Improving Outcomes in Hypertrophic Cardiomyopathy

Pieter Adriaan Vriesendorp

Improving outcomes in hypertrophic cardiomyopathy

ISBN 978-94-6299-403-4

Layout and printing: Ridderprint b.v., Ridderkerk, the Netherlands

Financial support for this thesis was generously provided by:
Cardialysis BV
Biotronik Nederland BV
Servier
ABN AMRO
Astra Zeneca
Boehringer Ingelheim
St. Jude Medical
Erasmus Universiteit Rotterdam
TomTec Imaging Systems

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged

Improving Outcomes in Hypertrophic Cardiomyopathy

Verbeteren van uitkomsten in hypertrofische cardiomyopathie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam

op gezag van de rector magnificus
prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
dinsdag 6 september 2016 om 13.30 uur

door

Pieter Adriaan Vriesendorp

geboren te Groningen

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotor
prof.dr. F. Zijlstra

Overige leden
prof.dr. A.J.J.C. Bogers
prof.dr. R.J.M. van Geuns
prof.dr. J. van der Velden

Copromotoren
dr. M. Michels
dr. A.F.L. Schinkel

ἄλλος γάρ τ᾽ ἄλλοισιν ἀνὴρ ἐπιτέρπεται ἔργοις.

Homer, the Odyssey (14:228)

TABLE OF CONTENTS

V – Discussion

VI – Epilogue

I – Introduction

GENERAL INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common (prevalence of 0.2%-0.5%) inheritable myocardial disease[1, 2], and is defined by left ventricular hypertrophy that is not explained by other conditions such as hypertension or aortic valve stenosis (FIGURE 1). HCM is a heterogeneous disease with a diverse spectrum of clinical manifestations. Patients may remain asymptomatic and have a normal life expectancy. A small subgroup of patients with HCM however may suffer from sudden cardiac death (SCD) as the first presentation. Other common symptoms are exertional dyspnea, chest pain, syncope and palpitations. The underlying pathophysiology exists of several components: left ventricular outflow tract obstruction, diastolic dysfunction, mitral regurgitation, myocardial ischemia, and atrial and ventricular arrhythmias.

First description of HCM

The modern description of this disease is credited to Donald Teare, a London pathologist who published his observations in 1958 in the *British Heart Journal*[3], and the comprehensive report by Eugene Braunwald in 1964 in *Circulation*.[4] However the concept of a hypertrophic heart disease was not new. Already in the Renaissance, several pieces of the puzzle were described.[5] William Harvey (1578-1657), the physician of the King of England, demonstrated in 1628 that the heart is a pump which causes blood to circulate through the body, an important breakthrough in the history of medicine. He also described a nobleman who was troubled by palpitations, chest pain, syncope and:

> *[…] the circulation of the blood being obstructed from the left ventricle in the artery.*[6]

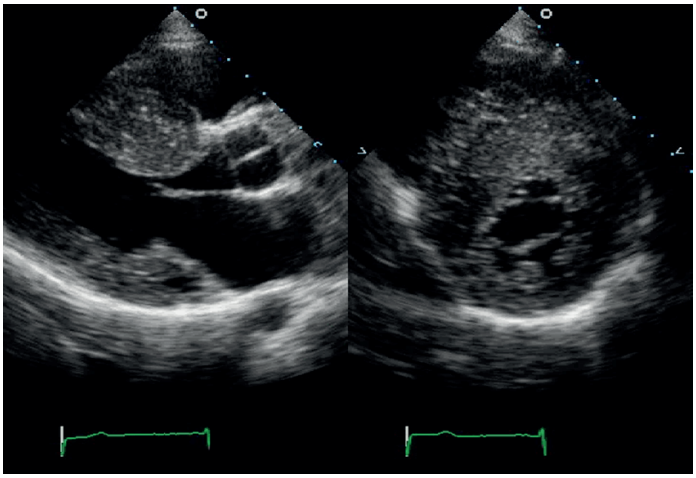


FIGURE 1 – Parasternal long and short axis 2D echocardiogram illustrating asymmetrical hypertrophy in a patient with HCM.

Other important contributions came from two Italian physicians: Giovanni Lancisi (1654-1720) and Giovanni Morgagni (1682-1771). Lancisi, the physician of Pope Clement XI, reported deaths due to left ventricular hypertrophy in his work on sudden death: *De subitaneis mortibus*, and was the first to mention a hereditary component in the disease.[7] Morgagni, celebrated as the father of modern anatomical pathology, continued on this work and in *De sedibus et causis morborum per anatomen indigatis* he wrote:

> *A coachman died suddenly in his carriage whose heart was larger than that of any bullock, another sudden death of a heart far exceeding its natural bulk.*[8]

Further groundwork was laid in the 18th and 19th century by several French and German physicians[5], and with each description of the disease a new or alternative name was proposed. After the reports by Teare and Braunwald, >80 different terms had been used, varying from 'primary muscular left sided conus stenosis?', 'asymmetrical hypertrophy of the heart' (by Teare), idiopathic hypertrophic subaortic stenosis (by Braunwald), and 'hypertrophic (obstructive) cardiomyopathy'. After its introduction in 1979 HCM has become the predominant formal term to describe this disease.[9, 10]

Diagnosis of HCM

In the following ±35 years the clinical perception of HCM has changed. It appeared to be an exotic disease with high mortality, and "no method of management that can specifically and favorably influence the course of a patient".[11, 12] But in these last 3 decades, scientific and technical advancements have altered the clinical course of patients with HCM.[12]

Improvement in imaging techniques facilitated a better and more early diagnosis. Until the development of echocardiography, diagnostic left ventricular catheterization was necessary to diagnose HCM. Electrocardiograms (ECG) in suspected patients showed signs of left ventricular hypertrophy, and ST- and T-wave abnormalities. It remained a sensitive but not-specific test, and the diagnosis could not be based on an abnormal ECG alone. When echocardiography came available, the diagnosis of HCM could be established safe and painless, but it could also characterize HCM much more precise. The asymmetry of the ventricular hypertrophy was easily demonstrated, in M-mode echocardiography. [13, 14] The ease of use of echocardiography, especially after development of 2D echocardiography led to its prominent position in the diagnosis and follow-up of patients with HCM. (FIGURE 1) It could also be used in asymptomatic family members to assess if they also had HCM. [14] Because a familial association with HCM was already suspected, and in 1961 Pare et al published a report describing a large family with HCM (in the report the disease is called hereditary cardiovascular dysplasia), and its transmission appeared to be autosomal dominant. [15] In 1989 the first pathogenic mutation was identified in the myosin heavy chain gene by Seidman et al.[16] Subsequent research had led to the discovery of >1500 mutations in > 20

genes and has increased the understanding of the complexity as well as the diversity of the disease.[17]

Therapeutic strategies

Initially therapeutic options were limited, but advancement in invasive techniques have also given us the possibility to treat patients diagnosed with HCM, especially in patients with extensive left ventricular outflow tract obstruction. Most symptoms related to this obstruction can be relieved by abolishing the obstruction, either by medical therapy or invasive septal reduction therapy. Medical therapy should be the first step in management of symptoms, and beta-blockers are the first line drugs to treat symptomatic LVOT obstruction. Alternatives such as verapamil and disopyramide are useful if beta-blocker therapy is causing side-effects or is ineffective. Invasive septal reduction therapy should only be considered for patients with severe, drug-refractory symptoms despite optimal medical therapy.[1]

Surgical myectomy was developed in 1961, a high risk procedure then, and only reserved for very symptomatic patients. Improvement of surgical techniques and periprocedural care made surgical myectomy a safe and effective procedure.[18-20] However, myectomy is open-heart surgery with relatively long rehabilitation, so in 1995 alcohol septal ablation, a percutaneous alternative, was developed. [21] This strategy was quickly adopted all over the world and the numbers of patients who received alcohol septal ablation quickly outnumbered the patients who underwent myectomy.[21-26] Concerns about alcohol septal ablation remain however, especially about the arrhythmogenic effect of the ablation scar in patients already at an increased risk of life-threatening arrhythmias.(FIGURE 2)[27-30]

Finally, the breakthrough of implantable cardioverter defibrillators (ICD) have further improved the prognosis of patients with HCM. In the 1980's the first report on ICDs by Mirowski et al. [31] was published. Interestingly, 3 of the 5 patients described herein, were patients with HCM and had survived 2 (!) cardiac arrests. The initial development of the device was focused on patients with ischemic heart disease, but in the last two decades more and more evidence demonstrated the efficacy of the ICD in patients with HCM in both primary and secondary prevention of SCD.[32-34] Nowadays the ICD is recommended in a selected group of HCM patients with increased SCD risk, a mere 300 years after the first description of this problem.[1, 10]

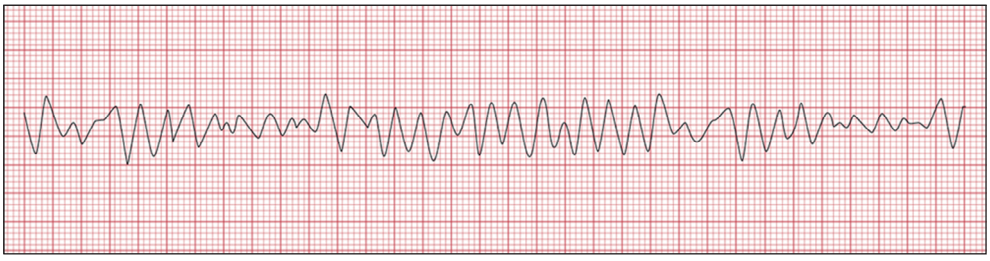


FIGURE 2 – An example of ventricular fibrillation.

OUTLINE OF THE THESIS

Several important questions in the management of the patient with HCM remain. The aim of this thesis is to approach these questions in a similar manner as we approach a patient with HCM. After a newly diagnosed patient presents itself, it is important to discuss the characteristics of the disease, the prognosis, and avoidance of competitive sports; and if necessary, medication can be started to treat symptoms. If optimal medical therapy remains insufficient, and patients remain severely symptomatic, an invasive approach should be considered. The next step is to improve the prognosis and prevent SCD in our patient. Finally, it is important to realize that behind every HCM patient is a potential HCM family; clinical and genetic screening can be used to identify family members at risk.

In PART II, we consider the invasive treatment of symptomatic left ventricular outflow tract obstruction. Although a large subset of patients will remain asymptomatic during their lifetime, in most cases HCM will be diagnosed when a symptomatic patient visits the outpatient clinic. These symptoms, such as dyspnea on exertion, chest pain, or syncope can be related to left ventricular outflow tract obstruction (FIGURE 1). The obstruction can be present during rest or after provocation, and 70% of the HCM population has obstructive physiology.[35] The first step is to alleviate symptoms by using beta-receptor antagonists, calcium channel blockers or disopyramide. If optimal medical therapy fails, an invasive approach is indicated. This can be a surgical or a percutaneous procedure. In CHAPTER 1 and CHAPTER 2 we evaluated and compared the long-term outcomes of both surgical myectomy and alcohol septal ablation. If there is concomitant mitral valve dysfunction, surgical myectomy can be combined with anterior mitral leaflet extension. This approach was developed in the Erasmus MC by van Herwerden, ten Cate, and de Jong,[36, 37] and the long term results, complications and examples of this surgical approach are described in CHAPTER 3 – 5. Alcohol septal ablation was developed 20 years ago, but concerns of increased risk of life-threatening arrhythmias remain. In CHAPTER 6 we evaluate the effect of high and low alcohol dosages used during the procedure. CHAPTER 7 describes the outcomes of alcohol septal ablation in the young and elderly. In CHAPTER 8 we explore the possibility of an alternative for alcohol, in this case septal microsphere embolization, to reduce procedure related arrhythmias.

The prevention and prediction of SCD in HCM is discussed in part III. SCD is a devastating expression of HCM, but the annual risk is low (<1%). There is a subset of patients with HCM at increased risk of sudden cardiac death, but identification of these patients may be challenging. In CHAPTER 9 we evaluate and validate the most recent risk prediction model, and the role of adverse left ventricular remodeling is analyzed in CHAPTER 10. ICDs can be used to prevent SCD, but this protection comes at a price of inappropriate shocks and device related complications. Our own results and a systematic review of ICD studies are discussed in CHAPTER 11 and 12.

Part IV considers the clinical implications of sarcomeric mutations. Genetic testing is used to identify family members at risk. In CHAPTER 13 we determine the incremental value of genetic testing, and to see if presence of a pathogenic sarcomere mutation affects outcome. The increased access to genetic screening has revealed family members with a pathogenic mutation, but without left ventricular hypertrophy. Follow-up of individuals with preclinical HCM is described in CHAPTER 14. Finally, in CHAPTER 15 we set out to improve our understanding of genotype-phenotype relations.

REFERENCES

1. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.
2. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol 2015;65:1249-54.
3. Teare D. Asymmetrical hypertrophy of the heart in young adults. Br Heart J 1958;20:1-8.
4. Braunwald E, Lambrew CT, Rockoff SD, Ross J, Jr., Morrow AG. Idiopathic Hypertrophic Subaortic Stenosis. I. A Description of the Disease Based Upon an Analysis of 64 Patients. Circulation 1964;30:SUPPL 4:3-119.
5. Coats CJ, Hollman A. Hypertrophic cardiomyopathy: lessons from history. Heart 2008;94:1258-63.
6. Harvey W. De Circl Sangu. Exercit 3 1647.
7. Lancisi G. De subitaneis mortibus libri duo. Latin edition. 1707.
8. Alexander B. The seats and causes of diseases investigated by anatomy Volume I of III. Translation of John Baptist Morgagni's book De sedibus et causis morborum per anatomen indigatis: Printed for A Miller and T Cadell, London 1769.
9. Maron BJ, Epstein SE. Hypertrophic cardiomyopathy: a discussion of nomenclature. Am J Cardiol 1979;43:1242-4.
10. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice G, American Association for Thoracic S, American Society of E, American Society of Nuclear C, Heart Failure Society of A, Heart Rhythm S, Society for Cardiovascular A, Interventions, Society of Thoracic S. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
11. Braunwald E, Brockenbrough EC, Morrow AG. Hypertrophic subaortic stenosis--a broadened concept. Circulation 1962;26:161-5.
12. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RHM, Garberich RF, Udelson JE, Maron MS. Hypertrophic Cardiomyopathy in Adulthood Associated With Low Cardiovascular Mortality With Contemporary Management Strategies. Journal of the American College of Cardiology 2015;65:1915-28.
13. ten Cate FJ, Hugenholtz PG, van Dorp WG, Roelandt J. Prevalence of dignostic abnormalities in patients with genetically transmitted asymmetric septal hypertrophy. Am J Cardiol 1979;43:731-7.
14. ten Cate FJ, Hugenholtz PG, Roelandt J. Ultrasound study of dynamic behaviour of left ventricle in genetic asymmetric septal hypertrophy. Br Heart J 1977;39:627-33.
15. Pare JA, Fraser RG, Pirozynski WJ, Shanks JA, Stubington D. Hereditary cardiovascular dysplasia. A form of familial cardiomyopathy. Am J Med 1961;31:37-62.
16. Jarcho JA, McKenna W, Pare JA, Solomon SD, Holcombe RF, Dickie S, Levi T, Donis-Keller H, Seidman JG, Seidman CE. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. N Engl J Med 1989;321:1372-8.
17. Ho CY. Genetic considerations in hypertrophic cardiomyopathy. Prog Cardiovasc Dis 2012;54:456-60.
18. Kirklin JW, Ellis FH, Jr. Surgical relief of diffuse subvalvular aortic stenosis. Circulation 1961;24:739-42.
19. Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, Itscoitz SB, Redwood DR. Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. Circulation 1975;52:88-102.

20. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ, Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470-6.
21. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211-4.
22. Maron BJ. Controversies in cardiovascular medicine. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. Circulation 2007;116:196-206; discussion
23. Fifer MA. Controversies in cardiovascular medicine. Most fully informed patients choose septal ablation over septal myectomy. Circulation 2007;116:207-16; discussion 16.
24. Fifer MA, Sigwart U. Controversies in cardiovascular medicine. Hypertrophic obstructive cardiomyopathy: alcohol septal ablation. Eur Heart J 2011;32:1059-64.
25. Maron BJ, Yacoub M, Dearani JA. Controversies in cardiovascular medicine. Benefits of surgery in obstructive hypertrophic cardiomyopathy: bring septal myectomy back for European patients. Eur Heart J 2011;32:1055-8.
26. Rigopoulos AG, Seggewiss H. A decade of percutaneous septal ablation in hypertrophic cardiomyopathy. Circ J 2011;75:28-37.
27. Boltwood CM, Jr., Chien W, Ports T. Ventricular tachycardia complicating alcohol septal ablation. N Engl J Med 2004;351:1914-5.
28. Kuhn H, Lawrenz T, Lieder F, Leuner C, Strunk-Mueller C, Obergassel L, Bartelsmeier M, Stellbrink C. Survival after transcoronary ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. Clin Res Cardiol 2008;97:234-43.
29. Sorajja P, Valeti U, Nishimura RA, Ommen SR, Rihal CS, Gersh BJ, Hodge DO, Schaff HV, Holmes DR, Jr. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2008;118:131-9.
30. ten Cate FJ, Soliman OI, Michels M, Theuns DA, de Jong PL, Geleijnse ML, Serruys PW. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail 2010;3:362-9.
31. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980;303:322-4.
32. Maron BJ, Shen WK, Link MS, Epstein AE, Almquist AK, Daubert JP, Bardy GH, Favale S, Rea RF, Boriani G, Estes NA, 3rd, Spirito P. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 2000;342:365-73.
33. Begley DA, Mohiddin SA, Tripodi D, Winkler JB, Fananapazir L. Efficacy of implantable cardioverter defibrillator therapy for primary and secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Pacing Clin Electrophysiol 2003;26:1887-96.
34. Jayatilleke I, Doolan A, Ingles J, McGuire M, Booth V, Richmond DR, Semsarian C. Long-term follow-up of implantable cardioverter defibrillator therapy for hypertrophic cardiomyopathy. Am J Cardiol 2004;93:1192-4.
35. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303.
36. van Herwerden LA, Ten Cate FJ. Combined anterior mitral leaflet extension and spark erosion myectomy in hypertrophic obstructive cardiomyopathy: Echo-enhanced surgery. Oper Tech Thorac Cardiovasc Surg 2004;9:310-9.
37. Kofflard MJ, van Herwerden LA, Waldstein DJ, Ruygrok P, Boersma E, Taams MA, Ten Cate FJ. Initial results of combined anterior mitral leaflet extension and myectomy in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 1996;28:197-202.

II – Invasive treatment of symptomatic left ventricular outflow tract obstruction

Chapter 1

Long-term outcome after medical and invasive treatment in patients with hypertrophic cardiomyopathy

Vriesendorp PA, Liebregts M, Steggerda RC, Schinkel AF, Willems R, Ten Cate FJ, van Cleemput J, Ten Berg JM, Michels M

JACC Heart Fail. 2014 Dec;2(6):630-6

ABSTRACT

Objectives

The aim of this study is to determine the long-term outcomes (all-cause mortality and sudden cardiac death (SCD)) after medical therapy, alcohol septal ablation (ASA) or myectomy in patients with hypertrophic cardiomyopathy (HCM).

Background

Therapy-resistant obstructive hypertrophic cardiomyopathy (HCM) can be treated both surgically and percutaneously. But there is no consensus on the long-term effects of ASA, especially on SCD.

Methods

This study included 1047 consecutive HCM patients (age 52 ±16 years, 61% male) from 3 tertiary referral centers. A total of 690 patients (66%) had a left ventricular outflow tract gradient ≥30 mmHg, of them 124 (12%) were treated medically, 316 (30%) underwent ASA and 250 (24%) underwent myectomy. Primary endpoints were all-cause mortality and SCD. Kaplan-Meier graphs and Cox-regression models were used for statistical analyses.

Results

Follow-up was 7.6 ± 5.3 years. The 10-year survival was similar in medically treated patients (84%), ASA patients (82%), myectomy patients (85%), and non-obstructive HCM patients (85%, log-rank p=0.5). Annual SCD-rate was low after invasive therapy: 1.0%/year in the ASA group, and 0.8%/year in the myectomy group. Multivariable analysis demonstrated that the risk of SCD was lower after myectomy compared with the ASA group (HR 2.1 [1.0-4.4], p=0.04), and the medical group (HR 2.3 [1.0-5.2], p=0.04).

Conclusions

Patients with obstructive HCM that are treated in referral centers for HCM care have a good survival and low SCD risk, similar to that of non-obstructive HCM patients. The SCD risk of patients after myectomy was lower than after ASA or in the medical group.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most prevalent inheritable myocardial disease, and (provocable) left ventricular outflow tract (LVOT) obstruction is present in the majority of HCM patients (±70%).[1] Not only is LVOT obstruction associated with symptoms such as dyspnea on exertion, fatigue, chest pain or syncope, but previous studies have also demonstrated that the presence of obstruction increases all-cause mortality and the occurrence of sudden cardiac death (SCD) in these patients,[2, 3] and it is included as a risk factor in the novel clinical risk prediction model presented by the HCM Outcomes Investigators.[4]

Therapy-resistant obstructive HCM can be treated both surgically and percutaneously and during the last years there is an intense and polarizing debate to define the best strategy.[5-8] Surgical approaches have been used for over 5 decades, and in experienced centers relief of obstruction can be achieved with minimal perioperative morbidity and mortality.[9-11] However, myectomy is open-heart surgery with relatively long rehabilitation, so in 1995 alcohol septal ablation (ASA), a percutaneous alternative, was developed. [12] This strategy was quickly adopted all over the world and the numbers of patients who received ASA quickly outnumbered the patients who underwent myectomy.[5-8, 12, 13] In some European countries ASA has fully replaced myectomy.[7] Concerns about ASA remain however, especially about the arrhythmogenic effect of the ablation scar in patients already at an increased risk of life-threatening arrhythmias.[14-17]

Although a randomized controlled trial does not seem feasible[18], and recent meta-analyses[19, 20] only evaluated short-term SCD rate and survival, there is no consensus on the long-term outcomes of ASA.[17, 21-24] The aim of the current study is therefore to determine the long-term effects of medical treatment, ASA and myectomy on all-cause mortality and SCD.

METHODS

Study design and population

An international multi-center, observational cohort design was used. The study conforms to the principles of the Helsinki Declaration. All patients gave informed consent for the intervention, and local institutional review board approval was obtained.

The study population consisted of 1065 consecutive HCM patients from the University Hospital Leuven, Leuven, Belgium (n=200), St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands (n=318), and the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands (n=547). Each patient had an established diagnosis of HCM, based on unexplained left ventricular hypertrophy of ≥15 mm, assessed by echocardiography.[25, 26] Patients with HCM linked to Noonan's syndrome, Fabry's disease, mitochondrial disease or congenital heart defects were excluded.

The LVOT gradient was measured in all patients using continuous wave Doppler-echocardiography, in rest and after provocative maneuvers. Patients were considered obstructive if LVOT gradient was ≥ 30 mmHg, at rest or after provocation. Invasive therapy was indicated if peak LVOT gradient was ≥ 50 mmHg, ventricular septal thickness ≥ 15 mm and persistent New York Heart Association (NYHA) class III/IV dyspnea, or Canadian Cardiovascular Society class III/IV angina despite optimal medical therapy.[26] Patients without an LVOT gradient ≥30 mmHg after provocation were considered non-obstructive and used as a control group.

Patients with obstructive HCM were classified in three groups based on the clinical treatment strategy: a medically treated group, an ASA group, and a myectomy group. Surgical septal myectomy was performed throughout the study period and as described previously[27, 28] and the postoperative care was in accordance with local protocols. ASA was performed starting from 1999 as described previously.[28, 29] Afterwards, all patients were monitored for at least 24 hours at the intensive coronary care unit.

Endpoints

The primary endpoints of this study were all-cause mortality and SCD-related events. The SCD endpoint was a composite endpoint, and consists of (1) instantaneous and unexpected death within 1 hour of a witnessed collapse in patients who were previously in a stable clinical condition, or nocturnal death with no antecedent history of worsening symptoms; (2) successful resuscitation after cardiac arrest; (3) appropriate internal cardioverter defibrillator (ICD) intervention for ventricular fibrillation (VF) or for fast VT (>200 bpm); and (4) unknown cause of death. Unknown death was included in the SCD endpoint to estimate the maximal occurrence of SCD in the population. We also evaluated periprocedural arrhythmic events and mortality, re-interventions, LVOT gradient reduction, and implantation of ICDs.

Mortality and adverse events were retrieved from hospital patient records at the center where follow-up occurred, from civil service population registers, and from information provided by patients themselves or their general practitioners. Cardiac transplantation was considered a HCM-related death, and patients were censored at the time of transplantation. All ICD interventions were evaluated by an experienced electrophysiologist.

Data collection and follow-up

Follow-up started at the time of intervention. In the medically treated cohort, follow-up started at the first outpatient clinic contact after January 1st, 1990. At baseline, all patients were evaluated for the following characteristics: NYHA class, maximum left ventricular wall thickness (LVWT), maximum (provocable) LVOT gradient, systolic and diastolic left ventricular function, and medication used. During follow-up, the established risk factors for SCD were evaluated.[25, 26] Other potential modifiers of SCD risk were also examined: atrial fibrillation and coronary artery disease. In patients treated with ASA, the dose of alcohol used was also collected.

If no endpoints occurred during follow-up, final censoring date was set at November 1st, 2012. If alternative septal reduction therapy was necessary (e.g. ASA after myectomy or vice versa) follow-up was censored at the date of the second intervention, due to the difficulty to attribute any later event to any intervention.

Statistical Analysis

SPSS version 20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for all statistical analyses. Categorical variables were summarized as percentages. Normality was assessed using the Shapiro-Wilk test combined with visual inspection of histogram and Q-Q plots. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median (interquartile range). To compare continuous variables Student *t* test, Mann-Whitney U-test and 1-way ANOVA were used. When appropriate, post-hoc comparisons were carried out using Bonferroni correction. To compare categorical variables, the χ^2-test was used. To identify clinical predictors of SCD mortality univariable and multivariable Cox regression analyses were used. Variables were selected for multivariable analysis if univariable p-value was < 0.10 and were expressed as hazard ratio (HR) with 95% confidence interval. The final number of variables was restricted according to the number of endpoint events to avoid overfitting the multivariable model. All tests were 2-sided and a p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

TABLE 1 lists the baseline characteristics of all patients. Of the 1065 patients (mean age 52 ± 16 years, 61% male) included in this study, 716 (67%) had obstructive HCM; in 269 (25%) LVOT obstruction was only present after provocation. Of these 716 patients, 142 (20%) were treated medically, 321 (45%) underwent ASA and 253 (35%) underwent myectomy. Patients in the ASA group were older (58 ± 14 years) than in the surgery group (52 ± 16 years, p<0.001) and in the medical group (53 ± 15 years, p=0.001). The majority of medically treated patients (124, 87%) reported no symptoms or mild (NYHA class I/II) symptoms at baseline, despite a mean LVOT gradient of 70 ± 32 mmHg. The other 18 patients (13%) had an indication for invasive treatment but were considered not eligible due to severe comorbidities (e.g. one patient had liver cirrhosis due to alcohol abuse and kidney failure) or patient refusal (several patients refused further invasive treatment, mostly because they were at old age, and preferred no further interventions). In this group mortality was high (8 deaths, 44%) and these patients were excluded from further analysis.

The distribution of established risk factors for SCD, among the 3 intervention groups and controls, is shown in TABLE 1. Complete risk stratification was not available for all patients: blood pressure response during exercise testing was available in 645 patients (61%), and documented rhythm information was available in 656 patients (62%). Significantly more patients in the myectomy group (44 patients (17%)) had ≥2 established risk factors for SCD than those in ASA group (32 patients (10%) p=0.009).

TABLE 1 – Baseline characteristics of 1065 HCM patients.

	Medical group	**ASA group**	**Myectomy group**	**Control (non-obstructive) group**
n=	*142*	*321*	*253*	*349*
Age, y	53 ± 15***	58 ± 14***	52 ± 16***	46 ± 16
Female	54 (38)*	143 (45)***	117 (46)***	98 (28)
NYHA III/IV	18 (13)	249 (78)***	165 (65)***	40 (11)
Atrial fibrillation	21 (15)**	76 (24)	62 (25)	103 (30)
Coronary artery disease	4 (3)	18 (6)**	25 (10)**	12 (3)
Maximum LVWT, mm	20 ± 5	21 ± 5***	21 ± 5***	20 ± 5
LVOT gradient, mmHg	70 ± 32***	102 ± 52***	92 ± 39***	9 ± 6
Systolic dysfunction (EF<50%)	17 (12)	18 (6)***	18 (7)***	63 (18)
Diastolic dysfunction	99 (70)**	130 (40)***	105 (42)**	190 (54)
Medication				
β-receptor antagonist	83 (58)*	218 (68)***	167 (66)***	166 (48)
Calcium-channel blocker	47 (33)***	116 (36)***	90 (36)***	49 (14)
Risk factors				
Survivor of sudden cardiac death	4 (3)*	7 (2)***	8 (3)*	29 (8)
Sudden death in family history	23 (16)	24 (7)***	42 (17)	81 (23)
Abnormal BP response	9 (6)	31 (10)	37 (15)	29 (8)
Maximum LVWT > 30 mm	9 (6)	22 (7)	18 (7)	19 (5)
Non-sustained VT	22 (15)**	41 (13)***	37 (15)	98 (28)
Syncope	10 (7)	52 (16)	41 (16)	45 (12)
0 risk factors	87 (61)**	188 (59)**	136 (54)*	158 (45)
≥ 2 risk factors	15 (11)*	32 (10)**	44 (17)	66 (19)

* = P < 0.05; ** = P < 0.01; *** = P < 0.001 (compared with controls). Data represented as n (percentage) unless stated otherwise. ASA: alcohol septal ablation, BP: blood pressure, EF: ejection fraction, HCM: hypertrophic cardiomyopathy, LVWT: left ventricular wall thickness, LVOT: left ventricular outflow tract, NYHA: New York Heart Association, VT: ventricular tachycardia

Procedural data

Invasive therapy was performed in 574 obstructive HCM patients. Periprocedural mortality was similar in ASA (5 patients, 1.6%) and myectomy (3 patients, 1.2%, p=0.7). In the first 30 days post-procedure, ventricular arrhythmias occurred more frequently in the ASA group (11 patients, 3.1%) than in the myectomy group (1 patient, 0.4%, p < 0.001). Cardiac resuscitation was necessary in 7 ASA patients (2.2%). Residual LVOT gradient was measured after 3 months, and was reduced after both ASA and myectomy: from 97 (66-130) mmHg to 10 (1-24) mmHg after ASA, and from 90 (70-100) mmHg to 9 (0-16) mmHg after myectomy. In 31 ASA patients (9.7%) additional septal reduction therapy was necessary, and this was higher than after myectomy (6 patients, 2.3%, p < 0.001; TABLE 2)

TABLE 2 – Invasive therapy in 574 HCM patients

	ASA group	**Myectomy group**
n=	*321*	*253*
Center		
Leuven	18 (6)	28 (11)
Nieuwegein	209 (65)	109 (43)
Rotterdam	94 (29)	116 (46)
Procedural details		
Volume of alcohol injected, median (IQR), mL	2.0 (1.0)†	NA
Residual LVOT gradient, median (IQR), mmHg	10 (24)	9 (16)**
Reduction in LVOT gradient, %	87 ± 30	90 ± 19**
Redo septal reduction therapy	31 (9.7)	6 (2.3)***
Periprocedural arrhythmic event		
Total	11 (3.1)	1 (0.4)***
Sudden cardiac death	3 (0.9)	1 (0.4)
Sustained VT	1 (0.3)	0 (0)
Resuscitated cardiac arrest	7 (2.2)	0 (0)
Periprocedural mortality		
Total	5 (1.6)	3 (1.2)
Sudden cardiac death	3 (0.9)	1 (0.4)
Heart failure death	0 (0)	2 (0.8)
Cardiac tamponade	2 (0.6)	0

* = P < 0.05; ** = P < 0.01; *** = P < 0.001. † In 53 patients (16.5%) the dose of alcohol could not be retrieved. Data are represented as n (percentage), unless stated otherwise. ASA: alcohol septal ablation, HCM: hypertrophic cardiomyopathy, IQR: interquartile range, LVOT: left ventricular outflow tract.

Mortality

In 1047 patients follow-up duration was 7.5 ± 5.3 years (maximum 22.8 years). There were 156 deaths in the entire cohort (TABLE 3): 8 (5%) were procedure-related, 80 (51%) were HCM-related, 56 (36%) patients died of non-cardiac causes, and unknown cause of death in 12 (8%). Twelve patients underwent cardiac transplantation, and were considered as HCM-related death. Kaplan-Meier estimates of survival are shown in FIGURE 1A. The 5-year and 10-year survival was similar after ASA, myectomy, medically treated patients in NYHA class I/II and non-obstructive HCM patients (TABLE 3). Independent predictors for all-cause mortality were: age (HR 1.05 95% CI 1.0-1.1, p<0.001); systolic dysfunction, with ejection fraction < 50% (HR 1.8 95% CI 1.2-2.6, p=0.005); and a trend towards diastolic dysfunction (HR 1.4 95% CI 0.98-1.88, p=0.07; TABLE 4).

TABLE 3 – Mortality and sudden cardiac death in 1047 HCM patients.

	Medical group	**ASA group**	**Myectomy group**	**Control (non-obstructive) group**
n=	*124*	*321*	*253*	*349*
Follow-up, mean (±SD), years	7.1 ± 4.8*	6.3 ± 3.6***	7.9 ± 6.1	8.7 ± 5.7
Mortality				
Periprodecural death	-	5 (1.6)	3 (1.2)	-
HCM-related death	11 (8.9)	12 (3.7)**	21 (8.4)	36 (10.3)
Non-cardiac death	8 (6.5)	23 (7.2)*	12 (4.8)	13 (3.7)
Unknown death	0 (0)	3 (0.9)	6 (2.4)	3 (0.8)
Total	**19 (15.3)**	**38 (11.8)**	**39 (15.6)**	**52 (14.9)**
5-year survival, %	89	91	92	95
10-year survival, %	84	82	85	85
Sudden cardiac death				
Sudden cardiac death	5 (4.0)	6 (1.9)	6 (2.4)	9 (2.6)
Resuscitated CA	1 (0.8)	2 (0.6)*	2 (0.8)	9 (2.6)
Appropriate ICD shock	5 (4.0)	8 (2.5)	1 (0.4)	12 (3.4)
Unknown death	0 (0)	3 (0.9)	6 (2.4)	3 (0.8)
Total	**11 (8.9)**	**19 (6.0)**	**15 (6.0)**	**31 (8.9)**
Annual SCD rate, %/year	1.26	0.96	0.75	1.02
ICD recipients	14(11.3)**	41 (13.0)***	29 (11.6)**	83 (23.8)

* = P < 0.05; ** = P < 0.01; *** = P < 0.001 (compared with controls). Data are represented as number (percentage) unless stated otherwise. CA: cardiac arrest, HCM: hypertrophic cardiomyopathy, ICD: implantable cardioverter-defibrillator, SD: standard deviation.

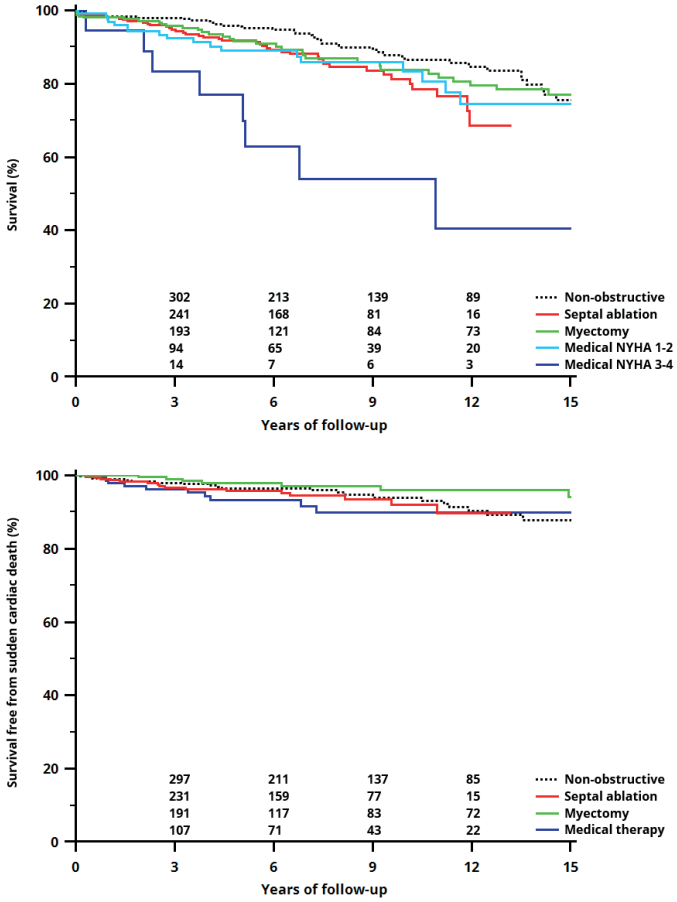


FIGURE 1 – Survival in 1047 HCM patients. Kaplan-Meier graphs of survival (A) and sudden cardiac death free survival (B) in 1047 hypertrophic cardiomyopathy (HCM) patients.

Sudden cardiac death

The SCD-endpoint occurred in 76 patients in 8003 patient-years (0.9%/year. Annual SCD rate was 0.96%/y after ASA, 0.76%/y after myectomy, 1.26%/y in medically treated groups, and 1.02%/y in non-obstructive HCM patients (p= 0.4). Appropriate ICD shocks were more common after ASA (in 8/41 patients (20%) than after myectomy (in 1/29 patients (3.4%, p=0.03). Other characteristics of SCD are described in TABLE 3. Kaplan-Meier estimates of survival free from SCD are shown in FIGURE 1B. Multivariable analysis identified the following independent predictors of SCD: patients who survived VF or sustained VT (HR 6.0 95% CI 3.4-10.6, p < 0.001); patients with ≥2 established risk factors (HR 2.7 95% CI 1.6-4.4, p < 0.001); patients with atrial fibrillation (HR 1.7 95%CI 1.1-2.8, p = 0.03); and when compared with myectomy: ASA (HR 2.1 95% CI 1.0-4.4, p = 0.04), and medically treated patients (HR 2.3 95% CI 1.1-5.1, p=0.04; TABLE 4).

TABLE 4 – Analysis of clinical variables associated with sudden cardiac death and all-cause mortality in 1047 hypertrophic cardiomyopathy patients.

	Univariable			*Multivariable*		
	HR	CI 95%	*p*	HR	CI 95%	*p*
Mortality (n=156)						
Age, y	1.05	1.03-1.06	< 0.001	**1.05**	**1.04-1.06**	**< 0.001**
Female	1.8	1.27-2.43	0.001	1.3	0.93-1.79	0.1
Atrial fibrillation	1.6	1.18-2.29	0.003	1.2	0.89-1.78	0.2
Coronary artery disease	1.9	1.25-2.74	0.002	1.4	0.94-2.08	0.1
Systolic dysfunction (EF < 50%)	2.2	1.51-3.22	< 0.001	**1.4**	**1.19-2.59**	**0.005**
Diastolic dysfunction	1.5	1.08-2.07	0.02	1.8	0.98-1.89	0.07
Myectomy (reference)	1.0		…	1.0		…
Alcohol septal ablation	1.3	0.79-2.02	0.3	1.0	0.65-1.61	0.9
Medical therapy NYHA I/II	1.3	0.73-2.20	0.4	1.2	0.68-2.13	0.5
Sudden cardiac death (n=76)						
Age, y	1.00	0.98-1.01	0.7			
Male	1.6	0.98-2.68	0.06	1.6	0.97-2.73	0.06
Left ventricular wall thickness, mm	1.03	0.98-1.08	0.2			
Atrial fibrillation	1.8	1.14-2.87	0.01	**1.7**	**1.06-2.75**	**0.03**
Coronary artery disease	1.8	1.06-3.20	0.03	1.7	0.98-3.04	0.06
Sudden cardiac death survivor	6.5	3.82-10.9	< 0.001	**6.0**	**3.43-10.7**	**< 0.001**
≥2 established risk factors	3.3	2.04-5.23	< 0.001	**2.7**	**1.65-4.44**	**< 0.001**
Myectomy (reference)	1.0		…	1.0		…
Alcohol septal ablation	2.0	0.99-4.25	0.05	**2.1**	**1.02-4.39**	**0.04**
Medical therapy NYHA I/II	2.2	0.99-4.91	0.05	**2.3**	**1.03-5.19**	**0.04**

Backwards multivariable Cox regression analysis was used. CI: confidence interval; EF: ejection fraction; HR: hazards ratio; NYHA: New York Heart Association.

DISCUSSION

The purpose of this investigation was to compare the long-term effects of medical treatment, ASA and myectomy on all-cause mortality and SCD in patients with obstructive HCM. There were two important results. First, the mortality rates in patients with prior ASA or myectomy, and medically treated patients in NYHA functional class I/II were similar to those of non-obstructive HCM patients. Second, the long-term risk of SCD is low both after myectomy (0.8%/year) and ASA (1.0%/year), a small but significant difference (HR for SCD after ASA vs myectomy: 2.1, p=0.04).

Low mortality in obstructive HCM patients

The observed survival after both myectomy (10-year survival of 85%) and ASA (82%, p=0.5), was similar to that of non-obstructive patients (85%, p=0.7 and p=0.2 respectively). This demonstrates that the survival disadvantage associated with LVOT obstruction can be effectively annulled by appropriate invasive therapy and management in referral centers for HCM care.[2] ASA was performed in carefully selected patients who were older and with more co-morbidities (61% of the deaths was due to non-cardiac causes), but despite this, the observed mortality after ASA was not significantly higher than in the other groups. The observed survival after invasive therapy in this study confirms other studies evaluating long-term outcomes for the individual approaches.[21-24]

The good survival of obstructive HCM patients who remain in NYHA I/II on optimal medical therapy (10-year survival of 84%) could imply that earlier intervention in asymptomatic or mildly symptomatic patients with obstructive HCM is not indicated, despite the low procedural mortality and morbidity of both invasive therapies.

Mortality, not surprisingly, was high (44%) in a limited group of patients (n=18, 13%) with an indication for invasive treatment (NYHA class III/IV despite optimal medical therapy), but who were deemed to be ineligible due to severe comorbidities.

Sudden cardiac death after alcohol septal ablation

Since the introduction of ASA there have been concerns regarding the arrhythmogenic effect of the ablation scar in patients already at an increased risk of life-threatening arrhythmias. Studies of short-term follow-up after ASA have described frequent episodes of sustained VT and VF.[14-17] Our findings confirm this, and show that although arrhythmic events were more frequent after ASA (3.1%) than after myectomy (0.4%, p<0.001), this had no effect on procedure-related mortality (1.6% vs. 1.2%, p= 0.7). The aim of this study was to assess the long-term effects of the different treatment modalities, especially because the long-term effect of ASA on SCD is unclear.

Two meta-analyses showed that the risk of SCD was not higher in ASA patients than in patients who underwent myectomy. These studies did not focus on long-term outcomes: average follow-up period across the cohorts in the study by Argawal et al.[19] was < 3 years, and in the study by Leonardi et al.[20] there was a significant difference in follow-up duration between the ASA and myectomy cohorts, with a median follow-up of 1266 patient-years in the myectomy studies and 51 patient-years in the ASA studies. Other concerns, especially about the calculated SCD risk have already been illustrated by Nishimura and Ommen.[30] The risk of SCD after myectomy has generally been low,[11] and the study by McLeod et al. even suggests that myectomy could decrease the risk of SCD.[31]

Our study found that the annual SCD rate (excluding periprocedural events) in patients who underwent ASA was 1.0%/year, which was similar to that of non-obstructive HCM patients and medically treated patients. The study by Ten Cate et al.[17], which included

a subset of the patients from the present study, reported a higher SCD rate than this study. The reason for this is twofold: (1) a separate endpoint for SCD (instead of a composite of cardiac mortality and SCD) was used, and (2) we excluded the periprocedural events from the final analysis to focus on the long-term effects of ASA. Two recently published studies with long-term follow-up, found that the risk of SCD was not high after ASA. Jensen et al.[23] examined 470 ASA patients, with an average follow-up of 8.4 years, and found an annual SCD rate of 0.5%/year. Sorajja et al.[24] examined 177 ASA patients and 177 age- and sex-matched myectomy patients, with an average follow-up of 5.7 years. They found annual SCD rates (including unknown death) of 1.3%/year after ASA and 1.1%/year after myectomy. The results of this study are in line with these findings, but the SCD risk after ASA is still higher than after myectomy (0.8%/year, HR for SCD after ASA vs myectomy: 2.1, p=0.04).

Patient selection and specialized care

The current findings may have implications for the clinical management of patients with obstructive HCM, who are considered for septal reduction therapy. Patient who underwent myectomy had a statistically significantly lower risk of SCD as compared with patients who underwent ASA.This, combined with a lower need for additional septal reduction therapy and lower periprocedural arrhythmic events, favors surgical myectomy over ASA when an invasive strategy is chosen, for example in younger and otherwise healthy patients. In older patients or patients with co-morbidities and drug-refractory symptoms, and appropriate septal anatomy, the expected survival after ASA is excellent, and in these patients ASA is a valuable therapy. Open heart surgery can be avoided and rehabilitation is much faster. We recommend that a multidisciplinary heart team (consisting of at least a cardiothoracic surgeon, an interventional cardiologist and a cardiologist specialized in the care of HCM patients) determines the optimal strategy for septal reduction. Also, in line with the 2003 ESC/ACC and 2011 ACCF/AHA guidelines,[25, 26] the procedure should be performed by experienced operators and confined to centers having substantial and specific experience with HCM care.

Study limitations

This study has several limitations. The 3 centers are all tertiary referral centers for the diagnostic and therapeutic care of HCM, and the patient population might not represent the general HCM population. This referral and selection bias could have influenced current results. Data collection was limited to variables that were routinely collected. As rhythm documentation of the event was not available for all SCD cases, it was not possible to ascertain that all deaths were arrhythmic in nature. Neither was it possible to correct for individual or local alterations of surgical or percutaneous technique, however all procedures were performed by experienced interventional cardiologist or cardiothoracic surgeons. This implies that our findings are more generalizable than those of single-center investigations.

CONCLUSION

Patients with obstructive HCM that are treated in referral centers for HCM care have a good survival and low SCD risk, similar to that of non-obstructive HCM patients. The SCD risk of patients after myectomy was lower than after ASA or in the medical group.

ACKNOWLEDGEMENTS

The authors would like to thank D.A.M.J. Theuns, O.I.I. Soliman, R.T. van Domburg, H. Heidbuchel, P.L. de Jong, A.J. Hauer and J.C. Balt and all treating physicians for providing additional data and assisting the authors in the realization of this study.

