance its role and make it a more desired device choice for HCM patients.

Noninvasive ECG technologies, including smart devices such as watches, may offer a new avenue for evaluation of HCM patients. These smart devices may help screen for atrial fibrillation and other arrhythmias and monitor activity levels.

The genetic basis for understanding the molecular mechanisms in disease has opened a new era. Notwithstanding, this knowledge needs to be further elucidated and translated into clinically relevant tools. Genetically based interventions have the potential to prevent disease progression or even obliterate the disease entirely. Recently, CRISPR-Cas9 based gene editing was applied in a human embryo to correct a gene mutation.[601]

Indeed, technological advances are needed to revolutionize treatments. At the same time, a holistic approach incorporated into the clinical management is warranted to understand the patients' perspectives and allocate resources for optimal care. A bright future for HCM patients depends on the implementation of current knowledge, appropriate resources, and innovation based on fruitful research collaborations.

12 CONCLUSIONS

The following conclusions of this thesis are based on Paper I-V.

● Patients to receive ICDs due to hypertrophic cardiomyopathy were based on known risk factors for sudden cardiac death at the time.

● ICDs effectively terminate potentially life-threatening ventricular arrhythmias in hypertrophic cardiomyopathy.

● The cumulative incidence of first appropriate ICD therapy in hypertrophic cardiomyopathy at 1 year, 3 years, and 5 years were 8%, 15%, and 21%, respectively.

● Left ventricular ejection fraction less than 50% and atrial fibrillation are strong predictors of appropriate ICD therapy.

● In hypertrophic cardiomyopathy patients with ICDs, the main cause of death is deterioration of systolic function leading to end-stage heart failure.

● The standardized mortality ratio is 3.4 in hypertrophic cardiomyopathy patients with ICD compared to the Swedish general population.

● Generic health-related quality of life, both mental and physical components, is lower in hypertrophic cardiomyopathy patients with ICDs than in Swedish population norms.

● Systolic heart failure and atrial fibrillation are determinants of low health-related quality of life, especially physical functioning.

● From a qualitative point of view, hypertrophic cardiomyopathy patients with ICDs perceive poor health due to limiting dyspnea.

● ICD patients with hypertrophic cardiomyopathy feel grateful for the device, even after experiencing inappropriate shocks, because it gives them hope during their life course despite necessary restrictions and adaptation.

● The knowledge about the disease hypertrophic cardiomyopathy and device therapy varies substantially among patients and the support from the health care providers is generally constrained to technical issues rather than an attempt at a holistic approach.

● Patients with hypertrophic cardiomyopathy and ICDs show decreased myocardial blood flow at stress, altered oxidative metabolism, and sympathetic denervation using the tracers ^{15}O-water, ^{11}C-acetate, and ^{11}C-HED during exams with positron emission tomography.

● The endocardium/epicardium myocardial blood flow gradient at stress is lower in hypertrophic cardiomyopathy patients with nonsustained ventricular tachycardia.