REFERENCES

1. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-9.
2. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303.
3. Elliott PM, Gimeno JR, Tome MT, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J 2006;27:1933-41.
4. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). Eur Heart J 2013.
5. Maron BJ. Controversies in cardiovascular medicine. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. Circulation 2007;116:196-206; discussion
6. Fifer MA. Controversies in cardiovascular medicine. Most fully informed patients choose septal ablation over septal myectomy. Circulation 2007;116:207-16; discussion 16.
7. Maron BJ, Yacoub M, Dearani JA. Controversies in cardiovascular medicine. Benefits of surgery in obstructive hypertrophic cardiomyopathy: bring septal myectomy back for European patients. Eur Heart J 2011;32:1055-8.
8. Fifer MA, Sigwart U. Controversies in cardiovascular medicine. Hypertrophic obstructive cardiomyopathy: alcohol septal ablation. Eur Heart J 2011;32:1059-64.
9. Kirklin JW, Ellis FH, Jr. Surgical relief of diffuse subvalvular aortic stenosis. Circulation 1961;24:739-42.
10. Morrow AG, Reitz BA, Epstein SE, et al. Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. Circulation 1975;52:88-102.
11. Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470-6.
12. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211-4.
13. Rigopoulos AG, Seggewiss H. A decade of percutaneous septal ablation in hypertrophic cardiomyopathy. Circ J 2011;75:28-37.
14. Boltwood CM, Jr., Chien W, Ports T. Ventricular tachycardia complicating alcohol septal ablation. N Engl J Med 2004;351:1914-5.
15. Kuhn H, Lawrenz T, Lieder F, et al. Survival after transcoronary ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. Clin Res Cardiol 2008;97:234-43.
16. Sorajja P, Valeti U, Nishimura RA, et al. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2008;118:131-9.
17. ten Cate FJ, Soliman OI, Michels M, et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail 2010;3:362-9.
18. Olivotto I, Ommen SR, Maron MS, et al. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Will there ever be a randomized trial? J Am Coll Cardiol 2007;50:831-4.
19. Agarwal S, Tuzcu EM, Desai MY, et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;55:823-34.
20. Leonardi RA, Kransdorf EP, Simel DL, et al. Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy: comparative rates of overall mortality and sudden cardiac death after treatment. Circ Cardiovasc Interv 2010;3:97-104.
21. Ball W, Ivanov J, Rakowski H, et al. Long-term survival in patients with resting obstructive hypertrophic cardiomyopathy comparison of conservative versus invasive treatment. J Am Coll Cardiol 2011;58:2313-21.

22. Nagueh SF, Groves BM, Schwartz L, et al. Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy. A multicenter North American registry. J Am Coll Cardiol 2011;58:2322-8.
23. Jensen MK, Prinz C, Horstkotte D, et al. Alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy: low incidence of sudden cardiac death and reduced risk profile. Heart 2013;99:1012-7.
24. Sorajja P, Ommen SR, Holmes DR, et al. Survival after Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy. Circulation 2012;126:2374-80.
25. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy - A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. European Heart Journal 2003;24:1965-91.
26. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
27. Maat LP, Slager CJ, van Herwerden LA, et al. Spark erosion myectomy in hypertrophic obstructive cardiomyopathy. Ann Thorac Surg 1994;58:536-40.
28. van der Lee C, ten Cate FJ, Geleijnse ML, et al. Percutaneous versus surgical treatment for patients with hypertrophic obstructive cardiomyopathy and enlarged anterior mitral valve leaflets. Circulation 2005;112:482-8.
29. van der Lee C, Scholzel B, ten Berg JM, et al. Usefulness of clinical, echocardiographic, and procedural characteristics to predict outcome after percutaneous transluminal septal myocardial ablation. Am J Cardiol 2008;101:1315-20.
30. Nishimura RA, Ommen SR. Septal reduction therapy for obstructive hypertrophic cardiomyopathy and sudden death: what statistics cannot tell you. Circ Cardiovasc Interv 2010;3:91-3.
31. McLeod CJ, Ommen SR, Ackerman MJ, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J 2007;28:2583-8.

EDITORIAL

Revisiting Arrhythmic Risk After Alcohol Septal Ablation : Is the Pendulum Finally Swinging…Back to Myectomy?

Maron BJ, Nishimura RA

JACC Heart Fail. 2014 Dec;2(6):637-40.

For the past 10 years, a debate has raged within the international cardiovascular medicine community regarding treatment options for severely symptomatic and drug-refractory patients with obstructive hypertrophic cardiomyopathy (HCM) [1-21]. Surgical myectomy has been the gold-standard treatment for this relatively small HCM subset since the early 1960s, with proven efficacy in abolishing left ventricular (LV) outflow gradients and heart failure symptoms, enhancing quality of life associated with long-term survival equivalent to the general population, and recently with low operative mortality (<1%) when performed by highly experienced surgeons [1- 6,20-22] (FIGURE 1).

Catheter-based alcohol septal ablation entered the therapeutic arena for HCM about 10 years ago, also with the capability for reducing gradient and symptoms, and became widely available, performed by many interventional cardiologists trained in standard percutaneous coronary interventions. [7-18] This introduction of alcohol ablation triggered a polarized and sometimes contentious debate focused on defining the most practical and effective strategy for severely symptomatic patients with obstructive HCM. [1-22] Advocates for septal ablation have underscored the less invasive nature of the technique, the shorter recovery time, as well

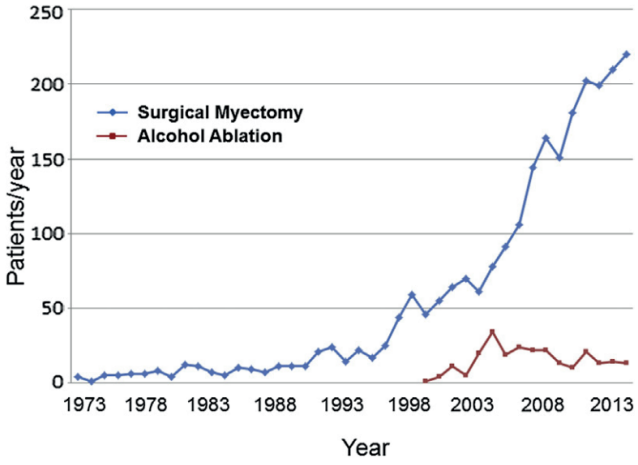


FIGURE 1 – Number of surgical myectomies versus alcohol ablation procedures performed at the mayo clinic (Rochester, Minnesota) by year, after an informed discussion of both options and shared decision-making.

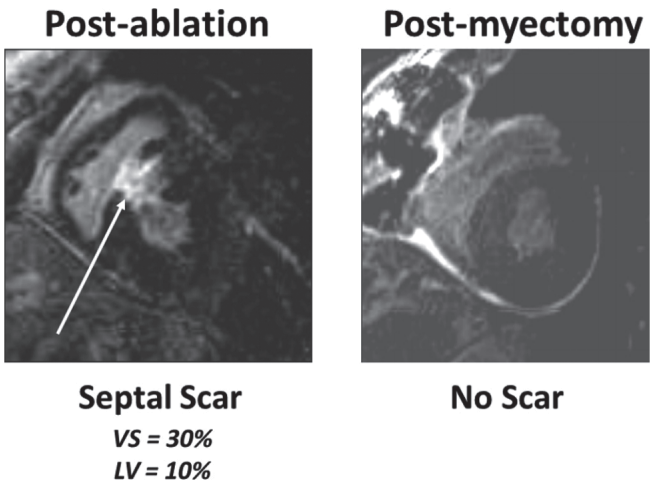


FIGURE 2 – Post-contrast CMR images show the distinctly different morphologic consequences of alcohol septal ablation and surgical myectomy. Alcohol ablation (left) produces a bright dense transmural scar (arrow), whereas intramyocardial scarring is absent after surgical myectomy and muscular resection (right). CMR = cardiovascular magnetic resonance; LV = left ventricular wall; VS = ventricular septum. Adapted with permission from Valeti et al.[23]

as its widespread availability. However, concern has been raised regarding the extensive use of alcohol ablation, given that it produces a sizable transmural myocardial infarction (on average 10% of LV mass and 30% of septum), potentially leading to increased arrhythmogenicity [23] (FIGURE 2). In addition, ablation is associated with an increased risk for complications such as heart block (requiring permanent pacing), generally less efficacious relief of gradient and symptoms, and the limited length of follow-up available for comparison with surgical myectomy.

Proponents of each strategy have argued their respective positions, and an extensive literature of almost 500 published papers has emerged. Notably, international consensus panels of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology have weighed in on the debate by interrogating the assembled data, unanimously judging septal myectomy to be the primary treatment option for most patients with HCM (particularly the young) experiencing unrelenting symptoms due to marked LV outflow tract gradients at rest and/or with physiologic (exercise) provocation, despite maximal medical management. [1-6,19,20,22,24] Alcohol septal ablation is regarded as a selective alternative to myectomy reserved for patients at unacceptable operative risk because of comorbidities, advanced age, or with strong aversion to surgery. [1-3]

Despite these recommendations, selection of patients for these management options has varied considerably in geographic terms. Surgical myectomy has been virtually abolished and replaced by alcohol ablation in much of Europe, including countries such as Germany and Switzerland, where myectomy programs had previously been robust. There is, however,

recent evidence of a resurgence in surgery for obstructive HCM in Italy, United Kingdom, and the Netherlands. [25] In the United States, alcohol septal ablation has been performed by interventional cardiologists at many institutions across the country, some of whom learn the technique from attending a conference. This is in contrast to septal myectomies performed primarily by the highly trained surgeons at HCM centers of excellence. The decision regarding which procedure a patient will undergo may depend more on the location, referral pattern, and current knowledge of the managing cardiologist rather than scientific evidence and shared decision-making.

In the report by Vriesendorp et al. [26] in this issue of JACC: Heart Failure, investigators from 3 tertiary institutions have joined together to describe their experience with HCM in >1,000 patients, including 566 with either myectomy or ablation: Thoraxcenter in Rotterdam, St. Antonius Hospital Nieuwegein (also in the Netherlands), and University Hospital Leuven in Belgium. This ambitious analysis focuses on the sudden death risk associated with both septal reduction procedures. Because HCM is characteristically a low–event-rate disease, it is not surprising that the investigators observed that the sudden death rate was generally low in patients with either surgery or ablation, as well as in a medically treated group with nonobstructive HCM.

However, most importantly, there are several novel observations in the Vriesendorp et al. [26] report regarding the arrhythmogenic potential of alcohol septal ablation compared to myectomy. First, on the basis of a multivariate analysis, there was a 2-fold increase in sudden death risk with alcohol ablation (hazard ratio: 2.1; 95% confidence interval: 1.0 to 4.4; $p = 0.04$) over the duration of the study, which could have been much higher if the investigators had included early life-threatening periprocedural arrhythmic complications (i.e., 11:1 for ablation to myectomy). The sudden death rate per year associated with alcohol ablation was 25% greater than with myectomy (1.0% vs. 0.8%). In terms of individual patients, sudden death events were 80% more common with ablation (16 vs. 9 with myectomy), including appropriate implantable cardioverter-defibrillator shocks for ventricular tachycardia or ventricular fibrillation that were 8:1 more frequent post-ablation. Finally, myectomy patients had a greater number of independent risk markers for sudden cardiac death but paradoxically fewer events than in the septal ablation patients.

Taken together, these observations support a level of arrhythmogenicity that is a direct consequence of the alcohol-induced transmural myocardial infarct. In addition, such a significant sustained occurrence of ventricular tachyarrhythmias after alcohol ablation in the Vriesendorp et al. [26] study is consistent with prior data from important centers at the Massachusetts General Hospital [15] and the Thoraxcenter [14,18], as well as in a study by Cuocco et al. [16] in which a large alcohol ablation population implanted with cardioverter-defibrillators is reported. In addition, a particularly low risk for sudden death and potentially lethal ventricular tachyarrhythmias has been reported after septal myectomy from the Mayo Clinic. [21,27] Indeed, the arrhythmogenic risk associated with alcohol septal ablation has

been an issue of concern since the inception of this procedure, [28,29] repeatedly raised by many clinicians and HCM experts, as well as by guideline and consensus panels.

The 250 patients with myectomy reported here from 3 institutions in the Netherlands and Belgium could reflect an emerging profile for this surgery in parts of Europe, although this is difficult to assess in precise terms because the investigators do not specify the period of time over which the procedures were performed. Nevertheless, myectomy was 2-fold more common in the Leuven group, and also constituted the majority of septal reduction procedures in Rotterdam. Indeed, in the United States, paradoxically, myectomy operations appear to have increased concomitant with the introduction of alcohol septal ablation [30] (FIGURE 1).

Furthermore, myectomy versus alcohol ablation decisions must be made weighing the risk with alcohol ablation for permanent pacemakers (10% to 15%), therapeutic failures with multiple procedures (12%), ineffective results in patients with particularly substantial LV hypertrophy (in whom adequate septal thinning cannot be achieved), and the potential for post-procedural arrhythmic risk, particularly in younger patients, against the inconvenience and post-operative rehabilitation required after open-heart surgery. [1-23] Also important, the heterogeneous and complex LV outflow tract morphology characteristic of obstructive HCM is often most amenable to the myectomy operation, for which the skilled and experienced surgeon has the distinct advantage of direct anatomic visualization, thereby increasing the likelihood of an optimal hemodynamic and symptomatic result. [1-6,19-21,28-31] In contrast, alcohol ablation is a "blind" approach restricted by the size and distribution of the septal perforator artery and its fixed anatomic relationship to the target site of outflow obstruction (where the anterior mitral leaflet contacts the septum in systole). [1-4,19, 20,28,29,31] Therefore, there will be patients in whom the optimal hemodynamic benefit will not be obtained by alcohol ablation because of these anatomic considerations.

Finally, Vriesendorp et al. [26] appropriately underscore the value of HCM subspecialty multidisciplinary teams at dedicated clinics and centers (e.g., with myectomy surgeons, interventional cardiologists, and cardiologists specialized in the care of patients with HCM) [32], creating an environment in which decisions between myectomy and alcohol ablation can be made effectively and in cooperation with fully informed patients [1,5,19].

In conclusion, the Vriesendorp et al. [26] data revisit the important issue of arrhythmogenicity associated with alcohol septal ablation and offer support to the consensus and guideline recommendations from the United States (2003 and 2011) [2,3] and Europe (2003) [2] panels that septal myectomy should be considered the treatment of choice for most patients with HCM and severe drug-refractory heart failure symptoms attributable to LV outflow obstruction. Although the myectomy–versus-ablation pendulum may be swinging back toward septal myectomy, the controversy will undoubtedly continue, although perhaps now in a more balanced environment, permitting greater repenetration of surgical myectomy into contemporary care for patients with HCM. This would represent a much anticipated adjustment in the management armamentarium of HCM, in the best interests of this patient population.

REFERENCES

1. B.J. Maron, M.S. Maron. Hypertrophic cardiomyopathy. Lancet, 381 (2013), pp. 242–255
2. B.J. Maron, W.J. McKenna, G.K. Danielson, et al.American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines Committee to Develop an Expert Consensus Document on Hypertrophic Cardiomyopathy. J Am Coll Cardiol, 42 (2003), pp. 1687–1713
3. B.J. Gersh, B.J. Maron, R.O. Bonow, et al. 2011 ACCF/AHA guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 124 (2011), pp. 2761–2796
4. B.J. Maron. Controversies in cardiovascular medicine. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. Circulation, 116 (2007), pp. 196–206
5. B.J. Maron, H. Rastegar, J.E. Udelson, J.A. Dearani, M.S. Maron. Contemporary surgical management of hypertrophic cardiomyopathy, the need for more myectomy surgeons and disease-specific centers, and the Tufts initiative. Am J Cardiol, 112 (2013), pp. 1512–1515
6. B.J. Maron, S.R. Ommen, C. Semsarian, P. Spirito, I. Olivotto, M.S. Maron. Hypertrophic cardiomyopathy present and future with translation into contemporary cardiovascular medicine. J Am Coll Cardiol, 64 (2014), pp. 83–99
7. U. Sigwart. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet, 346 (1995), pp. 211–214
8. P. Sorajja, S.R. Ommen, D.R. Holmes Jr., et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation, 126 (2012), pp. 2374–2380
9. P. Sorajja, U. Valeti, R.A. Nishimura, et al.Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation, 118 (2008), pp. 131–139
10. J.X. Qin, T. Shiota, H.M. Lever, et al. Outcome of patients with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery. J Am Coll Cardiol, 38 (2001), pp. 1994–2000
11. S.F. Nagueh, B.M. Groves, L. Schwartz, et al. Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy. A multicenter North American registry. J Am Coll Cardiol, 58 (2011), pp. 2322–2328
12. S. Agarwal, E.M. Tuzcu, M.Y. Desai, et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol, 55 (2010), pp. 823–834
13. D.H. Kwon, S.R. Kapadia, E.M. Tuzcu, et al. Long-term outcomes in high-risk symptomatic patients with hypertrophic cardiomyopathy undergoing alcohol septal ablation. J Am Coll Cardiol Intv, 1 (2008), pp. 432–438
14. F.J. ten Cate, O.I. Soliman, M. Michels, et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail, 3 (2010), pp. 362–369
15. P.A. Noseworthy, M.A. Rosenberg, M.A. Fifer, et al. Ventricular arrhythmia following alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Am J Cardiol, 104 (2009), pp. 128–132
16. F.A. Cuoco, W.H. Spencer III, V.L. Fernandes, et al. Implantable cardioverter-defibrillator therapy for primary prevention of sudden death after alcohol septal ablation of hypertrophic cardiomyopathy. J Am Coll Cardiol, 52 (2008), pp. 1718–1723
17. A. Ralph-Edwards, A. Woo, B.W. McCrindle, et al. Hypertrophic obstructive cardiomyopathy: comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score. J Thorac Cardiovasc Surg, 129 (2005), pp. 351–358

18. C. van der Lee, F.J. ten Cate, M.L. Geleijnse, et al.Percutaneous versus surgical treatmetn for patients with hypertrophic obstructive cardiomyopathy and enlarged anterior mitral valve leaflets. Circulation, 112 (2005), pp. 482–488
19. R.A. Nishimura, S.R. Ommen Septal reduction therapy for obstructive hypertrophic cardiomyopathy and sudden death: what statistics cannot tell you. Circ Cardiovasc Interv, 3 (2010), pp. 91–93
20. B.J. Maron, J.A. Dearani, S.R. Ommen, et al. The case for surgery in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol, 44 (2004), pp. 2044–2053
21. S.R. Ommen, B.J. Maron, I. Olivotto, et al.Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol, 46 (2005), pp. 470–476
22. B.J. Maron, E. Braunwald. Evolution of hypertrophic cardiomyopathy to a contemporary treatable disease. Circulation, 126 (2012), pp. 1640–1644
23. U.S. Valeti, R.A. Nishimura, D.R. Holmes, et al. Comparison of surgical septal myectomy and alcohol septal ablation with cardiac magnetic resonance imaging in patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol, 49 (2007), pp. 350–357
24. M.V. Sherrid, A. Shetty, G. Winson, et al. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with β-blockade or verapamil. Circ Heart Fail, 6 (2013), pp. 694–702
25. B.J. Maron, M. Yacoub, J.A. Dearani. Benefits of surgery for obstructive hypertrophic cardiomyopathy: bring septal myectomy back for European patients. Eur Heart J, 32 (2011), pp. 1055–1058
26. P.A. Vriesendorp, M. Liebregts, R.C. Steggerda, et al. Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol HF, 2 (2014), pp. 630–636
27. C.J. McLeod, S.R. Ommen, M.J. Ackerman, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J, 28 (2007), pp. 2583–2588
28. B.J. Maron. Role of alcohol septal ablation in treatment of obstructive hypertrophic cardiomyopathy. Lancet, 355 (2000), pp. 425–426
29. P. Spirito, B.J. Maron. Perspectives on the role of new treatment strategies in hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol, 33 (1999), pp. 1071–1075
30. B.J. Maron, S.R. Ommen, R.A. Nishimura, J.A. Dearani. Myths about surgical myectomy: rumor of its death have been greatly exaggerated. Am J Cardiol, 101 (2008), pp. 887–889
31. J.A. Dearani, S.R. Ommen, B.J. Gersh, H.V. Schaff, G.K. Danielson. Surgery insight: septal myectomy for obstructive hypertrophic cardiomyopathy—the Mayo Clinic experience. Nat Clin Pract Cardiovasc Med, 4 (2007), pp. 503–512
32. B.J. Maron. Hypertrophic cardiomyopathy centers. Am J Cardiol, 104 (2009), pp. 1158–1159

Chapter 2

A systematic review and meta-analysis of long-term outcomes after septal reduction therapy in patients with hypertrophic cardiomyopathy

Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AFL,
Michels M, Ten Berg JM

JACC Heart Fail. 2015 Nov;3(11):896-905

ABSTRACT

Objectives

The aim of this meta-analysis is to compare long-term mortality and SCD rates after myectomy and ASA in patients with HCM.

Background

Surgical myectomy and percutaneous alcohol septal ablation (ASA) are both accepted treatment options for medical therapy resistant obstructive hypertrophic cardiomyopathy (HCM). Questions remain however about the long-term outcomes, especially concerning the long-term risk of sudden cardiac death (SCD) after ASA.

Methods

A systematic review was conducted for eligible studies with a follow-up of at least 3 years. Primary outcomes were all-cause mortality and (aborted) SCD. Secondary outcomes were peri-procedural complications, LVOT gradient and NYHA class after ≥ 3 months, and re-intervention. Pooled estimates were calculated using a random effect meta-analysis.

Results

Sixteen myectomy cohorts (2791 patients, mean follow-up 7.4 years) and 11 ASA cohorts (2013 patients, mean follow-up 6.2 years) were included. Long-term mortality was found to be similarly low after ASA (1.5% per year) as compared to myectomy (1.4% per year, P=0.78). The rate of (aborted) SCD, including appropriate implantable cardioverter defibrillator shocks, was 0.4% per year after ASA and 0.5% per year after myectomy (P=0.47). Permanent pacemaker implantation was performed following ASA in 10% of the patients, compared to 4.4% after myectomy (P<0.001). Re-intervention was performed in 7.7% of the patients who underwent ASA, compared to 1.6% after myectomy (P=0.001).

Conclusion

Long-term mortality and (aborted) SCD rates after ASA and myectomy are similarly low. Patients who undergo ASA have over twice the risk of permanent pacemaker implantation and a 5 times higher risk of necessity for additional septal reduction therapy, as compared to those who undergo myectomy.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most prevalent inheritable myocardial disease, and (provokable) left ventricular outflow tract (LVOT) obstruction is present in the majority of HCM patients (±70%).(1) If patients with LVOT obstruction remain severely symptomatic despite optimal medical therapy, septal reduction therapy should be considered. This can be done, either by surgical myectomy or alcohol septal ablation (ASA).(2-4) Myectomy has been used for over 5 decades and in experienced centers relief of obstruction can be achieved with minimal perioperative morbidity and mortality.(5) In 1995 ASA was developed as a percutaneous alternative by Sigwart et al(6) and was quickly adopted all over the world. Now, after 20 years since its introduction the debate about the safety of ASA still continues, especially concerning the arrhythmogenic effect of the ablation scar in patients already at an increased risk of life-threatening arrhythmias. The two most recent meta-analyses date back to 2010, and only evaluated short-term outcomes.(7,8) The aim of this meta-analysis is to compare long-term outcomes after myectomy and ASA.

METHODS

Search strategy

Specific search terms were constructed, containing all synonyms for HCM in combination with all synonyms for myectomy and/or ASA, for the following databases: Embase, Medline, Cochrane, Web-of-science, Pubmed-publisher and Google Scholar. Search terms and amount of hits per database are shown in TABLE 1. Predetermined inclusion and exclusion criteria (TABLE 2) were applied by two independent reviewers. Because of our primary interest in long-term outcomes, a minimal mean follow-up was set on 3 years. Observational studies were included, in lack of randomized controlled trials.

Data extraction

Continuous variables were extracted as means or medians, and dichotomous variables were extracted in absolute numbers or percentages for each cohort.

Baseline patient characteristics of interest included age, sex, New York Heart Association (NYHA) functional class, maximal left ventricular wall thickness (LVWT), maximal LVOT gradient, a history of syncope, implantable cardioverter defibrillator (ICD), amount of alcohol used (ASA studies), and concomitant mitral valve surgery (myectomy studies).

Primary outcomes of interest were mortality, cause of death (cardiac/non-cardiac/unknown), sudden cardiac death (SCD), aborted SCD and appropriate ICD shocks. Cardiac death (syn. HCM related mortality) was defined as death due to heart failure, SCD, or death due to stroke associated with atrial fibrillation; SCD was defined as instantaneous and unex-

TABLE 1 – Search terms for systematic review per database with amount of corresponding hits.

Database	Hits	Search term
Embase.com	**1052**	('hypertrophic cardiomyopathy'/de OR 'familial hypertrophic cardiomyopathy'/de OR 'hypertrophic obstructive cardiomyopathy'/de OR (((hypertroph* OR obstruct*) NEAR/3 (cardiomyopath* OR 'subaortic stenosis' OR Asymmetric*)) OR hcm OR hocm OR ihss):ab,ti) AND ('muscle resection'/exp OR myotomy/de OR myomectomy/de OR (((septal OR alcohol) NEAR/3 ablat*) OR ((muscle OR septal) NEAR/3 (resect* OR cut* OR excis* OR extirpat* OR reduct*)) OR myectom* OR myotom* OR myomectom* OR morrow OR tash OR ASA OR PTSMA):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Conference Paper]/lim OR [Editorial]/lim)
Medline (OvidSP)	**910**	(exp Cardiomyopathy, Hypertrophic/ OR (((hypertroph* OR obstruct*) ADJ3 (cardiomyopath* OR subaortic stenosis OR Asymmetric*)) OR hcm OR hocm OR ihss).ab,ti.) AND ((((septal OR alcohol) ADJ3 ablat*) OR ((muscle OR septal) ADJ3 (resect* OR cut* OR excis* OR extirpat* OR reduct*)) OR myectom* OR myotom* OR myomectom* OR morrow OR tash OR ASA OR PTSMA).ab,ti.) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.
Cochrane	**24**	((((hypertroph* OR obstruct*) NEAR/3 (cardiomyopath* OR 'subaortic stenosis' OR Asymmetric*)) OR hcm OR hocm OR ihss):ab,ti) AND ((((septal OR alcohol) NEAR/3 ablat*) OR ((muscle OR septal) NEAR/3 (resect* OR cut* OR excis* OR extirpat* OR reduct*)) OR myectom* OR myotom* OR myomectom* OR morrow OR tash OR ASA OR PTSMA):ab,ti)
Web-of-science	**706**	TS=(((((hypertroph* OR obstruct*) NEAR/3 (cardiomyopath* OR "subaortic stenosis" OR Asymmetric*)) OR hcm OR hocm OR ihss)) AND ((((septal OR alcohol) NEAR/3 ablat*) OR ((muscle OR septal) NEAR/3 (resect* OR cut* OR excis* OR extirpat* OR reduct*)) OR myectom* OR myotom* OR myomectom* OR morrow OR tash OR ASA OR PTSMA))) AND LA=(english) AND DT=(Article)
PubMed publisher	**26**	((((hypertroph*[tiab] OR obstruct*[tiab]) AND (cardiomyopath*[tiab] OR subaortic stenosis OR Asymmetric*[tiab])) OR hcm OR hocm OR ihss)) AND ((((septal OR alcohol) AND ablat*[tiab]) OR ((muscle OR septal) AND (resect*[tiab] OR cut*[tiab] OR excis*[tiab] OR extirpat*[tiab] OR reduct*[tiab])) OR myectom*[tiab] OR myotom*[tiab] OR myomectom*[tiab] OR morrow OR tash OR ASA OR PTSMA)) AND english[la] AND publisher[sb]
Google Scholar	**200**	"hypertrophic cardiomyopathy" | "hypertrophic * cardiomyopathy" "septum | septic | alcohol resection | ablation" | myotomy | myomectomy | tash | ASA | PTSMA

pected death; and aborted SCD was defined as successful resuscitation after cardiac arrest. Secondary outcomes of interest were peri-procedural complications (death, permanent pacemaker implantation, stroke, tamponade, sustained ventricular tachycardia and ventricular fibrillation), days of hospitalization, LVOT gradient after ≥ 3 months, NYHA functional class after ≥ 3 months, and re-intervention (ASA or myectomy).

Statistical Analysis

Descriptive statistics of patients before the intervention are described with weighted medians and interquartile ranges. Standard errors for the differences in weighted medians between the ASA and myectomy group were estimated by 10.000 bootstraps of the weighted medians differences. P-values for the pooled incidence rate differences and weighted medians were calculated using the Wald test. Random-effect meta-analysis was conducted using "metan" function with "randomi" option in Stata version 12.1 (StataCorp LP, College Station, TX), which derives the estimates of heterogeniety from an inverse-variance fixed-effect model. Heterogeneity among studies was estimated by Chi-squared test and the I^2 statistics. Potential sources of heterogeneity were explored by meta-regression analysis, using "metareg" function in STATA. In all analyses, a P value of < 0.05 was considered significant.

RESULTS

Systematic review

The search strategy retrieved 2918 references. After elimination of double hits, a total of 1317 unique references remained (FIGURE 1). After applying the predetermined inclusion and exclusion criteria (TABLE 2) during the initial review, a total of 50 studies were selected for further evaluation. Twenty-two studies were subsequently excluded because of overlapping study periods with cohorts containing more patient-years of follow-up.(9-30) For the same reason only the ASA cohort from the study by Sorajja et al(31) was included. A study(32) on the outcome of patients who underwent myectomy between 1960 -1981, wasn't found eligible

TABLE 2 – Inclusion and exclusion criteria for meta-analysis.

Inclusion
Reporting on outcome of at least 5 patients undergoing ASA and/or surgical myectomy for treatment of medically refractory symptoms of obstructive HCM
Mean follow-up of at least 3 years
Exclusion
Use of ablative media other than ethanol (eg, cyanoacrylate, polyvinyl alcohol foam particles)
Enrolment primarily of patients undergoing rescue ablation after failed surgical myectomy or previous ASA, or vice versa of patients undergoing rescue myectomy after failed ASA or previous myectomy
Enrolment primarily of patients undergoing combined procedures (eg, simultaneous percutaneous coronary intervention or coronary bypass grafting for epicardial coronary disease, simultaneous percutaneous or surgical valve repair or replacement), patients selected for their high risk of sudden death (eg, patients with ICDs), or children
Publication in a non-English language without an available English translation

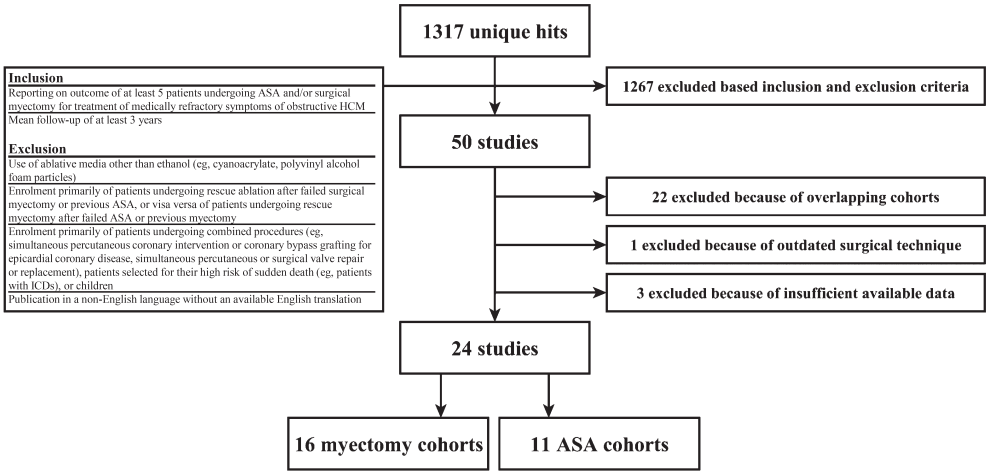


FIGURE 1 – Selection of studies for meta-analysis.

because 47% of the surgical procedures were performed using a transventricular or combined approach, unlike the myectomy techniques as described by Morrow(5) in the other studies. Two studies were excluded because of insufficient baseline characteristics,(33) and the exclusion of patients with a complete atrioventricular block after ASA.(34) Lastly, the study by Sathyamurthy et al(35) was excluded, in lack of an accurate description of the follow-up duration. Twenty-four studies were selected for inclusion, containing 11 ASA cohorts(31,36-45) and 16 myectomy cohorts.(42,43,45-58)

Study characteristics

The characteristics of the studies and their cohorts are shown in TABLE 3. The myectomy cohorts contain a total of 2791 patients, with a mean follow-up of 7.4 years. The ASA cohorts contain a total of 2013 patients, with a mean follow-up of 6.2 years. The median age in the ASA cohorts was 56 years, compared to 47 years in the myectomy cohorts (P = 0.009). Other baseline characteristics did not differ significantly between the ASA and myectomy cohorts.

Peri-procedural outcomes

Peri-procedural (< 30 days) outcomes are shown in TABLE 4. There were 61 peri-procedural deaths in the myectomy cohorts and 20 in the ASA cohorts. Weighted for cohort size, peri-procedural mortality was 1.3% (CI: 0.7-1.8) after ASA and 2.5% (CI: 1.4-3.6) after myectomy (P = 0.051). Cardiac mortality approximated all-cause mortality (1.1% vs. 2.5%; P = 0.035). Permanent pacemaker implantation was necessary after ASA in 10.0% (CI: 7.8-12.1) of patients compared to 4.4% (CI: 2.6-6.2) after myectomy (P < 0.001). The incidence of tamponade and stroke was similar and ≤ 1% after both ASA and myectomy (P = 0.50 and P = 0.15, respectively). Peri-procedural adverse arrhythmic events (AAE), comprising sustained ventricular

TABLE 3 – Baseline characteristics of studies included in meta-analysis.

First author / year	Region	Period	Patients n	Mean FU, y	Mean age	Women %	NYHA class	LVOTG mmHg	LVWT mm	Syncope %	ICD%	Alcohol, mL MV surgery, %
Alcohol septal ablation												
de la Torre Hernandez 2014[36]	Santander, Barcelona, Madrid, Valladolid & A Coruna, Spain	1998- 2003	45	12.3	62	68.8	-	101.0	22.0	-	-	3.7
Fernandes 2008[37]	Houston, Texas; Charleston, South Carolina	1996- 2007	629	4.6	54	49.4	2.8	78.0	21.0	-	-	2.6
Guo 2007[38]	Zhejiang, China; Fukui, Japan	before 2006	26	3.0	37	42.3	3.0	-	23.5	26.9	-	3.8
Jensen 2013[39]	Bad Oeynhausen, Germany; Copenhagen, Denmark	1996- 2010	470	8.4	56	45.0	-	114.0	20.0	26.0	3.0	2.5
Klopotowski 2010[40]	Warsaw, Poland	1997- 2003	61	9.7	48	44.3	-	76.0	21.0	9.8	-	2.7
Lyne 2010[41]	London, UK	1994- 2004	12	11.8	49	58.3	2.7	135.0	22.0	8.0	0.0	-
Samardhi 2014[42]	Brisbane, Australia	1981- 2012	47	3.6	57	44.7	-	72.8	20.3	57.5	6.4	1.8
Sedehi 2014[43]	Stanford, California	1972- 2006	52	3.2	57	44.0	3.0	104.4	21.3	-	11.5	3.3
Sorajja 2012[31]	Rochester, New York	1998- 2010	177	5.7	63	58.0	-	70.0	23.0	15.0	5.0	1.8
Veselka 2014[44]	Prague and Brno, Czech Republic	1998- 2013	178	4.8	58	53.0	2.9	68.0	21.0	15.0	2.2	1.7

TABLE 3 (continued)

First author / year	Region	Period	Patients n	Mean FU, y	Mean age	Women %	NYHA class	LVOTG mmHg	LVWT mm	Syncope %	ICD%	Alcohol, mL MV surgery, %
Vriesendorp 2014[45]	Rotterdam & Nieuwegein, the Netherlands; Leuven, Belgium	1990- 2012	316	6.3	58	45.0	3.0	102.0	21.0	16.0	-	2.0
		Weighted median: (IQR):			**56** (54-58)	**49.4** (45.0-49.4)	**2.8** (2.8-3.0)	**78.0** (78.0-104.4)	**21.0** (20.3-21.0)	**16.0** (15.0-26.0)	**3.0** (3.0-5.0)	**2.5** (2.0-2.6)
Surgical myectomy												
Cohn 1992[46]	Boston, Massachusetts	1972- 1991	31	6.5	55	48.4	3.1	96.0	-	-	-	0.0
Desai 2013[47]	Cleveland, Ohio	1997- 2010	699	6.2	47	37.0	-	103.0	22.1	21.0	10.0	26.0
Gol 1997[48]	Ankara, Turkey	1975- 1996	69	3.7	25	14.5	2.4	78.4	19.9	27.5	-	10.1
Havndrup 2000[49]	Copenhagen, Denmark	1991- 1998	11	3.6	44	63.6	2.4	100	23.0	27.3	9.1	27.3
Heric 1995[50]	Cleveland, Ohio	1975- 1993	178	3.7	-	50.0	2.8	93.0	-	-	-	11.2
Krajcer 1989[51]	Houston, Texas	1963- 1985	127	9.8	-	-	3.2	135.0	-	29.0	-	0.0
Lisboa 2011[52]	Sao Paulo, Brasil	1988- 2008	34	9.6	56	55.9	3.1	84.9	21.6	14.7	-	23.5
Merrill 2000[53]	Nashville, Tennessee	1981- 2000	22	6.6	31	36.3	-	-	-	-	-	4.5
Minami 2002[54]	Bad Oeynhausen, Germany	1985- 2000	75	5.4	53	49.3	3.3	125.0	22.8	-	-	0.0
Ommen 2005[55]	Rochester, New York	1983- 2001	289	5.8	45	49.0	2.9	67.3	23.5	-	-	0.0

TABLE 3 (continued)

First author / year	Region	Period	Patients n	Mean FU, y	Mean age	Women %	NYHA class	LVOTG mmHg	LVWT mm	Syncope %	ICD%	Alcohol, mL MV surgery, %
Samardhi 2014[42]	Brisbane, Australia	1981- 2012	23	3.8	47	56.5	-	78.4	22.6	17.4	13.0	13.0
Schonbeck 1998[56]	Zurich, Switzerland	1965- 1995	110	11.7	37	37.3	2.5	81.0	21.0	24.0	-	10.9
Schulte 1993[57]	Düsseldorf, Germany	1963- 1991	364	8.2	40	40.1	3.1	-	24.2	-	-	7.1
Sedehi 2014[43]	Stanford, California	1972- 2006	171	13.7	18	51.0	2.7	98.1	21.9	-	0.0	0.0
Vriesendorp 2014[45]	Rotterdam & Nieuwegein, the Netherlands; Leuven, Belgium	1990- 2012	250	7.9	52	46.0	2.7	92.0	21.0	16.0	-	-
Woo 2005[58]	Toronto, Canada	1978- 2002	338	7.7	47	40.0	-	65.6	22.7	39.0	-	4.0
		Weighted median: (IQR):			**47** (40-47)	**40.1** (37.0-49.0)	**2.9** (2.7-3.1)	**93.0** (67.3-103.0)	**22.1** (21.9-23.5)	**21.0** (21.0-29.0)	**10.0** (10.0-10.0)	**7.1** (0.0-26.0)
		P:			**0.009**	0.058	0.55	0.40	0.12	0.54	0.14	**-**

FU – follow-up; ICD – implanted cardioverter defibrillator; IQR – interquartile range; LVOT – left ventricular outflow tract; LVWT – left ventricular wall thickness; MV – mitral valve; NYHA – New York Heart Association; P = P-value for difference between ASA and myectomy groups.

TABLE 4 – Peri-procedural outcomes of studies included in meta-analysis.

Study	Pacemaker implantation	Tamponade	Stroke	sVT	VF	Total AAE	cardiac mortality	all cause mortality
ASA								
de la Torre Hernandez 2014[36]	5	1	0	1	0	1	0	0
Fernandes 2008[37]	52	0	0	0	3	3	5	6
Guo 2007[38]	1	0	0	0	1	1	0	0
Jensen 2013[39]	47	5	2	7	0	7	5	5
Klopotowski 2010[40]	11	0	0	0	0	0	0	0
Lyne 2010[41]	0	0	0	0	0	0	0	0
Samardhi 2014[42]	7	0	0	1	2	3	0	0
Sedehi 2014[43]	4	1	0	0	0	0	0	0
Sorajja 2012[31]	36	6	1	3	3	6	2	2
Veselka 2014[44]	14	0	0	6	1	7	1	2
Vriesendorp 2014[45]	-	2	-	1	10	11	5	5
Total:	**177**	**15**	**3**	**19**	**20**	**39**	**18**	**20**
% (CI):	**10.0** (7.8-12.1)	**0.6** (0.1-1.1)	**0.3** (0.0-0.8)	**0.8** (0.2-1.4)	**0.8** (0.2-1.4)	**2.2** (1.1-3.3)	**1.1** (0.6-1.6)	**1.3** (0.7-1.8)
Surgical myectomy								
Cohn 1992[46]	2	0	0	0	0	0	0	0
Desai 2013[47]	7	-	5	-	0	0	0	0
Gol 1997[48]	0	1	0	0	1	1	3	3
Havndrup 2000[49]	1	2	0	-	0	0	0	0
Heric 1995[50]	17	4	5	0	1	1	10	11

TABLE 4 (continued)

Study	Pacemaker implantation	Tamponade	Stroke	sVT	VF	Total AAE	cardiac mortality	all cause mortality
Krajcer 1989[51]	4	-	0	-	4	4	6	6
Lisboa 2011[52]	2	0	2	1	0	1	1	1
Merrill 2000[53]	0	1	0	0	0	0	0	0
Minami 2002[54]	6	0	0	0	0	0	0	1
Ommen 2005[55]	3	-	-	-	-	-	2	2
Samardhi 2014[42]	3	1	1	0	0	0	2	2
Schonbeck 1998[56]	5	1	0	0	1	1	4	4
Schulte 1993[58]	-	-	-	-	-	-	18	18
Sedehi 2014[43]	11	0	0	0	0	0	5	5
Vriesendorp 2014[45]	-	0	-	0	1	1	3	3
Woo 2005[58]	21	-	-	-	-	-	5	5
Total:	**82**	**10**	**13**	**1**	**8**	**9**	**59**	**61**
% (CI):	**4.4** (2.6-6.2)	**1.0** (0.0-2.0)	**0.9** (0.3-1.6)	**0.4** (0.0-1.4)	**0.3** (0.0-0.8)	**1.0** (0.1-1.8)	**2.5** (1.3-3.6)	**2.5** (1.4-3.6)
P:	**<0.001**	0.50	0.15	0.47	0.22	0.091	**0.035**	0.051

Values are n unless otherwise indicated; AAE – adverse arrhythmic events; ASA – alcohol septal ablation; CI – confidence interval; sVT – sustained ventricular tachycardia; VF – ventricular fibrillation; P = P-value for difference between ASA and myectomy groups.

tachycardia and ventricular fibrillation, were similar after ASA compared to myectomy (2.2% vs. 1.0%; P = 0.091). Hospitalization duration was only reported for two myectomy cohorts, and was therefore disregarded.

In light of potentially less developed peri-procedural care in the 20th century, when we excluded studies from before 2000, the peri-procedural mortality rate of myectomy further approximated that of ASA (1.1% vs. 1.3%, respectively; P = 0.75). Similarly, the rates of pacemaker implantation (4.0% vs 10.0% after ASA, P = <0.001) and peri-procedural AAE (0.6% vs 2.2% after ASA, P = 0.055) following myectomy were lower.

Long-term outcomes

Long-term outcomes per study are shown in TABLE 5. In the myectomy cohorts there were 302 all-cause deaths during follow-up (i.e., after 30 days post-procedure), of which 175 were HCM related. In the ASA cohorts 191 patients died, of which 76 were HCM related. Pooled all-cause mortality rates after myectomy and ASA were similar (1.44% per year vs. 1.52% per year; P = 0.78; FIGURE 2). The rate of HCM related mortality was 0.50% per year after ASA

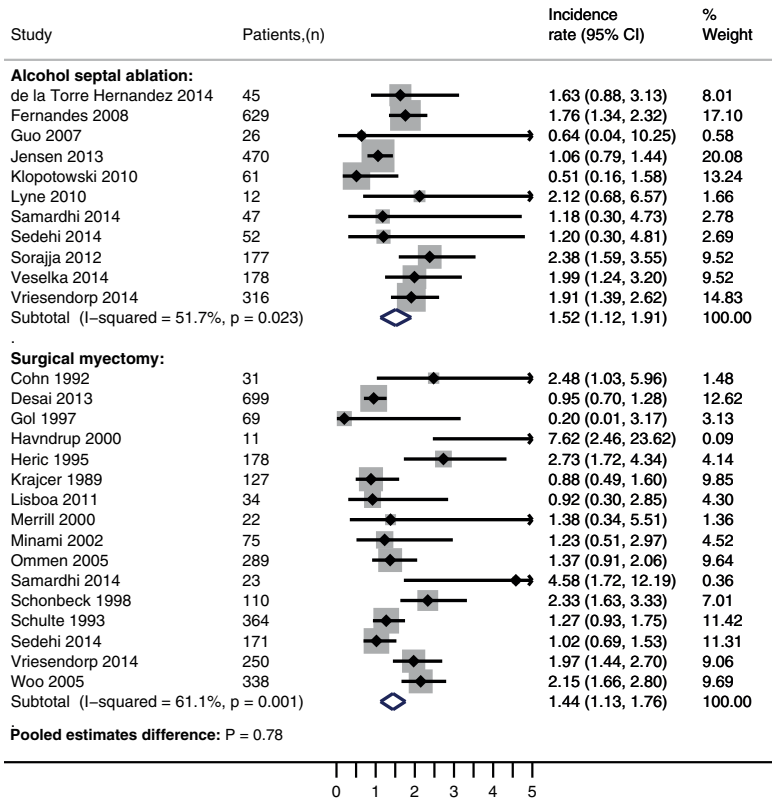


FIGURE 2 – Forest plots and pooled estimates of all-cause mortality rates after surgical myectomy and alcohol septal ablation.

TABLE 5 – Long-term outcomes of studies included in meta-analysis.

Study	SCD	ASCD	ICD shock	Total SCD (- ICD)	Total SCD (+ ICD)	cardiac mortality	noncardiac mortality	unknown mortality	all cause mortality
ASA									
de la Torre Hernandez 2014[36]	0	0	0	0	0	2	6	1	9
Fernandes 2008[37]	7	0	-	7	7	28	17	6	51
Guo 2007[38]	0	0	0	0	0	0	0	0	0
Jensen 2013[39]	16	0	3	16	19	16	0	26	42
Klopotowski 2010[40]	1	1	2	2	4	1	2	0	3
Lyne 2010[41]	2	0	0	2	2	2	1	0	3
Samardhi 2014[42]	0	0	-	0	0	1	1	0	2
Sedehi 2014[43]	-	-	-	-	-	0	0	2	2
Sorajja 2012[31]	1	1	1	2	3	1	11	12	24
Veselka 2014[44]	3	0	0	3	3	13	4	0	17
Vriesendorp 2014[45]	6	2	8	8	16	12	23	3	38
Total:	**36**	**4**	**14**	**40**	**54**	**76**	**65**	**50**	**191**
Surgical myectomy									
Cohn 1992[46]	0	0	-	0	0	4	1	0	5
Desai 2013[47]	32	11	10	43	53	35	0	6	41
Gol 1997[48]	0	0	-	0	0	0	0	0	0
Havndrup 2000[49]	1	0	0	1	1	2	1	0	3
Heric 1995[50]	2	0	0	2	2	4	9	5	18
Krajcer 1989[51]	5	0	-	5	5	9	2	0	11

TABLE 5 (continued)

Study	SCD	ASCD	ICD shock	Total SCD (- ICD)	Total SCD (+ ICD)	cardiac mortality	noncardiac mortality	unknown mortality	all cause mortality
Lisboa 2011[52]	0	0	-	0	0	2	1	0	3
Merrill 2000[53]	0	2	-	2	2	2	0	0	2
Minami 2002[54]	0	0	-	0	0	1	4	0	5
Ommen 2005[55]	5	0	-	5	5	7	16	0	23
Samardhi 2014[42]	0	0	-	0	0	3	1	0	4
Schonbeck 1998[56]	3	0	-	3	3	25	5	0	30
Schulte 1993[57]	11	0	-	11	11	17	20	1	38
Sedehi 2014[43]	-	-	-	-	-	0	0	24	24
Vriesendorp 2014[45]	6	2	1	8	9	21	12	6	39
Woo 2005[58]	13	0	-	13	13	43	13	0	56
Total:	**78**	**15**	**11**	**93**	**104**	**175**	**85**	**42**	**302**
P:	0.05	0.06	0.95	**0.013**	0.12	**0.013**	0.16	**0.002**	0.60

Values are n unless otherwise indicated; ASA – alcohol septal ablation; ASCD – aborted sudden cardiac death; ICD – implanted cardioverter defibrillator; SCD – sudden cardiac death; P = P-value for difference between ASA and myectomy groups.

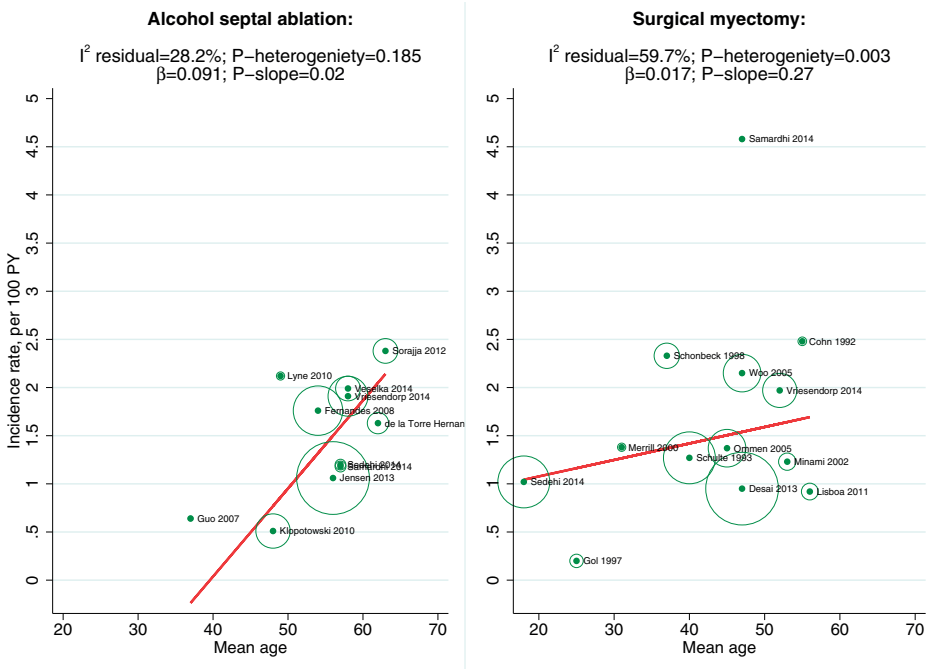


FIGURE 3 – All-cause mortality bubble plot for mean age in myectomy cohorts (left) and ASA cohorts (right), with fitted regression lines in red, and estimates from each cohort in green with the circles size being proportional to the inverse of each study variance. The myectomy study by Havendrup et al. was censored from the plots, but included in the estimates.

and 0.74% per year after myectomy (P = 0.013). There were significantly more unknown causes of death in the ASA cohorts (P = 0.002). Moderate heterogeneity was present for all-cause mortality in both the ASA (I^2 = 52%; P = 0.023) and the myectomy (I^2 = 61%; P = 0.001) groups. Meta-regression showed that ASA cohorts with older patients had higher all-cause mortality rates (P = 0.02), hence age explained some of the heterogeneity in this group (I^2 residual = 28%, P for heterogeneity = 0.19; FIGURE 3). None of the remaining study-level covariates depicted in TABLE 3 showed significant association with mortality across the ASA cohorts, nor were there any of the investigated covariates significantly related to mortality across myectomy cohorts.

The rate of (aborted) SCD during long-term follow-up was 0.41% per year after ASA, and 0.49% per year after myectomy (P = 0.47; FIGURE 4). The description of appropriate ICD shocks was incomplete and unevenly distributed over the two groups (8/11 of the ASA cohorts vs. 4/16 of the myectomy cohorts). In part, this can be explained by the fact that half of the myectomy cohorts are from the year 2000 or earlier, when ICD implantation was less common. When appropriate ICD shocks were excluded from the (aborted) SCD endpoint, the event rates were 0.34% per year after ASA, and 0.47% per year after myectomy (P = 0.16; FIGURE 5). Heterogeneity was present for SCD only in the myectomy cohorts when ICD

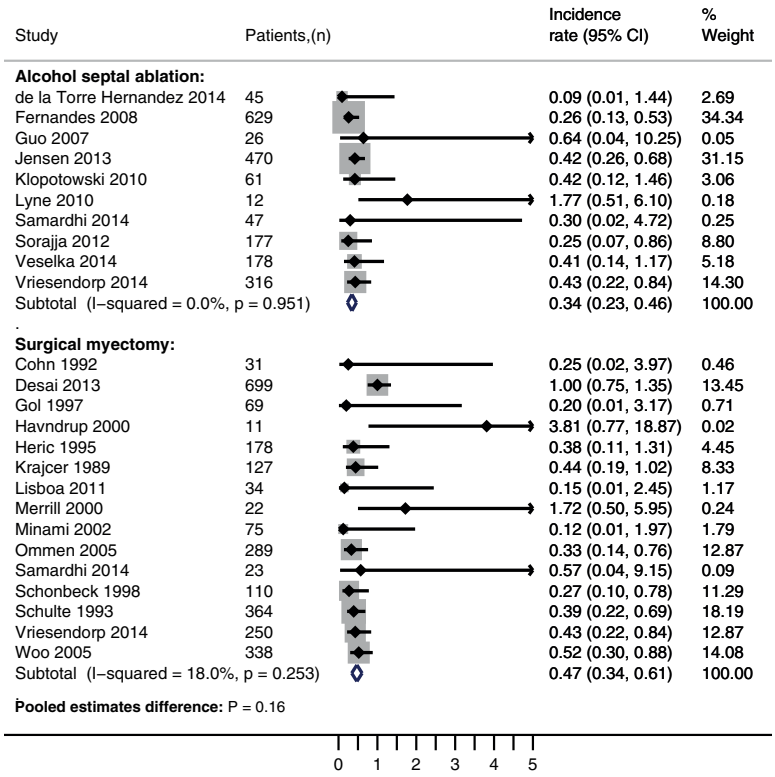


FIGURE 4 – Forest plots and pooled estimates of (aborted) SCD rates after surgical myectomy and alcohol septal ablation, including ICD shocks.

shocks were included (I^2 = 43%; P = 0.038). In meta-regression analysis this heterogeneity was not explained by any of the investigated study-level covariates.

Clinical efficacy

Improvement of functional status, LVOT gradient reduction, and need for re-intervention are depicted in TABLE 6. NYHA class during follow-up was reported either as mean class or in percentage of patients remaining in class III/IV, making comparisons difficult. The median reduction in NYHA class was 45% after both ASA and myectomy. The median amount of patients remaining in NYHA class III/IV was 8% after ASA and 5% after myectomy (P = 0.43). The reduction in LVOT gradient was 71% after ASA and 77% after myectomy (P = 0.63). The number of re-interventions (either ASA or myectomy) was significantly higher after ASA (n = 165) as compared to myectomy (n = 45). Weighted for cohort size this translated in a need for re-intervention in 7.7% (CI: 4.2-11.1) of the patients who underwent ASA, compared to 1.6% (CI: 0.6-2.6) after myectomy (P = 0.001).

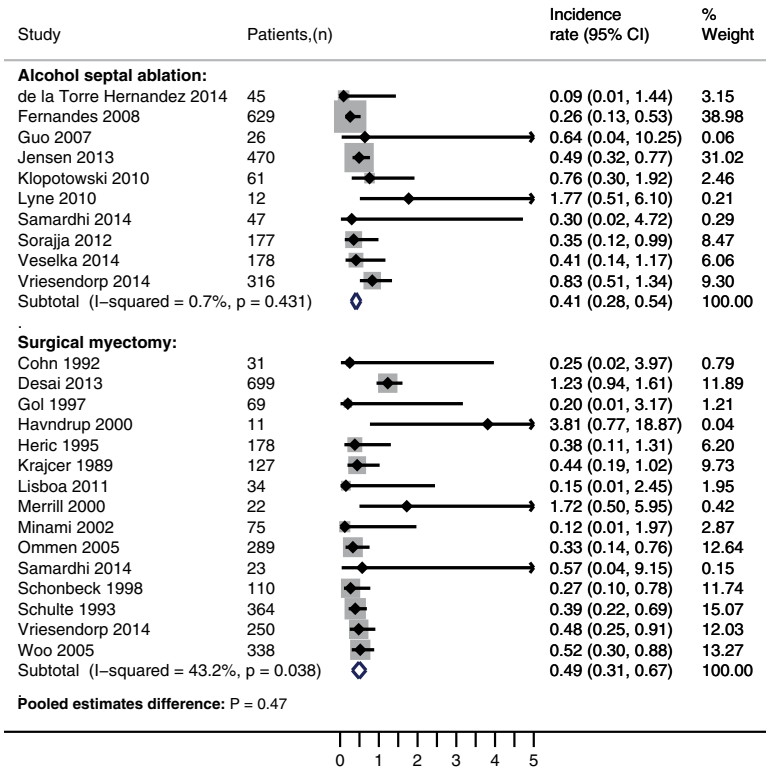


FIGURE 5 – Forest plots and pooled estimates of (aborted) SCD rates after surgical myectomy and alcohol septal ablation, excluding ICD shocks.

DISCUSSION

This is the first systematic review that considers the long-term outcomes after ASA and surgical myectomy. The most important finding of this analysis is that after ASA and myectomy, both mortality and SCD risk were found to be similarly low. Furthermore, we saw that patients who undergo ASA have a significantly higher risk of permanent pacemaker dependency and need for additional septal reduction therapy, as compared to those who undergo myectomy.

Sudden cardiac death after ASA and myectomy

Since the introduction of ASA there have been concerns regarding the arrhythmogenic effect of the ablation scar in patients already at an increased risk of life-threatening arrhythmias. Studies of short-term follow-up after ASA have described frequent episodes of AAE. (29,59,60) Our findings do not confirm this by showing a peri-procedural AAE rate of just 2%, similar to myectomy.

TABLE 6 – Clinical efficacy of ASA and myectomy.

Study	NYHA, %RED	NYHA III/IV, %	LVOT, %RED		Re-intervention
ASA					
de la Torre Hernandez 2014[36]	-	13	74		0
Fernandes 2008[37]	-	-	67		100
Guo 2007[38]	53	-	-		0
Jensen 2013[39]	-	8	90		-
Klopotowski 2010[40]	-	-	79		-
Lyne 2010[41]	63	0	80		2
Samardhi 2014[42]	-	5	63		8
Sedehi 2014[43]	50	-	66		0
Sorajja 2012[31]	-	-	-		15
Veselka 2014[44]	45	-	71		9
Vriesendorp 2014[45]	-	-	90		31
Weighted median: (IQR):	**45** (45-50)	**8.0** (8.0-8.0)	**71** (67- 90)	**Total: %** (CI):	**165 7.7** (4.2–11.1)
Surgical myectomy					
Cohn 1992[46]	45	19	95		0
Desai 2013[47]	-	5	69		8
Gol 1997[48]	38	5	77		0
Havndrup 2000[49]	38	9	83		0
Heric 1995[50]	50	6	77		22
Krajcer 1989[51]	34	27	74		0
Lisboa 2011[52]	55	-	77		0
Merrill 2000[53]	-	-	-		0
Minami 2002[54]	33	-	82		2
Ommen 2005[55]	48	6	96		-
Samardhi 2014[42]	-	0	83		0
Schonbeck 1998[56]	-	12	99		3
Schulte 1993[57]	45	4	-		3
Sedehi 2014[43]	44	-	66		0
Vriesendorp 2014[45]	-	-	90		6
Woo 2005[58]	-	17	-		1
Weighted median: (IQR):	**45** (44-48)	**4.5** (4.5-12)	**77** (69-90)	**Total: %** (CI):	**45 1.6** (0.6-2.6)
P:	0.94	0.43	0.63		**0.001**

Values are n unless otherwise indicated; ASA – alcohol septal ablation; CI – confidence interval; IQR – interquartile range; LVOT – left ventricular outflow tract; NYHA – New York Heart Association; RED – reduction; P = P-value for difference between ASA and myectomy groups.

Several meta-analyses comparing ASA and myectomy have been performed before,(7,8,61,62) but were only able to compare short-term results. Even the 2 meta-analyses published in 2010 did not reach a long enough cumulative follow-up time to make a definitive statement on long-term outcomes of ASA. The analysis by Agarwal et al.(7) had a mean follow-up period across the cohorts of 2.7 years, and the study by Leonardi et al(8) had a significant difference in follow-up duration between the ASA and myectomy cohorts, with a median follow-up of 1266 patient-years in the myectomy studies and 51 patient-years in the ASA studies.

There are two large studies in our analysis which compare the SCD risk of ASA to myectomy. Sorajja et al(31) examined 177 ASA patients and 177 age- and sex-matched myectomy patients, with an average follow-up of 5.7 years. They found annual SCD rates (including unknown deaths) of 1.3% per year after ASA and 1.1% per year after myectomy. Vriesendorp et al(45) examined 321 ASA patients and 253 myectomy patients, and compared their outcomes to 349 non-obstructive HCM patients, with an average follow-up of 7.6 years. They found annual SCD rates (including unknown deaths) of 1.0% per year after ASA and 0.8% per year after myectomy. The present meta-analysis confirms these findings that the long-term risk of SCD after both myectomy and ASA is low.

Peri-procedural complications and re-intervention

The main differences between the two interventions were found in the secondary endpoints. The most frequent peri-procedural complication was an atrioventricular block requiring permanent pacemaker implantation. This was performed in 10% of patients following ASA, compared to 4% after myectomy. Surgical myectomy was not significantly more effective in reducing NYHA functional class and LVOT gradient at ≥ 3 months. We think however that the need for re-intervention is the best clinical parameter for determining the overall efficacy of the procedures. Our results show that re-intervention was necessary after ASA in 7.7% of patients, compared to only 1.6% after myectomy.

We think these findings are important to discuss with patients when they are being informed about the possibilities and limitations of septal reduction therapy. Surgical myectomy is open heart surgery with relatively long rehabilitation. On the other hand, patients who undergo ASA have over twice the risk of permanent pacemaker implantation and a 5 times higher risk of necessity for additional septal reduction therapy (ASA or myectomy, depending on the presence of an additional suitable septal perforator). For these reasons, myectomy might be more suitable for younger patients. However, our results show that there is no elevated long-term risk for life-threatening arrhythmias after ASA, and that ASA is still effective for relief of symptoms in the majority of patients (92%) without need for pacemaker implantation in most (90%).

Patient selection and specialized care

Important developments in imaging and new procedural techniques have improved the efficacy and safety of both procedures. Guidance by myocardial contrast echocardiography made better predictions of the effect of ASA possible,(63) and recently developed peri-procedural image guidance does the same for myectomy.(64) Furthermore, new surgical techniques such as transatrial and transmitral myectomy (with or without robot-assistance), as alternatives to the traditional trans-aortic approach, make better visualization of the septum possible.(65,66) These advances reduce risks for both ASA and myectomy. In line with the 2011 American College of Cardiology(3) and the 2014 European Society of Cardiology(4) guidelines, we recommend that all patients considered for septal reduction therapy are assessed by a multidisciplinary heart team (consisting of at least one cardiothoracic surgeon, an interventional cardiologist, and a cardiologist specializing in the care of patients with HCM) to determine the most optimal therapy, by taking into account factors like mitral valve anatomy, septal thickness, age and comorbidities. Since the studies that were included in the systematic review were performed in centers with extensive experience in the treatment of HCM, the results from the meta-analysis primarily apply to such centers. We therefore recommend that surgical myectomy and ASA should be performed by experienced operators and confined to centers with substantial and specific expertise in HCM care.

Study limitations

As shown in TABLE 1 the patients who underwent ASA and myectomy are inherently different. The direct comparisons as drawn by meta-analysis are thereby harder to interpret. Most importantly the patients from the ASA cohorts were older than those from the myectomy cohorts (median age 56 vs. 47 years). In fact, in the meta-regression analysis ASA cohorts with older patients had higher all-cause mortality rates. Therefore, unmeasured, age-related confounders, such as comorbid illness, may have been more prevalent in ASA cohorts and may have increased all-cause mortality after ASA.

Another important limitation is the great dispersion in study periods between the myectomy and ASA cohorts, with half of the myectomy studies from the year 2000 or earlier. Although meta-regression analysis found no significant association between study period and all-cause mortality, the higher peri-procedural mortality of the myectomy cohorts might be explained by the less developed peri-procedural care in the early days of surgical myectomy. Indeed, the myectomy studies before 2000 all but one had above average peri-procedural mortality rates (Heric 6.2%, Schulte 4.9%, Krajcer 4.7%, Gol 4.3%, Schonbeck 3.6%). When we excluded studies from before 2000, the peri-procedural mortality rate of myectomy approximated that of ASA (1.1% vs. 1.3%, respectively). In doing so, the long-term mortality rate of myectomy was still similar to ASA (i.e., 1.42% per year after myectomy vs. 1.52% per year after ASA; $P = 0.73$).

Finally, because analyses were applied on cohort data instead of individual patient characteristics, the results of the regression models apply to cohorts rather than individual patients. The data shown here are therefore mainly descriptive, and conclusions should be drawn with caution.

CONCLUSION

Long-term mortality and (aborted) SCD rates after ASA and myectomy are similarly low. Patients who undergo ASA have over twice the risk of permanent pacemaker implantation and a 5 times higher risk of necessity for additional septal reduction therapy, as compared to those who undergo myectomy.

REFERENCES

1. Maron MS, Olivotto I, Zenovich AG et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-9.
2. Maron BJ, McKenna WJ, Danielson GK et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy - A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687-1713.
3. Gersh BJ, Maron BJ, Bonow RO et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58:2703-38.
4. Elliott PM, Anastasakis A BM, Borggrefe M et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.
5. Morrow AG, Reitz BA, Epstein SE et al. Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. Circulation 1975;52:88-102.
6. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211-4.
7. Agarwal S, Tuzcu EM, Desai MY et al. Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;55:823-34.
8. Leonardi RA, Kransdorf EP, Simel DL, Wang A. Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy comparative rates of overall mortality and sudden cardiac death after treatment. Circ Cardiovasc Interv 2010;3:97-104.
9. Brown ML, Schaff HV, Dearani JA, Li Z, Nishimura RA, Ommen SR. Relationship between left ventricular mass, wall thickness, and survival after subaortic septal myectomy for hypertrophic obstructive cardiomyopathy. J Thorac Cardiovasc Surg 2011;141:439-43.
10. Faber L, Seggewiss H, Gietzen FH et al. Catheter-based septal ablation for symptomatic hypertrophic obstructive cardiomyopathy: follow-up results of the TASH-registry of the German Cardiac Society. Z Kardiol 2005;94:516-23.
11. Fernandes VL, Nagueh SF, Wang W, Roberts R, Spencer WH 3rd. A prospective follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy--the Baylor experience (1996-2002). Clin Cardiol 2005;28:124-30.
12. Guo H, Wang J, Chen J, Shan J, Lee JD, Ueda T. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: Acute results and three-year noninvasive follow-up in 18 patients. Can J Cardiol 2004;20:779-82.
13. Jensen MK, Almaas VM, Jacobsson L et al. Long-term outcome of percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: a Scandinavian multicenter study. Circ Cardiovasc Interv 2011;4:256-65.
14. Jensen MK, Havndrup O, Hassager C et al. Survival and sudden cardiac death after septal ablation for hypertrophic obstructive cardiomyopathy. Scand Cardiovasc J 2011;45:153-60.
15. Krejci J, Gregor P, Zemanek D et al. Comparison of long-term effect of dual-chamber pacing and alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy. ScientificWorldJournal 2013;2013:629650.
16. Malek LA, Chojnowska L, Klopotowski M et al. Long-term follow-up of patients with hypertrophic obstructive cardiomyopathy treated with percutaneous alcohol septal ablation. Post Kardiol Interw 2009;5:167-71.

17. Minami K, Woltersdorf H, Kleikamp G, Bothig D, Koertke H, Koerfer R. Long-term results after myectomy in 64 patients with hypertrophic obstructive cardiomyopathy (HOCM). Morphological and hemodynamic aspects. J Cardiovasc Surg (Torino) 2000;41:801-6.
18. Mohr R, Schaff HV, Danielson GK, Puga FJ, Pluth JR, Tajik AJ. The outcome of surgical treatment of hypertrophic obstructive cardiomyopathy. Experience over 15 years. J Thorac Cardiovasc Surg 1989;97:666-74.
19. Robbins RC, Stinson EB. Long-term results of left ventricular myotomy and myectomy for obstructive hypertrophic cardiomyopathy. J Thorac Cardiovasc Surg 1996;111:586-94.
20. Rothlin ME, Gobet D, Haberer T, Krayenbuehl HP, Turina M, Senning A. Surgical treatment versus medical treatment in hypertrophic obstructive cardiomyopathy. Eur Heart J 1983;4:215-23.
21. Schulte HD, Borisov K, Gams E, Gramsch-Zabel H, Losse B, Schwartzkopff B. Management of symptomatic hypertrophic obstructive cardiomyopathy--long-term results after surgical therapy. Thorac Cardiovasc Surg 1999;47:213-8.
22. Seggewiss H, Rigopoulos A, Welge D, Ziemssen P, Faber L. Long-term follow-up after percutaneous septal ablation in hypertrophic obstructive cardiomyopathy. Clin Res Cardiol 2007;96:856-63.
23. Seiler C, Hess OM, Schoenbeck M et al. Long-term follow-up of medical versus surgical therapy for hypertrophic cardiomyopathy: a retrospective study. J Am Coll Cardiol 1991;17:634-42.
24. Shamim W, Yousufuddin M, Wang D et al. Nonsurgical reduction of the interventricular septum in patients with hypertrophic cardiomyopathy. New Engl J Med 2002;347:1326-33.
25. Smedira NG, Lytle BW, Lever HM et al. Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. Ann Thorac Surg 2008;85:127-33.
26. Sorajja P, Binder J, Nishimura RA et al. Predictors of an optimal clinical outcome with alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Catheter Cardiovasc Interv 2013;81:58-67.
27. Steggerda RC, Damman K, Balt JC, Liebregts M, Ten Berg JM, van den Berg MP. Periprocedural Complications and Long-Term Outcome After Alcohol Septal Ablation Versus Surgical Myectomy in Hypertrophic Obstructive Cardiomyopathy: A Single-Center Experience. JACC Cardiovasc Interv 2014;7:1227-34.
28. ten Berg JM, Suttorp MJ, Knaepen PJ, Ernst SM, Vermeulen FE, Jaarsma W. Hypertrophic obstructive cardiomyopathy. Initial results and long-term follow-up after Morrow septal myectomy. Circulation 1994;90:1781-5.
29. ten Cate FJ, Soliman OI, Michels M et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail 2010;3:362-9.
30. Veselka J, Duchonova R, Palenickova J et al. Impact of ethanol dosing on the long-term outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy: a single-center prospective, and randomized study. Circ J 2006;70:1550-2.
31. Sorajja P, Ommen SR, Holmes DR Jr. et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2012;126:2374-80.
32. Beahrs MM, Tajik AJ, Seward JB, Giuliani ER, McGoon DC. Hypertrophic obstructive cardiomyopathy: ten- to 21-year follow-up after partial septal myectomy. Am J Cardiol 1983;51:1160-6.
33. Zhu YB, Rajan S, Kurian VM, Liu ZY. Surgical outcomes and strategy of hypertrophic obstructive cardiomyopathy. J Zhejiang Univ Sci B 2006;7:148-53.
34. Chen SL, Ye F, Xu ZL et al. Midterm outcomes of percutaneous transluminal septal myocardial ablation in patients with hypertrophic obstructive cardiomyopathy refractory to medication. Chin Med J 2006;119:1121-4.
35. Sathyamurthy I, Nayak R, Oomman A et al. Alcohol septal ablation for hypertrophic obstructive cardiomyopathy - 8 years follow up. Indian Heart J 2014;66:57-63.
36. de la Torre Hernandez JM, Masotti Centol M, Lerena Saenz P et al. Effectiveness and safety beyond 10 years of percutaneous transluminal septal ablation in hypertrophic obstructive cardiomyopathy. Rev Esp Cardiol 2014;67:353-8.

37. Fernandes VL, Nielsen C, Nagueh SF et al. Follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy the Baylor and Medical University of South Carolina experience 1996 to 2007. JACC Cardiovasc Interv 2008;1:561-70.
38. Guo H, Wang P, Xing Y et al. Delayed electrocardiographic changes after percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy. J Electrocardiol 2007;40:356.
39. Jensen MK, Prinz C, Horstkotte D et al. Alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy: low incidence of sudden cardiac death and reduced risk profile. Heart 2013;99:1012-7.
40. Klopotowski M, Chojnowska L, Malek LA et al. The risk of non-sustained ventricular tachycardia after percutaneous alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy. Clin Res Cardiol 2010;99:285-92.
41. Lyne JC, Kilpatrick T, Duncan A, Knight CJ, Sigwart U, Fox KM. Long-term follow-up of the first patients to undergo transcatheter alcohol septal ablation. Cardiology 2010;116:168-73.
42. Samardhi H, Walters DL, Raffel C et al. The long-term outcomes of transcoronary ablation of septal hypertrophy compared to surgical myectomy in patients with symptomatic hypertrophic obstructive cardiomyopathy. Catheter Cardiovasc Interv 2014;83:270-7.
43. Sedehi D, Finocchiaro G, Tibayan Y et al. Long-term outcomes of septal reduction for obstructive hypertrophic cardiomyopathy [published online ahead of print september 18 2014]. J Cardiol 2014. doi: 10.1016/j.jjcc.2014.08.010.
44. Veselka J, Krejci J, Tomasov P, Zemanek D. Long-term survival after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a comparison with general population. Eur Heart J 2014;35:2040-5.
45. Vriesendorp PA, Liebregts M, Steggerda RC et al. Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. JACC Heart Fail 2014;2:630-6.
46. Cohn LH, Trehan H, Collins JJ Jr. Long-term follow-up of patients undergoing myotomy/myectomy for obstructive hypertrophic cardiomyopathy. Am J Cardiol 1992;70:657-60.
47. Desai MY, Bhonsale A, Smedira NG et al. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. Circulation 2013;128:209-16.
48. Gol MK, Emir M, Keles T et al. Septal myectomy in hypertrophic obstructive cardiomyopathy: late results with stress echocardiography. Ann Thorac Surg 1997;64:739-45.
49. Havndrup O, Pettersson G, Kjeldsen K, Bundgaard H. Outcome of septal myectomy in patients with hypertrophic obstructive cardiomyopathy. Scand Cardiovasc J 2000;34:564-9.
50. Heric B, Lytle BW, Miller DP, Rosenkranz ER, Lever HM, Cosgrove DM. Surgical management of hypertrophic obstructive cardiomyopathy. Early and late results. J Thorac Cardiovasc Surg 1995;110:195-206.
51. Krajcer Z, Leachman RD, Cooley DA, Coronado R. Septal myotomy-myomectomy versus mitral valve replacement in hypertrophic cardiomyopathy. Ten-year follow-up in 185 patients. Circulation 1989;80:57-64.
52. Lisboa LA, Dallan LA, Pomerantzeff PM, Oliveiras SA, Jatene FB, Stolf NA. Long term results of septal myectomy in the treatment of obstructive hypertrophic cardiomyopathy. Rev Bras Cir Cardiovasc 2011;26:86-92.
53. Merrill WH, Friesinger GC, Graham TP Jr. et al. Long-lasting improvement after septal myectomy for hypertrophic obstructive cardiomyopathy. Ann Thorac Surg 2000;69:1732-5.
54. Minami K, Boethig D, Woltersdorf H, Seifert D, Korfer R. Long term follow-up of surgical treatment of hypertrophic obstructive cardiomyopathy (HOCM): the role of concomitant cardiac procedures. Eur J Cardiothorac Surg 2002;22:206-10.
55. Ommen SR, Maron BJ, Olivotto I et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470-6.

56. Schonbeck MH, Brunner-La Rocca HP, Vogt PR et al. Long-term follow-up in hypertrophic obstructive cardiomyopathy after septal myectomy. Ann Thorac Surg 1998;65:1207-14.
57. Schulte HD, Bircks WH, Loesse B, Godehardt EA, Schwartzkopff B. Prognosis of patients with hypertrophic obstructive cardiomyopathy after transaortic myectomy. Late results up to twenty-five years. J Thorac Cardiovasc Surg 1993;106:709-17.
58. Woo A, Williams WG, Choi R et al. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. Circulation 2005;111:2033-41.
59. Kuhn H, Lawrenz T, Lieder F et al. Survival after transcoronary ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. Clin Res Cardiol 2008;97:234-43.
60. Sorajja P, Valeti U, Nishimura RA et al. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2008;118:131-9.
61. Alam M, Dokainish H, Lakkis NM. Hypertrophic obstructive cardiomyopathy alcohol septal ablation vs. myectomy: a meta-analysis. Eur Heart J 2009;30:1080-7.
62. Zeng Z,Wang F, Dou X, Zhang S, Pu J. Comparison of percutaneous transluminal septal myocardial ablation versus septal myectomy for the treatment of patients with hypertrophic obstructive cardiomyopathy: a meta analysis. Int J Cardiol 2006;112:80-4.
63. Faber L, Seggewiss H, Welge D et al. Echo-guided percutaneous septal ablation for symptomatic hypertrophic cardiomyopathy: 7 years of experience. Eur J Echocardiogr 2004;5:347-55.
64. Drake DH, Zimmerman KG, Hepner AM, Nichols CD. Echo-guided mitral reapair. Circ Cardiovasc Imaging 2014;7:132-41.
65. Mohr FW, Seeburger J, Misfeld M. Keynote lecture-transmitral hypertrophic obstructive cardiomyopathy (HOCM) repair. Ann Cardiothorac Surg 2013;2:729-32.
66. Khalpey Z, Korovin L, Chitwood WR Jr, Poston R. Robot-assisted septal myectomy for hypertrophic cardiomyopathy with left ventricular outflow tract obstruction. J Thorac Cardiovasc Surg 2014;147:1708-9.

Chapter 3

Long-term benefit of myectomy and anterior mitral leaflet extension in obstructive hypertrophic cardiomyopathy

Vriesendorp PA, Schinkel AF, Soliman OI, Kofflard MJ, de Jong PL, van Herwerden LA, Ten Cate FJ, Michels M

Am J Cardiol. 2015 Mar 1;115(5):670-5

ABSTRACT

Severely symptomatic patients with obstructive hypertrophic cardiomyopathy (HC) may benefit from surgical myectomy. In patients with enlarged mitral leaflets and mitral regurgitation, myectomy can be combined with anterior mitral leaflet extension (AMLE) to stiffen the mid-segment of the leaflet. The aim of this study was to evaluate the long-term results of myectomy combined with AMLE in patients with obstructive HC. This prospective observational single-center cohort study included 98 patients (49 ±14 years, 37% female) who underwent myectomy combined with AMLE between 1991 - 2012. Endpoints included all-cause mortality and change in clinical and echocardiographic characteristics. Mortality was compared with age-and gender matched non-obstructive HC patients and subjects from the general population. Long-term follow-up was 8.3 ±6.1 years. There was no operative mortality and NYHA class was reduced from 2.8 ±0.5 to 1.3 ±0.5 ($p<0.001$); left ventricular outflow tract gradient from 93 ±25 to 9 ±8 mmHg ($p<0.001$); mitral valve regurgitation from grade 2.0 ±0.9 to 0.5 ±0.8 ($p<0.001$); and systolic anterior motion of the mitral valve from grade 2.4 ±0.9 to 0.1 ±0.3 ($p<0.001$). The 1-, 5 -, 10-, and 15-year cumulative survival was 98%, 92%, 86%, and 83%, respectively; and did not differ from the general population (99%, 97 %, 92%, and 85%, respectively; $p=0.3$) or non-obstructive HC patients (98%, 97%, 88%, and 83%, respectively, $p=0.8$). In conclusion, in selected obstructive HC patients myectomy combined with AMLE is a low risk surgical procedure. It results in long-term symptom relief and survival similar to the general population.

INTRODUCTION

The aim of this study was to evaluate the long-term results of myectomy combined with anterior mitral leaflet extension (AMLE) in patients with obstructive hypertrophic cardiomyopathy (HC). In the current report long-term outcome after myectomy combined with AMLE was compared with age and gender matched patients with non-obstructive HC and subjects from the general Dutch population.

METHODS

The study conforms to the principles of the Helsinki Declaration. All patients gave informed consent for the intervention and prospective inclusion in a registry, and local institutional review board approval was obtained. A total of 139 obstructive HC patients underwent surgical myectomy between 1991 and December 2012. Myectomy with AMLE was performed in 98 patients (71%), isolated myectomy in 24 patients (17%), and myectomy combined with mitral valve replacement in 14 patients (12%).

Patients are selected for surgery at our HC center on the basis of the following indications: (1) peak left ventricular outflow tract (LVOT) gradient ≥ 50 mmHg at rest or on provocation and (2) presence of unacceptable symptoms despite maximally tolerated medications consisting of ß-blocking agents and/or calcium channel blockers. The decision to perform surgery was made after consensus of a heart team consisting of a cardiothoracic surgeon, an interventional cardiologist, and a cardiologist specialized in HC care.

Myectomy combined with AMLE is performed in patients with enlargement of the anterior mitral valve area (> 12 cm^2), calculated with the formula previously validated by Klues et al [1-3]. The surgical technique has been described previously [2,3]. In brief, an autologous pericardial patch is harvested, trimmed of fat and extraneous tissue, immersed for 6 minutes in 0.4 % glutaraldehyde, and then placed in a normal saline bath. After opening the ascending aorta by an oblique incision, myectomy is performed to the left of an imaginary line through the nadir of the right coronary cusp in the beginning with a locally designed electrocautery device [4], later by excision with scissors and a rongeur or surgical knife. After myectomy AMLE is performed. A gap is created in the anterior mitral leaflet by a longitudinal incision, starting at the sub aortic hinge point and ending just before the rough zone. Then, an oval autologous pericardial patch, of about 2.5 cm wide and 3 cm long, is grafted across the bending point of the mitral valve where the systolic anterior motion (SAM) is maximal to stiffen the buckling anterior mitral valve leaflet (AMVL). The patch extends the width but not the length of the AMVL, which shifts the centrally attached chordae laterally. As a result, the chordae are stretched and erected, which will enhance leaflet coaptation. Finally, because

force produced by blood flow against the leaflet is proportional to its area, the increased leaflet will be pressed posterior, with a decrease in SAM and MR. The surgical results were assessed with transoesophageal echocardiography immediately after weaning from cardiopulmonary bypass and at a systolic blood pressure of ≥ 100 mmHg.

The clinical characteristics collected before the intervention included assessment of symptoms, New York Heart Association (NYHA) functional class and prescribed drugs. Physical examination and baseline laboratory studies were performed, including electrocardiography, transthoracic echocardiography, and cardiac catheterization. The echocardiographic data were reviewed by a physician unaware of the patient's medical history. Echocardiography was performed in the month prior to surgery and after surgery repeated at 1 week, 3 months and at yearly intervals. Ventricular septum thickness was calculated at the site of myectomy from the septal width in diastole from both the parasternal short-axis and long-axis views. The severity of the mitral valve regurgitation (MR) was graded on a 0 to 4 scale by color flow Doppler echocardiography [5]. The severity of the SAM of the anterior mitral valve leaflet was determined from the 2D images and was graded on a scale from 0 to 3 depending on the mitral-septal distance (grade 0 indicating no SAM and grade 3 indicating prolonged contact between mitral valve and septum) [6]. The length of the anterior mitral valve leaflet was noted. Peak LVOT gradient was estimated with Doppler echocardiography by the modified Bernoulli equation ($P = 4v^2$), where P is the pressure gradient and v is Doppler-determined blood velocity.

The primary endpoint was all-cause mortality. Follow-up information was obtained at routine visits at the HC outpatient clinic. For 7 patients follow-up information was collected at their referring cardiologist. Follow-up vital status and cause of death was obtained by reviewing the hospital records, from general practitioners and civil registries. Sudden cardiac death (SCD) was defined as instantaneous and unexpected death within 1 hour after a witnessed collapse in patients who previously were in stable clinical condition, or nocturnal death with no antecedent history of worsening symptoms. Follow-up data were complete for all patients.

All statistics were performed using the SPSS 21 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Data are expressed as mean ± SD or number (percentage). The normal distribution for continuous data was examined with the Shapiro–Wilk test. Comparison of numerical variables was performed using the two-sided Student's t-test or Wilcoxon rank-sum test or ANOVA test, and the chi-square or Fisher's exact tests were used to compare qualitative variables. The p-values are two-sided; $p < 0.05$ was considered statistically significant. The survival analysis model used proportional hazards regression methodology; Kaplan-Meier survival curves were compared using log-rank statistics. Long-term survival of patients who underwent myectomy combined with AMLE was compared with age- and gender matched patients with non-obstructive HC and with the

expected survival curve for the general Dutch population. This expected survival curve was generated from the database of Statistics Netherlands, which incorporates all-cause mortality (www.cbs.nl). The administrative censoring date was set at August 1 2013. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

A total of 343 patients with obstructive HC (LVOT gradient > 50 mmHg) were evaluated at our center. Of these patients, 139 (41%) underwent myectomy, 97 (28%) underwent ASA, and 107

TABLE 1 – Clinical and demographic characteristics of 98 hypertrophic cardiomyopathy patients who received combined myectomy, 24 patients who underwent isolated myectomy, and 98 non-obstructive hypertrophic cardiomyopathy patients (controls).

Variable	**Combined myectomy**	**Isolated Myectomy**	**Non-obstructive**
	(n=98)	*(n=24)*	*(n=98)*
Age (years)	49 ± 14	48 ± 18	49 ± 15
Female	36 (37%)	10 (42%)	36 (37%)
NYHA III/IV	73 (74%)	19 (79%)	10 (10%)***
LV wall thickness (mm)	22 ± 5	20 ± 3	20 ± 5*
LV outflow tract gradient (mmHg)	93 ± 25	83 ± 20	8 ± 5***
Anterior mitral leaflet length (mm)	34 ± 4	29 ± 3***	28 ± 4***
Mitral regurgitation	2.0 ± 0.9	1.3 ± 0.9***	0.5 ± 0.7***
Medication			
β-receptor antagonist	67 (68%)	19 (79%)	38 (39%)***
Calcium-channel blocker	48 (49%)	13 (54%)	12 (12%)***
Follow-up			
Duration, y	8.3 ± 6.1	5.0 ± 6.0*	10.6 ± 5.5*
Cause of death			
Heart failure	6 (6%)	0	4 (4%)
Sudden death	3 (3%)	0	3 (3%)
Non-cardiac	1 (1%)	1 (4%)	6 (6%)

* = P < 0.05; ** = P < 0.01; *** = P < 0.001 (compared with combined myectomy). Data represented as n (percentage) unless stated otherwise. HC: hypertrophic cardiomyopathy, LV: left ventricular; NYHA: New York Heart Association

(31%) were treated medically. The majority of medically treated patients (91, 85%) reported no symptoms or mild (NYHA class I/II) symptoms at baseline, despite a mean LVOT gradient of 70 ± 24 mmHg. The other 16 patients (15%) had an indication for invasive treatment but were considered not eligible due to severe comorbidities (e.g. one patient had liver cirrhosis due to alcohol abuse and kidney failure) or patient refusal (several patients refused further invasive treatment, mostly because they were at old age, and preferred no further interventions).

The baseline characteristics of the 98 combined surgery patients, 24 isolated myectomy patients are listed in TABLE 1. Myectomy with additional coronary bypass grafting was performed in 3 patients (3%). In 14 patients, myectomy and MVR was performed directly, instead of AMLE. Reasons for direct mitral replacement were (among others): chordal rupture or prolapse of posterior leaflet, severe calcification of the valvular apparatus, and infective endocarditis with valvular destruction. In most of these cases, MVR was planned prior to surgery, but the final decision to perform AMLE was made intraoperatively by the surgeon after epicardial and/or transesophageal beating heart echocardiography and visual inspection of the arrested heart. In 8 patients (8%) myectomy and AMLE was performed after failed alcohol septal ablation (ASA) or embolization using coils.

Because advanced symptoms refractory to pharmacologic therapy represent the standard indication for operation, patients who underwent myectomy (both isolated and combined with AMLE) expectedly showed more severe functional disability at study entry than patients with non-obstructive HC; 74-79% in NYHA class III or IV compared with 7% in the non-obstructive group ($p<0.001$). The length of the anterior mitral valve leaflet prior to surgery was longer in patients who underwent combined surgery, compared with the isolated myec-

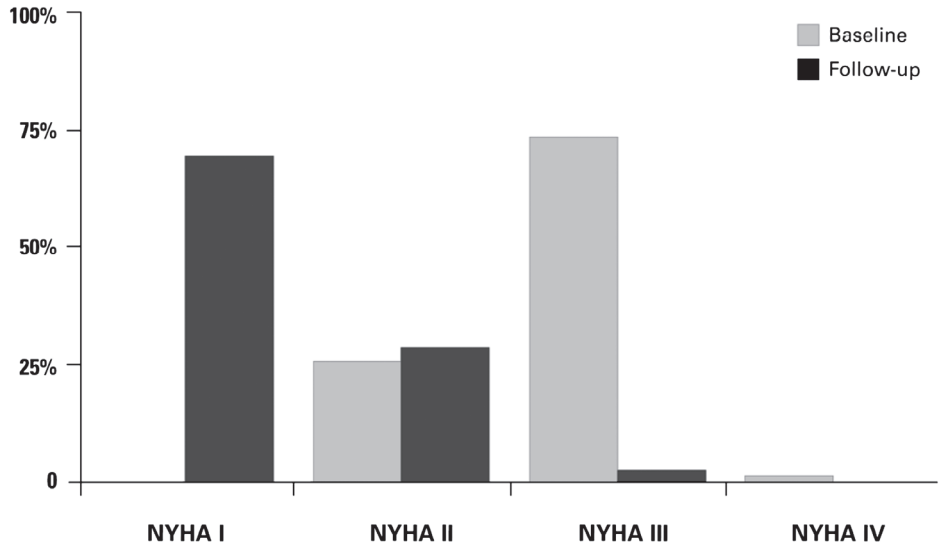


FIGURE 1 – NYHA functional class at baseline and at latest follow-up in patients with obstructive hypertrophic cardiomyopathy treated with myectomy and mitral leaflet extension.

TABLE 2 – Long-term echocardiographic follow-up in 98 obstructive hypertrophic cardiomyopathy patients treated with myectomy combined with anterior mitral valve leaflet extension.

Variable	**Baseline**	**Follow-up**	
	(n=98)	*(n=86)*	*P*
Ventricular septum (mm)	22 ± 5	16 ± 4	**< 0.001**
LV end diastolic diameter (mm)	44 ± 6	49 ± 7	**< 0.001**
LV outflow tract gradient (mmHg)	93 ± 25	9 ± 8	**< 0.001**
Left atrial size (mm)	48 ± 8	49 ± 11	0.5
Systolic anterior motion (grade)	2.4 ± 0.9	0.1 ± 0.3	**< 0.001**
Mitral valve regurgitation (grade)	2.0 ± 0.9	0.5 ± 0.8	**< 0.001**

LV: left ventricular

tomy and non-obstructive patients. Mitral valve regurgitation (prior to surgery) was also more severe in patients who underwent combined surgery (TABLE 1).

The myectomy combined with AMLE group experienced substantial symptomatic and hemodynamic improvement after surgery; 73 (74%) patients were in NYHA functional class III or IV before operation, whereas only 2 of 89 (2%) remaining patients at latest follow-up were in NYHA class III. (FIGURE 1). Compared with preoperative data, there were significant changes in peak LVOT gradient, MR severity and presence of systolic anterior motion of the mitral valve at latest follow-up compared with pre-operative state (TABLE 2).

Long-term follow-up was 8.3 ±6.1 years or 809 patient-years. Four patients (2 of those were operated after failed ASA) developed complete heart block during surgery. Three patients received a permanent pacemaker, in the remaining patient combined with an implantable cardioverter defibrillator (ICD) because of a high risk status for SCD. An ICD was implanted in 17 more patients for primary prevention of SCD. One patient received appropriate ICD-shocks during follow-up. Paroxysmal or persistent atrial fibrillation occurred in 36 (37%) patients during follow-up. Of these patients, in 21 (21%) AF occurred during follow-up, and 15 (15%) patients only had an episode of post-operative AF (6 of these had a prior history of AF). Electric cardioversion during post-operative recovery was necessary in 7 patients (7%).

None of the patients had an indication for reinstitution of cardiopulmonary bypass. Perfect mitral competence (grade 0 MR) was present in 57 (58%) of patients and only 2 (2%) had grade 3+ MR at latest follow-up. In 1 patient (1%) early valve repair failure, due to rupture of the new chordae (13 days after initial surgery), leading to mitral valve replacement was necessary. Other indications of re-surgery are shown in TABLE 3.

None of the patients died during surgery or in hospital. Twelve (12 %) patients died during follow-up; 3 suffered SCD, respectively after 1.9, 2.8, and 16.9 years. Six (6%) patients died of end-stage heart failure, after a median of 5.1 years (TABLE 3). Three patients (3%) died of non-cardiac causes. The shortest time to death after the procedure was 3 months after surgery

TABLE 3 – Events during 20-year follow-up in 98 obstructive hypertrophic cardiomyopathy patients treated with myectomy and mitral valve leaflet extension

Latest Follow-up	
Total mortality	12 (12%)
Operative mortality	0
Sudden cardiac death	3 (3%)
End-stage heart failure	6 (6%)
Non-cardiac	3 (3%)
Atrial fibrillation	36 (37%)
Pacemaker	4 (4%)
Implantable cardioverter-defibrillator	18 (18%)
Re-operation	17 (17%)
Mitral valve replacement	3 (3%)
Pericardial effusion	3 (3%)
Heart transplantation	2 (2%)
Patch-dehiscence	2 (2%)
Bleeding	4 (4%)
Mediastinitis	2 (2%)
Residual obstruction	1 (1%)

Data represented as n (percentage).

in the patient with LVEF of 30% and grade III diastolic dysfunction. In the isolated myectomy group, 1 (4%) patient died due to a non-cardiac cause.

As seen in FIGURE 2; the 1-, 5 -, 10-, and 15- year cumulative survival after myectomy combined with AMLE was 98%, 92%, 86%, and 83%, respectively and did not differ from the general population (99%, 97 %, 92%, and 85%, respectively; log-rank p = 0.3). Likewise, the 1-, 5 -, 10-, and 15- year cumulative survival (98%, 97%, 88%, and 83%, respectively, log-rank p = 0.8) of age- and gender-matched non-obstructive HC patients was not different from the patients who underwent myectomy combined with AMLE. The number of cardiac related deaths in both groups was identical; however in the non-obstructive HC group more patients died from non-cardiac causes during long-term follow-up.