13 ABSTRACT IN SWEDISH (SAMMANFATTNING)

Bakgrund. Hypertrofisk kardiomyopati (HCM) är ett heterogent tillstånd med olika sjukdomsuttryck inklusive plötslig hjärtdöd, vilket dock kan förebyggas med en implanterbar kardiell defibrillator (ICD). **Syfte.** Det övergripande syftet med avhandlingen var att belysa olika aspekter av ICD-behandling hos patienter med HCM. Detta innefattar ICD-användning vid HCM med tonvikt på riskvärdering avseende ventrikulära arytmier, mortalitet och dödsorsaker, mätning av hälsorelaterad livskvalitet, kvalitativa aspekter av hur det är att leva med en ICD, karakterisering med positronemissionstomografi (PET) och undersökning av riskmarkörer för plötslig död. **Metod.** Det svenska pacemaker och ICD registret användes för att identifiera tänkbara patienter. Socialstyrelsens patientregister, dödsorsaksregistret, Statistiska centralbyrån och journaler användes. SF-36 användes för att kvantifiera hälsorelaterad livskvalitet. Intervjuer analyserades kvalitativt med hermeneutik och innehållsanalys. PET och ekokardiografi genomfördes. **Resultat och Slutsatser.** I *delarbete I*, baserat på den nationella kohorten av oselekterade patienter med hypertrofisk kardiomyopati, konstaterades att riskvärdering avseende ICD skedde utifrån, vid tidpunkten, etablerade riskfaktorer avseende plötslig död. ICD bryter effektivt potentiellt livshotande ventrikeltakykardi hos patienter med HCM. Den kumulativa incidensen av första adekvata ICD-behandlingen vid 1, 3 och 5 år var 8 %, 15 % respektive 21 %. Ejektionsfraktion under 50 % och förmaksflimmer utgör starka prediktorer för adekvat ICD-behandling. I *delarbete II* visades att för HCM patienter med ICD var huvudsakliga dödsorsaken försämring av systolisk funktion som leder till terminal hjärtsvikt. Däremot upphör närmast plötslig hjärtdöd till följd av arytmi. Alltjämt föreligger en förhöjd dödsrisk (standardiserad mortalitetskvot 3.4) jämfört med svenska befolkningsdata matchad avseende kön, ålder och kalendertid. I *delarbete III*, var generisk hälso-relaterad livskvalitet, både mental och fysisk, lägre hos patienter med HCM och ICD än svensk ålders och könsmatchad normpopulation. Systolisk hjärtsvikt och förmaksflimmer var utslagsgivande för låg hälsorelaterad livskvalitet, särskilt fysisk funktionsförmåga. I *delarbete IV* baserat på kvalitativ innehållsanalys av intervjuer med HCM patienter med ICD konstaterades försämrad hälsa till följd av begränsande andfåddhet men de anpassade sig och accepterade dessa livsstilsförändringar. De var tacksamma för ICD:n som gav dem känsla av hoppfullhet under livets trots nödvändiga restriktioner och anpassning, till och med efter inadekvata chockbehandlingar. Kunskapen om sjukdomen och ICD varierar påtagligt och stöd från sjukvården är vanligen begränsat till tekniska delar snarare än försök till holistisk ansats. I *delarbete V*, visade sig HCM-patienter med ICD representera allvarlig sjukdom uttryckt som minskat myokardiellt blodflöde vid adenosinstress, förändrad oxidativ metabolism och sympatikoton denervering vid användande av de radioaktiva spårämnena ^{15}O-vatten, ^{11}C-acetat och ^{11}C-HED vid PET undersökning. Kvoten myokardiellt blodflöde endokardium/epikardium vid adenosinstress är lägre hos patienter som har icke-ihållande ventrikeltakykardi vilket utgör en potentiell markör för att förbättra riskvärdering avseende plötslig hjärtdöd.

14 POPULAR SCIENCE SUMMARY

Hypertrophic cardiomyopathy (HCM) is a varied disease, often with symptoms such as shortness of breath and risk of sudden death due to cardiac arrhythmias mainly from the ventricles of the heart. An implantable cardioverter defibrillator (ICD) has the capacity to terminate such arrhythmias by either overdrive pacing or an electrical shock. The aim of this doctoral thesis was to elucidate different aspects of ICD treatment in patients with HCM. It focuses on risk stratification for life-threatening arrhythmias, mortality and cause of death, assessment of quality of life, qualitative aspects of living with an ICD, and characterization using imaging tools such as positron emission tomography (PET) to explore risk markers for sudden death. The Swedish Pacemaker and ICD Registry was retrieved to identify eligible patients. Data from the National Patient Registers, the Cause of Death Register, Statistics Sweden, and medical records were used. Quality of life was assessed using the questionnaire SF-36. Interviews were analyzed by hermeneutics and latent content analysis. PET and echocardiography exams were performed.

In *Paper I*, the nationwide sample of all HCM patients with ICDs was based on established risk factors for SCD at the time. ICDs effectively terminate life-threatening ventricular arrhythmias in hypertrophic cardiomyopathy. After 1, 3 and 5 years, 8%, 15%, and 21% of the patients, respectively, had experienced appropriate ICD therapy. The study used the ejection fraction, which is the proportion of blood in the heart's large lower left chamber that is ejected out into the body with each cardiac contraction. The ejection fraction is typically measured with echocardiography. An ejection fraction below 50% and/or atrial fibrillation are strong predictors that an ICD patient will receive appropriate therapy from the device at some point. In *Paper II,* it was shown that for hypertrophic cardiomyopathy patients with ICDs, the main cause of death is deterioration of the ejection fraction, leading to end-stage heart failure. The ICD is very effective at terminating arrhythmias, so the risk of sudden death is almost gone. Still, there is an increased risk of death, more than threefold compared to the Swedish general population with the same age, sex at the same time period. In *Paper III*, quality of life, both mental and physical components, was shown to be lower in HCM patients with ICDs than in Swedish population norms of the same age and sex. Low ejection fraction and atrial fibrillation are also determinants of low quality of life. This is more pronounced in physical functioning. In *Paper IV*, HCM patients with ICDs appear to perceive that they are in poor health due to limiting shortness of breath, but they nevertheless accept the change in life style. They feel grateful for their ICD device, which gives them hope even after experiencing inappropriate shocks and despite necessary restrictions and adaptation. The knowledge about the disease and device therapy varies substantially and the support from health care providers is generally constrained to technical issues rather than an attempt to achieve a holistic approach. In *Paper V*, HCM patients with ICDs represent advanced disease expression determined as decreased myocardial blood flow at stress, altered metabolism, and impairment of the sympathetic nervous system that controls the heart. This was measured using radiolabeled tracers in PET exams. The endocardium/epicardium myocardial blood flow gradient (i.e. the inner half of the heart muscle divided by the outer half) at stress is lower in hypertrophic cardiomyopathy patients with a certain type of arrhythmia (ventricular tachycardia that lasts less than 30 s). This knowledge can be used to improve risk stratification in HCM and select the right candidates for ICDs.