DISCUSSION

This study shows that myectomy combined with AMLE, which stiffens the mid-segment of the anterior leaflet, is an effective procedure to remove the LVOT obstruction in selected HC

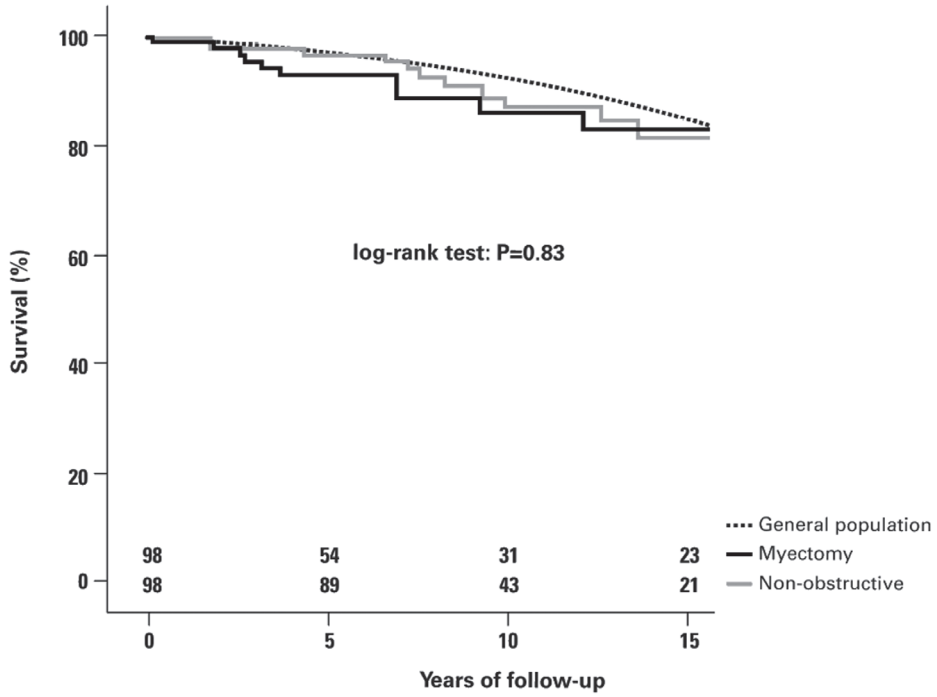


FIGURE 2 – Kaplan-Meier event-free survival comparison between patients with obstructive hypertrophic cardiomyopathy treated with myectomy and mitral leaflet extension, non-obstructive hypertrophic cardiomyopathy patients, and the general population.

patients. The operation can be performed at the cost of acceptable morbidity and very low operative mortality. It leads to long-term symptom relief and comparable survival to age and sex-matched patients with non-obstructive HC and subjects from the general Dutch population.

LVOT obstruction is an important pathophysiological component of HC. Clinical studies performed in large HC populations have identified a consistent relationship between LVOT gradients at rest and heart failure symptoms and cardiovascular events; including overall probability of death due to heart failure, stroke and progression to NYHA functional class III or IV [7,8]. Severely symptomatic drug-refractory obstructive HC patients are candidates for invasive septal reduction interventions as surgical myectomy or ASA.

The current study consisted of consecutive patients with enlarged anterior mitral leaflets and typical SAM as described in previous reports from our institute treated with myectomy combined with AMLE [3] (FIGURE 3). The immediate reduction of the LVOT gradient after surgical myectomy (with AMLE) has positive effects on LV filling pressures, heart failure symptoms and exercise capacity in patients with drug-refractory obstructive HC [9-11]. In this study there was a clear improvement in hemodynamics and NYHA class, and these benefits continue in 74% up to 20 years.

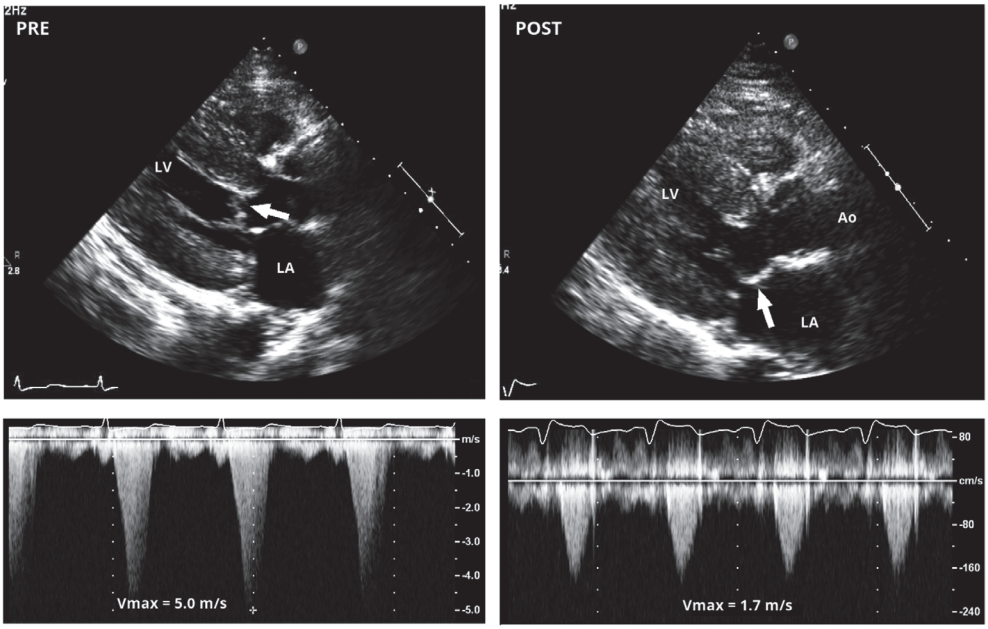


FIGURE 3 – Preoperative and postoperative 2D Parasternal long-axis view (top) and Continuous Wave Doppler (bottom) echocardiograms in patient treated with combined myectomy and mitral valve leaflet extension with successful reduction of the left ventricular outflow tract gradient. Left arrow shows systolic anterior motion of the mitral leaflet. Right arrow indicates the patch in the mitral leaflet (Ao: Aorta; LA: left atrium; LV: left ventricle; PRE: preoperative; POST: postoperative).

The procedure was without operative mortality in this cohort, with an excellent long-term cumulative survival equal to general Dutch population of age-and gender matched patients and comparable with non-obstructive HC patients. This outcome is comparable with the reported long-term survival benefit of obstructive HC patients who underwent isolated myectomy in the Mayo Clinic and Toronto General Hospital [12,13]. In the larger Mayo Clinic series 10-year overall survival was 83%, which was equivalent to expected in the matched general U.S. population. In the latter study, patients who underwent myectomy combined with concurrent operative procedures were excluded [13].

However, obstructive HC can also be associated with a variety of intrinsic abnormalities of the mitral valve, including increased mitral leaflet area [1,14]. These abnormalities may predispose to residual SAM and result in suboptimal outcome after isolated myectomy [15,16]. Our results show a post-operative reduction of SAM from 2.4 ±0.9 to 0.1 ± 0.3, and in only 1 patient re-resection of the septum to further reduce the LVOT gradient was necessary. In the study performed by Wan et al [17], mitral valve repair was performed instead of AMLE. In 6 of the 32 patients (19%) SAM was present post-operatively. In our study, only 7 patients (7%) had SAM after surgery. Balaram et al. performed mitral plication in 132 patients, and showed a similar reduction in MR severity (from 2.3 ± 0.9 to 0.5 ± 0.6), and need for re-resection (2

patients, 1.5%) [18]. We do not propose myectomy combined with AMLE to be performed in all obstructive HC patients, but this technique can be a safe and valuable addition in the treatment of LVOT obstruction, especially in patients with enlarged mitral leaflets.

Other studies with patients who underwent myectomy and mitral valve repair with different techniques show similar survival and improvement in functional class, LVOT gradient, SAM and mitral valve regurgitation at follow-up [19,20]. A study by Kaple et al. reports overall survival after myectomy combined with a number of repair techniques at 1-, 5 - and 10 years of respectively 91%, 81% and 66%; the patients in this study were however significantly (59±14 versus 49±14, $p<0.001$) older than those in the current study [14]. The current study is to our knowledge the first to describe equivalent survival to the general population in obstructive HC patients undergoing a myectomy combined with AMLE. During long-term follow-up 88% patients were free of reoperation, which is comparable with the results of combined surgery in obstructive HC reported by others at 3 years follow-up [14].

In comparison with the age-and gender matched patients with non-obstructive HC cardiac related mortality in both groups was similar. The annual mortality rate of the operated patients (1.4%/year) was similar to previously reported mortality rates in HC patients during long-term follow-up [12,21,22]. We did find that end-stage heart failure was the most common cause of death after myectomy with AMLE, but it was similar to non-obstructive patients ($p=0.5$), and median time to death was >5 years after surgery.

The majority of the patients were in NYHA class III/IV prior to surgery, and mortality related to end-stage heart failure in these patients is high and patients suffer from debilitating symptoms [7]. The outcome of this study, in line with aforementioned literature concerning isolated myectomy or surgical plication of the AMVL, shows that myectomy (with AMLE) delays or even averts the onset of heart-failure in patients with obstructive HC, and improves quality of life in these patients.

This is a single institution's consecutive experience with myectomy combined with AMLE in a relatively small number of selected obstructive HC patients. These patients were deemed not acceptable candidates at our institution for isolated myectomy or ASA because of mitral valve abnormalities. We included a third group of obstructive HC patients treated by isolated myectomy, however this group was relatively small because between 1999 and 2007 almost all patients (> 90 patients) suitable for isolated myectomy underwent ASA at our center, mostly because of patient preference [23]. Due to small sample size further analysis on comparing isolated and combined myectomy in our population was not appropriate. Based on the experience in our center with this specific technique there is also a referral bias; especially obstructive HC patients with enlarged mitral valve leaflets are being referred for surgery. Despite the lack of a statistically significant difference in the Kaplan-Meir survival analysis between patients who underwent myectomy combined with AMLE and the general Dutch population, the study may not be powered enough to detect such a difference.

REFERENCES

1. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. *Circulation* 1992;85:1651-1660.
2. Van Herwerden LA, Ten Cate FJ. Combined anterior mitral leaflet extension and spark erosion myectomy in hypertrophic obstructive cardiomyopathy: Echo-enhanced surgery. In*: Operative Techniques in Thoracic and Cardiovascular Surgery. A Comparative Atlas*. Sundt III TM ed. Vol.9,No.4,310-319,2004
3. van der Lee C, Kofflard MJ, van Herwerden LA, Vletter WB, ten Cate FJ. Sustained improvement after combined anterior mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy. *Circulation* 2003;108:2088-2092.
4. Maat LP, Slager CJ, van Herwerden LA, Schuurbiers JC, van Suylen RJ, Kofflard MJ, ten Cate FJ, Bos E. Spark erosion myectomy in hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg* 1994;58:536-540.
5. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, American Society of E. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777-802.
6. Gilbert BW, Pollick C, Adelman AG, Wigle ED. Hypertrophic cardiomyopathy: subclassification by m mode echocardiography. *Am J Cardiol* 1980;45:861-872.
7. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348:295-303.
8. Autore C, Bernabo P, Barilla CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. *J Am Coll Cardiol* 2005;45:1076-1080.
9. Monteiro PF, Ommen SR, Gersh BJ, Dearani JA, Schaff HV, Nishimura RA, Tajik AJ. Effects of surgical septal myectomy on left ventricular wall thickness and diastolic filling. *Am J Cardiol* 2007;100:1776-1778.
10. Ommen SR, Nishimura RA, Squires RW, Schaff HV, Danielson GK, Tajik AJ. Comparison of dual-chamber pacing versus septal myectomy for the treatment of patients with hypertrophic obstructive cardiomyopathy: a comparison of objective hemodynamic and exercise end points. *J Am Coll Cardiol* 1999;34:191-196.
11. Firoozi S, Elliott PM, Sharma S, Murday A, Brecker SJ, Hamid MS, Sachdev B, Thaman R, McKenna WJ. Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy. A comparison of clinical, haemodynamic and exercise outcomes. *Eur Heart J* 2002;23:1617-1624.
12. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ, Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;46:470-476.
13. Woo A, Williams WG, Choi R, Wigle ED, Rozenblyum E, Fedwick K, Siu S, Ralph-Edwards A, Rakowski H. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. *Circulation* 2005;111:2033-2041.
14. Kaple RK, Murphy RT, DiPaola LM, Houghtaling PL, Lever HM, Lytle BW, Blackstone EH, Smedira NG. Mitral valve abnormalities in hypertrophic cardiomyopathy: echocardiographic features and surgical outcomes. *Ann Thorac Surg* 2008;85:1527-1535
15. Yu EH, Omran AS, Wigle ED, Williams WG, Siu SC, Rakowski H. Mitral regurgitation in hypertrophic obstructive cardiomyopathy: relationship to obstruction and relief with myectomy. *J Am Coll Cardiol* 2000;36:2219-2225.

16. Smedira NG, Lytle BW, Lever HM, Rajeswaran J, Krishnaswamy G, Kaple RK, Dolney DO, Blackstone EH. Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg* 2008;85:127-133.
17. Wan CK, Dearani JA, Sundt TM, 3rd, Ommen SR, Schaff HV. What is the best surgical treatment for obstructive hypertrophic cardiomyopathy and degenerative mitral regurgitation? *Ann Thorac Surg* 2009;88:727-731
18. Balaram SK, Ross RE, Sherrid MV, Schwartz GS, Hillel Z, Winson G, Swistel DG. Role of mitral valve plication in the surgical management of hypertrophic cardiomyopathy. *Ann Thorac Surg* 2012;94:1990-1997
19. Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, Homel P, Balaram SK, Swistel DG. Treatment of Obstructive Hypertrophic Cardiomyopathy Symptoms and Gradient Resistant to First-Line Therapy With beta-Blockade or Verapamil. *Circ Heart Fail* 2013;6:694-702.
20. Iacovoni A, Spirito P, Simon C, Iascone M, Di Dedda G, De Filippo P, Pentiricci S, Boni L, Senni M, Gavazzi A, Ferrazzi P. A contemporary European experience with surgical septal myectomy in hypertrophic cardiomyopathy. *Eur Heart J* 2012;33:2080-2087.
21. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. *J Am Coll Cardiol* 2003;41:987-993.
22. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation* 2000;102:858-864.
23. van der Lee C, ten Cate FJ, Geleijnse ML, Kofflard MJ, Pedone C, van Herwerden LA, Biagini E, Vletter WB, Serruys PW. Percutaneous versus surgical treatment for patients with hypertrophic obstructive cardiomyopathy and enlarged anterior mitral valve leaflets. *Circulation* 2005;112:482-488.

Chapter 4

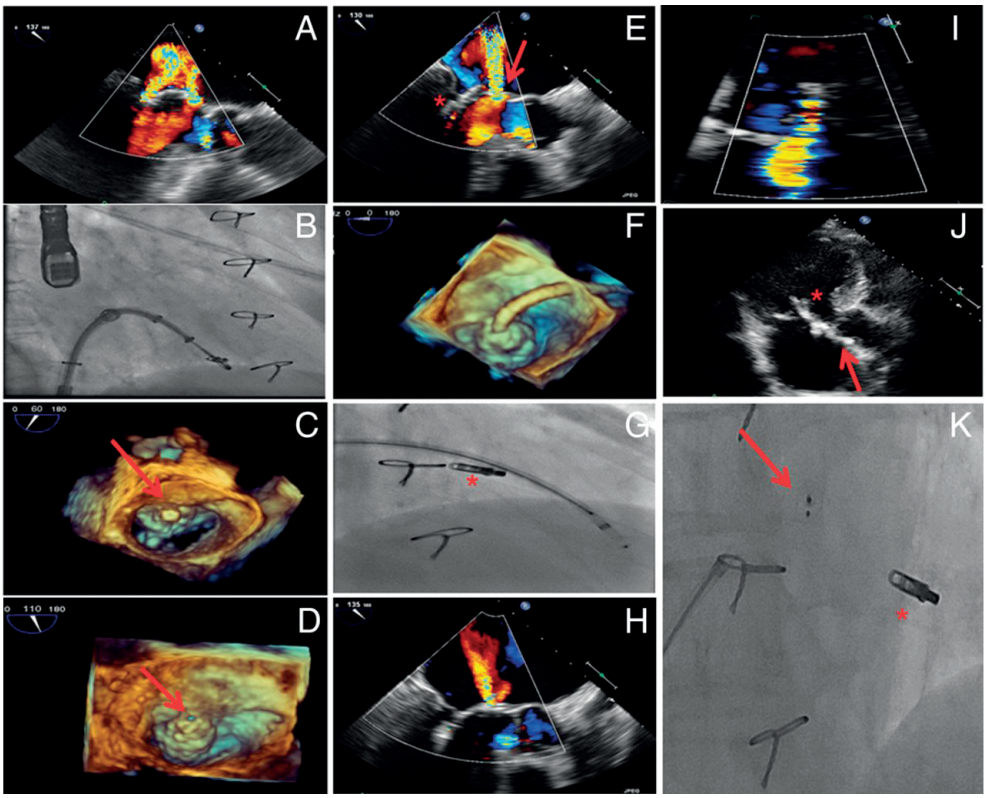
Completely percutaneous repair of a failing surgical mitral valve repair

Bergoli LC, Vriesendorp PA, Rodríguez-Olivares R,
Van Mieghem NM.

Eur Heart J. 2015 Feb 14;36(7):433

A 70-year-old female patient with hypertrophic cardiomyopathy was admitted 18 months after surgical septal myectomy, venous bypass of the left circumflex artery, and mitral valve repair using an autologous pericardial patch extension of the anterior mitral leaflet. Echocardiogram revealed severe mitral insufficiency with a central regurgitation based on malcoaptation of the mitral leaflets and an additional leak due to a perforation in the anterior leaflet patch (*Panel A*). The heart team agreed upon Mitraclip implantation and plug closure of the patch perforation.

Panel B demonstrates the mitraclip opening in the left ventricle before leaflet grasping. The mitral double orifice after Mitraclip implantation as seen by three-dimensional by transoesophageal echocardiography (TOE) is shown in *Panel C*. *Panels D* and *E* display the residual leak through the patch (red arrow) after mitraclip (arrowhead) implantation. The patch perforation is crossed by a 6-French multipurpose diagnostic catheter (*Panel F*—TOE, *Panel G* Fluoroscopy, note mitraclip (*) in situ). A 8 × 6 mm AMPLATZER™ Duct Occluder (St Jude Medical, St Paul, MN, USA) is deployed in the patch perforation with initially mild residual patch leakage (*Panel H*—TOE). Transthoracic echocardiography 4 days later confirms mild central mitral regurgitation with no residual patch leakage (*Panel I*). *Panel J* (TTE) and *K*(fluoroscopy) illustrate the mitraclip (*) and duct occluder within the patch (arrow) *in situ*.



Chapter 5

Combining myectomy and mitral leaflet extension in the treatment of a true obstructive cardiomyopathy patient

Vriesendorp PA, Vriesendorp MD, Schinkel AFL, De Jong PL, Michels M

submitted

ABSTRACT

Left ventricular outflow tract obstruction is an important pathophysiological component of hypertrophic cardiomyopathy, and can be treated with surgical septal myectomy, with or without papillary muscle repositioning and mitral valve repair. In this report we describe the treatment of a patient with severe LVOT obstruction and grade 3 mitral regurgitation, but without hypertrophy: a case of true obstructive cardiomyopathy. The procedure, myectomy combined with mitral leaflet extension, resolved the mitral regurgitation and no LVOT obstruction was present afterwards. This illustrates the value of mitral leaflet extension in selected patients, especially when there is only borderline hypertrophy.

REPORT

Obstruction of the left ventricular outflow tract (LVOT) is present in the majority of the patients with hypertrophic cardiomyopathy (HCM) and is a major determinant of outcome.1 The obstruction is caused by a combination of muscular hypertrophy of the ventricular septum, systolic anterior motion (SAM) of the anterior mitral valve leaflet (AMVL) and anomalous papillary muscle insertion. The first step in the treatment of LVOT obstruction is to alleviate symptoms by using β-receptor antagonists, verapamil or disopyramide. If this is not sufficient and patients remain in NYHA or CCS class III/IV, and have an LVOT gradient of >50 mmHg, patients are eligible for invasive therapy. This can be surgical septal myectomy or alcohol septal ablation. The 2011 ACCF/AHA guidelines 2 recommend transaortic septal myectomy as the most appropriate treatment for these patients. This procedure was developed by Morrow over 5 decades ago, and initially a 3-cm long resection was performed. Currently, a more extended myectomy is performed, with a resection of about 7 cm. In addition to the myectomy, papillary muscles can be repositioned and at the Thoraxcenter in patients with elongated AMVL, a mitral valve extension, made from autologous pericardial tissue, is performed.3 Long-term outcome after surgical myectomy are excellent and the procedure plays a central role in the treatment of obstructive HCM.However, in this report we describe the treatment of a patient with severe LVOT obstruction and grade 3 mitral regurgitation, but without hypertrophy: a case of true obstructive cardiomyopathy.

A 44-year old man was referred to our hospital with invalidating symptoms of dyspnea on exertion in NYHA class III. Family history was inconclusive. On clinical examination there was a systolic ejection murmur grade 3/6, which increased during Valsalva-maneuver. The electrocardiogram was slightly abnormal: a sinusbradycardia, with a normal QRS-complex, and a negative T-wave in aVF. Echocardiography revealed a normal systolic and diastolic function with a wall thickness of 9-10 mm, except a borderline hypertrophy of the basal ventricular septum (14 mm). However, there was a clear SAM of the AMVL with mitral-septal contact, and a grade III mitral regurgitation. The LVOT obstruction increased from 55mmHg at rest to 75 mmHg after Valsalva (FIGURE 1). The patient was already treated with metoprolol and verapamil by his referring cardiologist at maximal tolerable dosages, and was accepted for surgery. Cardiac surgery was performed with standard techniques of cardiopulmonary bypass with moderate hypothermia and myocardial preservation. After aortotomy, myectomy was attempted, but the septum was minimally resected, due to the lack of evident hypertrophy. Next, all abnormal papillary muscles were resected from the anterior wall, and a mitral leaflet extension, as described above, was performed. Postoperative results were assessed by transesophageal echocardiography and demonstrated a mild MR (grade I) and LVOT gradient of ±10 mmHg. The further recovery was uneventful, and the patient was discharged without any complications. The patient continued to visit the outpatient clinic, and in the following 7 years the patient remained asymptomatic. Latest

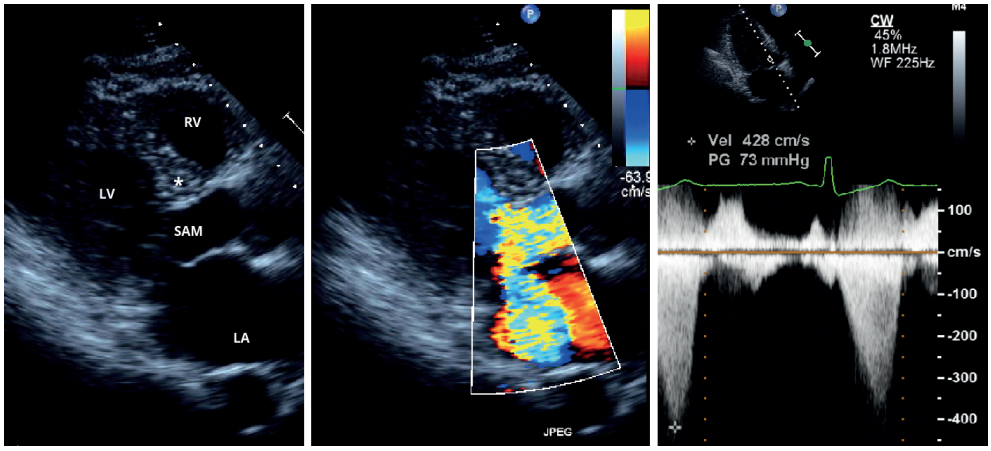


FIGURE 1 – Preoperative 2D and doppler echocardiography, demostrating a clear systolic anterior motion (SAM, left panel), severe mitral regurgitation (middle panel) and high left ventricular outflow tract obstruction (right panel). LA: left atrium; LV: left ventricle; RV: right ventricle.

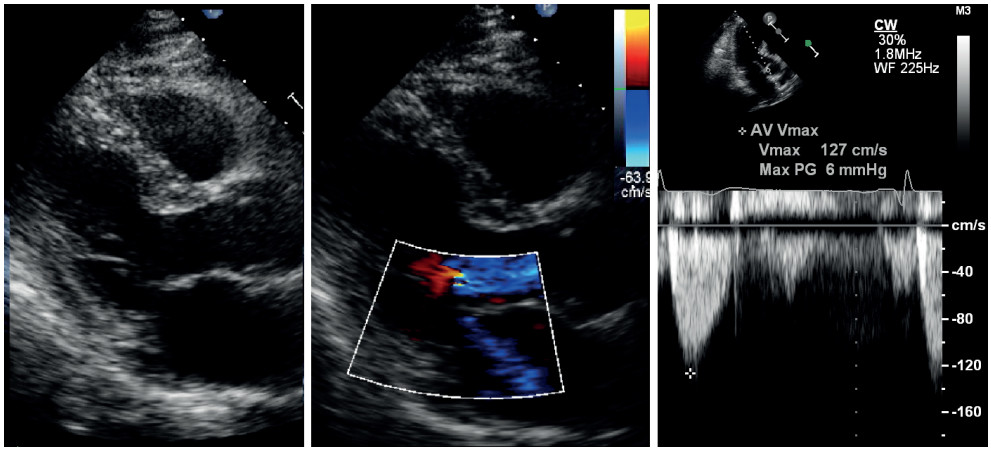


FIGURE 2 – Post-operative 2D and doppler echocardiography, in which no SAM or mitral regurgation is present. Left ventricular outflow tract gradient is not increased.

echocardiographic control showed no SAM and minimal MR. There was no LVOT obstruction (FIGURE 2).

DISCUSSION

This case of obstructive cardiomyopathy, with only borderline hypertrophy of the basal septal wall, illustrates the role of the mitral valve apparatus and abnormal papillary muscle anatomy in LVOT obstruction. And although LVOT obstruction without hypertrophy is not a com-

mon finding, even in the absence of muscular hypertrophy it can still cause invalidating and drug-refractory symptoms. This case also shows that an isolated myectomy, or alcohol septal ablation, would not have been sufficient to relieve symptoms in this patient. The additional advantages of myectomy combined with mitral leaflet extension (MLE) are gained by the insertion of the pericardial patch on the central part of the AMVL. This stiffens the lax leaflet and thus prevents SAM, also the greater leaflet area reduces the mitral regurgitation.3

There is a certain controversy around this procedure. Other groups, for example the Mayo Clinic series, have excellent results without touching the mitral valve, and advocate that if the myectomy is sufficiently extended, there will be no remaining LVOT obstruction.4 But in patients with not a very thick septum, such as the patient in this case, there might not be enough muscle to remove. At our center there is ± 20 years of experience with myectomy combined with MLE, and long-term outcome is comparable to the non-obstructive HCM population.5 On the other hand, myectomy combined with MLE should not be performed in all obstructive HCM patients. If there is limited (or no) hypertrophy, and the presence of enlarged mitral leaflets, MLE can be a safe and valuable addition to treat the LVOT obstruction.

In conclusion, myectomy combined with mitral leaflet extension, resolved the mitral regurgitation, and no LVOT obstruction was present afterwards. This illustrates the value of mitral leaflet extension in selected patients, especially when there is only borderline hypertrophy.

REFERENCES

1. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348:295-303.
2. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761-2796.
3. van der Lee C, Kofflard MJ, van Herwerden LA, Vletter WB and ten Cate FJ. Sustained improvement after combined anterior mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy. Circulation. 2003;108:2088-2092.
4. Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46:470-476.
5. Vriesendorp PA, Schinkel AF, Soliman OI, et al. Long-term benefit of myectomy and anterior mitral leaflet extension in obstructive hypertrophic cardiomyopathy. Am J Cardiol. 2015;115:670-675.

Chapter 6

Effect of alcohol dosage on long-term outcomes after alcohol septal ablation in patients with hypertrophic cardiomyopathy

Liebregts M, Vriesendorp PA, Steggerda RC, Schinkel AFL,
Balt JC, Ten Cate FJ, Michels M, Ten Berg JM

Catheter Cardiovasc Interv. 2016 Mar 4. [Epub ahead of print]

ABSTRACT

Objectives

The aim of this study is to assess the long-term effects of alcohol dosage in alcohol septal ablation (ASA) on mortality and adverse arrhythmic events (AAE).

Background

ASA can be performed to reduce left ventricular outflow tract (LVOT) obstruction in patients with hypertrophic cardiomyopathy (HCM). However, the effect of alcohol dosage on long-term outcomes is unknown.

Methods

This retrospective cohort study includes 296 HCM patients (age 60 ± 22 years, 58% male) who underwent ASA because of symptomatic LVOT obstruction. 29 patients (9.8%) were excluded because the alcohol dosage could not be retrieved. Primary endpoints were all-cause mortality and AAE.

Results

During 6.3 ± 3.7 years of follow-up all-cause mortality and AAE rates were similar in patients who received ≤2.0 mL (n= 142) and >2.0 mL (n= 121) alcohol during ASA. Age was the only independent predictor of mortality (HR 1.1 95% CI 1.0-1.1, p< 0.001). Predictors of AAE were maximum CK-MB >240 U/L (HR 3.3 95% CI 1.5-7.2, p= 0.003), and sudden cardiac death survivor (HR 5.9 95% CI 1.7-20.3, p= 0.004). There was a mild to moderate correlation between CK-MB levels and amount of alcohol (Spearman's ρ 0.39, p< 0.001), cross-sectional area of the target septal branch ostium/ostia (Spearman's ρ 0.19, p= 0.003), and maximum ventricular wall thickness (Spearman's ρ 0.17, p= 0.006).

Conclusions:

Alcohol dosage appears not to have a long-term effect on mortality and AAE. A larger infarct size created by ASA increases the risk of AAE, and extended monitoring of these patients is advised.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is an inheritable myocardial disease present in one in 500 of the general population (1). HCM is characterized by left ventricular hypertrophy and is often associated with (provocable) left ventricular outflow tract (LVOT) obstruction (2). Symptoms such as dyspnea (on exertion), syncope and angina due to LVOT obstruction can be alleviated by the use of β-receptor antagonists, verapamil or disopyramide. If patients remain severely symptomatic despite optimal medical therapy, septal reduction therapy should be considered, either by surgical myectomy or alcohol septal ablation (ASA) (3-6). ASA was introduced as a percutaneous alternative to surgical myectomy, and has shown to be effective in reducing LVOT obstruction and associated symptoms (7-9). In the 20 years since its introduction, ASA has become a valuable alternative in the management of HCM patients, and important developments (e.g. the use of intramyocardial ultrasound contrast agents) have improved the safety and efficacy of the technique (8-10). Concerns about ASA remain however, especially regarding the possible arrhythmogenic effect of the ablation scar in patients already at an increased risk of life-threatening arrhythmias (11). The effect of the dosage of intracoronary alcohol in this context remains controversial, and long-term results are scarce (12-15). The aim of this study is to evaluate the long-term effects of alcohol dosage in ASA on mortality and adverse arrhythmic events (AAE).

MATERIALS AND METHODS

Study design and patient population

A two-center, observational cohort design was used. The study population consisted of 296 consecutive HCM patients who underwent ASA in the St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands (n = 209), and the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands (n = 87). All patients met the criteria for invasive treatment: (i) ventricular septal thickness ≥ 15 mm, (ii) (provocable) LVOT gradient ≥ 50 mmHg, and (iii) persistent New York Heart Association (NYHA) class III/IV dyspnea or Canadian Cardiovascular Society class III/IV angina despite optimal medical therapy (3-5). The choice of ASA instead of surgical myectomy was based on patient profile (age, comorbidities, etc.) and patient preference. Patients were divided in 2 groups, based on the amount of alcohol received: a high dose group (> 2.0 mL) and a low dose group (≤ 2.0 mL). A 2.0 mL cut-off was chosen because this was the median amount of intracoronary alcohol used in the entire cohort (range 0.75-8 mL), and because this was in line with previous studies (12-13). Patients where the alcohol dosage could not be retrieved were excluded. The study conforms to the principles of the Helsinki Declaration. All patients gave informed consent prior to the procedure, and local institutional review board approval was obtained.

The procedure

ASA was performed as described previously (16-17). After placement of a temporary right ventricular pacing lead, a double lumen pigtail catheter was advanced in the left ventricle allowing for simultaneous pressure recordings in the left ventricle and ascending aorta. Coronary angiography was then performed and after visual assessment of the septal perforator branches of the left anterior descending artery the first or second septal perforator was wired with a 0.014" coronary guidewire introduced into an over-the-wire (OTW) balloon. After removal of the coronary guidewire, 2 mL of echo contrast agent (Sonovue, Bracco Diagnostics, Milan, Italy) was selectively injected into the septal perforator through the inner lumen of the OTW balloon to allow for echocardiographic identification of the basal left ventricular septum as appropriate anatomical target. If the area of perfusion on the septum was not the area of contact by systolic anterior motion of the anterior leaflet of the mitral valve, another septal perforator was cannulated. Subsequent dosages of 0.5 mL of absolute alcohol were injected slowly over 1-15 minutes in the septal perforator under continuous echocardiographic guidance, after which the balloon remained in place for 10 more minutes. After the balloon was deflated, gradient reduction was assessed, and coronary angiography was repeated to confirm the occlusion of the septal branch and patency of the left anterior descending coronary artery. If significant LVOT gradient would remain afterwards, additional septal perforators could be treated. The temporary pacemaker lead was kept in place for at least 24 hours. All patients were monitored for at least 24 hours at the intensive coronary care unit afterwards.

Follow-up and endpoints

Follow-up started at the time of ASA, and the first procedures were performed in 1999. Baseline patient characteristics of interest included age, sex, NYHA class, maximum left ventricular wall thickness (LVWT), maximum (provocable) LVOT gradient, left ventricular ejection fraction, atrial fibrillation, coronary artery disease, medication used, conventional risk factors for sudden cardiac death (SCD) (3-5), amount of intracoronary alcohol used during the procedure and the cross-sectional area of the ostium/ostia of the target septal perforator(s).

The primary endpoints were all-cause mortality and AAE during long-term follow-up. AAE consisted of SCD, resuscitated cardiac arrests due to ventricular fibrillation

(VF) or tachycardia, and appropriate implantable cardioverter-defibrillator (ICD) firing. Secondary endpoints were periprocedural (< 30 days) mortality and AAE, LVOT gradient reduction, maximum CK-MB, temporary atrioventricular (AV) block, permanent pacemaker implantation, re-intervention (ASA or myectomy) and HCM-related death (death due to heart failure, stroke or SCD).

Mortality and adverse events were retrieved from hospital patient records at the center where follow-up occurred, from civil service population registers, and from information provided by patients themselves and/or their general practitioners. All ICD shocks were evalu-

ated by an experienced electrophysiologist, unaware and independent of the study purpose and endpoints. If no events occurred during follow-up, the administrative censoring date was set at November 1st, 2012.

Statistical Analysis

SPSS version 20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for all statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median ± interquartile range. To compare continuous variables Student t test or Mann-Whitney U-test were used, and to compare categorical variables the $\chi 2$-test was used. To identify clinical predictors of all-cause mortality and AAE univariable and multivariable Cox regression analysis was used. Variables were selected for multivariable analysis if the univariable p-value was < 0.10 and were expressed as hazard ratio (HR) with 95% confidence interval. The final number of variables was restricted according to the number of endpoint events to avoid overfitting the multivariable model. For correlation analysis, spearman's ρ was calculated in case of a non-linear relationship between the variables, or if the variables were non-normally distributed. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

In the cohort of 296 patients, 29 (9.8%) were excluded because no alcohol dosage could be retrieved. Of these 29 patients (age 60 ± 22, 44% male), 1 experienced periprocedural VF and 3 patients died (none in the first 30 days). The cause of death was SCD in 1 patient, and non-cardiac in the others.

The baseline characteristics of the remaining 267 patients (age 61 ± 14, 58% male) are found in TABLE 1. Patients in the low dose group (n = 143) were older (63 ± 24 years) than those from the high dose group (n = 124, age 58 ± 22 years, p = 0.005). Conversely, fewer patients from the low dose group were in NYHA class III/IV (76% vs. 85%, p = 0.05) or had systolic dysfunction on echocardiography (2% vs. 9%, p = 0.03).

Procedural outcomes

Over time a reduction of the mean amount of alcohol used for ASA was seen (FIGURE 1, p < 0.001). This was irrespective of the pre- and post-procedural LVOT gradient (FIGURE 2). The infarct size after a high amount of alcohol was greater than after a low dose (maximum CK-MB levels 213 ± 137 U/L vs. 152 ± 91 U/L, p < 0.001), which resulted in a slightly greater reduction in LVOT gradient (95% vs. 86%, p < 0.001). The NYHA class post-procedure was

TABLE 1 – Baseline characteristics of 267 alcohol septal ablation patients.

	n =	**Low alcohol group (≤ 2.0 mL)**	**High alcohol group (> 2.0 mL)**	
		143	*124*	*P*
Age, median ± IQR, years		63 ± 24	58 ± 22	**0.005**
Female		63 (44)	50 (40)	0.5
NYHA III/IV		108 (76)	105 (85)	**0.05**
Maximum LVWT, median ± IQR, mm		20 ± 5	20 ± 6	0.1
LVOT gradient, median ± IQR, mmHg		90 ± 86	100 ± 42	0.8
Systolic dysfunction (EF < 50%)		3 (2)	11 (9)	**0.03**
Coronary artery disease		34 (24)	23 (19)	0.3
Atrial fibrillation		37 (26)	24 (19)	0.2
Medication				
β-receptor antagonist		92 (64)	87 (70)	0.3
Calcium-channel blocker		54 (38)	41 (33)	0.4
Risk factors				
Sudden cardiac death survivor		4 (3)	3 (2)	1.0
≥ 2 conventional risk factors for SCD		13 (9)	14 (11)	0.4
Procedure				
Volume of alcohol injected, median ± IQR, mL		2 ± 0	3 ± 1.5	**< 0.001**
Mean volume of alcohol injected, mL		1,8	3,7	
Ostium area, median ± IQR, mm^2		1.8 ± 1.4	2.3 ± 1.4	**< 0.001**

Data represented as n (percentage) unless stated otherwise. EF: ejection fraction, IQR: interquartile range, LVOT: left ventricular outflow tract, LVWT: left ventricular wall thickness, NYHA: New York Heart Association, SCD: sudden cardiac death.

similar in both groups though (p = 0.08), and more re-intervention (ASA or myectomy) was necessary in patients who received a high dose compared with the low dose group (15% vs. 6%, p = 0.01) (TABLE 2). The maximum CK-MB level was correlated with amount of alcohol (Spearman's ρ 0.39, p < 0.001), cross-sectional area of the target septal branch ostium (Spearman's ρ 0.19, p = 0.003), and maximum LVWT (Spearman's ρ 0.17, p = 0.006). Amount of alcohol and maximum LVWT were not associated (Spearman's ρ 0.09, p = 0.15).

Temporary periprocedural AV block was present in 78 patients (29%). This resulted in permanent pacemaker implantation in 14 patients (10%) of the low dose group and 9 patients (7%) of the high dose group (p = 0.5). Within the first 30 days of follow-up 4 patients died, of

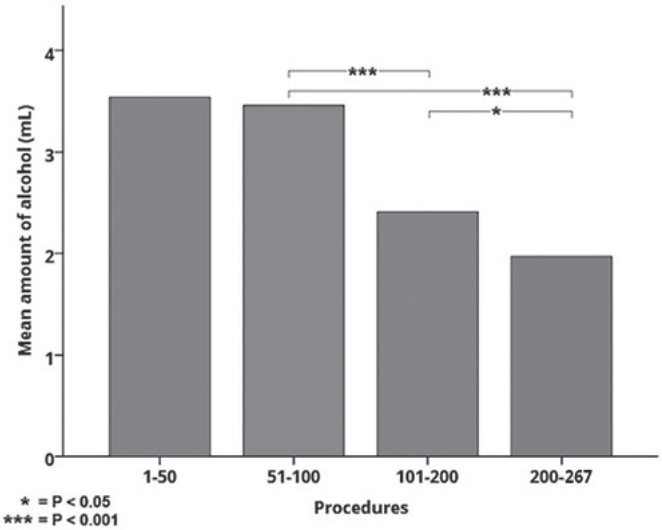


FIGURE 1 – The learning-curve effect. Showing systematic reduction of the mean amount of alcohol injected during the procedure over time.

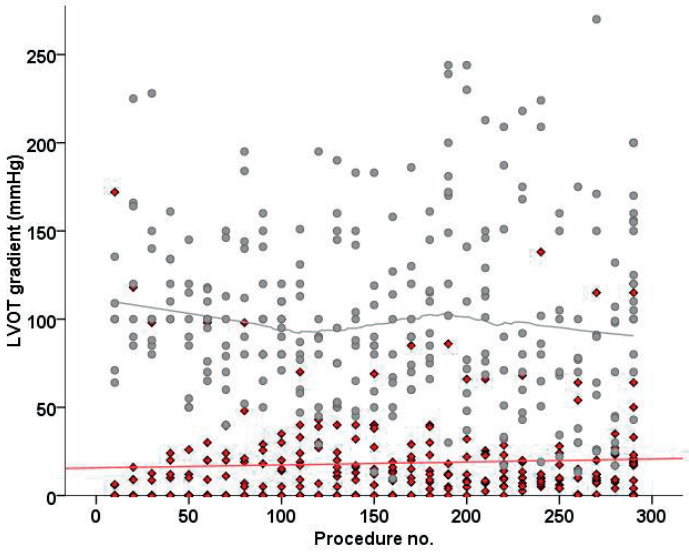


FIGURE 2 – LVOT gradient reduction. Pre-procedure LVOT gradient (grey circles) and post-procedure LVOT gradient (red squares) over time.

which 3 received a high amount of alcohol (p = 0.3). The causes of death were peri-procedural VF in 2 patients, tamponade one day post-procedure in 1 patient, and ventricular tachycardia with deterioration to VF two days post-procedure in 1 patient. AAE occurred in 10 patients, of which 6 received a high amount of alcohol (p = 0.3) (TABLE 3). Besides the above, these comprised of peri-procedural VF with successful defibrillation in 3 patients, and VF dur-

TABLE 2 – Long-term outcomes after alcohol septal ablation in 263 patients.

	Low alcohol group (≤ 2.0 mL)	High alcohol group (> 2.0 mL)	
n =	*142*	*121*	*P*
Years of follow-up, median ± IQR	4.9 ± 6.1	7.6 ± 4.1	**< 0.001**
Residual LVOT gradient > 3 months post-procedure, median ± IQR, mmHg	11 ± 18	6 ± 20	**< 0.001**
Reduction in LVOT gradient > 3 months post-procedure, median ± IQR, %	86 ± 25	95 ± 21	**< 0.001**
NYHA class III/IV > 3 months post-procedure	8 (6)	15 (12)	0.08
Redo septal reduction therapy	8 (6)	18 (15)	**0.01**
Mortality			
Total mortality	17 (12)	21 (17)	0.2
HCM-related death	5 (4)	8 (7)	0.2
Non-cardiac	11 (8)	11 (9)	0.7
Unknown	1 (1)	2 (2)	0.5
5-year survival, %	94	91	0.5
10-year survival, %	89	85	0.8
Adverse arrhythmic events (> 30 days post-procedure)			
Total adverse events	7 (5)	9 (7)	0.4
Sudden cardiac death	2 (1)	3 (2)	0.5
Resuscitated cardiac arrest	2 (1)	1 (1)	1.0
Appropriate ICD shocks	2 (1)	4 (3)	1.0
Annual events, %/year	0.91	0.99	0.4

Data are represented as n (percentage), unless stated otherwise. HCM: hypertrophic cardiomyopathy, ICD: internal cardioverter defibrillator, IQR: interquartile range, LVOT: left ventricular outflow tract, NYHA: New York Heart Association.

ing the first week post-procedure with successful resuscitation in 4 patients. The latter all received an ICD for secondary prevention.

Long-term outcomes

Of the 267 patients, follow-up was completed in 263 patients (99%) with a median follow-up duration of 6.3 ± 3.7 years. The 4 patients lost to follow-up had moved abroad and could not be reached. During follow-up there was a total of 38 deaths in the entire cohort (TABLE 2): 13 (34%) were HCM-related, 22 (58%) patients died of certified non-cardiac causes, and no cause of death could be identified in 3 (8%). Kaplan-Meier estimates of survival are shown in

TABLE 3 – Periprocedural (< 30 days) outcomes after alcohol septal ablation in 267 patients.

	n =	**Low alcohol group (≤ 2.0 mL)**	**High alcohol group (> 2.0 mL)**	
		143	*124*	*P*
Maximal CK-MB levels, median ± IQR, U/L		152 ± 91	213 ± 137	**< 0.001**
Atrioventricular block		46 (32)	32 (26)	0.2
Pacemaker implantation		14 (10)	9 (7)	0.5
Periprocedural mortality				
Total mortality		1 (1)	3 (2)	0.3
Sudden cardiac death		1 (1)	2 (2)	0.5
Cardiac tamponade		-	1 (1)	-
Periprocedural adverse arrhythmic events				
Total adverse events		4 (3)	6 (5)	0.3
Sudden cardiac death		1 (1)	2 (2)	0.5
Sustained ventricular tachycardia		2 (1)	-	-
Resuscitated cardiac arrest		1 (1)	4 (3)	0.2

Data are represented as n (percentage) unless stated otherwise. IQR: interquartile range.

FIGURE 3. All-cause mortality was similar in patients who received ≤ 2.0 mL and patients who received > 2.0 mL intracoronary alcohol during ASA (p = 0.2). The same applied for HCM-related mortality (p = 0.2). The 5- and 10-year survival for patients receiving a low amount of alcohol was 94% and 89%, respectively. Which was similar to the 91% and 85% for patients receiving a high amount of alcohol (p = 0.5 and p = 0.8, respectively). The only independent predictor of all-cause mortality was age (HR 1.1 95% CI 1.0-1.1, p < 0.001). A persisting high post-procedural LVOT gradient (≥ 50 mmHg) showed a trend towards increased mortality (p = 0.06) (TABLE 4).

AAE during long-term follow-up were also similar in the two groups: 7 events (5%) occurred in the low dose group and 9 events (7%) in the high dose group (p = 0.4). This translates in an annual event rate of 0.91% after ASA with < 2.0 mL alcohol and 0.99% after ASA with > 2.0 mL alcohol. Five patients died of SCD, 3 patients were resuscitated from cardiac arrest, and 6 patients received an appropriate ICD shock (TABLE 2). Multivariable analysis identified the following independent predictors of AAE: maximum CK-MB > 240 U/L (HR 3.3 95% CI 1.5-7.2, p = 0.003), and SCD survivor (HR 5.9 95% CI 1.7-20.3, p = 0.004) (TABLE 4).

TABLE 4 – Predictors of all-cause mortality and adverse arrhythmic events - Analysis of clinical variables associated with all-cause mortality and adverse arrhythmic events in 263 patients after ASA.

	Univariable			Multivariable		
	HR	**CI 95%**	**P**	**HR**	**CI 95%**	**P**
Mortality (n = 38)						
Age	1.06	1.03-1.09	**< 0.001**	1.07	1.04-1.10	**< 0.001**
Female	2.2	1.12-4.13	**0.02**	1.2	0.56-2.64	0.6
High dose alcohol (> 2.0 mL)	1.0	0.53-1.93	1.0			
Post-procedure NYHA III/IV	1.7	0.64-4.38	0.3			
Post-procedure LVOT gradient > 50 mmHg	2.8	1.09-7.35	**0.03**	2.6	0.97-6.78	0.06
Coronary artery disease	2.2	1.15-4.30	**0.02**	1.6	0.78-3.30	0.2
Adverse arrhythmic events (n = 26)						
Age	0.99	0.97-1.02	0.6			
Female	0.8	0.40-1.93	0.7			
High alcohol dose (> 2.0 mL)	1.3	0.63-2.99	0.4			
CK-MB > 240 U/L	4.5	2.02-10.1	**< 0.001**	3.3	1.51-7.16	**0.003**
Ostium area > 2 mm^2	1.9	0.90-4.10	0.09	1.7	0.77-3.79	0.2
Atrial fibrillation	1.2	0.51-2.90	0.7			
Coronary artery disease	0.8	0.33-2.35	0.8			
Sudden cardiac death survivor	6.8	2.02-22.9	**0.002**	5.9	1.74-20.3	**0.004**
≥ 2 conventional risk factors for SCD	3.8	1.66-8.83	**0.002**	2.2	0.66-7.05	0.2

Backwards multivariable Cox regression analysis was used. CI: confidence interval, HR: hazards ratio, LVOT: left ventricular outflow tract, NYHA: New York Heart Association, SCD: sudden cardiac death.

DISCUSSION

The most important finding of this study was that long-term mortality and AAE rates after ASA were not increased if a higher dose of alcohol was used. Also, periprocedural AAE and mortality, AV-blocks and pacemaker implantations were similar in both high dose alcohol and low dose alcohol groups.

ASA and alcohol dosage

ASA was introduced in 1995 as an alternative to surgical myectomy (7). Initially, relatively high doses of alcohol were used (3-6 mL). Over time clinical experience combined with better strategies to identify the target septal branches (e.g. the use of intramyocardial ultrasound

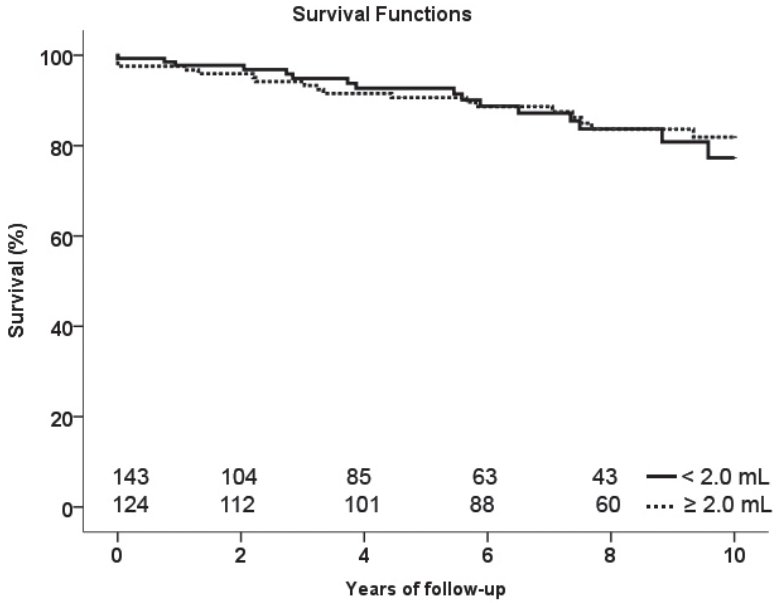


FIGURE 3 – Survival after Alcohol septal ablation. Kaplan Meier graphs showing 10-year survival in 263 patients after alcohol septal ablation.

contrast agents) led to the use of lower doses of alcohol during ASA (8-10). The subsequent "learning curve" of the centers participating in this study is shown in FIGURE 1.

The first study to investigate the correlation between amount of intracoronary alcohol and outcome of ASA was conducted by Kuhn et al (12). This retrospective study comprises two series: 329 patients treated in a dose finding strategy with decreasing amounts of alcohol until 2001, and 315 patients of the "low alcohol dose era" treated until 2005. Patients treated with high amounts of alcohol (> 2.0 mL) had a higher mortality rate than those treated with less alcohol. The mean follow-up of this cohort was no more than 2.1 years though. Also, the patients treated with a high dose of alcohol were by definition the first patients to undergo ASA at this center.

Veselka et al (13) conducted a prospective study with 76 patients who were randomized into two equal groups, and subsequently treated with ≤ 2.0 mL and > 2.0 mL intracoronary alcohol. They found no differences in post-procedural complications between both groups and after a median follow up of 7 years all-cause mortality was equal. Though these findings are in line with this study, the small size of the study doesn't allow for a reliable survival analysis and the study may not be powered enough to detect this difference.

In the study by ten Cate et al (11), which included a subset of the patients included in this study, ASA was associated with an increased risk for SCD. The study was criticized for the use of high amounts of alcohol (3.5 ± 1.5 mL) in its ASA patients. In their analysis no effect

of alcohol dosage on their primary endpoint (composite of cardiac death and aborted SCD including appropriate ICD firing) was observed however.

ASA and infarct size

We found that higher CK-MB levels after ASA predicted AAE during follow-up. Although no direct effect of alcohol dosage on AAE was observed, a higher amount of intracoronary alcohol was associated with higher CK-MB levels. This is in line with previous studies (18-20). In addition to amount of alcohol, caliber of the target septal perforator(s) and LVWT also showed a positive correlation with CK-MB levels. The infarct size and concomitant risk of AAE may therefore be the resultant of a combination of these variables. Since the separate correlations are mild to moderate at best however, the infarct size for an individual patient can still be hard to predict. On the contrary, finding high CK-MB levels post-procedure could warrant extended monitoring or preventive ICD implantation, especially in the presence of other risk factors for SCD.

A low dose of intracoronary alcohol in ASA can be as effective as a high dose. Veselka et al (14) showed that the use of a very low dose of alcohol (mean 1.0 ± 0.1 mL) is as effective in reducing the LVOT gradient as using a mean dose of 2.5 ± 0.8 mL. Boekstegers et al (15) came to the same conclusion after treating 50 patients with a mean amount of 1.9 ± 0.7 mL intracoronary alcohol. These findings are in line with our study. Despite a slightly lower gradient at follow-up in the high dose group, this did not lead to a difference in NYHA class at follow-up, nor to a lower rate of re-do procedures. In fact, re-interventions were even more common in the high dose group compared with the low dose group (15% vs. 6%). Furthermore, we found no association between amount of alcohol and LVWT. In other words, thicker intraventricular septa did not per definition require more intracoronary alcohol. Consequently, the fact that more alcohol leads to higher CK-MB levels may indicate that a high amount of alcohol leads to infarction of unnecessary septal tissue.

This circumstantial evidence suggests that the smallest effective infarct size should be pursued. This may be achieved by using a low dose of alcohol, more distally in the target septal perforator(s).

Study limitations

This study has several limitations. Data collection was limited to variables that were routinely collected. The study was performed in 2 referral centers for the care of HCM, and selection and referral bias can be present. It was not possible to correct for individual or local alterations of percutaneous technique. However, all procedures were performed by experienced interventional cardiologists, plus this implies that our findings are more generalizable than those of single-center investigations. Furthermore, like in the study by Kuhn et al (12) most of the patients treated with a high dose of alcohol underwent ASA in the early days of our experience (FIGURE 1). The cause of death could not be determined in 3 of the 38 deaths (8%)

that occurred. In addition there was a large group (10%) in which no dose of alcohol could be retrieved, however events in this group were low (1 case of SCD). Finally, the cut-off value of 2.0 mL of alcohol was arbitrarily chosen because this was the median alcohol dose in this ASA cohort and previous studies have used this cutoff value, facilitating comparison to these studies. Choosing a cut-off value of 3.0 mL however, didn't result in a significant difference in long-term mortality and AAE either.

CONCLUSION

Alcohol dosage appears not to have a long-term effect on mortality and AAE. A larger infarct size created by ASA increases the risk of AAE, and extended monitoring of these patients is advised.

REFERENCES

1. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CARDIA study. Coronary artery risk development in (young) adults. Circulation 1995;92:785-789.
2. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-2239.
3. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH 3rd, Spirito P, Ten Cate FJ, Wigle ED; Task Force on Clinical Expert Consensus Documents. American College of Cardiology; Committee for Practice Guidelines. European Society of Cardiology. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687-1713.
4. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-2796.
5. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European society of cardiology (ESC). Eur Heart J 2014;35:2733-2779.
6. ten Berg JM, Steggerda RC, Siebelink HM. Myocardial disease: the patient with hypertrophic cardiomyopathy. Heart 2010;96:1764-1772.
7. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211-214.
8. Fifer MA, Sigwart U. Controversies in cardiovascular medicine. Hypertrophic obstructive cardiomyopathy: alcohol septal ablation. Eur Heart J 2011;32:1059-1064.
9. Rigopoulos AG, Seggewiss H. A decade of percutaneous septal ablation in hypertrophic cardiomyopathy. Circ J 2011;75:28-37.
10. Faber L, Seggewiss H, Welge D, Fassbender D, Schmidt HK, Gleichmann U, Horstkotte D. Echo-guided percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy: 7 years of experience. Eur J Echocardiogr 2004;5:347-355.
11. ten Cate FJ, Soliman OI, Michels M, Theuns DA, de Jong PL, Geleijnse ML, Serruys PW. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail 2010;3:362-369.
12. Kuhn H, Lawrenz T, Lieder F, Leuner C, Strunk-Mueller C, Obergassel L, Bartelsmeier M, Stellbrink C. Survival after transcoronary ablation of septal hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. Clin Res Cardiol 2008;97:234-243.
13. Veselka J, Tomašov P, Zemánek D. Long-term effects of varying alcohol dosing in percutaneous septal ablation for obstructive hypertrophic cardiomyopathy: a randomized study with a follow up to 11 years. Can J of Cardiol 2011;27:763-767.

14. Veselka J, Zemánek D, Tomasov P, Duchonová R, Linhartová K. Alcohol septal ablation for obstructive hypertrophic cardiomyopathy: ultra-low dose of alcohol (1 ml) is still effective. Heart vessels 2009;24:27-31.
15. Boekstegers P, Steinbigler P, Molnar A, Schwaiblmair M, Becker A, Knez A, Haberl R, Steinbeck G. Pressure guided nonsurgical myocardial reduction induced by small septal infarctions in hypertrophic cardiomyopathy. J Am Coll Cardiol 2001;38:846-853.
16. van der Lee C, ten Cate FJ, Geleijnse ML, Kofflard MJ, Pedone C, van Herwerden LA, Biagini E, Vletter WB, Serruys PW. Percutaneous versus surgical treatment for patients with hypertrophic obstructive cardiomyopathy and enlarged anterior mitral valve leaflets. Circulation 2005;112:482-488.
17. van der Lee C, Scholzel B, ten Berg JM, Geleijnse ML, Idzerda HH, van Domburg RT, Vletter WB, Serruys PW, ten Cate FJ. Usefulness of clinical, echocardiographic, and procedural characteristics to predict outcome after percutaneous transluminal septal myocardial ablation. Am J Cardiol 2008;101:1315-1320.
18. Li ZQ, Cheng TO, Liu L, Jin YZ, Zhang M, Guan RM, Yuan L, Hu J, Zhang WW. Experimental study of relationship between intracoronary alcohol injection and the size of the resultant myocardial infarction. Int J Cardiol 2003;91:93-96.
19. van Dockum WG, ten Cate FJ, ten Berg JM, Beek AM, Twisk JW, Vos J, Hofman MB, Visser CA, van Rossum AC. Myocardial infarction after percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: evaluation by contrast-enhanced magnetic resonance imaging. J Am Coll Cardiol 2004;43:27-34.
20. Veselka J, Procházková S, Duchonová R, Bolomová-Homolová I, Pálenícková J, Tesar D, Cervinka P, Honek T. Alcohol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy: Lower Alcohol Dose Reduces Size of Infarction and Has Comparable Hemodynamic and Clinical Outcome. Catheter Cardiovasc Interv 2004;63:231-235.

Chapter 7

Long-term outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy in the young and the elderly

Liebregts M, Steggerda RC, Vriesendorp PA , Van Velzen HG, Schinkel AFL, Willems R, Van Cleemput J, Van den Berg MP, Michels M, Ten Berg JM

JACC Cardiovasc Interv. 2016 Mar 14;9(5):463-9

ABSTRACT

Objectives

The aim of this study is to compare outcomes of alcohol septal ablation (ASA) in young and elderly patients with obstructive hypertrophic cardiomyopathy (HCM).

Background:

The ACCF/AHA guidelines reserve ASA for elderly patients and patients with serious comorbidities. Information on long-term age-specific outcomes after ASA is scarce.

Methods:

This cohort study included 217 HCM patients (54±12 years) who underwent ASA because of symptomatic left ventricular outflow tract (LVOT) obstruction. Patients were divided in a young (≤55 years) and elderly (>55 years) group, and matched by age in a 1:1 fashion to non-obstructive HCM patients.

Results:

Atrioventricular block following ASA was more common in elderly patients (43% vs. 21%, P=0.001), resulting in pacemaker implantation in 13% and 5%, respectively (P=0.06). Residual LVOT-gradient, post-procedural NYHA class, and necessity for additional septal reduction therapy was comparable between age groups. During a follow-up of 7.6 ± 4.6 years, 54 patients died. Five- and 10-year survival following ASA was 95% and 90% in patients ≤55 years, and 93% and 82% in patients >55 years, comparable to their control groups. The annual adverse arrhythmic event (AAE) rate following ASA was 0.7%/year in young patients, and 1.4%/year in elderly patients, comparable to their control groups.

Conclusion:

ASA is similarly effective for reduction of symptoms in young and elderly patients, however younger patients have a lower risk of procedure-related atrioventricular conduction disturbances. The long-term mortality rate and risk of AAE following ASA are low, both in young and elderly patients, and comparable to age-matched non-obstructive HCM patients.

INTRODUCTION

If patients with obstructive hypertrophic cardiomyopathy (HCM) remain severely symptomatic despite optimal medical therapy, septal reduction therapy should be considered. This can be done, either by surgical myectomy or alcohol septal ablation (ASA).(1,2) ASA was introduced as a percutaneous alternative to surgical myectomy, and has shown to be effective in reducing left ventricular outflow tract (LVOT) obstruction and associated symptoms in the 20 years since.(3-5) Concerns about ASA remain however, especially about the possible arrhythmogenic effect of the ablation scar in patients already at an increased risk of life-threatening arrhythmias.(6) The American College of Cardiology Foundation/American Heart Association guidelines on HCM state that ASA should be reserved for elderly patients and patients with serious comorbidities.(1)

Little is known about the differences in outcome of the procedure between young and elderly patients. The aim of this study is to compare complication rates, symptom relief and long-term outcomes of ASA in young and elderly patients.

METHODS

Study design and patient population

A multicenter observational cohort design was used. The study population consisted of 217 consecutive HCM patients who underwent ASA in the St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands (n = 147), or the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands (n = 70). All patients met the criteria for invasive treatment: (i) ventricular septal thickness ≥15 mm, (ii) (provocable) LVOT gradient ≥50 mmHg, and (iii) persistent New York Heart Association (NYHA) class III/IV dyspnea or Canadian Cardiovascular Society class III/IV angina despite optimal medical therapy.(1,2) The choice of ASA instead of surgical myectomy was based on patient profile (age, comorbidities, etc.) and patient preference. ASA was performed as described previously.(7,8)

All patients gave informed consent prior to the procedure. Local institutional review board approval was obtained. Patients were divided in a ≤ 55 years group and a group >55 years of age. A 55-year cut-off was chosen because this was the median age of the study population (range 18-80 years). For the long-term outcomes two control groups were selected from a cohort of 349 non-obstructive HCM patients, also used as control group in a previous analysis.(9) These patients, from the St. Antonius Hospital Nieuwegein, Erasmus Medical Center Rotterdam, and University Hospital Leuven (Belgium), all had a LVOT gradient of <30 mmHg after provocation. They were matched by age in a 1:1 fashion to patients who underwent ASA.

Follow-up and endpoints

Follow-up started at the time of ASA or, for the non-obstructive patients, at first outpatient clinic contact after January 1st, 1990. At baseline all patients were evaluated for the following characteristics: age, sex, NYHA class, maximum left ventricular wall thickness (LVWT), maximum (provocable) LVOT gradient, left ventricular function, coronary artery disease, atrial fibrillation, and conventional risk factors for sudden cardiac death (SCD).(1)

The primary endpoints of this study were all-cause mortality and adverse arrhythmic events (AAE) during long-term follow-up (i.e., after 30-days post-procedure). AAE consisted of: SCD, resuscitated cardiac arrests due to ventricular fibrillation or tachycardia, and appropriate implantable cardioverter-defibrillator (ICD) shock. Secondary endpoints were HCM-related death (death due to heart failure, stroke or SCD), peri-procedural (<30 days) AAE and mortality, new right bundle branch block, (temporary) atrioventricular block, permanent pacemaker implantation, ICD implantation, reduction in LVWT, LVOT gradient and NYHA class >3 months post-procedure, and re-intervention (ASA or myectomy).

Mortality and adverse events were retrieved from hospital patient records at the center where follow-up occurred, from civil service population registers, and from information provided by patients themselves and/or their general practitioners. All ICD shocks were evaluated by an experienced electrophysiologist, unaware and independent of the study purpose and endpoints. If no events occurred during follow-up, the administrative censoring date was set at November 1st, 2012.

Statistical Analysis

SPSS version 20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for all statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median ± interquartile range. To compare continuous variables Student t test or Mann-Whitney U-test were used, and to compare categorical variables the $\chi 2$-test was used. Kaplan-Meier graphs were used to show survival rates. In all analyses, a P value of <0.05 was considered significant.

RESULTS

Clinical characteristics

The baseline characteristics of the 217 patients who underwent ASA and their age matched control groups are shown in TABLE 1. The mean age of the patients ≤55 years was 43 ± 8 years, and the mean age of the patients >55 years was 64 ± 6 years. There were more non-obstructive patients with systolic dysfunction, as compared to patients who underwent ASA. A higher alcohol dose was used for ASA in patients ≤55 years, compared to patients >55 years (P = 0.013).

TABLE 1 – Baseline characteristics of 107 patients ≤55 years and 110 patients > 5 years

	< 55 years			> 55 years			P
	ASA	controls		ASA	controls		
n=	107	107	P	110	110	P	
Age, years	43 ± 8	43 ± 8	0.99	64 ± 6	64 ± 6	0.98	<0.001
Female	21 (20)	30 (28)	0.20	54 (49)	39 (36)	0.056	<0.001
NYHA III/IV	90 (84)	9 (8)	<0.001	84 (76)	18 (16)	<0.001	0.21
Maximum LVWT, mm	20 ± 6	18 ± 5	<0.001	19 ± 4	18 ± 5	0.17	0.001
Maximum LVOT gradient, mmHg	65 ± 56	6 ± 5	<0.001	60 ± 63	7 ± 5	<0.001	0.68
Systolic dysfunction (EF < 50%)	2 (2)	15 (14)	0.002	10 (9)	25 (23)	0.010	0.042
Coronary artery disease	8 (8)	12 (11)	0.48	37 (34)	18 (16)	0.005	<0.001
Atrial fibrillation	20 (19)	29 (27)	0.19	26 (24)	47 (43)	0.004	0.47
Sudden cardiac death survivor	4 (4)	8 (8)	0.38	2 (2)	11 (10)	0.022	0.44
≥ 2 conventional risk factors for SCD	16 (15)	16 (15)	1.0	9 (8)	22 (20)	0.020	0.18
Amount of alcohol, mL	3.0 ± 1.0	-	-	2.0 ± 1.0	-	-	0.013

Values are mean ± SD, n (percentage), or median (interquartile range) for skewed distributions. ASA = alcohol septal ablation; EF = ejection fraction; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; NYHA = New York Heart Association; SCD = sudden cardiac death.

Procedural outcomes

Procedural outcomes of the patients who underwent ASA are shown in TABLE 2. Atrioventricular block following ASA was more common in patients >55 years compared to patients ≤55 years (43% vs. 21%, P = 0.001), resulting in permanent pacemaker implantation in 13% and 5%, respectively (P = 0.06). Other peri-procedural complications, including AAE and mortality, were similar in both groups. Residual LVWT, LVOT gradient and NYHA class >3 months post-procedure were comparable in both age groups, as was necessity for additional septal reduction therapy.

Long-term outcomes

During a mean follow-up of 7.6 ± 4.6 years there was a total of 20 deaths in the ASA cohorts, and 34 deaths in the control groups. Follow-up was complete in 98% of patients. The 5- and 10-year survival following ASA of patients ≤55 years was 94.9% (95% CI, 90.4%-100.0%) and 90.2% (95% CI, 82.2%-98.1%), respectively, compared to 98.0% (95% CI, 95.4%-100.0%) and 88.1% (95% CI, 80.1%-96.1%) in the control group (P = 0.87, FIGURE 1). The 5- and 10-year survival following ASA of patients >55 years was 93.2% (95% CI, 88.0%-98.5%) and 81.9% (95% CI, 71.8%-91.9%), respectively, compared to 91.7% (95% CI, 86.1%-97.3%) and 82,7% (95% CI,

TABLE 2 – Procedural outcomes after alcohol septal ablation in 107 patients ≤55 years and 110 patients >55 years.

	ASA ≤ 55 years	ASA > 55 years	
n =	107	110	P
Peri-procedural(<30 days) complications			
New right bundle branch block	42 (39)	39 (36)	0.66
(temporary) atrioventricular block	22 (21)	47 (43)	0.001
Permanent pacemaker implantation	5 (5)	14 (13)	0.063
ICD implantation	15 (14)	11 (10)	0.48
Adverse arrhythmic events	8 (8)	8 (7)	1.0
Mortality	2 (2)	0 (0)	0.24
Procedure efficacy			
Residual LVWT > 3 months post-procedure, mm	14 ± 5	14 ± 4	0.45
Residual LVOT gradient > 3 months post-procedure, mmHg	12 ± 27	10 ± 27	0.99
Reduction in LVOT gradient > 3 months post-procedure, %	78 ± 60	76 ± 60	0.68
NYHA class III/IV > 3 months post-procedure	5 (5)	9 (9)	0.43
Redo septal reduction therapy	14 (13)	13 (12)	0.94

Values are n (percentage), or median (interquartile range). ASA = alcohol septal ablation; ICD = internal cardioverter defibrillator; LVOT = left ventricular outflow tract; LVWT = left ventricular wall thickness; NYHA = New York Heart Association.

72.9%-92.6%) in the control group (P = 0.51, FIGURE 2). The annual AAE rate following ASA in patients ≤55 years was 0.7% per year, compared to 1% per year in the control group (P = 0.6). The annual AAE rate following ASA in patients >55 years was 1.4% per year, compared to 0.5% per year in the control group (P = 0.07).

DISCUSSION

The most important result of this 7.6-year follow-up study is that long-term survival following ASA in young and elderly patients is comparable to survival in age matched non-obstructive HCM patients, and the same holds true for AAE rates. Furthermore, ASA is similarly effective for reduction of symptoms in young and elderly patients, although younger patients have a lower risk of procedure related atrioventricular conduction disturbances.

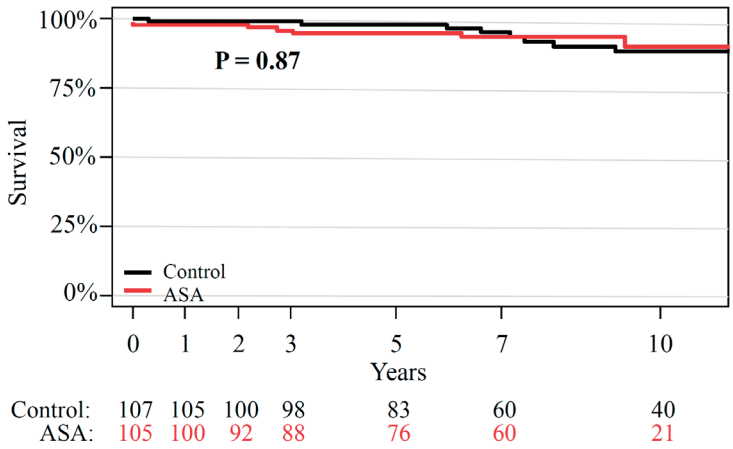


FIGURE 1 – Kaplan-Meier graph of all-cause survival in patients ≤ 55 years who underwent ASA vs. age-matched non-obstructive HCM patients

Previous age specific ASA studies

Currently, information on the long-term age-specific outcomes after ASA in patients with obstructive HCM is scarce. Two previous studies(10,11) have evaluated age specific outcomes of ASA patients during a follow-up period of respectively 1 and 5.1 years. Leonardi et al(10) compared the outcomes of 360 HCM patients undergoing ASA of 3 age categories (<45, 45-64, and >65 years). Likewise, they found that the reduction in LVOT gradient and NYHA class following ASA was similar independent of age, and that elderly patients more often required pacemaker implantation after the procedure. There were no control groups however, and not surprisingly the mortality rate after a follow-up of 1 year was highest in patients >65 years. Veselka et al(11) assessed the 5.1-year outcomes following ASA in 75 patients aged 42 ± 7 years, which is comparable to the mean age of our young patients. They found a survival free of all-cause mortality at 5- and 10 years of 94% each, in line with our findings. No comparisons with elderly patients were made however.

Current guidelines

The American College of Cardiology Foundation/American Heart Association guidelines on HCM of 2011 state that ASA should be reserved for elderly patients and patients with serious comorbidities, and gives a class III recommendation (level of evidence C) to ASA for younger patients if myectomy is a viable option.(1) The procedural mortality rate is reported to be <1% for myectomy versus up to 4% for ASA.(1,12-14) Larger, more recent ASA studies have shown rates of 0.3%-0.6%, however.(15,16) Also, a recent meta-analysis comparing ASA to myectomy showed similarly low peri-procedural and long-term mortality rates.(17) Furthermore, subsequent to the publication of the 2011 guidelines, the post-ASA prognosis was

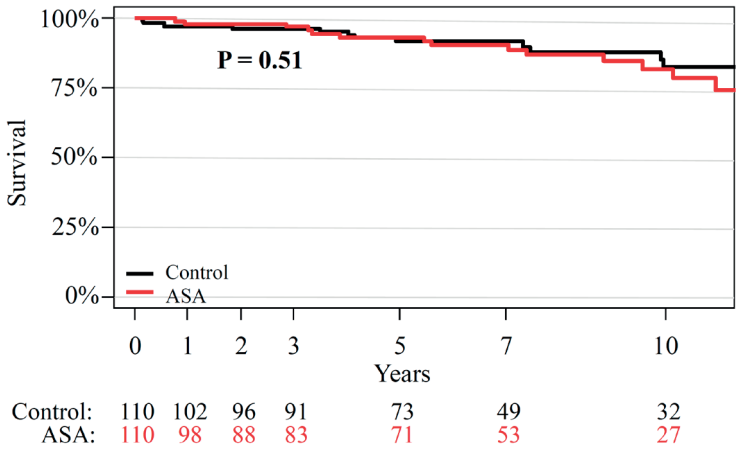


FIGURE 2 – Kaplan-Meier graph of all-cause survival in patients >55 years who underwent ASA vs. age-matched non-obstructive HCM patients.

demonstrated to be comparable with the sex- and age-matched population,(15,16,18) and with matched post-myectomy patients.(18) Notably, these and other studies(15,16,19) showed that age was the only independent predictor of mortality following ASA. Implying that survival in patients after ASA is not determined by ASA, but HCM itself.

One of the main concerns about ASA in younger patients is the potential arrhythmogenic effect of the ablation scar in patients already at an increased risk of life-threatening arrhythmias.(6) Recent studies have shown however, that the long-term risk of SCD after ASA is low and comparable to patients who undergo myectomy.(9,17,18) This study showed an annual AAE rate following ASA of 0.7% per year in the young patients, which was similar to age-matched non-obstructive HCM patients, and half the rate of elderly patients.

Another conceivable reason to choose myectomy instead of ASA in younger patients is the >2 times higher risk of atrioventricular block requiring pacemaker implantation following ASA.(17,20) This higher need for pacemaker implantation may at least partly be explained by the higher age of the patients undergoing ASA: the ASA patients from both meta-analyses were on average 9 years older than the myectomy patients. The present and previous studies have shown that atrioventricular conduction disturbances following ASA are mainly seen in elderly patients,(10,21) with a need for pacemaker implantation in only 5% of the young patients. This, despite the use of a higher amount of alcohol in the young patients. Large outcome studies following myectomy in HCM patients of similar age categories (mean age 37-47 years) showed incidences of atrioventricular block requiring pacemaker implantation of 1-6%.(12,13,22,23)

Since the improvement in functional status following ASA in young and elderly patients is similarly good as well, we propose that the indication for ASA can be broadened to younger patients. In other words, younger age alone should not be a reason not to consider ASA. For

children and adolescents however, little to no results are available following ASA, while there is substantial experience with myectomy.(24) We therefore recommend against ASA in this age group, until studies have proven the safety and efficacy of the procedure in these very young patients.

Patient selection and specialized care

In line with the 2011 American College of Cardiology(1) and the 2014 European Society of Cardiology(2) guidelines, we recommend that all patients considered for septal reduction therapy are assessed by a multidisciplinary heart team (consisting of at least one cardiothoracic surgeon, an interventional cardiologist, and a cardiologist specialized in the care of patients with HCM) to determine the optimal therapy, by taking into account not only age, but also factors like mitral valve anatomy, coronary anatomy, septal thickness, and comorbidities. When both procedures are possible, shared decision making between the informed patient and treating physician should also be part of the equation. Furthermore, septal reduction therapy should be performed by experienced operators and confined to centers with substantial and specific expertise in HCM care.

TABLE 3 – Long-term outcomes after alcohol septal ablation in 107 patients ≤55 years compared to their age matched control group.

	ASA ≤ 55 years	control ≤ 55 years	
n =	**107**	107	**P**
Years of follow-up	7.2 ± 3.4	9.2 ± 5.6	
Mortality (>30 days post-procedure)			
Total mortality	5 (5)	15 (14)	**0.036**
HCM-related death	3 (3)	11 (10)	0.055
Non-cardiac	2 (2)	4 (4)	0.68
5-year survival, %	93	97	0.87
10-year survival, %	90	75	0.87
Adverse arrhythmic events (>30 days post-procedure)			
Total adverse events	5 (5)	9 (8)	0.41
Sudden cardiac death	2 (2)	4 (4)	0.68
Resuscitated cardiac arrest	1 (1)	2 (2)	1.0
Appropriate ICD shocks	2 (2)	3 (3)	1.0
Annual events, %/year	0.7	1.0	0.58

Values are median (interquartile range), or n (percentage), unless stated otherwise. ASA = alcohol septal ablation; HCM: hypertrophic cardiomyopathy, ICD: internal cardioverter defibrillator.

TABLE 4 – Long-term outcomes after alcohol septal ablation in 107 patients >55 years compared to their control group.

	ASA > 55 years	**control > 55 years**	
n =	*110*	110	*P*
Years of follow-up	6.5 ± 3.8	7.5 ± 4.8	
Mortality(>30 days post-procedure)			
Total mortality	15 (14)	19 (17)	0.58
HCM-related death	4 (4)	10 (9)	0.17
Non-cardiac	11 (10)	8 (7)	0.63
5-year survival, %	92	90	0.51
10-year survival, %	79	80	0.51
Adverse arrhythmic events (>30 days post-procedure)			
Total adverse events	10 (9)	4 (4)	0.17
Sudden cardiac death	3 (3)	0 (0)	0.25
Resuscitated cardiac arrest	2 (2)	1(1)	1.0
Appropriate ICD shocks	5 (5)	3 (3)	0.72
Annual events, %/year	1.4	0.5	0.070

Values are median (interquartile range), or n (percentage), unless stated otherwise. ASA = alcohol septal ablation; HCM: hypertrophic cardiomyopathy, ICD: internal cardioverter defibrillator.

Study limitations

There were significant differences in baseline characteristics between the young and elderly patients who underwent ASA. Besides the to be expected differences in prevelance of systolic dysfunction and coronary artery disease, we noted a use of higher amounts of alcohol in the ≤55 years population. The same also held true in a recent study comparing the use of low (≤2.0 mL) versus high (>2 mL) doses of alcohol for ASA.(25) In this study of same patient population as the present study, patients from the high dose group were significantly younger than those from the low dose group. Although the two groups did not differ in maximal LVWT or LVOT gradient, the patient from the high dose group did have a larger caliber of the target septal perforator(s), which might explain the difference. This study has several other limitations. The study was performed in tertiary referral centers for the care of HCM, and the patient population might not represent the general HCM population. This referral and selection bias could have influenced the results. Data collection was limited to variables that were routinely collected. It was not possible to correct for individual or local alterations of percutaneous technique. However, all procedures were performed by experienced interventional cardiologists, plus this implies that our findings are more generalizable than those of single-center investigations.

CONCLUSION

ASA is similarly effective for reduction of symptoms in young and elderly patients, however younger patients have a lower risk of procedure related atrioventricular conduction disturbances. The long-term mortality rate and risk of AAE following ASA is low, both in young and elderly patients, and comparable to age matched non-obstructive HCM patients. We propose that the indication for ASA can be broadened to younger patients.

ACKNOWLEDGEMENTS

The authors would like to thank Hans Kelder for his statistical assistance.

REFERENCES

1. Gersh BJ, Maron BJ, Bonow RO et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
2. Elliott PM, Anastasakis A, Borger MA et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European society of cardiology (ESC). Eur Heart J 2014;35:2733-79.
3. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211-4.
4. Fifer MA, Sigwart U. Controversies in cardiovascular medicine. Hypertrophic obstructive cardiomyopathy: alcohol septal ablation. Eur Heart J 2011;32:1059-64.
5. Rigopoulos AG, Seggewiss H. A decade of percutaneous septal ablation in hypertrophic cardiomyopathy. Circ J 2011;75:28-37.
6. ten Cate FJ, Soliman OI, Michels M et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail 2010;3:362-9.
7. van der Lee C, ten Cate FJ, Geleijnse ML et al. Percutaneous versus surgical treatment for patients with hypertrophic obstructive cardiomyopathy and enlarged anterior mitral valve leaflets. Circulation 2005;112:482-8.
8. van der Lee C, Scholzel B, ten Berg JM et al. Usefulness of clinical, echocardiographic, and procedural characteristics to predict outcome after percutaneous transluminal septal myocardial ablation. Am J Cardiol 2008;101:1315-20.
9. Vriesendorp PA, Liebregts M, Steggerda RC et al. Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. JACC Heart Fail 2014;2:630-6.
10. Leonardi RA, Townsend JC, Patel CA et al. Alcohol septal ablation for obstructive hypertrophic cardiomyopathy: outcome in young, middle-aged, and elderly patients. Catheter Cardiovasc Interv 2013;82:838-45.
11. Veselka J, Krejci J, Tomasov P et al. Survival of patients ≤50 years of age after alcohol septal ablation for hypertrophic obstructive cardiomyopathy. Can J Cardiol 2014;30:634-8.
12. Ommen SR, Maron BJ, Olivotto I et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470-6.
13. Woo A, Williams WG, Choi R et al. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. Circulation 2005;111:2033-41.
14. Lakkis NM, Nagueh SF, Dunn JK, Killip D, Spencer WH 3rd. Nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy: one-year follow-up. J am Coll Cardiol 2000;36:852-5.
15. Jensen MK, Almaas VM, Jacobsson L et al. Long-term outcome of percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: a Scandinavian multicenter study. Circ Cardiovasc Interv 2011;4:256-65.
16. Veselka J, Krejči J, Tomašov P, Zemánek D. Long-term survival after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a comparison with general population. Eur Heart J 2014;35:2040-5.
17. Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AFL, Michels M, ten Berg JM. A Systematic Review and Meta-analysis of Long-term Outcomes After Septal Reduction Therapy in Patients with Hypertrophic cardiomyopathy [published online October 7 2015]. JACC Heart Fail 2015. doi:10.1016/j.jchf.2015.06.011.
18. Sorajja P, Ommen SR, Holmes DR, Jr. et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation 2012;126:2374-80.
19. Kwon DH, Kapadia SR, Tuzcu EM et al. Long-term outcomes in high-risk symptomatic patients with hypertrophic cardiomyopathy undergoing alcohol septal ablation. JACC Cardiovasc Interv 2008;1:432-8.

20. Leonardi RA, Kransdorf EP, Simel DL, Wang A. Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy: comparative rates of overall mortality and sudden cardiac death after treatment. Circ Cardiovasc Interv 2010;3:97-104.
21. Lawrenz T, Lieder F, Bartelsmeier M et al. Predictors of complete heart block after transcoronary ablation of septal hypertrophy: Results of a prospective electrophysiological investigation in 172 patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 2007;49:2356–63.
22. Desai MY, Bhonsale A, Smedira NG et al. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. Circulation 2013;128:209-16.
23. Schonbeck MH, Brunner-La Rocca HP, Vogt PR et al. Long-term follow-up in hypertrophic obstructive cardiomyopathy after septal myectomy. Ann Thorac Surg 1998;65:1207-14.
24. Altarabsheh SE, Dearani JA, Burkhart HM et al. Outcome of septal myectomy for obstructive hypertrophic cardiomyopathy in children and young adults. Ann Thorac Surg 2013;95:663-9.
25. Liebregts M, Vriesendorp PA, Steggerda RC et al. Effect of alcohol dosage on long-term outcomes after alcohol septal ablation in patients with hypertrophic cardiomyopathy. Catheter Cardiovasc Interv;In Press..

EDITORIAL

Patient selection for alcohol septal ablation: does age matter?

Eleid MF, Nishimura RA
JACC Cardiovasc Interv. 2016 Mar 14;9(5):470-1

> *Age is an issue of mind over matter. If you don't mind, it doesn't matter.*
> — Mark Twain [1]

Septal reduction therapy plays an important role in the treatment of patients with hypertrophic cardiomyopathy (HCM) and symptoms due to a dynamic left ventricular outflow tract obstruction refractory to medical therapy. Surgical resection of septal hypertrophy has been an established treatment for over 5 decades, with excellent symptomatic and hemodynamic improvement and a mortality rate of 0.4% among the most experienced centers [2]. Although percutaneous transcatheter alcohol septal ablation (ASA) was first introduced 20 years ago [3], data regarding the long-term outcome of patients receiving this treatment have become available only in recent years [4,5]. The 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the diagnosis and treatment of hypertrophic cardiomyopathy had previously recommended ASA as an alternative to myectomy in the presence of advanced age or other comorbidities (Class IIa) or due to patient preference (Class IIb) [6]. These recommendations were made on the basis of: 1) the lack of long-term follow-up with concern regarding long-term arrhythmic potential related to iatrogenic infarction; and 2) lesser efficacy in terms of symptom relief, particularly in the younger patient.

The study by Liebregts et al. [7] in this issue of JACC: Cardiovascular Interventions is a valuable contribution to the accumulating knowledge regarding long-term outcome of patients undergoing ASA. In their retrospective observational study at 2 tertiary referral centers, the outcomes of young (<55 years) and older (>55 years) patients undergoing ASA (n = 217) were compared with nonobstructive HCM patients managed medically. Five- and 10-year survival following ASA in young (95% and 90%, respectively) and older (93% and 82%, respectively) groups were quite favorable and were similar to an age-matched control group of patients with nonobstructive HCM. Furthermore, short-term procedural efficacy was similar between young and older patients (>90% of patients having New York Heart Association (NYHA) functional class I or II symptoms after 3 months of follow-up), as was the rate of additional septal reduction therapy (13% and 12%, respectively). The mean maximal left ventricular septal wall thickness was similar in young and older patients (20 ± 6 and 19 ± 4 mm, respectively). As expected, the rate of atrioventricular block requiring permanent pacemaker implantation appeared to be higher in older (13%) compared with younger patients (5%).

This study provides some reassurance regarding longer-term survival and procedural efficacy in young patients undergoing ASA, challenging the recommendation that ASA be

reserved for older patients [6]. However, despite the low event rate observed in the present study (5 arrhythmic events and 3 cardiac deaths), it is difficult to ignore prior warnings of increased ventricular arrhythmogenicity following ASA [8-10], compared with a signal for reduced rates of ventricular arrhythmia following myectomy [11], when considering treatment options for a young individual with many decades of a good quality of life ahead of them. On the basis of results to date, it is probable that ASA does not increase the overall risk of malignant arrhythmias, but myectomy may decrease this risk [12,13]. The ACCF/AHA guidelines also hinge on the concept that septal myectomy is a more effective procedure, with a higher percentage of patients having complete relief of symptoms as well as a lower rate of repeat procedures compared with ASA, particularly for younger patients <65 years of age [14]. The study by Liebregts et al. [7] did not include a surgical myectomy group for comparison, and thus, conclusions regarding the efficacy of ASA relative to myectomy in this population cannot be drawn from this investigation. Although the outcome measures of NYHA functional class at 3 months were promising, what patients really desire is long-term durability of symptom relief to allow return to a normal lifestyle, which was not addressed.

At HCM centers of excellence where both myectomy and ASA are offered, patient selection for septal reduction therapy is highly nuanced and patient-centered, with a shared decision-making approach. Older patients and those with multiple comorbidities may be at higher risk for complications from septal myectomy, making a less-invasive option potentially more attractive for these patients [6]. Multiple other factors must be taken into consideration, including the degree of septal hypertrophy, the location and size of septal perforators relative to septal hypertrophy, concomitant mitral valve pathology including aberrant papillary muscle insertion, as well as baseline conduction system disease and patient preference, which all may affect the risk–benefit ratio of ASA. Accordingly, age may only be 1 factor in the integration of all clinical data to arrive at a patient-centered recommendation for therapy. Local institutional expertise is another critical factor weighing on the choice of septal reduction therapy. At a HCM center of excellence with experience in septal myectomy, the weight of evidence continues to favor this option for a young patient being considered for septal reduction therapy, due to very low operative mortality, superior efficacy and lesser need for subsequent procedures. However, growing evidence supports that ASA is not fraught with the high risk that had been suspected and that long-term survival after ASA may be comparable to that of myectomy, potentially opening this treatment modality to a younger population as well as to centers that do not have the surgical expertise. It must be remembered that, as with any interventional technique, outcomes are highly dependent upon the knowledge and experience of the operators, and the excellent results in this study may not necessarily be extrapolated to all other centers.

Future studies comparing the long-term clinical outcomes of ASA directly with surgical myectomy in patients across a broad age spectrum at institutions with expertise in both techniques may help answer the question of whether ASA should be considered in a younger

population. Additionally, even longer-term data will be required to determine the lasting impact of the iatrogenic septal infarction of ASA on lifetime arrhythmogenic risk in a younger population. Until that time, the question of how much age really matters in patient selection for ASA will remain.

REFERENCES

1. Twain M. Available at: www.brainyquote.com/search_results.html?q=mark+twain%2C+aging. Accessed February 17, 2016.
2. B.J. Maron, J.A. Dearani, S.R. Ommen, et al. Low operative mortality achieved with surgical septal myectomy: role of dedicated hypertrophic cardiomyopathy centers in the management of dynamic subaortic obstruction. J Am Coll Cardiol, 66 (2015), pp. 1307–1308
3. U. Sigwart. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet, 346 (1995), pp. 211–214
4. R.A. Leonardi, J.C. Townsend, C.A. Patel, et al.Alcohol septal ablation for obstructive hypertrophic cardiomyopathy: outcomes in young, middle-aged, and elderly patients. Catheter Cardiovasc Interv, 82 (2013), pp. 838–845
5. P. Sorajja, S.R. Ommen, D.R. Holmes Jr., et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation, 126 (2012), pp. 2374–2380
6. B.J. Gersh, B.J. Maron, R.O. Bonow, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 124 (2011), pp. 2761–2796
7. M. Liebregts, R.C. Steggerda, P.A. Vriesendorp, et al. Long-term outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy in the young and the elderly. J Am Coll Cardiol Intv, 9 (2016), pp. 463–469
8. F.A. Cuoco, W.H. Spencer 3rd, V.L. Fernandes, et al. Implantable cardioverter-defibrillator therapy for primary prevention of sudden death after alcohol septal ablation of hypertrophic cardiomyopathy. J Am Coll Cardiol, 52 (2008), pp. 1718–1723
9. P.A. Noseworthy, M.A. Rosenberg, M.A. Fifer, et al. Ventricular arrhythmia following alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Am J Cardiol, 104 (2009), pp. 128–132
10. F.J. ten Cate, O.I. Soliman, M. Michels, et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail, 3 (2010), pp. 362–369
11. C.J. McLeod, S.R. Ommen, M.J. Ackerman, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J, 28 (2007), pp. 2583–2588
12. M.Y. Desai, N.G. Smedira, A. Bhonsale, M. Thamilarasan, B.W. Lytle, H.M. Lever. Symptom assessment and exercise impairment in surgical decision making in hypertrophic obstructive cardiomyopathy: relationship to outcomes. J Thorac Cardiovasc Surg, 150 (2015), pp. 928–935.e1
13. R.A. Nishimura, H.V. Schaff. Septal myectomy for patients with hypertrophic cardiomyopathy: a new paradigm. J Thorac Cardiovasc Surg, 151 (2016), pp. 303–304
14. P. Sorajja, U. Valeti, R.A. Nishimura, et al. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation, 118 (2008), pp. 131–139

Chapter 8

Microsphere embolisation as an alternative for alcohol in percutaneous transluminal septal myocardial ablation

Vriesendorp PA, Van Mieghem NM, Vletter WB, Ten Cate FJ, de Jong PL, Schinkel AF, Michels M.

Neth Heart J. 2013 May;21(5):245-8

ABSTRACT

Background

Percutaneous transluminal septal myocardium ablation using microsphere embolization is a new interventional technique to treat patients with hypertrophic obstructive cardiomyopathy

Methods and Results

In two patients, considered at high risk for myectomy, targeted septal perforators were occluded with microsphere embolization instead of alcohol ablation to reduce left ventricular outflow gradient. In both cases the left ventricular outflow tract gradient immediately was reduced. No adverse events occurred.

Conclusion

This is the first clinical experience with Embozene® Microspheres in the Netherlands as an alternative for alcohol septal ablation. In both cases it resulted in immediate improvement in hemodynamics, without any adverse events.

INTRODUCTION

Dynamic obstruction of the left ventricular outflow tract (LVOT) is an important component of the pathophysiology of hypertrophic cardiomyopathy (HCM) and is described in almost 70% of HCM-patients.[1] Therapy in severely symptomatic patients aims at reducing the extent of the LVOT obstruction, either medically using negative inotropic drugs or invasively by either myectomy or percutaneous transluminal septal myocardium ablation (PTSMA) using alcohol.[2, 3] PTSMA precludes general anesthesia, sternotomy and cardiopulmonary bypass and thus results in overall shorter in-hospital stay as compared to surgical myectomy. Conversely, PTSMA may be associated with a higher permanent pacemaker implantation rate for total atrioventricular block. [4] Furthermore there is ongoing debate on the long-term impact of the resultant myocardial scar with arrhythmogenic potential.[5] In the current guidelines PTSMA is an alternative intervention for selected patients who are no optimal surgical candidates.[2, 3]

Alcohol has been traditionally used for PTSMA. Its inherent cardiotoxicity and the risk of procedural alcohol spilling into the left anterior descending artery (LAD) have spurred interest in reliable and potentially safer embolic alternatives. There is a vast experience with microspheres as an embolic agent to control bleeding or occlude the blood supply of certain tumours or arteriovenous malformations. Microspheres allow for an easy, safe and targeted delivery.[6, 7] Recently, Embozene® Microspheres have been demonstrated by Latsios et al. [8] as a potential alternative for alcohol in PTSMA. The aim of this report is to demonstrate the safety and efficacy of PTSMA using Embozene® Microspheres.

MATERIAL AND METHODS

Microspheres

Embozene® Microspheres are specially designed spherical embolic agents, developed by CeloNova Biosciences Inc. (San Antonio, TX, USA). The microspheres are hydrogel cores with an anorganic polymer surface (Polyzene®-F), which is biocompatible and not absorbable. There are several different sizes, which range from 40μm to 900μm in diameter, and each size has a different colour. For PTSMA the use of the 75μm-microspheres is recommended. A total of 0.6 mL Microspheres solution is diluted with 6 mL of contrast agent for optimal deliverability and visualization.

Patients

Two HCM patients (age 64 and 77 years) with severe LVOT obstruction (>90 mmHg at rest) were selected for PTSMA because of invalidating symptoms (NYHA functional class IV) despite optimal medical therapy. Based on multiple co-morbidities both patients were refused

for surgery by multidisciplinary heart-team consensus and thus considered for PTSMA. Both patients provided written informed consent for the procedure.