15 POPULAR SCIENCE SUMMARY IN SWEDISH (POPULÄRVETENSKAPLIG SAMMANFATTNING)

Hypertrofisk kardiomyopati (HCM) är ett heterogent tillstånd med olika sjukdomsuttryck inklusive plötslig hjärtdöd vilket dock kan förebyggas med en implanterbar kardiell defibrillator (ICD) som har förmåga att bryta rytmrubbningar. Det övergripande syftet med avhandlingen var att belysa olika aspekter av ICD-behandling hos patienter med HCM. Detta innefattar ICD-användning vid HCM med tonvikt på riskvärdering avseende livshotande rytmrubbning, dödlighet och dödsorsaker, mätning av livskvalitet och aspekter av hur det är att leva med en ICD, karakterisering med bildavgivningssättet positronemissionstomografi (PET) och undersökning av riskmarkörer för plötslig död. Det svenska pacemaker och ICD registret användes för att identifiera tänkbara patienter. Socialstyrelsens patientregister, dödsorsaksregistret, Statistiska centralbyrån och journaler användes. SF-36 användes för att beräkna livskvalitet. Intervjuer analyserades kvalitativt med hermeneutik och innehållsanalys. PET och hjärtultraljud genomfördes.

I *delarbete I*, baserat på den nationella kohorten av oselekterade patienter med hypertrofisk kardiomyopati, konstaterades att riskvärdering avseende ICD skedde utifrån, vid tidpunkten, etablerade riskfaktorer avseende plötslig död. ICD bryter effektivt potentiellt livshotande rytmrubbning hos patienter med HCM. Efter 1, 3 och 5 år hade 8 %, 15 % respektive 21 % haft adekvat ICD-behandling till följd av rytmrubbning. Ejektionsfraktion (ett mått på andelen blodvolym som pumpas ut i varje hjärtslag) under 50 % och förmaksflimmer har ett starkt samband med adekvat ICD-behandling. I *delarbete II* visades att för HCM patienter med ICD var den huvudsakliga dödsorsaken försämring av pumpkraft mätt som ejektionsfraktion vilket leder till dödlig hjärtsvikt. Däremot försvinner närmast plötslig hjärtdöd som dödsorsak. Alltjämt föreligger en förhöjd dödsrisk, drygt trefaldig jämfört med övrig befolkning med samma kön och ålder. I *delarbete III*, sågs att mental och fysisk hälsorelaterad livskvalitet var lägre hos patienter med HCM och ICD än övrig jämförbar befolkning. Nedsatt ejektionsfraktion och förmaksflimmer var förknippat med låg livskvalitet, särskilt fysisk funktionsförmåga. I *delarbete IV* baserat på intervjuer av HCM patienter med ICD framkom försämrad hälsa till följd av begränsande andfåddhet men de anpassade sig och accepterade dessa livsstilsförändringar. De var tacksamma för ICD:n som gav dem känsla av hoppfullhet under livets nödvändiga restriktioner och anpassning, till och med efter inadekvata chockbehandlingar. Kunskapen om sjukdomen och ICD varierar påtagligt och stöd från sjukvården var vanligen begränsat till tekniska delar snarare än försök till holistisk ansats. I *delarbete V*, visade sig HCM-patienter med ICD representera allvarlig sjukdom uttryckt som försämrat blodflöde i hjärtmuskeln vid stresspåslag, förändrad ämnesomsättning och försämring av nervsystemet som styr hjärtat när det undersöktes med radioaktiva spårämnen i PET-kameran. Kvoten blodflöde endokardium/epikardium (det vill säga innerhalvan dividerad med ytterhalvan) vid stresspåslag var lägre hos patienter som har kammarytmrubbning som varar mindre än 30 sekunder. Denna kunskap kan användas för att förbättra riskvärdering vid HCM och välja ut de som behöver en ICD.

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