Intervention

The invasive PTSMA procedure evolves under transthoracic echocardiographic monitoring and conscious sedation. The right and left femoral artery and right femoral vein are cannulated using standard Seldinger technique. A temporary pacemaker lead is placed in the apex of the right ventricle. Full anticoagulation is obtained with heparine aiming for an activated clotting time between 250 and 300 seconds. A 6F double lumen Langston™ pigtail catheter is advanced into the left ventricle allowing for simultaneous pressure recordings in the left ventricle and the ascending aorta. The LVOT gradient is measured invasively and simultaneously with continuous wave Doppler throughout the procedure. The Brockenbrough-Braunwald-Morrow sign is assessed at baseline by artificially provoking ventricular ectopy (FIGURE 1). The left main coronary artery is selectively engaged with a 6F Judkins left guiding catheter. After visual assessment of the septal perforator branches of the left anterior descending artery the first or second septal perforator is wired with a 0.014" hydrophilic coronary guidewire introduced into a 1.50 X 15mm over-the-wire (OTW) Balloon (Trek™, Abbott Vascular). The OTW balloon is advanced into the septal perforator and inflated up to 6 atmospheres. After removal of the coronary guidewire, 2mL of echo contrast (Sonovue, Bracco Diagnostics, Milan, Italy) is selectively injected into the septal perforator through the inner lumen of the OTW balloon to allow for echocardiographic identification of the basal left ventricular septum as appropriate anatomical target for the microspheres (FIGURE 2). Subsequently, with the balloon still inflated 0.6 ml of Embozene Microspheres are injected. Filling of the septal perforator with eventual stasis of the injected solution is confirmed by fluoroscopy and continuous invasive hemodynamic monitoring demonstrates progressive reduction in LVOT gradient. The OTW balloon is deflated and removed. FIGURE 3 illustrates a favorable reduction in LVOT gradient from 65 mmHg to 5 mmHg and abolition of the 1st septal perforator.

RESULTS

Safety

Both procedures evolved uneventful. No allergic reactions were reported after the use of microspheres. Transient per-procedural atrioventricular conduction disturbances were noted in 1 patient. The temporary pacemaker wire could be safely removed after 24 hours. No patient required a permanent pacemaker implantation.

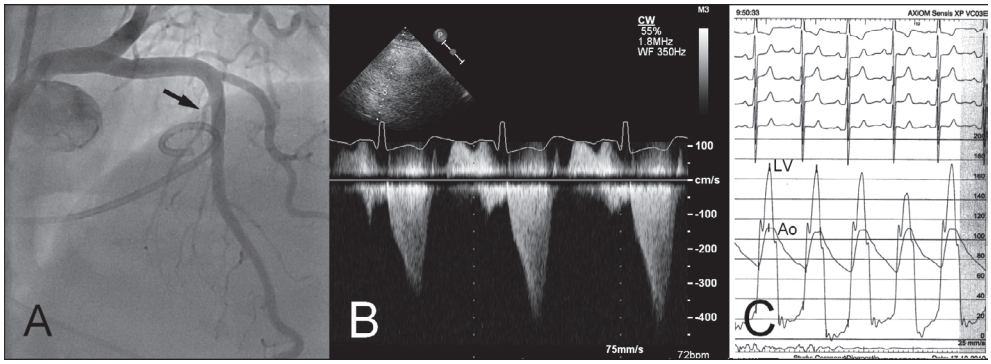


FIGURE 1 – Baseline coronary angiography (A) of the targeted septal artery (black arrow) and left ventricular outflow tract gradient measured with continuous wave Doppler (B) and invasively (C) direct before the procedure.

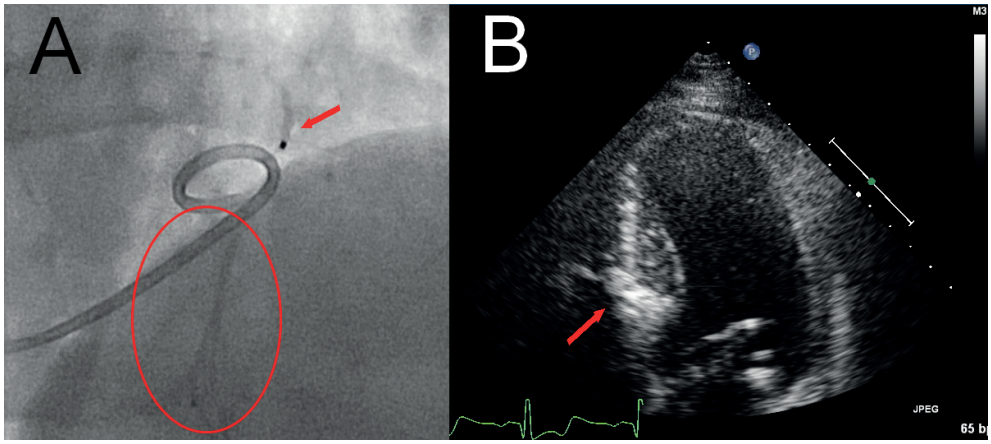


FIGURE 2 – Balloon inflation (A) in targeted septal artery (red arrow) and contrast agent downstream of the balloon (red circle). Opacification of the targeted septal area on 2D echocardiography (B).

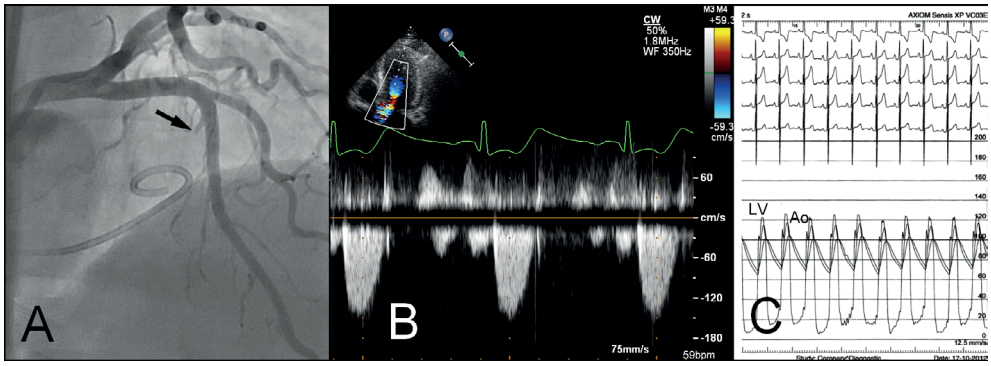


FIGURE 3 – Post-procedural situation with angiography (A) showing that targeted septal artery is no longer visible (black arrow) and decrease in left ventricular outflow tract gradient measured with continuous wave Doppler (B) and invasively (C) directly after the procedure.

Efficacy

Continuous recording of LVOT gradient revealed an almost instant reduction of the LVOT pressure gradient (-50 mmHg and -60 mmHg) in both patients. Focal septal wall infarction was obtained as demonstrated by peak CK-MB levels (20 resp. 227 μg/L) and echocardiographic confirmation of hypokinesis and thinning of the basal septal wall.

DISCUSSION

Alcohol injection in the septal artery is the most commonly used technique of PTSMA in patients with hypertrophic obstructive cardiomyopathy (HOCM). However due to the direct toxicity of the alcohol on the myocardial tissue and the risk of leakage in the LAD with subsequent anterior wall infarction this procedure is not without risks. Coil embolization has been proposed as an alternative for alcohol. Coils,

like microspheres, may provide the opportunity to create a more controlled infarction. However drawbacks of this technique are persistence or reoccurrence of LVOT obstruction during long-term follow-up and the risk of periprocedural migration of coils to the LAD with subsequent complications such as myocardial infarction and rarely a ventricular septal defect. [9, 10]

For the first time in the Netherlands, we used Embozene® Microspheres as an alternative for alcohol to perform PTSMA in 2 patients and confirm its feasibility corroborating the findings by the Siegburg group, where in one patient the LVOT obstruction was reduced from 70 to 10 mmHg without any complications.[8] The immediate improvement in hemodynamics and decrease of LVOT gradient is most likely caused by the focal infarction and subsequent akinesia of the septal wall. Long-term results need further research, but it is expected that due to thinning of the myocardium the LVOT gradient will further decrease.

Microsphere embolization in these two patients was safe and effective in inducing focal basal septal wall infarction. Its higher viscosity makes it safe to inject and reduces the risk of spilling into the LAD. Also the absence of intrinsic cardiotoxic effects (as seen with alcohol) may preclude untoward acute myocardial damage and create a more controlled infarction.

CONCLUSION

This is the first clinical experience with Embozene® Microspheres in the Netherlands as an alternative for the use of alcohol in PTSMA in severely symptomatic patients with HOCM. In both cases it resulted in immediate improvement in hemodynamics, without any adverse events.

REFERENCES

1. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-9.
2. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
3. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. Eur Heart J 2003;24:1965-91.
4. Chen AA, Palacios IF, Mela T, et al. Acute predictors of subacute complete heart block after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Am J Cardiol 2006;97:264-9.
5. ten Cate FJ, Soliman OI, Michels M, et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail 2010;3:362-9.
6. Stampfl U, Radeleff B, Sommer C, et al. Midterm results of uterine artery embolization using narrow-size calibrated embozene microspheres. Cardiovasc Intervent Radiol 2011;34:295-305.
7. Stampfl U, Stampfl S, Bellemann N, et al. Experimental liver embolization with four different spherical embolic materials: impact on inflammatory tissue and foreign body reaction. Cardiovasc Intervent Radiol 2009;32:303-12.
8. Latsios G, Gerckens U, Mueller R, et al. Substitution of ethanol with specially designed microspheres in a TASH procedure. EuroIntervention 2011;6:889-92.
9. Carrel T, Schmidli J. Septal myectomy for hypertrophic obstructive cardiomyopathy: coil, boil and the role of rescue surgery. Eur J Cardiothorac Surg 2009;36:210-1.
10. Durand E, Mousseaux E, Coste P, et al. Non-surgical septal myocardial reduction by coil embolization for hypertrophic obstructive cardiomyopathy: early and 6 months follow-up. Eur Heart J 2008;29:348-55.

III – Prediction and prevention of sudden cardiac death

Chapter 9

Validation of the 2014 ESC guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy

Vriesendorp PA, Schinkel AF, Liebregts M, Theuns DAMJ,
van Cleemput J, Ten Cate FJ, Willems R, Michels M

Circ Arrhythm Electrophysiol. 2015 Aug;8(4):829-35

ABSTRACT

Background

The recently released 2014 ESC guidelines of hypertrophic cardiomyopathy (HCM) use a new clinical risk prediction model for sudden cardiac death, based on the HCM Risk-SCD study. Our study is the first external and independent validation of this new risk prediction model.

Methods and results

The study population consisted of a consecutive cohort of 706 HCM patients without prior SCD event, from 2 tertiary referral centers. The primary endpoint was a composite of SCD and appropriate ICD therapy, identical to the HCM Risk-SCD endpoint. The 5-year SCD risk was calculated using the HCM Risk-SCD formula. ROC curves and C-statistics were calculated for the 2014 ESC guidelines, and risk stratification methods of the 2003 ACC/ESC guidelines and 2011 ACCF/AHA guidelines.

During follow-up of 7.7 ±5.3 years, SCD occurred in 42 (5.9%) of 706 patients (age 49 ±16 years, 34% female). The C-statistic of the new model was 0.69 (95% CI 0.57-0.82, p = 0.008), which performed significantly better than the conventional risk factor models based on the 2003 guidelines (C-statistic of 0.55 95% CI 0.47-0.63, p = 0.3), and 2011 guidelines (C-statistic of 0.60, 95% CI 0.50-0.70, p = 0.07).

Conclusion

The HCM Risk-SCD model improves the risk stratification of HCM patients for primary prevention of SCD, and calculating an individual risk estimate contributes to the clinical decision making process. Improved risk stratification is important for the decision making before ICD implantation for the primary prevention of SCD.

INTRODUCTION

Sudden cardiac death (SCD) is a relatively rare but devastating clinical event in hypertrophic cardiomyopathy (HCM) with an incidence of 0,5-1%/year in patients with HCM.[1] High risk patients can be protected from SCD by implantable cardioverter-defibrillators (ICD), but this protection comes at a price of inappropriate shocks and device related complications.[2]

Originally, in the 2003 ACC/ESC guidelines and 2011 ACCF/AHA guidelines, the identification of high-risk patients was based on five clinical characteristics: a family history of SCD in first-degree relatives < 40 years of age, maximal left ventricular wall thickness (LVWT) of >30 mm, unexplainable syncope, non-sustained ventricular tachycardia (nsVT) and abnormal blood pressure response during exercise.[3, 4] Although it was clear that the risk of SCD increases with increasing number of risk factors, O'Mahony et al.[5] demonstrated that both 2003 and 2011 guidelines distinguish high and low risk patients with only limited power. Recently the HCM Outcomes Investigators presented a novel clinical risk prediction model for SCD (HCM Risk-SCD), based on a cohort of 3675 patients from six centers.[6] This model provides an individualized 5-year risk, based on most of the aforementioned risk factors, combined with left ventricular outflow tract (LVOT) gradient, left atrial (LA) diameter, and age at evaluation. This new model was more accurate in predicting SCD compared with the conventional risk factors, and the recently released 2014 ESC guidelines incorporated the HCM Risk-SCD model to classify patients as low risk (5-year risk of SCD <4%), intermediate risk (5-year risk of SCD 4-6%) or high risk (5-year risk of SCD >6%). ICD implantation was respectively a IIB or IIA recommendation in the latter groups.

This improvement of identification of high risk patients is a promising development in the prevention of SCD in HCM, but the final model needs external validation for generalizability. The aim of this study is to perform an external and independent validation of the novel clinical risk prediction model, and to compare it with the 2003 and 2011 guidelines.

METHODS

Study design and population

An international two-center, observational cohort design was used. The study conforms to the principles of the Helsinki Declaration and local institutional review board approval was obtained.

The study population consisted of 747 adult (≥16 years of age) consecutively evaluated patients with HCM at the University Hospital Leuven, Leuven, Belgium and the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. The same inclusion and exclusion criteria as described in the HCM Risk-SCD study were used, and 41 patients with a history of SCD prior to or as first contact were excluded.[6] Each patient had an established diagnosis of HCM, based on unexplained left ventricular hypertrophy of ≥15 mm, assessed

by echocardiography.[3, 4] Patients with HCM linked to Noonan's syndrome, Fabry's disease, mitochondrial disease or congenital heart defects were excluded. All patients with a history of cardiac arrest or sustained ventricular tachycardia were also excluded.

Outcomes and follow-up

The primary endpoint of SCD was equivalent to the endpoint used in the HCM Risk-SCD study. It was a composite endpoint and consists of (1) instantaneous and unexpected death within 1 hour of a witnessed collapse in patients who were previously in a stable clinical condition, or nocturnal death with no antecedent history of worsening symptoms; (2) successful resuscitation after cardiac arrest; and (3) appropriate ICD interventions for VF or fast VT (>200 bpm), in line with previous studies.[6, 7] Mortality and adverse events were retrieved from hospital patient records at the center where follow-up occurred, from civil service population registers, and from information provided by patients themselves or their general practitioners. For primary prevention, a cut-off rate for ventricular tachycardia (VT) detection of 175–180 b.p.m. with a series of antitachycardia pacing (ATP) bursts followed by shocks was programmed. Detection for ventricular fibrillation (VF) was usually set at 220 b.p.m. with direct shock application. All ICD interventions were evaluated by an experienced electrophysiologist at each center. Follow-up extended from first evaluation up to an endpoint or the administrative censoring date, set at November 1st, 2012. If patients were lost to follow-up, the patient would be censored at last known contact date.

Risk factors and profiles

Risk factors for SCD were evaluated at baseline and based on the conventional risk factors and the variables described in the HCM Risk-SCD study. The following risk factors were identified: (1) age at evaluation; (2) a family history of SCD in ≥ 1 first-degree relatives < 40 years of age or in a first degree relative with confirmed HCM at any age; (3) maximal LVWT; (3) history of unexplainable syncope, (4) documented nsVT ≥ 3 beats at a rate of ≥ 120 bpm; (5) maximal LVOTO gradient (either resting or provocable gradient); (6) LA diameter measured in parasternal long axis; and (7) abnormal blood pressure response during exercise was also identified (as a conventional risk factor). The 5-year risk of SCD for individual patients were calculated using the HCM Risk-SCD formula: $\hat{P}_{\text{SCD at 5 years}} = 1 - 0.998^{\exp(\text{Prognostic Index})}$, where Prognostic Index = 0.15939858*maximal LVWT (mm) – 0.00294271*maximal LVWT^2 (mm^2) + 0.0259082*LA diameter (mm) + 0.00446131*maximal LVOT gradient (mmHg) + 0.4583082*Family history of SCD+0.82639195*nsVT + 0.71650361*unexplained syncope-0.01799934*age at evaluation (years); (The ESC calculator is available at http://www.doc2do.com/hcm/webHCM.html). Additionally, risk profiles based on 2003 ACC/ESC guideline and 2011 ACCF/AHA guideline were calculated. In the 2003 guideline, each risk factor was of equal weight and the profile was calculated as the sum of all risk factors present in the patient. The approach for the 2011 guideline was similar, except that documented nsVT

and abnormal blood pressure response during exercise only were considered if at least one of the other risk factors was present.

Statistical Analysis

SPSS version 21 (IBM, Armonk, NY, USA), R version 3.1.1 (The R Foundation, Vienna, Austria) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for all statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median (interquartile range). To compare continuous variables between groups Student t test or Mann-Whitney U-test were used, and to compare categorical variables the χ^2-test was used. The performance of the novel risk model, and the models based on conventional risk factors, was determined by the C-statistic, which indicates how well a model discriminates here between high and low risk for SCD in HCM patients. A C-statistic of 0.5 indicates no predictive value, and 1.0 indicates perfect performance. A receiver operating characteristic (ROC) curve was constructed to visualize the model performances, by plotting the sensitivity against 1-specificity. The C-statistic was based on a Cox regression model, using R's survival and survivalROC packages. Kaplan-meier estimates were calculated, and compared using the log-rank test. Univariable cox regression analysis was performed to identify predictors of outcome. All tests were 2-sided and a p-value <0.05 was considered statistically significant. To deal with missing data, we used a similar approach outlined in the HCM Risk-SCD study: missing data was identified and imputed using multiple imputation. A total of 25 imputed data sets were generated and pooled. Patients with 50% missing predictors were excluded from model development.

RESULTS

Clinical characteristics

The final study population consisted of 706 HCM patients (age 49 ± 16, 66% male) and TABLE 1 lists the baseline characteristics of these patients. A baseline LVOT gradient ≥ 30 mmHg was present in 375 patients (53%). During follow-up 109 patients (15%) underwent septal ablation and 139 patients (20%) underwent surgical myectomy. Atrial fibrillation was documented in 170 patients (24%) during follow-up. A total of 524 patients (74%) were treated with at least a β-receptor antagonist or verapamil. An ICD was implanted for primary prevention in 117 patients (17%). Risk stratification was not complete in all patients: in 107 patients (15%) the exercise testing was lacking, in 116 patients (16%) the Holter-monitoring, in 52 patients (7.3%) there was LVOT gradient, and in 52 patients LA diameter was missing. No patients were excluded because of missing data. Predictors of missingness were: age at first contact, gender, and NYHA class, and date of exit of the study.

TABLE 1 – Clinical characteristics of 706 HCM patients

	All	Patients with SCD	Patients without SCD
n=	*706*	*42*	*664*
Female	242 (34)	10 (24)	232 (35)
Age, y	49 ± 16	44 ± 17	50 ± 16
NYHA III/IV	232 (33)	19 (41)	213 (32)
Atrial fibrillation	170 (24)	15 (36)	155 (23)
Left ventricular wall thickness, mm	20 ± 5	23 ± 5	20 ± 5
Left atrial diameter, mm	45 ± 8	49 ± 9	45 ± 7
Maximal LVOT gradient, mmHg	48 ± 44	48 ± 43	48 ± 44
Surgical myectomy	139 (20)	6 (14)	133 (20)
Septal ablation	109 (15)	10 (24)	99 (15)
Family history of SCD	141 (20)	14 (33)	127 (19)
Syncope	72 (10)	7 (17)	65 (10)
Left ventricular wall thickness ≥30mm	46 (7)	8 (19)	38 (6)
Non-sustained ventricular tachycardia	157 (22)	16 (38)	141 (21)
Abnormal blood pressure during exercise	89 (13)	5 (12)	84 (13)
0 Risk factors	345 (49)	12 (29)	333 (50)
1 Risk factor	245 (35)	17 (40)	228 (34)
≥ 2 Risk factors	116 (16)	13 (31)	103 (16)

Data are represented as n (percentage) unless stated otherwise. LVOT: left ventricular outflow tract; SCD: sudden cardiac death.

Sudden cardiac death

Follow-up was 7.7 ±5.3 years (range 22.7), with a total of 5438 patient-years. During follow-up 42 patients (5.9%) reached the SCD endpoint. Of these, 4 (10%) had successful cardiac resuscitation, 16 (38%) had appropriate ICD shocks and 22 (52%) died suddenly. Patients with SCD were younger (44 vs 50 years), had increased LVWT (23 vs 20 mm) and left atrial diameter (49 vs 45 mm). Twenty patients (28%) reached the SCD endpoint in the first 5 years after initial risk stratification. Univariable Cox-regression analysis identified only left ventricular wall thickness as a predictor for SCD (TABLE 2).

HCM Risk-SCD score and the 2003 and 2011 guidelines

In the patients reaching the SCD endpoint, mean calculated 5-year SCD risk was 4.9% (IQR 3.8%) and these patients had a median of 1 (IQR 2) established risk factor. In patients without SCD calculated 5-year risk was 2.8% (IQR 3.0%; p = 0.002), with a median of 0 (IQR 1) established risk factors (p=0.03).

TABLE 2 – Univariable Cox regression model of predictors for SCD in 706 HCM patients.

	HR	CI 95%	p
Age, y	0.98	0.96-1.01	0.2
Male	3.0	0.87-10.1	0.08
Left ventricular wall thickness, mm	1.09	1.02-1.17	0.009
Left atrial diameter, mm	1.05	0.99-1.10	0.09
Maximal LVOT gradient, mmHg	1.01	1.00-1.02	0.1
Family history of SCD	1.7	0.66-4.45	0.3
Syncope	1.6	0.47-5.51	0.4
Left ventricular wall thickness ≥30mm	4.6	1.68-12.7	0.003
Non-sustained ventricular tachycardia	1.2	0.46-3.21	0.7
Abnormal blood pressure during exercise	0.7	0.17-3.13	0.7

CI: confidence interval; HCM: Hypertrophic cardiomyopathy; HR: hazard ratio; LVOT: left ventricular outflow tract; SCD: sudden cardiac death.

The C-statistic for the HCM Risk-SCD model was 0.69 (95% CI 0.57-0.82, p=0.008). The C-statistic was also calculated for the 2003 guidelines: 0.55 (95% CI 0.47-0.63, p=0.3); and for the 2011 guidelines: 0.60 (95% CI 0.50-0.70, p=0.07). The ROC curves are shown in FIGURE 1. We also examined whether using the HCM Risk-SCD score results in correct reclassification of high-risk patients. Net reclassification index (NRI) was 0.27 (95% CI -0.02 – 0.57, p=0.07)

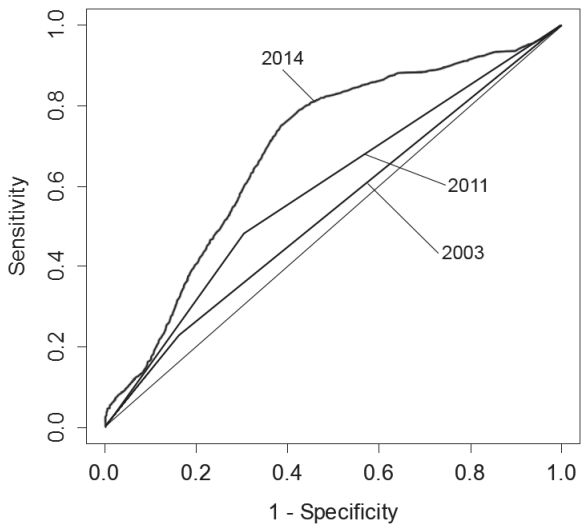


FIGURE 1 – Time-dependent receiver operating characteristic curves for the risk prediction models of the 2014 ESC guidelines (AUC=0.69), 2003 ACC/ESC guidelines (AUC=0.55), and 2011 ACCF/AHA guidelines (AUC=0.60), and the reference line (AUC=0.5).

TABLE 3 – Reclassification of predicted risk among cases (patients with SCD-event) and controls.

	Predicted risk classified downward in new model	Predicted risk not changed in new model	Predicted risk classified upward in new model	Total
2014 vs. 2003 guidelines model				
Cases (SCD-patients), n (%)	0 (0) †	11 (55)	9 (45)*	20
Controls, n (%)	12 (2)*	540 (79)	134 (20) †	686
2014 vs. 2011 guidelines model				
Cases (SCD-patients), n (%)	2 (10) †	12 (60)	6 (30)*	20
Controls, n (%)	75 (11)*	513 (75)	98 (14) †	686

* indicates correct reclassifications in the new model. † indicates incorrect reclassifications in the new model. SCD = sudden cardiac death †

compared with 2003 guidelines and NRI was 0.16 (95% CI -0.17 – 0.45, p=0.2) compared with 2011 guidelines. A complete overview is shown in TABLE 3.

Risk groups and clinical implications

The predicted and observed risk per group are illustrated in FIGURE 2, SCD risk was over-estimated, especially in the high risk group. Optimal sensitivity and specificity of the HCM Risk-SCD model in the original study was determined at ≥4% per 5-year, with a sensitivity and specificity of 71% and 70%. In this study a calculated 5-year SCD risk of 4% showed similar sensitivity (70%) and specificity (67%, FIGURE 1), and was a significant predictor for SCD (HR 4.2 95% CI 1.6-11.0, p=0.003). In contrast, the presence of ≥1 (HR 2.2 95% CI 0.9-5.3, p=0.08; 2011 guidelines) or ≥2 (HR 1.7 95% CI 0.6-4.6, p=0.3; 2003 guidelines) risk factors were not predictive of SCD. Kaplan-Meier estimates for risk of SCD are shown in FIGURE 3.

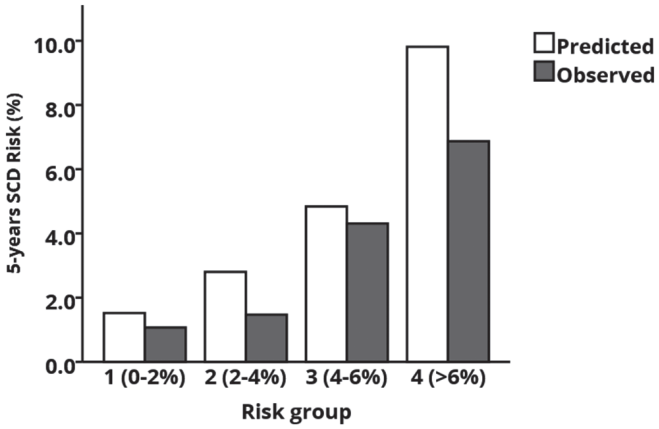


FIGURE 2 – Predicted and observed risk of SCD in the different risk groups.

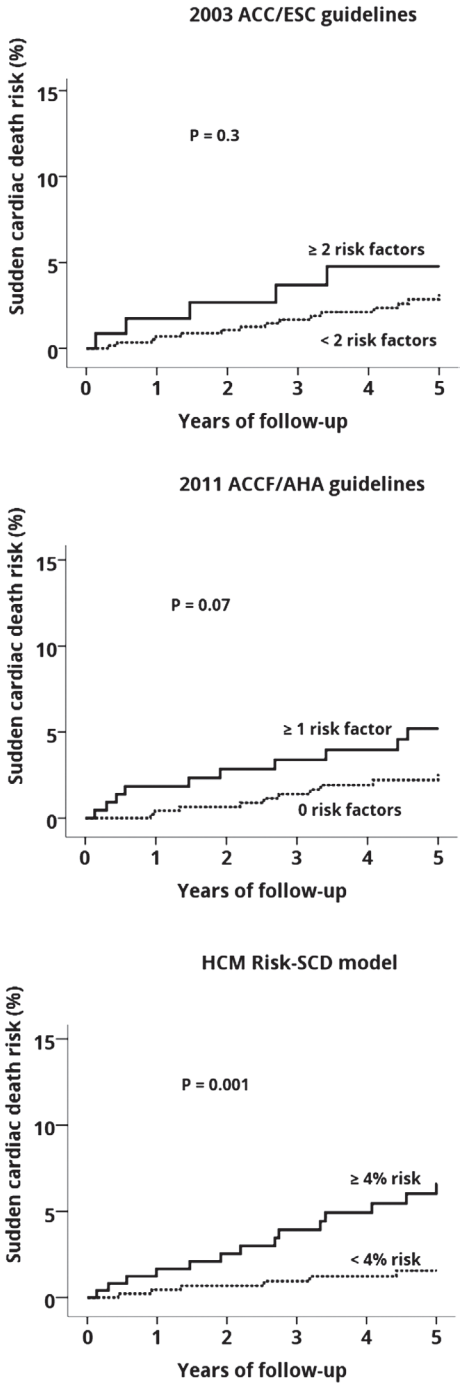


FIGURE 3 – Kaplan Meier estimates of SCD risk in 706 HCM patients, based on the 2003 ACC/ESC guidelines, 2011 ACCF/AHA guidelines, and HCM Risk-SCD model (SCD risk ≥4%/5-year).

TABLE 4 – ICD implantations and 5-year risk of SCD based on the HCM Risk-SCD model, and 2003 and 2011 risk prediction models

	Patients with SCD		Patients without SCD	
n = 706	**ICD**	**No ICD**	**ICD**	**No ICD**
2003 guidelines (≥2 established risk factors)	5 (25)	15 (75)	111 (16)	575 (84)
2011 guidelines (≥1 established risk factor)	10 (50)	10 (50)	210 (31)	476 (69)
HCM Risk-SCD score ≥4%	14 (70)	6 (30)	229 (33)	457 (67)

Data are represented as number (percentage). HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; SCD: sudden cardiac death.

To prevent 1 case of SCD in 5 years, 17 ICD implantations are necessary when using the ≥4% cut-off. The 2003 guideline model requires 22 ICD implantations to prevent 1 SCD and the 2011 guideline model requires 20 ICD implantations (TABLE 4).

DISCUSSION

This study is the first independent and external validation of the novel clinical risk prediction model (HCM Risk-SCD) used in the 2014 ESC guidelines.[1, 6] The most important finding of this study is that in an independent setting, the HCM Risk-SCD score discriminates better between patients with high or low SCD risk, than the risk stratification models proposed by older clinical guidelines.

Identification of high risk patients

The 2003 and 2011 guidelines[3, 4] are based on the five aforementioned established risk factors to determine whether or not patients with HCM are at increased risk of SCD. O'Mahony et al. demonstrated in 2013 that both models are limited to discern high from low risk patients[5]. The HCM Risk-SCD model was developed to improve the risk stratification of HCM patients. Instead of an algorithm based on the sum of the established risk factors, as those guidelines do, this model calculates individual 5-year SCD risk estimates. Our results show that, in an independent setting, the ability to predict SCD by using the HCM Risk-SCD model (C-statistic = 0.69) is improved when compared with current guidelines (C-statistic = 0.55-0.60).

The biggest changes in the HCM Risk-SCD model, compared with the risk stratification models proposed by the older guidelines are the following: (1) abnormal blood pressure response during exercise is no longer included in the risk stratification; (2) increasing age is a protective factor; (3) LVWT is no longer regarded as dichotomous, but as a continuous variable; and (4) LA diameter and LVOT gradient are added as continuous risk factors. All

clinical variables are easily obtained, especially since abnormal blood pressure response during exercise is no longer a risk factor. Although there was a univariable association between blood pressure response and SCD[8], it remained unclear if it was only of clinical importance in patients ≤40 years old[7], or how the finding was related to the increase in dynamic LVOT gradient. In the 2011 guidelines the usefulness of ICD implantation in the presence of an abnormal blood pressure response as only risk factor was deemed uncertain (Class IIb, level of evidence C)[4], and it was excluded as potential risk factor in the HCM Risk-SCD model because it was not associated with SCD in any multivariable survival analyses[7, 9, 10]. Age is considered to be protective of SCD in this model. A number of studies have demonstrated that a younger age is associated with an increased risk of SCD[11-13], and a recent study showed a very low SCD risk in patients >60 years of age[14].

Cardiac remodeling and SCD

Another advantage of the new model is that the effects of cardiac remodeling on SCD are now considered. HCM is not a static disease and Olivotto et al. identified 4 clinical stages of HCM and demonstrated that disease progression is associated with an increase of SCD risk: from 0.5%-1%/year in patients with classic phenotype to 10%/year in patients with overt dysfunction[15]. This increase of risk is not considered in the conventional risk prediction models. The new HCM Risk-SCD model is partially based on factors of disease progression including maximal LVWT, LA diameter and LVOT gradient. These factors are, as mentioned above, included in the model as continuous variables, and changes herein are reflected in the SCD risk score.

ICD implantation for primary prevention of SCD

Patients that are considered at high risk for SCD should be considered for ICD implantation, after taking into account the potential complications of long-term ICD implantation[2]. The improved discriminatory power of the HCM Risk-SCD model might imply that more patients at increased risk (both intermediate and high risk) of SCD (a 5-year risk of 4-6% and ≥6%) are correctly identified and become eligible for ICD implantation, but also that unnecessary and potential harmful ICD implantations in patients without increased risk of SCD can be avoided. In our population, for every 17 ICD's implanted in patients with a 5-year risk of ≥ 4%, 1 patient could be saved from SCD at 5 years. This is similar with the 16 ICD implantations needed to prevent 1 SCD in the HCM Risk-SCD study, and lower than current risk stratification models. It is important to note that the calculated risk score is not a replacement of clinical judgment, but should be used as the authors state: "to complement clinical reasoning by providing objective individualized prognostic information."[6] This is in line with the 2011 guidelines that state: "The decision for placement of primary prevention ICD in HCM often involves a large measure of individual clinical judgment, particularly when evidence for risk is ambiguous. The potential for SCD needs to be discussed with each fully informed HCM

patient and family member in the context of their concerns and anxieties and should be balanced against the risks and benefits of proposed prophylactic ICD strategy."[4]

Model limitations and future developments

Further development of the model will determine the role of other clinical variables. SCD in HCM is assumed to originate from the myocardial disarray and scar tissue[7], 16, which is, for example, more present in patients with increased LVWT. Several studies have shown that the presence of extensive fibrosis, demonstrated by delayed gadolinium enhancement on cardiac magnetic resonance imaging, might increase the risk of SCD[17-20], but a recent meta-analysis did not show any relationship with SCD[21]. There is a relationship however between extensive delayed enhancement and progression to heart failure[22]. The additional value of delayed enhancement in the prediction of SCD could be assessed in a future version of the risk prediction model.

A similar approach can be used for genetics: it is not evident whether genetic information is predictive of outcome. Genotype was not predictive of appropriate ICD interventions[23], but patients with double or triple mutations are at increased risk of end-stage progression and ventricular arrhythmias[24]. Current DNA sequencing is expensive and time-consuming; especially if analysis has to be continued after the first mutation has been found. With next-generation sequencing it will be possible to screen for a larger number of genes, and it will possibly lead to identification of more patients carrying mutations. It might become easier to identify patients with multiple mutations and include this information in the individual risk stratification. In addition, specific electrocardiographical features, such as paced electrogram fractionation analysis, may provide further improvement of the risk model.[25] Finally, it is unclear how septal reduction therapy (both surgical myectomy and septal ablation) influences the individual SCD risk, and whether or not it is suffice to calculate the new 5-year risk by using the post-procedural LVOT gradient and LVWT. Several studies demonstrated that SCD rates after myectomy are low, but the SCD risk after septal ablation is more controversial.[26-29]

Study limitations

This study has several limitations. The comparison between different risk models is limited due to the small numbers of SCD events. Both participating centers are tertiary referral centers for the diagnostic and therapeutic care of HCM, and due to this selection and referral bias, the patient population might not represent the general HCM population. As rhythm documentation of the event was not available for all SCD cases, it was not possible to ascertain that all deaths were arrhythmic in nature. Also a more conservative setting would have influenced the occurrence of ICD interventions. Risk stratification was not complete in all patients: in 107 patients (15%) the exercise testing was lacking, and in 116 patients (16%) the Holter-monitoring. The same approach to missing data was used as in the HCM Risk-SCD study.[6]

CONCLUSION

The HCM Risk-SCD model improves the risk stratification of HCM patients, and calculating an individual risk estimate contributes to the clinical decision making process. Improved risk stratification is important for the decision making before ICD implantation for primary prevention of SCD.

REFERENCES

1. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C and Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2733-2779.
2. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, Ten Cate FJ and Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail. 2012;5:552-559.
3. Maron BJ, McKenna WJ, Danielson GK, Kappenberger JKB, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, Spirito P, Cate FJT and Wigle ED. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy - A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. European Heart Journal. 2003;24:1965-1991.
4. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice G, American Association for Thoracic S, American Society of E, American Society of Nuclear C, Heart Failure Society of A, Heart Rhythm S, Society for Cardiovascular A, Interventions and Society of Thoracic S. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761-2796.
5. O'Mahony C, Tome-Esteban M, Lambiase PD, Pantazis A, Dickie S, McKenna WJ and Elliott PM. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. Heart. 2013;99:534-541.
6. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM and Hypertrophic Cardiomyopathy Outcomes I. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J. 2014;35:2010-2020.
7. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG and McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36:2212-2218.
8. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP and McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation. 1997;96:2987-2991.
9. Gimeno JR, Tome-Esteban M, Lofiego C, Hurtado J, Pantazis A, Mist B, Lambiase P, McKenna WJ and Elliott PM. Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. Eur Heart J. 2009;30:2599-2605.
10. Efthimiadis GK, Parcharidou DG, Giannakoulas G, Pagourelias ED, Charalampidis P, Savvopoulos G, Ziakas A, Karvounis H, Styliadis IH and Parcharidis GE. Left ventricular outflow tract obstruction as a risk factor for sudden cardiac death in hypertrophic cardiomyopathy. Am J Cardiol. 2009;104:695-699.
11. Maki S, Ikeda H, Muro A, Yoshida N, Shibata A, Koga Y and Imaizumi T. Predictors of sudden cardiac death in hypertrophic cardiomyopathy. Am J Cardiol. 1998;82:774-778.

12. Kofflard MJ, Ten Cate FJ, van der Lee C and van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. J Am Coll Cardiol. 2003;41:987-993.
13. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barilla CS, Biagini E, Quarta G, Conte MR, Bruzzi P and Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119:1703-1710.
14. Maron BJ, Rowin EJ, Casey SA, Haas TS, Chan RH, Udelson JE, Garberich RF, Lesser JR, Appelbaum E, Manning WJ and Maron MS. Risk stratification and outcome of patients with hypertrophic cardiomyopathy >=60 years of age. Circulation. 2013;127:585-593.
15. Olivotto I, Cecchi F, Poggesi C and Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail. 2012;5:535-546.
16. Stroumpoulis KI, Pantazopoulos IN and Xanthos TT. Hypertrophic cardiomyopathy and sudden cardiac death. World J Cardiol. 2010;2:289-298.
17. Olivotto I, Maron BJ, Appelbaum E, Harrigan CJ, Salton C, Gibson CM, Udelson JE, O'Donnell C, Lesser JR, Manning WJ and Maron MS. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106:261-267.
18. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E and Maron MS. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation. 2014;130:484-495.
19. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, Das B, Khwaja J, Alpendurada FD, Wage R, Roughton M, McKenna WJ, Moon JC, Varnava A, Shakespeare C, Cowie MR, Cook SA, Elliott P, O'Hanlon R, Pennell DJ and Prasad SK. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. Heart. 2014;100:1851-1858.
20. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, Lesser JR, Hanna CA, Udelson JE, Manning WJ and Maron MS. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51:1369-1374.
21. Green JJ, Berger JS, Kramer CM and Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012;5:370-377.
22. Bruder O, Wagner A, Jensen CJ, Schneider S, Ong P, Kispert EM, Nassenstein K, Schlosser T, Sabin GV, Sechtem U and Mahrholdt H. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;56:875-887.
23. Vriesendorp PA, Schinkel AF, Van Cleemput J, Willems R, Jordaens LJ, Theuns DA, van Slegtenhorst MA, de Ravel TJ, ten Cate FJ and Michels M. Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications. Am Heart J. 2013;166:496-502.
24. Girolami F, Ho CY, Semsarian C, Baldi M, Will ML, Baldini K, Torricelli F, Yeates L, Cecchi F, Ackerman MJ and Olivotto I. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol. 2010;55:1444-1453.
25. Saumarez RC, Pytkowski M, Sterlinski M, Bourke JP, Clague JR, Cobbe SM, Connelly DT, Griffith MJ, McKeown PP, McLeod K, Morgan JM, Sadoul N, Chojnowska L, Huang CL and Grace AA. Paced ventricular electrogram fractionation predicts sudden cardiac death in hypertrophic cardiomyopathy. Eur Heart J. 2008;29:1653-1661.

26. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ and Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46:470-476.
27. ten Cate FJ, Soliman OI, Michels M, Theuns DA, de Jong PL, Geleijnse ML and Serruys PW. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail. 2010;3:362-369.
28. Veselka J, Tomasov P and Zemanek D. Long-term effects of varying alcohol dosing in percutaneous septal ablation for obstructive hypertrophic cardiomyopathy: a randomized study with a follow-up up to 11 years. Can J Cardiol. 2011;27:763-767.
29. Jensen MK, Prinz C, Horstkotte D, van Buuren F, Bitter T, Faber L and Bundgaard H. Alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy: low incidence of sudden cardiac death and reduced risk profile. Heart. 2013;99:1012-1017.

EDITORIAL

Prophylactic implantable defibrillators for hypertrophic cardiomyopathy: disarray in the era of precision medicine

Grace A

Circ Arrhythm Electrophysiol. 2015 Aug;8(4):763-6

Discussions with individuals and families affected by hypertrophic cardiomyopathy (HCM) concerning prophylactic implantable defibrillators (ICDs) will on occasion offer some new challenges. In a bold attempt to provide categorical answers, the European Society of Cardiology have incorporated a mathematical approach to risk prediction into their 2014 guidelines [1] that includes some risk factors (RFs) that are not broadly agreed and without any prior independent testing.[2] Furthermore, 2 groups have now examined how the guidance would have performed in their patients and arrived at essentially polar opposite conclusions on utility.[3,4]

HCM is common with a broad clinical expression and overall an annual sudden cardiac death (SCD) risk that is <1%.[5,6] It is the exemplar monogenic cardiac disorder and study of the underlying genetics has enhanced understanding of disease pathophysiology opening up candidate therapeutic approaches.[7] More complete follow-up along with multidisciplinary considerations of the range of treatment options has allowed better timing of surgical/non-surgical interventions.[1,6] Such progress has had a significant impact on improving patient outcomes, but there is the critical issue that we remain only modestly capable of identifying accurately the small subset that will benefit from an ICD.[1,3,4,8]

Why risk prediction remains so difficult has been extensively considered.[1,5] Despite large patient cohorts, it is the phenotypic diversity of HCM, the low SCD event rates, the long recruitment periods, evolving assessment methods and corresponding incomplete data that have all confounded clear answers. The only option for the provision of protection is the ICD and prospective, randomized comparisons have not been possible.[9] Accordingly, guidance has relied on cumulative clinical observation.[5,6,8] What is agreed is that individual RFs that have been associated with risk have low positive predictive power, in the range of 10% to 20%,5 and even with aggregate RF assessment sensitivity and specificity in regard to the prediction of SCD remains poor.[5] Family history is undoubtedly relevant, but epigenetic and other acquired influences have substantially greater impact on risk so that genetic studies have few roles in SCD risk assessment in the propositus.[1]

Possible RFs have been the subject of long-standing dispute on both their definition and relative importance.[1,4,10] These include syncope,[10] ventricular wall thickness, exercise-associated blood pressure responses, nonsustained ventricular tachycardia, and left ventricular outflow tract (LVOT) obstruction.11 One point that is striking is that neither the nature nor the number of RFs predicts ICD discharge.[9,12] Furthermore, factors previously not considered risk markers, eg, fractional shortening, have been associated with appropri-

ate shocks thereby again questioning individual RF validity.[12] Simply stacking up RFs has low predictive power strongly supported by an observational, retrospective, cohort study of 1606 patients in whom 5 RFs were assessed in their capacity to predict risk.[13] Although risk was seen to increase with multiple RFs, the C-statistic obtained from the receiver operating characteristic curve (in the range 0.61 to 0.64 at 5 years) indicated limited capacity to resolve risk.[13] These data essentially recapitulate prior evidence provided from a prospective evaluation of the same RFs.14 The results taken together provide substantial support for the view that softer but nonetheless effective contributions such as physician experience are crucial to making the right decisions.[1,4,5]

The HCM Risk-SCD algorithm has been presented with an aim "to develop and validate a new SCD prediction model that provides individualized risk estimates"[2] and is the basis of the European Society of Cardiology 2014 risk guidance.[1]The algorithm is based on a Cox proportional hazards model internally validated with boot strapping. The data populating the model was obtained from a retrospective, multicenter, longitudinal cohort study involving 3675 consecutively presenting patients. The model was developed across 5 sites (2082 patients) with validation at a further participating center (1593 patients). Seven continuous or binary RFs (age, maximal LV wall thickness, left atrial [LA] size, max. LVOT gradient, family history of SCD, nonsustained ventricular tachycardia, and unexplained syncope) derived from the literature and each independently associated with SCD in at least one multivariable survival analysis were then assessed in respect of the occurrence of SCD or appropriate ICD shocks. These events occurred in [almost equal to]5% of patients over a median follow-up of 5.7 years. Patients were then banded into one of 3 groups based on 5-year risks of SCD. If the 5-year risk was calculated at <4%, an ICD would not be recommended; if in the range 4% to 6%, it would be contingent; and if >6%, an ICD would be recommended. The C-statistic reported using this modified approach was 0.70. RFs can now be inputted into an online calculator and a recommendation obtained as to whether to recommend or seek out ICD implantation.[1]

The predictor variables included in the HCM Risk-SCD algorithm that have probably attracted most comment are LA enlargement and LVOT obstruction. At first pass, LA enlargement is not the most intuitively obvious potential predictor of the risk of SCD. The incorporation in the algorithm has been justified by a single observation in which LA enlargement conferred a relative risk of 1.03 (confidence interval, 1.00–1.06; P<0.04).[10] LA enlargement has been used, rather than the presence of atrial fibrillation, as we are told: "LA enlargement predisposes to atrial fibrillation and contained less missing data."[2] A further problem is that the association between atrial fibrillation and SCD in HCM has never been robust and in a recent study of 3673 patients, although atrial fibrillation enhanced overall risk, there was no significant influence on the risk of SCD.[15] The problems raised by the inclusion of LVOT obstruction mainly relate to frequency of occurrence, variability, and modest impact.[4]

The performance of the HCM Risk-SCD algorithm has now been assessed in an observational cohort design conducted in twin tertiary referral centers.[3] A total of 706 HCM

patients who had been under consideration for a prophylactic ICD have been included, and the end points of SCD-equivalent event (SCD, appropriate ICD discharge) was observed in 5.9% of patients at follow-up. Interestingly, basal LVOT gradient was >30 mm in 53% patients, and >30% of patients underwent interventions that could have had a significant impact on key inputs into the algorithm (LVOT gradient, LA size). Of course, we already know that relief of LVOT obstruction with myectomy is associated with subsequent low rates of SCD.[16] The research provides similar results to those in the first description of HCM Risk-SCD 2 with an improved C-statistic (0.69) when compared with derivations based on the 2003 [17] (C-statistic, 0.55) and 2011 [5] guidance (C-statistic, 0.60). Using this approach still required the implantation of 17 ICDs to save one life at the end of 5 years.

To directly test the algorithm, a US group has also retrospectively examined the clinical prediction capabilities of HCM Risk-SCD in 1629 consecutive patients followed up for a median of 6.4 years of whom 460 received ICDs.[4] Forty-six patients went on to receive appropriate ICD interventions, but 27 (59%) of this group had low HCM Risk-SCD scores that would have precluded an ICD recommendation. In addition, only 16 of the total of 81 (20%) who had an SCD-equivalent event had a high HCM Risk-SCD score along with a definite ICD recommendation. This group also tested the algorithm in a series of simulations providing examples of patients with large single RFs (who would not receive an ICD according to HCM Risk-SCD) and situations such as a combination of relative youth, LVOT obstruction, and increased LA size (who would not currently receive an ICD but in whom with uncritical application of HCM Risk-SCD would now get an ICD). The main conclusion was that application of HCM Risk-SCD might reduce the number of inappropriate ICDs but was thoroughly insensitive to the accurate identification of high-risk patients.[4]

In view of these various continuing issues, it is likely that most of us will (for now) steer clear of an algorithmic approach that might obscure useful raw data.[1,2] Some patients will undoubtedly access the HCM Risk-SCD algorithm, input their own data, and raise possibly challenging questions that will need to be addressed. To minimize such occurrences, a single, inclusive community effort in guideline formulation based on international cooperation should again be our aim.[17] Most experienced physicians will continue to take a careful history probing difficult aspects (family history, syncope), review all the data in multidisciplinary discussion, and reach a measured conclusion to take back to the well-informed patient. Patients without manifest RFs will be reassured in the knowledge that their risk is low and not too far away from the general population mean.[5] The question of risk will be revisited at future visits in the light of their further test results and accumulating research findings.[5] In those in whom an ICD is thought likely to provide net benefit, the simplest device possible for that patient should be used to minimize adverse risks.[12]This may be a single ventricular lead, single-coil transvenous unit but consideration should be made of the subcutaneous ICD, especially in young patients who will be especially prone to the issues emerging from both acute and progressive lead failure.[9,12,18,19]

The variable performance of the HCM risk-SCD algorithm again highlights the need for new methods to identify those at risk of ventricular fibrillation.[20] It is universally agreed that the source of risk is myocardial, and that the presence of myofibrillar disarray is a key determinant yet no current assessment method addresses this aspect directly.[5,6,14] The use of late gadolinium enhancement as a possible means of risk stratification is of great interest, but it is unlikely to be sensitive to the presence of disarray.21 Gadolinium is taken up into expanded extracellular spaces and detects large areas of scar tissue during washout but smaller patches of collagen, interstitial fibrosis, and disarray may not be detected.[21,22]Late gadolinium enhancement is, however, relevant to HCM-related heart failure outcomes,[22] and although the relationship to SCD outcomes is not yet secure and probably again modest, it associates with potential surrogates of SCD (hypertrophy, nonsustained ventricular tachycardia).22,23 The American College of Cardiology/American Heart Association guidelines support a potential role of late gadolinium enhancement in decision making 5 although whether the absence of late gadolinium enhancement predict those at low risk remains a point of much discussion.[8,23,24] The National Institutes of Health–funded HCMR (Novel Predictors of Outcome in HCM) study plans to recruit 2750 subjects with 5-year follow-up to address the question of the best use of advanced imaging in risk stratification and is due for completion in 2018.[25]

Developments of cardiac MRI technology, eg, T1 mapping,[26] will no doubt usefully input into phenotypic categorization. It would, however, appear that the architectural pattern not the density of fibrosis had the most impact on the electrophysiology of human cardiomyopathic hearts when studied ex vivo.[27,28] So while diffuse, short-strand fibrosis had marginal effects on conduction delay, patchy fibrosis with long fibrotic strands substantially delayed conduction [27] and such patterns are more likely to facilitate wavebreak and fibrillation.[29] The direction of wavefront activation is also of relevance to the occurrence of nonuniform anisotropic conduction with effects being the most prominent with activation perpendicular to fiber direction.[27] Clearly, some elements of this complex structural/functional milieu are going to be more amenable to noninvasive imaging than others.

Invasive electrophysiological assessment of patients with HCM is not usually recommended having fallen out of favor after disappointing, contentious responses to conventional ventricular stimulation.[1,5] Nonetheless, evidence of regional voltage variation, increased latency, and delayed conduction has been consistently observed.30,31 In addition, the feasibility of invasive assessment of electrograms with the aim of addressing the functional significance of myofibrillar disarray without arrhythmia induction has been reported.[14] The capacity of such approaches to enhance risk prediction was strongly supported in a prospective study of 179 patients followed up over 4 years. This investigation demonstrated that the electrophysiological approach predicted outcome with a high PPV (C-statistic, 0.88) although further validation is required.[14]

The ICD provides an effective means of protecting HCM patients from SCD but we must precisely target high-risk subcategories of the disease to gain most benefit.[32] To make further significant progress, we require a focus on deep phenotyping (imaging/electrophysiology) directed to the heart muscle to address the prognostic consequences of myofibrillar disarray. In the interim, as Spiegelhalter has pointed out, we should be cautious in the use of large data sets as "precision will delude us if selection bias and overinterpretation of associations as causation are not properly taken into account." [33]

REFERENCES

1. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2733–2779
2. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PMHypertrophic Cardiomyopathy Outcomes Investigators. . A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J. 2014;35:2010–2020
3. Vriesendorp PA, Schinkel AFL, Liebregts M, Theuns DAMJ, van Cleemput J, ten Cate FJ, Willems R, Michels M. Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol. 2015;8:829–835
4. Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent assessment of the european society of cardiology sudden death risk model for hypertrophic cardiomyopathy [published online ahead of print June 4, 2015]. Amer J Cardiol. 2015
5. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CWAmerican College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. . 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e783–e831
6. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RH, Garberich RF, Udelson JE, Maron MS. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. J Am Coll Cardiol. 2015;65:1915–1928
7. Ashrafian H, McKenna WJ, Watkins H. Disease pathways and novel therapeutic targets in hypertrophic cardiomyopathy. Circ Res. 2011;109:86–96
8. McKenna WJ, Nagueh SF. Cardiac magnetic resonance imaging and sudden death risk in patients with hypertrophic cardiomyopathy. Circulation. 2014;130:455–457
9. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes NA III, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298:405–412
10. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barillà CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119:1703–1710
11. Elliott P, Gimeno J, Tomé M, McKenna W. Left ventricular outflow tract obstruction and sudden death in hypertrophic cardiomyopathy. Eur Heart J. 2006;27:3073
12. O'Mahony C, Lambiase PD, Quarta G, Cardona M, Calcagnino M, Tsovolas K, Al-Shaikh S, Rahman SM, Arnous S, Jones S, McKenna W, Elliott P. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. Heart. 2012;98:116–125

13. O'Mahony C, Tome-Esteban M, Lambiase PD, Pantazis A, Dickie S, McKenna WJ, Elliott PM. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. Heart. 2013;99:534–541
14. Saumarez RC, Pytkowski M, Sterlinski M, Bourke JP, Clague JR, Cobbe SM, Connelly DT, Griffith MJ, McKeown PP, McLeod K, Morgan JM, Sadoul N, Chojnowska L, Huang CL, Grace AA. Paced ventricular electrogram fractionation predicts sudden cardiac death in hypertrophic cardiomyopathy. Eur Heart J. 2008;29:1653–1661
15. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. J Am Heart Assoc. 2014;3:e001002
16. McLeod CJ, Ommen SR, Ackerman MJ, Weivoda PL, Shen WK, Dearani JA, Schaff HV, Tajik AJ, Gersh BJ. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J. 2007;28:2583–2588
17. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH III, Spirito P, Ten Cate FJ, Wigle EDTask Force on Clinical Expert Consensus Documents. American College of Cardiology; Committee for Practice Guidelines. European Society of Cardiology. . American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2003;42:1687–1713
18. Burke MC, Gold MR, Knight BP, Barr CS, Theuns DA, Boersma LV, Knops RE, Weiss R, Leon AR, Herre JM, Husby M, Stein KM, Lambiase PD. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE Study and EFFORTLESS Registry. J Am Coll Cardiol. 2015;65:1605–1615
19. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. Circulation. 2007;115:2474–2480
20. Grace AA, Roden DM. Systems biology and cardiac arrhythmias. Lancet. 2012;380:1498–1508
21. Moon JC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, Petrou M, Pennell DJ. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;43:2260–2264
22. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, Das B, Khwaja J, Alpendurada FD, Wage R, Roughton M, McKenna WJ, Moon JC, Varnava A, Shakespeare C, Cowie MR, Cook SA, Elliott P, O'Hanlon R, Pennell DJ, Prasad SK. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. Heart. 2014;100:1851–1858
23. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation. 2014;130:484–495
24. Maron MS, Maron BJ. . Clinical impact of contemporary cardiovascular magnetic resonance imaging in hypertrophic cardiomyopathy. Circulation. 2015;132:292–298
25. US National Institutes of Health. . HCMR: Novel Markers of Prognosis in Hypertrophic Cardiomyopathy. https://clinicaltrials.gov/ct2/show/NCT01915615 Accessed July 25, 2015.

26. Puntmann VO, Voigt T, Chen Z, Mayr M, Karim R, Rhode K, Pastor A, Carr-White G, Razavi R, Schaeffter T, Nagel E. Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy. JACC Cardiovasc Imaging. 2013;6:475–484
27. Kawara T, Derksen R, de Groot JR, Coronel R, Tasseron S, Linnenbank AC, Hauer RN, Kirkels H, Janse MJ, de Bakker JM. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. Circulation. 2001;104:3069–3075
28. Glukhov AV, Fedorov VV, Kalish PW, Ravikumar VK, Lou Q, Janks D, Schuessler RB, Moazami N, Efimov IR. Conduction remodeling in human end-stage nonischemic left ventricular cardiomyopathy. Circulation. 2012;125:1835–1847
29. Engelman ZJ, Trew ML, Smaill BH. Structural heterogeneity alone is a sufficient substrate for dynamic instability and altered restitution. Circ Arrhythm Electrophysiol. 2010;3:195–203
30. Schumacher B, Gietzen FH, Neuser H, Schümmelfeder J, Schneider M, Kerber S, Schimpf R, Wolpert C, Borggrefe M. Electrophysiological characteristics of septal hypertrophy in patients with hypertrophic obstructive cardiomyopathy and moderate to severe symptoms. Circulation. 2005;112:2096–2101
31. Sakamoto N, Kawamura Y, Sato N, Nimura A, Matsuki M, Yamauchi A, Kanno T, Tanabe Y, Takeuchi T, Natori S, Saijo Y, Aburano T, Hasebe N. Late gadolinium enhancement on cardiac magnetic resonance represents the depolarizing and repolarizing electrically damaged foci causing malignant ventricular arrhythmia in hypertrophic cardiomyopathy. Heart Rhythm. 2015;12:1276–1284
32. Ashley EA. The precision medicine initiative: a new national effort. JAMA. 2015;313:2119–2120 doi: 10.1001/jama.2015.3595
33. Spiegelhalter DJ. Statistics. The future lies in uncertainty. Science. 2014;345:264–265

Chapter 10

Impact of adverse left ventricular remodeling on the risk of sudden cardiac death in patients with hypertrophic cardiomyopathy

Vriesendorp PA, Schinkel AF, de Groot NM, van Domburg RT, Ten Cate FJ, Michels M.

Clin Cardiol. 2014 Aug;37(8):493-8

ABSTRACT

Background:

Adverse left ventricular (LV) remodeling predicts heart failure symptoms and overt LV dysfunction in patients with hypertrophic cardiomyopathy (HCM), but its influence on the occurrence of SCD is unknown.

Hypothesis:

The aim of this study is to investigate the effect of adverse LV remodeling on sudden cardiac death (SCD) risk in patients with HCM.

Methods:

This study included 41 patients with HCM who experienced SCD; each case was matched with 3 controls based on age, gender, and time of first contact. In this population of 164 patients, predictors of SCD were identified using univariable and multivariable logistic regression and expressed as odds ratio (OR) with 95% confidence interval.

Results:

Baseline characteristics, such as NYHA class, systolic and diastolic left ventricular function, left ventricular wall thickness, left atrial size, atrial fibrillation and established risk factors for SCD, were similar in cases and controls. Independent predictors of SCD during follow-up (median follow-up: 7.7 ± 6.5 years) were : increase in NYHA class (OR 8.7 [2.5-30.5], p=0.001), decrease of fractional shortening (per % decrease, OR 1.09 [1.03-1.14], p=0.001), and decrease of diastolic function (OR 3.5 [1.2-10.2], p=0.02).

Conclusion:

This study shows that SCD risk in HCM increases when adverse remodeling occurs. Since cases and controls were similar at baseline, these findings emphasize the importance of vigilant follow-up of HCM patients and could aid clinical decision-making concerning ICD implantation, especially in patients with moderate risk for SCD.

INTRODUCTION

Sudden cardiac death (SCD) is the most devastating expression of hypertrophic cardiomyopathy (HCM). The annualized rate of SCD in HCM patients is presumed to be ± 1% per year.[1,2] Implantable cardioverter defibrillators (ICDs) have proven to be an effective way of preventing SCD in HCM patients, both in primary as in secondary prevention.[3-5] For secondary prevention there is universal agreement that ICDs should be implanted. The SCD risk in primary prevention is assessed by risk stratification based on the work of Elliott et al in 2000 [1,6] and updated to its current form in the 2011 ACCF/AHA guidelines.[7]

HCM is not a static disease and the guidelines recommend to repeat the risk stratification every 12-24 months. Recently Olivotto et al. [8] identified 4 clinical stages of HCM: non-hypertrophic HCM, classic phenotype, adverse remodeling and overt dysfunction. Adverse remodeling is characterized by the presence of unfavorable structural and functional changes and patients with adverse remodeling are presumed to be at increased risk of heart failure and overt dysfunction.[8-11] Characteristics of adverse remodeling as described by Olivotto et al. are the following: a decrease in systolic and diastolic left ventricular function (LVF) [11], left atrial (LA) and left ventricular (LV) dilatation[9,12], an increase in symptoms and functional limitations[9], the occurrence of atrial fibrillation (AF)[13], reduction or loss of LVOT obstruction[10,14] and thinning of LV walls[10]. The SCD risk increases from 0.5-1%/year for patients with the classic phenotype to 10%/year for patients with overt dysfunction, but the SCD risk of patients with adverse remodeling is unknown.[8] We performed therefore a case-control study to investigate the relation between adverse LV remodeling and the risk of SCD in HCM patients.

METHODS

Study design and patient population

This study included 41 patients with HCM who died because of SCD and 123 age and gender-matched control patients with HCM attending the adult outpatient clinic at the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands between January 1st, 1995 and December 31st, 2011. Each patient had an established diagnosis of HCM, based on unexplained left ventricular hypertrophy of ≥ 15 mm.[15] Patients with HCM linked to Noonan's syndrome, Fabry's disease, mitochondrial disease or congenital heart defects were excluded. Patients younger than 16 years were excluded. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board.

Cases were defined as HCM patients with SCD and controls as HCM patients without SCD. Patients with a prior SCD event before the study period or first contact were excluded. Cases were identified at the time of SCD and chart review was done retrospectively. SCD

is defined as death occurring < 1 hour from the onset of symptoms in patients who had previously experienced a relatively stable or uneventful clinical course. In this study SCD also included successfully resuscitated cardiac arrest or appropriate ICD intervention for ventricular fibrillation (VF) or fast (≥ 200 bpm) ventricular tachycardia (VT). Each case was matched with 3 controls based on the following parameters: age (± 1 years) and gender, and year of first contact (± 3 years).

Assessment of Adverse Remodeling

The following clinical characteristics and signs of adverse remodeling were examined at baseline and at last documented contact before SCD or end of follow-up: New York Heart Association (NYHA) functional class, maximal left ventricular wall thickness (LVWT), end systolic diameter (ESD), end diastolic diameter (EDD), LA size, LVOT gradient during rest and/or exercise, systolic LVF, diastolic LVF, the occurrence of AF (either persistent or paroxysmal), medical therapy and a history of septal reduction therapy (SRT), either alcohol septal ablation or myectomy.

Systolic LVF was evaluated by visual assessment of ejection fraction (EF) and scored as normal (EF > 55%), mildly reduced (EF 45-55%), moderate (EF 30-45%) and poor LVF (EF < 30%).[16] Additionally fractional shortening (FS) was calculated. Decrease of systolic LVF was defined as the decrease of >1 classification during follow-up (e.g. from normal to mildly reduced). Diastolic LVF was described as normal, abnormal relaxation (stage I), pseudo-normalization (stage II) and restrictive filling (stage III) and was based on the latest guidelines.[17,18] Decrease of diastolic LVF was defined as the decrease of ≥ 1 stage (e.g. from normal to abnormal relaxation).

Patient follow-up

Mortality was provided from civil service population registers and information provided by general practitioners and at the center where follow-up occurred. Clinical characteristics were retrieved from hospital patient records provided by the center where follow-up occurred.

Echocardiographic evaluation was independently performed by cardiologists with extensive experience in reading echocardiograms, who were blinded to clinical data. The administrative censoring date for follow-up in the control group was November 1st, 2012.

Statistical Analysis

SPSS version 20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for all statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data was expressed as median ± interquartile range. For comparing variables, means and medians χ^2-test, Student *t* test or Mann-Whitney U-test were used, for categorical and continuous data respectively. To identify clinical predic-

tors of SCD univariable and multivariable logistic regression analysis were used. Clinical variables - from last contact prior SCD or censoring date - were selected for backward stepwise multivariable analysis if univariable p-value was < 0.1 and were expressed as odds ratio (OR) with 95% confidence interval (CI). The final number of variables was restricted according to the number of end-points to avoid overfitting the multivariable model. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 41 cases of SCD were identified. Seventeen patients died, 11 were successfully resuscitated after cardiac arrest and 13 patients had appropriate ICD intervention for either VF or fast VT (> 200 bpm). Three controls per case were identified based on age, gender, and year of first contact, and thus the total study population consisted of 41 cases and 123 controls (TABLE 1). The majority of cases and controls were male (112 (66%) patients) with an average age of 46 ± 15 years (range 16-73) at baseline. No significant differences were described at baseline between cases and controls in NYHA class, diastolic LVF, EDD, ESCD, fractional shortening, LVOT gradient, maximal LVWT, and LA size. More cases had systolic impairment at baseline (9 (21%) patients and 9 (7%) patients, p=0.03). Both groups had similar numbers of patients with a family history for SCD, unexplained syncope and LVWT ≥ 30mm,

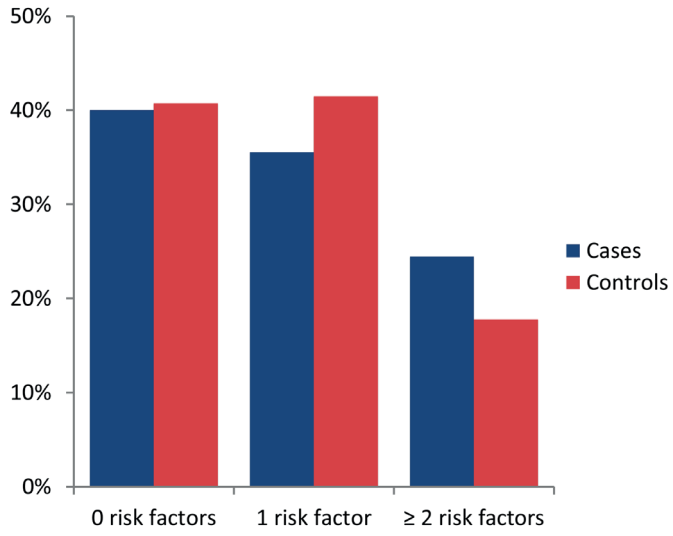


FIGURE 1 – Distribution of risk factors – Showing the distribution of the number of established risk factors for sudden cardiac death in 41 cases and 123 controls.

TABLE 1 – Baseline characteristics of 41 cases (SCD) and 123 controls (no SCD)

	SCD	*No SCD*	*p*
n =	*41*	*123*	
Age, y	45.6 ± 15	45.6 ± 15	1.0
Male	27 (66)	81 (66)	1.0
NYHA III/IV	18 (44)	41 (33)	0.2
Maximum LVWT, mm	22 ± 5	21 ± 5	0.4
Left atrial size, mm	48 ± 10	45 ± 8	0.07
LVOT gradient, mmHg	54 ± 48	51 ± 44	0.9
Left ventricular function			
End diastolic diameter, mm	45 ± 6	42 ± 6	0.07
Fractional shortening, %	45 ± 9	42 ± 9	0.2
Reduced ejection fraction (<55%)	9 (17)	9 (7)	**0.02**
Diastolic dysfunction	21 (51)	70 (57)	0.7
Risk factors for SD			
SCD in family history	9 (22)	21 (17)	0.5
nsVT on Holter-monitoring	9 (22)	19 (15)	0.3
Abnormal exercise BP response	5 (12)	7 (6)	0.6
Syncope	12 (30)	23 (19)	0.08
LVWT ≥ 30 mm	8 (20)	10 (8)	0.2
≥ 2 risk factors	11 (27)	17 (14)	0.06
Medication:			
Betablocker	14 (34)	60 (49)	0.1
Calcium channel blocker	11 (27)	35 (28)	0.8
Amiodarone	4 (10)	4 (3)	0.09

Data are presented as number (percentage) unless stated otherwise. BP: blood pressure; LVOT: left ventricular outflow tract; LVWT: left ventricular wall thickness; nsVT: non-sustained ventricular tachycardia; NYHA: New York Heart Association; SCD: sudden cardiac death

and distribution of major risk factors was comparable (FIGURE 1). The medication used to alleviate symptoms was not significantly different in both groups.

Follow-up

The median follow-up was 7.7 ± 6.5 years, 6.6 ± 8.0 years for cases and 7.9 ± 5.8 years for controls (p=0.01). Compared to the controls the cases showed increase of NYHA class,

TABLE 2 – Clinical characteristics at last evaluation of 41 cases (SCD) and 123 controls (no SCD)

	SCD	*No SCD*	*p*
n =	*41*	*123*	
Age, y	51.9 ± 16	53.8 ± 15	0.4
duration of follow-up, y	6.6 ± 8.0	7.9 ± 5.8	**0.01**
NYHA III/IV	14 (34)	7 (6)	**< 0.001**
Maximum LVWT, mm	20 ± 5	19 ± 4	**0.09**
Left atrial size, mm	52 ± 12	47 ±8	**0.01**
Atrial fibrillation	15 (37)	16 (13)	**0.001**
LVOT gradient, mmHg	29 ± 35	27 ± 30	0.8
Left ventricular function:			
End-diastolic diameter, mm	50 ± 10	45 ± 7	**0.002**
Fractional shortening, %	32 ± 10	42 ± 10	**< 0.001**
Reduced ejection fraction (< 55%)	18	19	**< 0.001**
Diastolic dysfunction	35	78	**< 0.02**
Septal reduction:			
Alcohol septal ablation	10 (24)	21 (17)	0.3
Myectomy	9 (22)	20 (16)	0.4

Data are presented as number (percentage) unless stated otherwise. LVOT: left ventricular outflow tract; LVWT: left ventricular wall thickness; NYHA: New York Heart Association; SCD: sudden cardiac death

TABLE 3 – Characteristics of adverse remodeling between 41 cases (SCD) and 123 controls (no SCD)

	SCD	*No SCD*	*p*
n =	*41*	*123*	
Increase of NYHA class, n (%)	13 (32)	9 (7)	**< 0.001**
Decrease of LVWT, mm	1 ± 5	2 ± 4	0.6
Increase of left atrial size, mm	4 ± 7	1 ± 5	**0.04**
Increase of end-diastolic diameter, mm	6 ± 9	2 ± 5	**0.04**
Decrease of fractional shortening, %	10 ± 11	0 ± 10	**< 0.001**
Decrease of systolic LV function, n (%)	17 (41)	13 (11)	**< 0.001**
Decrease of diastolic LV function, n (%)	19 (46)	29 (24)	**0.004**
Atrial fibrillation, n (%)	15 (37)	16 (13)	**0.001**

LV: left ventricular; LVWT: left ventricular wall thickness; NYHA: New York Heart Association; SCD: sudden cardiac death

decreased systolic and diastolic LVF, increased EDD, increased left atrial size, decrease of fractional shortening and a higher incidence of AF. Septal reduction therapy was performed in 19 (46%) cases and in 41 (33%) controls (p=0.3). (TABLE 2 and 3). LVOT gradient reduction in this group was from 93 ±36mmHg at baseline to 28 ±33 mmHg at last follow-up, and procedure was successful in 45 patients (76%). During follow-up, an ICD was implanted in 27 patients, in 19 (46%) cases and 8 (7%) controls (p < 0.001).

Predictors of SCD

TABLE 4 summarizes the results of univariable and multivariable analysis. Characteristics of adverse remodeling such as decrease in systolic and diastolic function, advancement of NYHA class, left atrial and ventricular dilation and decrease of fractional shortening were all significant predictors in univariable analysis. In multivariable analysis independent predictors for SCD were: fractional shortening (per % decrease, OR 1.09 [1.03-1.14], p=0.001), decrease of diastolic function (OR 3.5 [1.2-10.1], p =0.02), and increase of NYHA functional class (OR 8.7 [2.5-30.5], p=0.001).

Table 4. Analysis of clinical variables associated with sudden cardiac death in 164 HCM patients (41 cases and 123 controls)

	Univariate			*Multivariate*		
Predictor	OR	CI 95%	p	OR	CI 95%	p
Indicators of adverse LV remodeling:						
Increase of NYHA Class	5.8	2.2-14.9	**< 0.001**	8.7	2.5-30.5	**0.001**
Decrease of systolic left ventricular function	6.0	2.6-14.0	**< 0.001**			
Decrease of diastolic left ventricular function	3.0	1.3-6.4	**0.005**	3.5	1.2-10.1	**0.02**
Decrease of LVWT (per mm)	1.0	0.9-1.1	0.5			
Increase of end-diastolic diameter (per mm)	1.09	1.02-1.15	**0.008**	1.01	0.93-1.09	0.8
Decrease of fractional shortening (per %)	1.09	1.04-1.15	**< 0.001**	1.08	1.03-1.14	**0.003**
Increase of left atrial diameter (per mm)	1.07	1.01-1.14	**0.02**			
Atrial fibrillation	3.9	1.7-8.8	**0.001**	2.3	0.5-10.7	0.3
Additional predictors:						
Alcohol septal ablation	1.6	0.7-3.7	0.3			
Surgical myectomy	1.4	0.6-3.5	0.4			
≥2 risk factors	2.3	1.0-5.4	0.06			

CI: confidence interval; HCM: hypertrophic cardiomyopathy; LA: left atrial; LVOT: left ventricular outflow tract; LVWT: left ventricular wall thickness; NYHA: New York Heart Association; OR: odds ratio

DISCUSSION

The findings of this study suggest that the presence of signs of adverse LV remodeling in HCM patients increases the risk for SCD. Additionally, deterioration of the NYHA functional class and decrease of systolic and diastolic LV function are predictors of SCD in HCM patients.

A decrease of systolic function (in this study identified by LV dilatation, a decrease in fractional shortening and visual assessment of the EF) is more prevalent in the cases than in the controls. The increased risk of SCD in HCM patients with a low EF is already established, not only in general heart disease but also in HCM [9-11,19]. Our findings suggest that not only a low EF but the decrease of systolic function (EF < 55%) on its own increases the risk of SCD. The same statement can be made for diastolic dysfunction. Not only is a severe diastolic dysfunction a strong independent predictor for SCD, [20] but deterioration of diastolic LV function indicates an increased risk of SCD.

Current risk stratification for SCD is based on 5 major risk factors identified in the last two decades. This includes a detailed family history of SCD, a personal history of unexplained syncope, the assessment of maximal LVWT, Holter monitoring and blood pressure response to exercise. HCM patients are at increased risk in case of a family history of SCD in first-degree relatives, an LVWT of ≥ 30 mm and a personal history of syncope. In these patients ICD implantation is considered reasonable (Class IIa, level of evidence: C). Other indications are the presence of non-sustained ventricular tachycardia on Holter-monitoring or abnormal blood pressure response during exercise-testing, especially in presence of other potential risk modifiers for SCD, such as the presence of left ventricular outflow tract (LVOT) obstruction ≥ 30 mmHg, left ventricular apical aneurysms or delayed enhancement on magnetic resonance imaging [7,21]. The presence of delayed enhancement correlates with ECG changes[22], and has an trend toward significance for the risk of SCD [23]. Although SCD does occur in patients with no risk factors, there is consensus not to implant an ICD in these patients.

Risk stratification in patients with only 1 risk factor remains a gray area, in which the presence of the aforementioned potential arbitrators may lead to implantation of an ICD. This is a relevant clinical challenge as in our population 72 (40%) patients had only 1 major risk factor (FIGURE 1). The presence of signs of adverse LV remodeling could aid clinical decision making in these patients. If signs of adverse LV remodeling are present, it could be considered an additional argument towards implanting an ICD. In patients with no classic risk factors, the presence of signs of adverse remodeling could trigger repeating the risk stratification.

Both guidelines [1,7] advise to repeat the risk stratification every 12-24 months. However, this is an arbitrary time-interval, and with the results of our study it should be advised to repeat the risk stratification when the aforementioned signs of adverse LV remodeling are identified. Additionally, as our results imply that adverse LV remodeling is also a potential arbitrator, it should be evaluated at every repeated risk stratification.

Furthermore, it is important to note that at baseline both cases and controls were similar and no independent predictors for SCD could be identified. It was only during follow-up that differences between both groups were identified. This underscores the importance of vigilant follow-up of HCM patients, not only repeating the SCD risk stratification and evaluating systolic and diastolic LVF and symptoms to determine if adverse LV remodeling is present.

Limitations

This study has several limitations. This study was performed in a referral center for patients with HCM, therefore selection bias may have influenced the study results. The findings in this study will not be helpful in the first assessment of the patient, as baseline characteristics should be known, and the patient should be followed over time. This made data collection limited to variables that were routinely collected and novel developments during follow-up period were difficult to include. For this reason, advanced echocardiographic imaging such as strain rate imaging and cardiac magnetic resonance information was insufficient to use in this study. Rhythm documentation of the event was not available for all SCD cases. Considering appropriate ICD shocks as SCD endpoint could overestimate the SCD rate. A greater proportion of patients in the SCD group had septal ablation (24% vs. 17%) or myectomy (22% vs. 16%) than those without SCD. Although the incidence of septal reduction therapy was not statistically significant between the groups, the confounding effect of septal reduction therapy cannot be excluded, because the study may not be powered sufficiently to adjust for this variable in the multivariable model.

CONCLUSION

Adverse LV remodeling is not only a predictor for heart-failure and overt dysfunction in HCM patients, but these patients are also at increased risk for SCD. This can only be identified during vigilant follow-up of HCM patients as initial screening might not show any signs of adverse remodeling. During follow-up not only should current risk stratification be repeated, but signs of adverse remodeling should be evaluated. It also implies that SCD occurs not only in the young and asymptomatic but especially when the disease progresses.

REFERENCES

1. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, 3rd, Spirito P, Ten Cate FJ, Wigle ED, Task Force on Clinical Expert Consensus Documents. American College of C, Committee for Practice Guidelines. European Society of C. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687-713.
2. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308-20.
3. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes NA, 3rd, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007;298:405-12.
4. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, Ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail 2012;5:552-9.
5. Vriesendorp PA, Schinkel AF, Van Cleemput J, Willems R, Jordaens LJ, Theuns DA, van Slegtenhorst MA, de Ravel TJ, Ten Cate FJ, Michels M. Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: Patient outcomes, rate of appropriate and inappropriate interventions, and complications. Am Heart J 2013;166:496-502.
6. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, Mahon NG, McKenna WJ. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212-8.
7. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice G, American Association for Thoracic S, American Society of E, American Society of Nuclear C, Heart Failure Society of A, Heart Rhythm S, Society for Cardiovascular A, Interventions, Society of Thoracic S. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
8. Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 2012;5:535-46.
9. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation 2006;114:216-25.
10. Maron BJ, Spirito P. Implications of left ventricular remodeling in hypertrophic cardiomyopathy. Am J Cardiol 1998;81:1339-44.
11. Olivotto I, Maron BJ, Appelbaum E, Harrigan CJ, Salton C, Gibson CM, Udelson JE, O'Donnell C, Lesser JR, Manning WJ, Maron MS. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. Am J Cardiol 2010;106:261-7.
12. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, Conte MR, Casazza F, Galderisi M, Maron BJ, Cecchi F. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol 2006;98:960-5.
13. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 2001;104:2517-24.
14. Ciro E, Maron BJ, Bonow RO, Cannon RO, Epstein SE. Relation between marked changes in left ventricular outflow tract gradient and disease progression in hypertrophic cardiomyopathy. Am J Cardiol 1984;53:1103-9.

15. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-6.
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing G, American Society of Echocardiography's G, Standards C, European Association of E. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
17. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.
18. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-50.
19. Melacini P, Basso C, Angelini A, Calore C, Bobbo F, Tokajuk B, Bellini N, Smaniotto G, Zucchetto M, Iliceto S, Thiene G, Maron BJ. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. Eur Heart J 2010;31:2111-23.
20. Biagini E, Spirito P, Rocchi G, Ferlito M, Rosmini S, Lai F, Lorenzini M, Terzi F, Bacchi-Reggiani L, Boriani G, Branzi A, Boni L, Rapezzi C. Prognostic implications of the Doppler restrictive filling pattern in hypertrophic cardiomyopathy. Am J Cardiol 2009;104:1727-31.
21. Maron BJ. Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Circulation 2010;121:445-56.
22. Song BG, Yang HS, Hwang HK, Kang GH, Park YH, Chun WJ, Oh JH. Correlation of electrocardiographic changes and myocardial fibrosis in patients with hypertrophic cardiomyopathy detected by cardiac magnetic resonance imaging. Clin Cardiol 2013;36:31-5.
23. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging 2012;5:370-7.

Chapter 11

Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis.

Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ,
ten Cate FJ, Michels M.

Circ Heart Fail. 2012 Sep 1;5(5):552-9

ABSTRACT

Background

Previous observational studies demonstrated that hypertrophic cardiomyopathy (HCM) patients at risk for sudden cardiac death (SCD) may benefit from implantable cardioverter defibrillator (ICD) therapy. A complete overview of outcome and complications after ICD therapy is currently not available. This study pools data from published studies on outcome and complications after ICD therapy in patients with HCM.

Methods and Results

A PubMed database search returned 27 studies on 16 cohorts reporting outcome and/or complications after ICD therapy in HCM patients. In case of >1 publications on a particular cohort, the publication with the largest number of patients was included in the meta-analysis. ICD interventions, complications, and mortality rates were extracted, pooled and analyzed. There were 2190 patients (mean age 42 y, 38% women), most of whom (83%) received an ICD for primary prevention of SCD. Risk factors for SCD were left ventricular wall thickness ≥30 mm (20%), family history of SCD (43%), non-sustained ventricular tachycardia (46%), syncope (41%), and abnormal blood pressure response (25%). During 3.7 year follow-up, annualized cardiac mortality rate was 0.6%, non-cardiac mortality rate 0.4%, and appropriate ICD intervention rate 3.3 %. Annualized inappropriate ICD intervention rate was 4.8% and annualized ICD related complication rate was 3.4%.

Conclusion

This meta-analysis demonstrates a low cardiac and non-cardiac mortality rate after ICD therapy in patients with HCM. Appropriate ICD intervention occurred at a rate of 3.3%/year, thereby most probably preventing SCD. Inappropriate ICD intervention and complications are not uncommon.

INTRODUCTION

Patients with hypertrophic cardiomyopathy (HCM) are at increased risk for sudden cardiac death (SCD), mostly caused by ventricular arrhythmias. SCD may occur as the initial presentation of HCM, often in asymptomatic or mildly symptomatic patients (1). In fact, HCM is the most frequent cause of SCD in young people, including trained athletes (2,3). Implantable cardioverter defibrillator (ICD) therapy may effectively terminate potentially life threatening ventricular arrhythmias, thereby preventing SCD and prolonging life. Still, ICD therapy is not without risk, because inappropriate interventions and device related complications may occur.

Previous observational studies have reported on the use of ICD therapy for primary and secondary prevention of SCD in HCM (4-30). A complete overview of outcome and complications after ICD therapy in HCM patients at risk for SCD is currently not available. The goal of this analysis was to pool the individual studies in an effort to examine the precise rate of cardiac and non-cardiac mortality, appropriate and inappropriate interventions, and complications. This knowledge may aid clinical decision making and counselling in HCM patients at increased risk for SCD considered for ICD therapy.

METHODS

Study Design

This systematic review and meta-analysis included all available original studies reporting clinical outcome and/or complications in HCM patients who underwent ICD implantation. Studies that did not provide data on outcome or complications and review manuscripts were excluded. Studies focussing on SCD in HCM patients without ICD were excluded.

Literature search

The online MEDLINE database was searched for literature in March 2012 using PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, Maryland). The search strategy was: "hypertrophic cardiomyopathy" and "defibrillator". No time restriction for publication dates was used. All titles and abstracts of the articles were evaluated. After exclusion based on the title and abstract, full articles were evaluated, and articles meeting the inclusion criteria were identified. In addition, a manual search of the reference lists of the identified studies was performed, and references were evaluated using the same inclusion and exclusion criteria.

Data Extraction

Selected studies were reviewed and relevant patient characteristics, known risk factors for SCD, and follow-up duration were registered. Extracted outcome parameters were: cardiac mortality, non-cardiac mortality, heart transplant, appropriate ICD intervention, inappropriate ICD intervention, and complication including lead malfunction, infection, lead displacement, psychological complication and total complications. The outcome parameter total complications included all reported ICD related complications, except inappropriate ICD intervention, this parameter was registered separately. No time restriction for complications was used; both early and late complications were included in the analysis. Studies with overlapping data were identified, and in cases of apparent serial reporting of a particular patient cohort, only the publication with the largest number of patients was included in the meta-analysis. However, all serial publications on a particular cohort were registered and tabulated.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington) and SPSS version 15.0 (SPSS Inc., Chicago, Illinois). Continuous variables were reported as mean. Categorical variables were summarized as percentages. The total number of risk factors for SCD was divided by the total number of patients to assess the average number of risk factors per patient. Heterogeneity among the studies was assessed using the Q test and I^2 index. Random effects model was used to calculate summary estimates of the outcome data. From the pooled data, summary estimates of patient characteristics and risk factors for SCD were calculated. Meta-analysis of the outcome data was performed and weighted event rates and weighted annualized event rates were calculated. Forest plots were constructed using the method of Neyeloff et al. (31).

RESULTS

Search Results

The literature search yielded 469 articles (FIGURE 1). After review, exclusion, and cross-referencing, a total of 27 observational studies were included in the systematic review (TABLE 1). Overall, 16 different patient cohorts were identified in these 27 studies (4-30). Because of apparent serial reporting of patient cohorts, and to avoid duplicate entering of data, only 1 study per patient cohort was included in the meta-analysis. Hence, the summary estimate of clinical data and outcome is based on 16 studies (4,7,9,12-14,16,18-20,24-28,30). Thirteen (81%) studies reported on a population of HCM patients with an ICD for primary or secondary prevention of SCD, 1 (8%) study focused on HCM patients with an ICD for primary prevention of SCD, 2 (13%) studies reported on hypertrophic obstructive cardiomyopathy (HOCM) patients who underwent alcohol septal ablation (ASA), and had received an ICD.

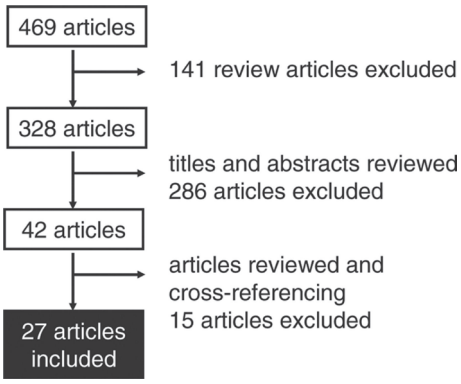


FIGURE 1 – Flow chart of the literature searches and study selection. The initial search yielded 469 eligible studies, 141 review articles were excluded. The remaining 328 studies were evaluated, and on basis of title and abstract, 286 articles were considered unrelated and were excluded. The remaining 42 articles were evaluated and after cross-referencing, a total of 27 articles were included in the systematic review and meta-analysis. A total of 15 articles were excluded, because of the following reasons: not all patients had HCM (n = 2), not all patients had an ICD (n = 4), no follow-up data (n = 1), study on socio-economical aspects (n = 2), editorial or case-report (n = 6).

Patient Characteristics

There were 2190 patients (mean age 42 y, 38% women), most of whom (83%) received an ICD for primary prevention of SCD. Risk factors for SCD were left ventricular wall thickness ≥30 mm (20%), family history of SCD (43%), non-sustained ventricular tachycardia (46%), syncope (41%), and abnormal blood pressure response (25%). Patients had on average 1.8 risk factors for SCD. HOCM was present in 27% of the patients.

ICD Interventions and Outcome

During 3.7 year follow-up, 311 of 2190 (14%) of the patients had an appropriate ICD intervention (TABLE 2). Annualized appropriate ICD intervention rate was 3.3% (FIGURE 2). Data on inappropriate ICD intervention was available in 13 studies. Inappropriate ICD intervention occurred in 388 of 1966 (20%) of the patients. Annualized inappropriate ICD intervention rate was 4.8% (FIGURE 3). Mortality data was reported in 13 studies: there were 53 (3%) cardiac deaths and 49 (2%) non-cardiac deaths. Annualized cardiac mortality rate was 0.6%, and annualized non-cardiac mortality rate was 0.4%. Five studies reported follow-up data on heart transplantation, this occurred in 28 of 1214 patients (2%), and annualized heart transplantation rate was 0.5%.

Complications

Information on ICD related complications was available in 9 of 16 studies including a total of 1691 patients (TABLE 2). Of them, 260 (15%) had any form of ICD related complication. The most frequently observed complication was lead malfunction in 118 (7%). Other complications

TABLE 1 – Summary of the studies reporting ICD therapy in patients with hypertrophic cardiomyopathy.

Cohort	Region	Author	Year	Population	n	Mean age (y)	Women %	Primary prevention %	Secondary prevention %	LVWT ≥30 mm %	Family history of SCD %	NSVT %	Syncope %	Abnormal BPresponse %	HOCM %
Aalst, Barcelona	Belgium, Spain	Primo (4)	1998	HCM and ICD	13	48	38	77	23	0	NA	NA	46	NA	38
London	UK	Elliott (5)	1999	HCM with VT/VF	6	19	NA	100	0	NA	17	33	50	67	NA
		Pablo Kaski (6)	2007	ICD in children with HCM	22	14	41	77	23	50	55	5	32	68	36
		O'Mahony (7)	2012	HCM and ICD	334	40	38	92	8	15	51	48	39	33	23
ICD in HCM Registry	US, Italy	Maron (8)	2000	HCM and ICD	128	40	31	66	34	8	30	25	32	NA	18
	US, Europe, Australia	Maron (9)	2007	HCM and ICD	506	42	36	76	24	24	51	46	47	NA	5
	US, Australia	Maron (10)	2009	HCM and appropriate ICD intervention	63	43	29	65	35	NA	NA	NA	NA	NA	14
	US, Australia	Sherrid (11)	2009	HCM and ICD	330	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NIH	US	Begley (12)	2003	HCM and ICD	132	34	39	36	64	23	41	63	39	26	38
Sydney	Australia	Jayatilleke (13)	2004	HCM and ICD	22	NA	NA	82	18	50	36	27	41	23	NA
Minneapolis	US	Almquist (14)	2005	HCM and ICD	75	37	35	95	5	29	NA	NA	NA	NA	20
		Maron (15)	2009	HCM and VT/VF	39	34	44	46	54	23	41	47	NA	NA	16
Bielefeld	Germany	Lawrenz (16)	2005	HOCM, ICD, and ASA	15	53	47	40	60	NA	33	33	33	17	100
Warsaw	Poland	Przybylski (17)	2005	HCM and ICD	46	32	59	39	61	17	50	54	63	70	17
		Syska (18)	2010	HCM and ICD	104	35.6	55	75	25	NA	NA	65	NA	NA	NA

TABLE 1 – continued

Cohort	Region	Author	Year	Population	n	Mean age (y)	Women %	Primary prevention %	Secondary prevention %	LVWT ≥30 mm %	Family history of SCD %	NSVT %	Syncope %	Abnormal BPresponse %	HOCM %
Alicante, Murcia, La Coruna	Spain	Marin (19)	2006	HCM and ICD	45	42.8	38	60	40	29	31	64	47	56	44
Sao Paulo	Brazil	Medeiros (20)	2006	HCM and ICD	26	42.7	54	62	38	19	58	46	77	NA	NA
Rochester	US	Cha (21)	2007	HCM and ICD for primary prevention	68	43	40	100	0	NA	56	62	29	5	NA
		McLeod (22)	2007	HCM and ICD	125	41.0	38	94	6	6	49	38	36	26	56
		Kiernan (23)	2008	HCM, ICD, and no ASA or myectomy	69	43.5	29	97	3	1	54	46	30	30	20
		Lin (24)	2009	HCM and ICD	181	44	38	86	14	16	56	41	40	1	20
Toronto	Canada	Woo (25)	2007	HCM and ICD	61	46	34	82	18	15	46	5	25	NA	NA
Charleston	US	Cuoco (26)	2008	HCM, ASA and ICD for primary prevention	123	48	34	100	0	11	38	NA	63	34	100
10 centers	UK, Poland, France	Saumarez (27)	2008	HCM and ICD for primary prevention	179	NA	44	100	0	16	13	35	19	22	NA
7 centers	US	Hauser (28)	2008	HCM and ICD	324	47	33	91	9	NA	NA	NA	NA	NA	30
Minneapolis, Rochester	US	Bos (29)	2010	HCM and ICD for primary prevention	177	45.3	37	100	0	14	51	36	43	11	24
Bad Oeynhausen	Germany	Prinz (30)	2010	HCM and ICD	50	44	34	96	4	26	28	44	36	30	50
Summary estimate (16 cohorts)					2190	42.3	38	83	17	20	43	46	41	25	27

TABLE 2 – Summary of clinical outcome.

\	Author	Year	Follow-up (y)	Appropriate intervention %	Inappropriate intervention %	Complications %				Mortality %			
						Lead malfunction	Infection	Lead displacement	Psychological	Any	Cardiac	Non-cardiac	Heart transplant %
Aalst, Barcelona	Primo (4)	1998	2.2	15	23	0	0	8	NA	8	0	0	NA
London	Elliott (5)	1999	6.1	50	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Pablo Kaski (6)	2007	1.7	18	18	5	5	NA	8	18	0	0	0
	O'Mahony (7)	2012	3.6	8	16	5	6	4	NA	18	3	1	3
ICD in HCM Registry	Maron (8)	2000	3.1	23	25	9	2	NA	1	14	NA	NA	NA
	Maron (9)	2007	3.7	20	27	7	4	NA	NA	12	4	4	2
	Maron (10)	2009	NA	100	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Sherrid (11)	2009	3.7	17	NA	NA	NA	NA	NA	NA	NA	NA	NA
NIH	Begley (12)	2003	4.8	20	23	5	3	NA	4	28	3	2	2
Sydney	Jayatilleke (13)	2004	2.9	32	9	NA	5	NA	NA	5	NA	NA	NA
Minneapolis	Almquist (14)	2005	3.6	7	NA	3	NA	3	NA	8	3	0	NA
	Maron (15)	2009	9.4	41	28	NA	NA	NA	NA	NA	13	5	NA
Bielefeld	Lawrenz (16)	2005	3.4	27	20	NA	NA	NA	NA	NA	0	20	NA
Warsaw	Przybylski (17)	2005	2.4	28	30	7	4	2	NA	13	0	2	4
	Syska (18)	2010	4.6	26	35	13	5	2	NA	24	2	2	NA
Alicante	Marin (19)	2006	2.7	22	29	NA	2	NA	NA	NA	0	4	NA
Sao Paulo	Medeiros (20)	2006	1.6	15	NA	NA	NA	NA	NA	NA	4	0	NA

TABLE 2 – continued

\	Author	Year	Follow-up (y)	Appropriate intervention %	Inappropriate intervention %	Complications %				Mortality %			
						Lead malfunction	Infection	Lead displacement	Psychological	Any	Cardiac	Non-cardiac	Heart transplant %
Rochester	Cha (21)	2007	3.4	13	15	NA	NA	NA	NA	NA	NA	NA	NA
	McLeod (22)	2007	4.4	10	NA	NA	NA	NA	NA	NA	2	2	NA
	Kiernan (23)	2008	4.4	17	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Lin (24)	2009	4.9	16	23	13	4	NA	NA	26	3	8	2
Toronto	Woo (25)	2007	3.3	13	33	13	NA	NA	NA	NA	2	0	2
Charleston	Cuoco (26)	2008	2.9	7	NA	NA	NA	NA	NA	NA	NA	NA	NA
10 centers	Saumarez (27)	2008	4.3	3	3	NA	NA	NA	NA	NA	1	0	NA
7 centers	Hauser (28)	2008	3.3	11	12	5	0.3	3	NA	7	1	2	NA
Minneapolis, Rochester	Bos (29)	2010	4.6	14	27	NA	NA	NA	NA	NA	3	5	NA
Bad Oeynhausen	Prinz (30)	2010	2.0	10	6	NA	NA	NA	NA	NA	NA	NA	NA
Event rate (95% CI)				13.7 (9.9-17.5)	19.0 (12.6-25.4)	6.2 (4.1-8.3)	3.1 (1.2-5.0)	2.7 (1.6-3.9)	3.8 (0.5-7.1)	14.9 (9.9-19.9)	2.2 (1.5-2.8)	1.4 (0.8-1.9)	2.2 (1.3-3.0)
Annualized event rate				3.3 (2.2-4.4)	4.8 (2.9-6.7)	1.5 (0.9-2.1)	0.6 (0.1-1.0)	1.0 (0.5-1.4)	0.8 (-0.8-2.3)	3.4 (2.5-4.3)	0.6 (0.2-0.9)	0.4 (0.1-0.7)	0.5 (0.1-1.0)

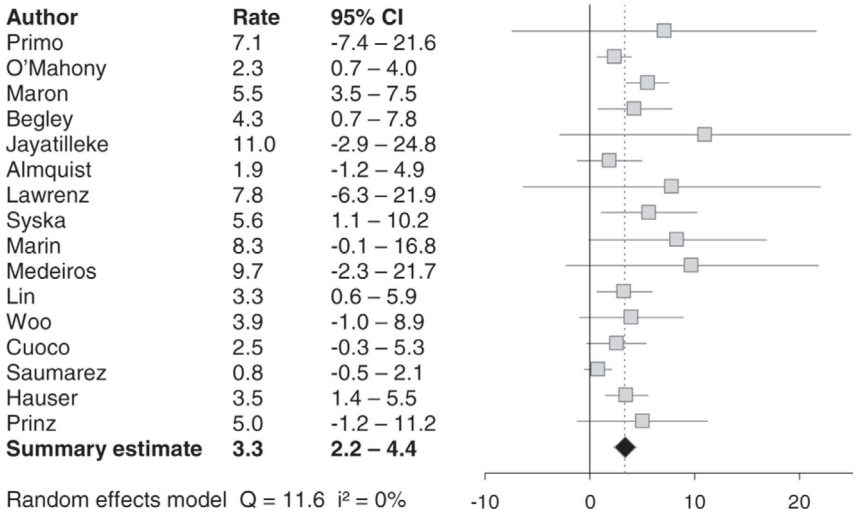


FIGURE 2 – Forest plot of annualized appropriate ICD intervention rate (%/year).

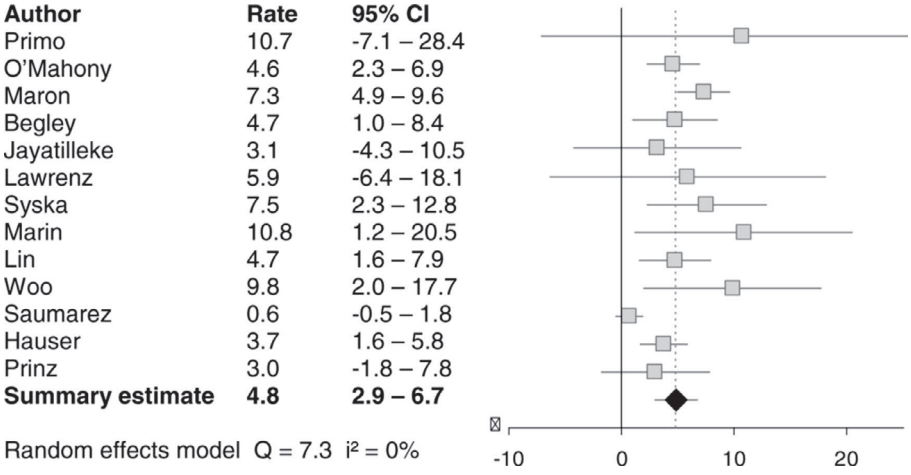


FIGURE 3 – Forest plot of annualized inappropriate ICD intervention rate (%/year).

were infection in 59 (3%) and lead displacement in 28 (3%). Only 1 study provided information on psychological complications, these occurred in 5 of 132 (4%) patients.

DISCUSSION

This meta-analysis demonstrates a low cardiac and non-cardiac mortality rate after ICD therapy in patients with HCM. In HCM patients with on average 1.8 risk factors for SCD,

appropriate ICD intervention occurred at a rate of 3.3%/year, thereby most probably preventing SCD. These findings emphasize the importance of ICD therapy in HCM patients at risk for SCD.

Current ACCF/AHA guidelines (32) recommend comprehensive SCD risk stratification at initial evaluation and on a periodic basis (every 12 to 24 months) for patients with HCM. A personal history for ventricular fibrillation, sustained VT or SCD is recommended and established risk factors for SCD should be evaluated. ICD placement is recommended (class I recommendation) for patients with HCM and prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant VT. A comparable decision strategy for ICD implantation for secondary prevention of SCD was applied in the studies included in the present analysis. In the pooled analysis, 17% of the HCM patients received an ICD for secondary prevention of SCD.

For primary prevention of SCD in HCM patients, the guideline state that it is reasonable to recommend (class IIa recommendation) an ICD for patients with HCM with SCD presumably related to HCM in ≥1 first-degree relatives, or a maximum LV wall thickness ≥30 mm, or ≥1 recent unexplained syncopal episodes (32). An ICD can be useful in select patients with NSVT in the presence of other SCD risk factors or modifiers, or with an abnormal blood pressure response to exercise in the presence of other SCD risk factors or modifiers. It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation.

In the present analysis, the majority of the studies did not provide clear information on the clinical decision strategy for ICD implantation for primary prevention of SCD. Complete information on all 5 established risk factors for SCD in HCM patients was available in only 7 of 16 (44%) cohorts. Primary prevention of SCD in HCM patients depends on the presence of SCD risk factors and modifiers; therefore complete information on all established risk factors is highly relevant. All reported cohorts were collected before publication of the current practice guideline on HCM, and it is not certain that the results from the pooled analysis also apply to HCM patients that currently receive an ICD. Nevertheless, the present analysis demonstrates that HCM patients with an ICD had on average 1.8 risk factors for SCD. Consequently the population in the pooled analysis was at high-risk for SCD, and is probably comparable to the population that should be considered for ICD implantation according to the current guideline (32).

The pooled analysis demonstrates that inappropriate ICD intervention and complications are not uncommon (4.8%/year and 3.4%/year respectively). Previous studies suggested that HCM patients are more vulnerable to ICD related complications and inappropriate ICD therapy because of young age at implant and increased prevalence of atrial fibrillation (24). Reports from large ICD registries including predominantly patients with ischemic heart disease demonstrate an early complication rate varying from 3.3% to 11% during the hospital

admission for ICD implantation (33, 34). Long-term follow-up data on ICD-related complications in general practice are not available, hampering comparison of the inappropriate ICD intervention and ICD-related complication rates observed in HCM patients. Most HCM patients who underwent ICD implantation were young (mean age 42 y), and therefore the risk of ICD related complications should be carefully considered and discussed with the patient during the decision making process before implantation. This is particularly relevant because of the long periods that young patients will live with the implanted device and leads. Only 1 study (6) reported the occurrence of ICD related psychological complications. The psychological and behavioural aspects of ICD therapy in HCM patients should receive more attention because many HCM patients considered for ICD therapy are otherwise healthy and often asymptomatic young individuals.

Limitations

This systematic review and meta-analysis has inherent limitations. The data were extracted from observational studies. A potential risk of pooling data from different studies is to mix patients with different clinical characteristics and SCD risk profile. The decision strategy for ICD implantation was not specified in most studies. The currently available studies have reported on outcome and complications after ICD therapy in populations with predominantly adult HCM patients, except the study of Pablo Kaski (6). More information is desired concerning ICD therapy in children and adolescents with HCM. Data on cycle length of the arrhythmia and type of arrhythmia were not available in the majority of the studies. Finally, the first report was from 1998, and over the years significant progress in ICD devices and leads has been made, and experience with implantation and follow-up has increased.

Future studies

ICD therapy has proven benefits in HCM patients at increased risk for SCD. Future studies on ICD therapy for prevention of SCD in HCM patients are needed to refine risk stratification for SCD, and to define the role of other risk markers including cardiac magnetic resonance imaging. There are indications that HCM patients with extensive delayed enhancement on contrast-enhanced cardiac magnetic resonance imaging are at increased risk of ventricular arrhythmias. Efforts to further reduce inappropriate ICD intervention and complication rates may have substantial clinical and financial benefits. Authors of future reports on ICD therapy in HCM patients are encouraged to provide complete information on clinical characteristics of the study population, established clinical risk factors for SCD, decision strategy for ICD implantation, and device related complications and outcome (including at least appropriate and inappropriate ICD intervention, and cardiac and non-cardiac mortality).

CONCLUSIONS

This meta-analysis demonstrates a low cardiac and non-cardiac mortality rate after ICD therapy in patients with HCM. Appropriate ICD intervention occurred at a rate of 3.3%/year, thereby most probably preventing SCD. Inappropriate ICD intervention and complications are not uncommon (4.8%/year and 3.4%/year respectively). The benefits and risks of ICD therapy in HCM patients should be carefully weighted.

REFERENCES

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA.* 2002;287:1308-1320.
2. Maron BJ. Sudden death in young athletes. *N Engl J Med.* 2003;349:1064-1075.
3. Kim JH, Malhotra R, Chiampas G, d'Hemecourt P, Troyanos C, Cianca J, Smith RN, Wang TJ, Roberts WO, Thompson PD, Baggish AL; Race Associated Cardiac Arrest Event Registry (RACER) Study Group. Cardiac arrest during long-distance running races. *N Engl J Med.* 2012;366:130-140.
4. Primo J, Geelen P, Brugada J, Filho AL, Mont L, Wellens F, Valentino M, Brugada P. Hypertrophic cardiomyopathy: role of the implantable cardioverter-defibrillator. *J Am Coll Cardiol.* 1998;31:1081-1085.
5. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1999;33:1596-1601.
6. Pablo Kaski J, Tomé Esteban MT, Lowe M, Sporton S, Rees P, Deanfield JE, McKenna WJ, Elliott PM. Outcomes after implantable cardioverter-defibrillator treatment in children with hypertrophic cardiomyopathy. *Heart.* 2007;93:372-374.
7. O'Mahony C, Lambiase PD, Quarta G, Cardona M, Calcagnino M, Tsovolas K, Al-Shaikh S, Rahman SM, Arnous S, Jones S, McKenna W, Elliott P. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. *Heart.* 2012;98:116-125.
8. Maron BJ, Shen WK, Link MS, Epstein AE, Almquist AK, Daubert JP, Bardy GH, Favale S, Rea RF, Boriani G, Estes NA 3rd, Spirito P. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342:365-373.
9. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, Boriani G, Estes NA 3rd, Favale S, Piccininno M, Winters SL, Santini M, Betocchi S, Arribas F, Sherrid MV, Buja G, Semsarian C, Bruzzi P. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA.* 2007;298:405-412.
10. Maron BJ, Semsarian C, Shen WK, Link MS, Epstein AE, Estes NA 3rd, Almquist A, Giudici MC, Haas TS, Hodges JS, Spirito P. Circadian patterns in the occurrence of malignant ventricular tachyarrhythmias triggering defibrillator interventions in patients with hypertrophic cardiomyopathy. *Heart Rhythm.* 2009;6:599-602.
11. Sherrid MV, Cotiga D, Hart D, Ehlert F, Haas TS, Shen WK, Link MS, Estes NA 3rd, Epstein AE, Semsarian C, Daubert JP, Winters SL, Giudici MC, Maron BJ. Relation of 12-lead electrocardiogram patterns to implanted defibrillator-terminated ventricular tachyarrhythmias in hypertrophic cardiomyopathy. *Am J Cardiol.* 2009;104:1722-1726.
12. Begley DA, Mohiddin SA, Tripodi D, Winkler JB, Fananapazir L. Efficacy of implantable cardioverter defibrillator therapy for primary and secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol.* 2003;26:1887-1896.
13. Jayatilleke I, Doolan A, Ingles J, McGuire M, Booth V, Richmond DR, Semsarian C. Long-term follow-up of implantable cardioverter defibrillator therapy for hypertrophic cardiomyopathy. *Am J Cardiol.* 2004;93:1192-1194.
14. Almquist AK, Montgomery JV, Haas TS, Maron BJ. Cardioverter-defibrillator implantation in high-risk patients with hypertrophic cardiomyopathy. *Heart Rhythm.* 2005;2:814-819.
15. Maron BJ, Haas TS, Shannon KM, Almquist AK, Hodges JS. Long-term survival after cardiac arrest in hypertrophic cardiomyopathy. *Heart Rhythm.* 2009;6:993-997.
16. Lawrenz T, Obergassel L, Lieder F, Leuner C, Strunk-Mueller C, Meyer Zu Vilsendorf D, Beer G, Kuhn H. Transcoronary ablation of septal hypertrophy does not alter ICD intervention rates in high risk patients with hypertrophic obstructive cardiomyopathy. *Pacing Clin Electrophysiol.* 2005;28:295-300.

17. Przybylski A, Małecka L, Pytkowski M, Chojnowska L, Lewandowski M, Sterliński M, Maciag A, Ruzyłło W, Szwed H. Implantable cardioverter-defibrillators in patients with hypertrophic cardiomyopathy -- dilemmas and difficulties. *Kardiol Pol.* 2005;63:391-397.
18. Syska P, Przybylski A, Chojnowska L, Lewandowski M, Sterliński M, Maciag A, Gepner K, Pytkowski M, Kowalik I, Maczyńska-Mazuruk R, Ruzyłło W, Szwed H. Implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy: efficacy and complications of the therapy in long-term follow-up. *J Cardiovasc Electrophysiol.* 2010;21:883-889.
19. Marín F, Gimeno JR, Payá E, García-Alberola A, Pérez-Alvarez L, Fernández X, de la Morena G, Sogorb F, Castro-Beiras A, Valdés M, Martínez JG, Monserrat L. The implantable cardioverter-defibrillator and hypertrophic cardiomyopathy. Experience at three centers. *Rev Esp Cardiol.* 2006;59:537-544.
20. Medeiros P de T, Martinelli Filho M, Arteaga E, Costa R, Siqueira S, Mady C, Piegas LS, Ramires JA. Hypertrophic cardiomyopathy: the importance of arrhythmic events in patients at risk for sudden cardiac death. *Arq Bras Cardiol.* 2006;87:649-657.
21. Cha YM, Gersh BJ, Maron BJ, Boriani G, Spirito P, Hodge DO, Weivoda PL, Trusty JM, Friedman PA, Hammill SC, Rea RF, Shen WK. Electrophysiologic manifestations of ventricular tachyarrhythmias provoking appropriate defibrillator interventions in high-risk patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol.* 2007;18:483-487.
22. McLeod CJ, Ommen SR, Ackerman MJ, Weivoda PL, Shen WK, Dearani JA, Schaff HV, Tajik AJ, Gersh BJ. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. *Eur Heart J.* 2007;28:2583-2588.
23. Kiernan TJ, Weivoda PL, Somers VK, Ommen SR, Gersh BJ. Circadian rhythm of appropriate implantable cardioverter defibrillator discharges in patients with hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol.* 2008;31:1253-1258.
24. Lin G, Nishimura RA, Gersh BJ, Phil D, Ommen SR, Ackerman MJ, Brady PA. Device complications and inappropriate implantable cardioverter defibrillator shocks in patients with hypertrophic cardiomyopathy. *Heart.* 2009;95:709-714.
25. Woo A, Monakier D, Harris L, Hill A, Shah P, Wigle ED, Rakowski H, Rozenblyum E, Cameron DA. Determinants of implantable defibrillator discharges in high-risk patients with hypertrophic cardiomyopathy. *Heart.* 2007;93:1044-1045.
26. Cuoco FA, Spencer WH 3rd, Fernandes VL, Nielsen CD, Nagueh S, Sturdivant JL, Leman RB, Wharton JM, Gold MR. Implantable cardioverter-defibrillator therapy for primary prevention of sudden death after alcohol septal ablation of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2008;52:1718-1723.
27. Saumarez RC, Pytkowski M, Sterlinski M, Bourke JP, Clague JR, Cobbe SM, Connelly DT, Griffith MJ, McKeown PP, McLeod K, Morgan JM, Sadoul N, Chojnowska L, Huang CL, Grace AA. Paced ventricular electrogram fractionation predicts sudden cardiac death in hypertrophic cardiomyopathy. *Eur Heart J.* 2008;29:1653-1661.
28. Hauser RG, Katsiyiannis WT, Gornick CC, Almquist AK, Kallinen LM. Deaths and cardiovascular injuries due to device-assisted implantable cardioverter-defibrillator and pacemaker lead extraction. *Europace.* 2010;12:395-401.
29. Bos JM, Maron BJ, Ackerman MJ, Haas TS, Sorajja P, Nishimura RA, Gersh BJ, Ommen SR. Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. *Am J Cardiol*. 2010;106:1481-1486.
30. Prinz C, Vogt J, Bitter T, Muntean BG, Hering D, Horstkotte D, Faber L. Incidence of adequate ICD interventions in patients with hypertrophic cardiomyopathy supposed to be at high risk for sudden cardiac death. *Acta Cardiol.* 2010;65:521-525.

31. Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and Forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. *BMC Res Notes.* 2012;5:52.
32. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011;124:e783-831.
33. Reynolds MR, Cohen DJ, Kugelmass AD, Brown PP, Becker ER, Culler SD, Simon AW. The frequency and incremental cost of major complications among medicare beneficiaries receiving implantable cardioverter-defibrillators. *J Am Coll Cardiol.* 2006;47:2493-2497.
34. Peterson PN, Daugherty SL, Wang Y, Vidaillet HJ, Heidenreich PA, Curtis JP, Masoudi FA; National Cardiovascular Data Registry. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. *Circulation.* 2009;119:1078-1084.

Chapter 12

Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications.

Vriesendorp PA, Schinkel AF, Van Cleemput J, Willems R, Jordaens LJ, Theuns DA, van Slegtenhorst MA, de Ravel TJ, ten Cate FJ, Michels M.

Am Heart J. 2013 Sep;166(3):496-502

ABSTRACT

Background

Sudden cardiac death (SCD) is the most devastating complication of hypertrophic cardiomyopathy (HCM) but this can be prevented by an implantable cardioverter-defibrillator (ICD). The aim of this study is to evaluate HCM patients with ICDs for primary or secondary prevention of SCD.

Methods

The study population consisted of all HCM patients with an ICD in 2 tertiary referral clinics. Endpoints during follow-up were total and cardiac mortality, appropriate and inappropriate ICD intervention, and device related complications. Cox-regression analysis was performed to identify predictors of outcome.

Results

ICDs were implanted in 134 HCM patients (mean age 44 ± 17 years, 34% women, 4.2 ± 4.8 years follow-up). Annualized cardiac mortality rate was 3.4%/year and associated with NYHA class III/IV (HR 5.2 [2.0-14, p=0.002]) and cardiac resynchronization therapy (HR 6.3 [2.1-20, p=0.02]). Appropriate ICD interventions occurred in 38 patients (6.8%/year) and was associated with implantation for secondary prevention of SCD (HR 4.0 [1.8-9.1], p=0.001) and male gender (HR 3.3 [1.2-9.0], p=0.02). Inappropriate ICD intervention occurred in 21 patients (3.7%/year) and in 20 patients device related complications were documented (3.6%/year).

Conclusion

ICDs successfully abort life-threatening arrhythmias in HCM patients at increased risk of SCD with an annualized intervention rate of 6.8%/year. End-stage heart failure is the main cause of mortality in these patients. The annualized rate of inappropriate ICD intervention was 3.7%/year, whereas device related complications occurred 3.6%/year.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most prevalent (1:500 individuals) inheritable myocardial disease and the most common cause of sudden cardiac death (SCD) in young people and trained athletes.[1-3] The use of an implantable cardioverter-defibrillator (ICD) may prevent SCD and prolong life in HCM patients by terminating life-threatening arrhythmias.[4-6] With an incidence of SCD in HCM patients of 0.7-1.0% per year, careful selection of patients considered for ICD therapy is needed.[7-9] Moreover, ICD therapy has its drawbacks, as patients are subject to inappropriate interventions and device-related complications.[10]

Previous observational studies have confirmed that ICD therapy effectively prevents SCD in HCM patients.[6,11-16] However most of these previous studies did not provide a complete overview of total mortality, cardiac mortality, appropriate ICD interventions, inappropriate ICD interventions, and complications. Additionally, complete information on established risk factors[17] for SCD was not available in 44% of the studies in a recent meta-analysis.[18]

The goals of the current study are therefore: (1) to provide a complete overview of outcome and complications after ICD therapy in HCM patients at increased risk of SCD based on the established risk factors and (2) to identify predictors of outcome and complications in these patients.

METHODS

Study design and patient population

The study population consisted of 152 consecutive HCM patients who received an ICD between April 1994 and December 31st, 2011 at the Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands or the University Hospitals Leuven, Leuven, Belgium. All patients gave written informed consent for ICD implantation and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the institutional review board. Each patient had an established diagnosis of HCM, based on unexplained left ventricular hypertrophy of ≥ 15 mm.[9] Patients with HCM linked to Noonan's syndrome, Fabry's disease, mitochondrial disease or congenital heart defects were excluded.

ICDs were implanted for primary prevention of SCD, based on the presence of established major risk factors for SCD (non-sustained ventricular tachycardia (VT) on Holter-monitoring, unexplained syncope, abnormal blood pressure response during exercise testing, left ventricular wall thickness (LVWT) ≥ 30 mm or a family history of ≥ 1 HCM-related SCD in close relatives), or for secondary prevention of SCD in patients with a history of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT).[19,20] ICDs were also implanted in HCM patients who developed complete AV-block after alcohol septal ablation (ASA).

The following clinical characteristics and other less well-established risk factors for SCD were examined: gender, age at implantation, New York Heart Association (NYHA) functional class, indication for cardiac resynchronization therapy (CRT), atrial fibrillation (AF), left ventricular outflow tract (LVOT) obstruction, history of myectomy or ASA, the presence of delayed gadolinium enhancement on MRI, genotype, coronary artery disease (CAD), inducible VF during electrophysiological testing, and anti-arrhythmic medication used by patients. If genetic testing was applied, the following genes were screened for mutations: *cardiac myosin binding protein C* (MYBPC3), *β-cardiac myosin heavy chain* (MYH7), *myosin regulatory light chain* (MYL2), *cardiac troponin T* (TNNT2), *cardiac troponin* I (TNNI3), *α-actin,* and *α-tropomyosin*.

No extramural funding was used to support this work and the authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

Devices

Patients received single or dual-chamber ICDs, or biventricular ICDs if CRT was indicated[21], with transvenous lead systems. All devices were capable of antitachycardia and antibradycardia pacing, and can deliver shock therapy. The rate cutoff for detection of VF or VT and activation of antitachycardia pacing (ATP) was set at the discretion of the treating electrophysiologist.

Endpoints

Endpoints were total and cardiac mortality, appropriate ICD intervention, appropriate ICD shocks, inappropriate ICD shocks, and ICD related complications. Cardiac mortality was defined as SCD, death from stroke, death from end-stage heart failure, and heart transplantation. Patients undergoing heart-transplantation were censored at the time of the procedure. Mortality, ICD interventions, and complications were retrieved from hospital patient records, from civil service population registers, and from information provided by general practitioners or other centers where follow-up had occurred. All ICD interventions were evaluated by an experienced electrophysiologist. Appropriate ICD intervention was defined as an intervention (either shock or ATP) triggered by an arrhythmia that was ventricular in origin. Appropriate ICD shock was defined as an ICD shock triggered by a sustained ventricular arrhythmia. Inappropriate ICD shock was defined as ICD shocks triggered by non-sustained ventricular arrhythmias, supraventricular arrhythmias, sinus tachycardia, oversensing or device malfunction (e.g. lead fracture leading to inappropriate shocks). If revision or hospital readmission related to the device was required, it was identified as a major complication. Follow-up started at the time of ICD implantation. The administrative censoring date was set at July 1st, 2012.

Statistical Analysis

SPSS version 20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for all statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data was expressed as median ± interquartile range (IQR). For comparing variables either χ^2-test or Mann Whitney U-test were used, for categorical and continuous data respectively. Estimated survival and actuarial event-free rates from ICD intervention were calculated according to the Kaplan-Meier method and were compared using the log-rank test. Patients who underwent heart transplantation were censored alive on the day of transplantation. Cox regression analysis was used to determine predictors of outcome. Variables were selected for multivariable analysis if univariable p-value was < 0.10 and were expressed as hazard ratio (HR) with 95% confidence interval. The final number of variables was restricted according to the number of endpoint events to avoid overfitting the multivariable model. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

In total 152 HCM patients with an ICD were identified. Fifteen patients were excluded because they were lost to follow-up when they moved abroad and access to full medical records was not possible. Three patients with a subcutaneous ICD were also excluded for further analysis, although there were no events in these patients. In the final group of 134 patients, 93 patients (69%) received an ICD for primary prevention and 41 patients (31%) for secondary prevention. Patients who received an ICD for primary prevention (age 49 ± 16 years) tended to be older at implantation than patients who received an ICD for secondary prevention (age 44 ± 19 years, p = 0.08). The majority of patients was male (66%) and LVOT obstruction was present in 62 patients (46%). The clinical characteristics of these patients are summarized in TABLE 1.

Total follow-up time was 602 patient-years with a median follow-up of 4.2 ± 4.8 years and follow-up was completed in all included patients. Genetic analysis was performed in 85 patients and mutations were identified in 63 patients (47%); of these, 86% had mutations in the MYBPC3 and MYH7 genes. CRT was deemed necessary in 7 patients (5%, 4 males) according to the guidelines. These patients were in NYHA class III or IV at the time of implantation, EF ≤ 35% and there was a wide QRS-complex (≥ 120 ms). In two of these patients an initial dual chamber ICD was upgraded to a CRT device.

TABLE 1 – Baseline characteristics of 137 patients with hypertrophic cardiomyopathy and implantable defibrillators

Patients	**All patients**	**Primary prevention**	**Secondary prevention**
	134	*93*	*41*
Age at implant, y	47 ±17	49 ±16	44 ±19
Male gender	89 (66)	63 (68)	26
NYHA class III/IV	32 (24)	28 (30)	4 (10) *
Indication for CRT	7 (5)	6 (6)	1 (2)
Atrial fibrillation	43 (32)	33 (35)	10 (24)
Coronary artery disease	16 (12)	9 (10)	7 (17)
LVOT obstruction (> 30 mmHg)	62 (46)	45 (48)	17 (41)
Surgical myectomy	28 (21)	21 (23)	7 (17)
Alcohol septal ablation	23 (17)	18 (19)	5 (12)
Confirmed genetic mutation:			
- MyBPC3	43 (32)	28 (30)	15 (37)
- MyH7	11 (8)	9 (10)	2 (5)
- Other	6 (4)	5 (5)	1 (2)
Anti-arrhythmic medication:			
- β-blocker	91 (68)	68 (73)	23 (56)
- Amiodarone	23 (17)	16 (17)	7 (17)
- Calcium channel blocker	20 (15)	15 (16)	5 (12)
Risk factors:			
- Non-sustained ventricular tachycardia	58 (43)	55 (59)	3 (7) †
- Unexplained syncope	34 (25)	26 (28)	8 (20)
- Abnormal BP response at exercise	25 (19)	19 (20)	6 (15)
- Maximum LVWT ≥ 30 mm	10 (7)	9 (10)	1 (2)
- Family history of SCD	36 (27)	30 (32)	6 (15) *
- Total risk factors	1.2 ± 0.9	1.5 ± 0.9	0.6 ± 0.7 †

Data are presented as number (percentage) unless stated otherwise. *: p-value < 0.05; †: p-value < 0.001; BP: blood pressure; CRT: cardiac resynchronization therapy; LVOT: Left ventricular outflow tract; LVWT: left ventricular wall thickness; MyBPC3: Myosin bindin protein C-gene; MyH7: Myosin heavy chain-gene; NYHA: New York Heart Association; SCD: sudden cardiac death

Risk profile for SCD

The distribution of risk factors among 93 patients who received an ICD for primary prevention is shown in FIGURE 1; Non-sustained ventricular tachycardia (59%) was most frequently identified. On average patients had 1.5 ± 0.9 major risk factors for SCD; 29 patients (31%) had 1 risk factor and 50 patients (54%) had ≥ 2 risk factors. Fourteen patients (15%) received an ICD after ASA complicated by total AV-block. In the patients with 1 major risk factor the decision to implant an ICD was based on potential modifiers such as late gadolinium enhancement on MRI or the presence of inducible VF during electrophysiological testing (only performed in the years 2000-2005).

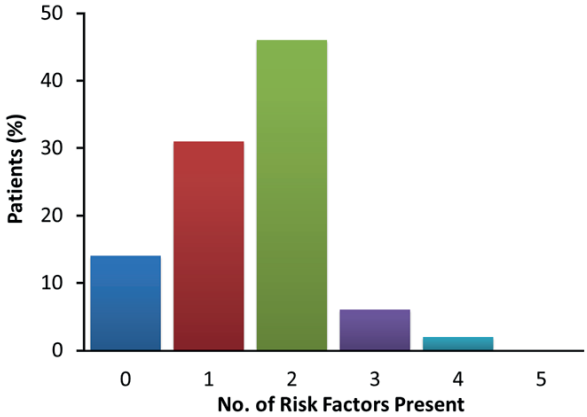


FIGURE 1 – The distribution of major risk factors for SCD in patients who received an ICD for primary prevention of SCD.

Cardiac mortality

During the median follow-up of 4.2 ± 4.8 years 14 patients (10.4%) died and in 11 patients (8.2%) the cause of death was cardiac and 3 patients (2.2%) died of non-cardiac causes. End-stage heart failure was the main cause for cardiac mortality leading to death in 9 patients (6.6%). The two other patients died as a consequence of having had VF, despite restoration of cardiac rhythm by ICD intervention. One patient with end-stage disease had no return of cardiac output, in the other the arrhythmia caused a severe motor vehicle accident because of syncope and ultimately leading to death. Also 8 patients (6.0%) underwent heart-transplantation. The annualized rate for the combined cardiac mortality endpoint was 3.4%/year. Multivariable analysis demonstrated that NYHA functional class III or IV (FIGURE 2A) and the indication for CRT were independent predictors of mortality. (TABLE 2)

Appropriate ICD interventions

Appropriate ICD interventions occurred in 38 patients (6.8%/year). The median time to first appropriate ICD intervention was 3.2 ± 4.5 years. Appropriate ICD shocks occurred in 29

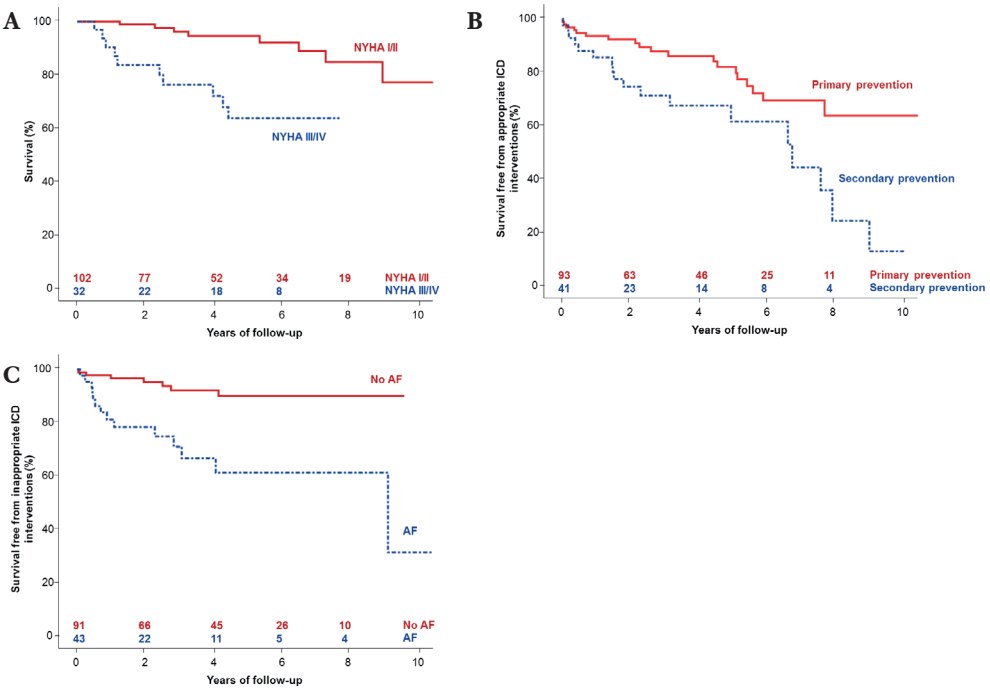


FIGURE 2 – Kaplan-Meier event-free survival for (A) the endpoint of cardiac mortality in patients with NYHA class I/II and II/IV at implantation, (B) the endpoint of appropriate ICD intervention in patients who received an ICD for primary or secondary prevention of SCD, and (C) the endpoint of inappropriate ICD intervention comparing patients with and without atrial fibrillation (AF).

patients. Of these patients, 18 (62%) received more than one appropriate ICD shock. In 15 patients (52%), the arrhythmia leading to the shock was VF. Multivariable analysis demonstrated that male gender and implantation of the ICD for secondary prevention were independent predictors of appropriate ICD intervention. (TABLE 3) The Kaplan-Meier curves demonstrating the event-free survival in patients who received an ICD for primary or secondary prevention of SCD are shown in FIGURE 2B. Twenty (22%) patients who received an ICD for primary prevention of SCD had an appropriate ICD intervention (5.1%/year), 13 patients (14%) received an appropriate ICD shock (3.3%/year).

Inappropriate ICD shocks

Inappropriate ICD shocks occurred in 21 patients (3.7%/year) and was caused by AF in 50% of the cases. The median time to first inappropriate shock was 3.3 ± 4.2 years after implantation. Fifteen (71%) of these patients had >1 inappropriate ICD shock. Patients with pre-existent AF (FIGURE 2C) were at increased risk for inappropriate ICD shock as were patients after surgical myectomy with or without mitral valve repair. (TABLE 4)

TABLE 2 – Analysis of clinical variables associated with cardiac mortality (19 events in 134 patients with hypertrophic cardiomyopathy)

Predictor	*Univariable*			*Multivariable*		
	HR	CI 95%	*p*	HR	CI 95%	*p*
Age at implantation, y	1.00	0.98-1.04	0.7			
Female	2.5	1.0 -6.3	0.06	2.3	0.9-5.8	0.09
NYHA III/IV	5.2	2.0-13.7	**0.001**	4.9	1.8-13.2	**0.002**
CRT-D	6.3	2.1-19.7	**0.001**	4.1	1.3-13.4	**0.02**
Atrial fibrillation	1.8	0.7-4.5	0.2			
Coronary artery disease	1.9	0.6-5.8	0.3			
LVOTO ≥ 30 mmHg	0.8	0.3-2.3	0.8			
Surgical myectomy	2.8	1.1-7.5	**0.04**	1.6	0.6-4.3	0.4
Alcohol septal ablation	0.03	0.0-3.1	0.1			
Sudden death survivor	0.6	0.2-1.8	0.4			
≥2 risk factors	2.4	0.9-6.1	0.08			
Genetic mutations:						
- MYBPC3	1.7	0.6-4.9	0.3			
- MYH7	3.4	0.9-13.5	0.08			
- MYL2	6.0	0.7-50.1	0.1			

Backwards multivariable Cox regression analysis was used. CI: confidence interval; CRT-D: cardiac resynchronization therapy – defibrillator; HR: hazard ratio; LVOTO: left ventricular outflow tract obstruction, MYBPC3: cardiac myosin binding protein; MYH7: myosin heavy chain; MYL2: myosin light chain; NYHA: New York Heart Association

In 89 patients (65%) the ICD was programmed in a dual-zone configuration with a median cycle length set for the VF-zone of 290ms (IQR 280-300) and 350ms (336-360) for VT-zone. Device settings, such as longer cycle length for VF-zone (HR 0.82, p=0.655) or VT-zone (HR 0.83, p=0.726), did not influence the frequency of inappropriate ICD shock. The amount of inappropriate ICD shocks was similar in patients with an atrial lead and patients without (14% vs. 17%, p = 0.7).

ICD related complications

ICD related complications are shown in FIGURE 3 and were diverse: pocket-infection, lead failure or dislocation, pneumothorax, and minor pocket related problems: pocket hematoma, severe wound pain requiring prolonged hospital stay, allergic reactions to device material, and migration of the device. Revision was necessary in 15 patients (11%), mostly because of lead dislocation/fracture or pocket related problems. During follow-up complications occurred

TABLE 3 – Analysis of clinical variables associated with appropriate ICD interventions (38 events in 134 patients with hypertrophic cardiomyopathy)

Predictor	*Univariable*			*Multivariable*		
	HR	CI 95%	*p*	HR	CI 95%	*p*
Age at implantation, y	0.99	0.97-1.01	0.3			
Male	2.8	1.2-6.5	**0.01**	3.3	1.2-9.0	**0.02**
NYHA III/IV	0.6	0.2-1.6	0.3			
Atrial fibrillation	1.1	0.6-2.2	0.8			
Coronary artery disease	4.1	0.9-18.6	0.06	1.9	0.4-8.7	0.4
LVOTO ≥ 30 mmHg	1.6	0.8-3.0	0.2			
Surgical myectomy	0.9	0.4-2.1	0.9			
Alcohol septal ablation	0.6	0.3-1.5	0.3			
Sudden death survivor	2.5	1.3-4.8	**0.005**	4.0	1.8-9.1	**0.001**
≥2 risk factors	0.9	0.5-1.8	0.8			
Genetic mutations:						
- MYBPC3	1.7	0.9-3.4	0.1			
- MYH7	1.0	0.2-4.1	0.9			
- MYL2	3.3	0.4-25.3	0.3			
- TNNI3	1.9	0.2-14.3	0.5			

Backwards multivariable Cox regression analysis was used. CI: confidence interval; HR: hazard ratio; LVOTO: left ventricular outflow tract obstruction, MYBPC3: cardiac myosin binding protein; MYH7: β-cardiac myosin heavy chain; MYL2: myosin regulatory light chain; NYHA: New York Heart Association; TNNI3: cardiac troponin I

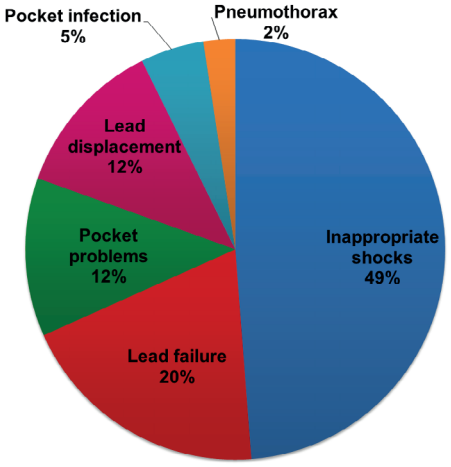


FIGURE 3 – Distribution of adverse events in 134 HCM patients with an ICD.

TABLE 4 – Analysis of clinical variables associated with inappropriate ICD interventions (21 events in 134 patients with hypertrophic cardiomyopathy)

Predictor	*Univariable*			*Multivariable*		
	HR	CI 95%	*p*	HR	CI 95%	*p*
Age at implantation, y	1.00	0.97-1.03	0.9			
Male	0.8	0.3-1.9	0.6			
NYHA III/IV	0.8	0.3-2.4	0.7			
Atrial fibrillation	5.4	2.2-13.4	**< 0.001**	5.4	2.2-13.4	**< 0.001**
Coronary artery disease	2.5	0.3-19.8	0.4			
Surgical myectomy	2.8	1.2-6.9	0.02	3.1	1.2-7.6	**0.02**
Alcohol septal ablation	0.4	0.09-1.6	0.2			
Sudden death survivor	0.9	0.3-2.3	0.8			
≥2 risk factors	0.6	0.2-1.5	0.3			
Device-related:						
Single lead (VVI)	1.2	0.5-2.8	0.7			
Atrial lead (DDD)	0.8	0.3-2.0	0.7			
CRT-D	1.0	0.1-7.2	1.0			
Implantation before 2007	2.2	0.9-5.6	0.09	2.4	0.9-6.0	0.07
VF-zone only	1.2	0.5-2.9	0.7			
VF-zone cycle length > 290 ms	0.8	0.3-1.9	0.6			

Backwards multivariable Cox regression analysis was used. CI: confidence interval; CRT-D: cardiac resynchronization therapy – defibrillator; HR: hazard ratio; LVOTO: left ventricular outflow tract obstruction; NYHA: New York Heart Association; VF: ventricular fibrillation

in 20 patients (3.5%/year) with lead failure in one third of the cases. None of the patients died because of device-related complications or required admission to an intensive care unit. Combining inappropriate ICD therapy and device-related complications, adverse ICD events occurred in 36 patients (6.4%/year). There was no difference in devices implanted before or after 2007 (HR 0.6, p=0.2).

DISCUSSION

The findings in this study demonstrate that in a consecutive group of HCM patients considered at increased risk of SCD, appropriate ICD interventions happened frequently (6.8%/year) and ICD interventions were effective at restoring sinus rhythm and cardiac output. With a median time to first shock of 3.2 years (3.4 years in primary prevention patients and

3.2 years in secondary prevention patients) this was remarkably longer than the time to first shock in ischemic cardiomyopathy: in the MADIT-trial 60% of the patients received the first appropriate ICD therapy in the first two years.[22] With SCD being prevented, the main cause of mortality in these patients was severe heart failure. Patients who received an ICD for secondary prevention of SCD more frequently had appropriate ICD interventions. This confirms that a history of VF or sustained VT is a strong predictor of having subsequent episodes as compared with primary prevention patients.

A recent meta-analysis[18] pooled the results of 16 studies reporting the outcome and complications of ICD therapy in a total of 2190 HCM patients (mean age 42 y, 38% women). Schinkel et al. found that the majority of patients (83%) received an ICD for primary prevention. During an average follow-up of 3.7 years, annualized cardiac mortality rate was 0.7%, non-cardiac mortality rate 0.7%, and appropriate ICD intervention rate 3.9 %. The relatively high appropriate ICD intervention rate found in our study may be caused by the fact that a larger proportion of our study population had an ICD for secondary prevention of SCD (31%). Also, the duration of our follow-up was somewhat longer and most arrhythmic events seem to occur several years after implantation.

The drawbacks of ICD therapy – inappropriate ICD shocks (3.7%/year) and device-related complications (3.5%/year) – were not uncommon. The rate of annualized inappropriate ICD shocks and ICD-related complications were similar between the findings of Schinkel et al.[18] and our study. These annual rates are substantial, and especially in young HCM patients the probability of complications cumulates considerably during lifetime. We found that patients with pre-existent AF were at increased risk for inappropriate ICD shocks, which has previously been reported both for HCM and non-HCM patients.[23,24] The presence of an atrial lead did not reduce the frequency of inappropriate ICD shocks in these patients significantly. Thus to prevent inappropriate ICD shocks, strict rate or rhythm control in HCM patients with AF is necessary, and so is good device programming.[25] In drug-refractory AF radiofrequency ablation can be attempted but it is in these patients still in a preliminary stage: its success-rate are mediocre and redo procedures are often necessary.[26]

The effectiveness of ICDs in HCM patients with an increased risk for SCD and the high appropriate ICD intervention rate show the importance of ICD therapy in these patients. In both centers the decision to implant an ICD was based on the latest recommendations or – after they were established – European guidelines.[19] Implantation for primary prevention was advised if ≥ 2 major risk factors were present or in the presence of 1 major risk factor and other individual SCD risk modifiers. In 29 patients (31%) the presence of 1 major risk factor and other less well-established risk factors was sufficient to implant an ICD. In this group the appropriate ICD intervention rate was 4.0%/year. Patients who received an ICD after ASA, even with no other risk factors present, showed comparable appropriate ICD intervention rates as other patients (respectively 14% and 13%). This suggests that ASA might be a potential risk factor on its own.[27] Recent findings link the amount (but not the presence) of

late gadolinium enhancement with an increased risk for SCD.[28] In our population there were insufficient MRI-data available to evaluate this.

We also found that genotype was not predictive of mortality or appropriate ICD interventions. Patients with double or triple mutations are at increased risk of end-stage progression and ventricular arrhythmias.[29] Current DNA sequencing is expensive and time-consuming, especially if analysis has to be continued after the first mutation has been found. With next-generation sequencing it will be possible to screen for a larger number of genes and it will possibly lead to identification of more patients carrying mutations and it might become easier to identify patients with multiple mutations and include this information in the individual risk stratification.

Limitations

This is a retrospective study and data collection is restricted to those variables that were routinely collected. For this reason, information from magnetic resonance imaging and echocardiographic information (e.g. ejection fractions) were not included. In 15 patients follow-up could not have been completed and were excluded from the analyses. This could have influenced the current results, especially concerning appropriate and inappropriate ICD interventions. Finally, this study covers a 17-year period in which there has been a considerable evolution in devices and expertise in implantation, which could have affected the outcome. But there was no difference in ICD-related complications or inappropriate interventions in ICDs implanted before or after 2007.

CONCLUSION

ICDs successfully abort life-threatening arrhythmias in HCM patients at increased risk of SCD with an annualized intervention rate of 6.8%/year. End-stage heart failure is the main cause of mortality in these patients. The annualized rate of inappropriate ICD intervention was 3.7%/year, whereas device related complications occurred in 3.6%/year.

REFERENCES

1. Maron BJ. Hypertrophic Cardiomyopathy. Circulation 2002;106:2419-21.
2. Maron BJ. Sudden death in young athletes. N Engl J Med 2003;349:1064-75.
3. Kim JH, Malhotra R, Chiampas G, et al. Cardiac arrest during long-distance running races. N Engl J Med 2012;366:130-40.
4. Maron BJ, Shen WK, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 2000;342:365-73.
5. Jayatilleke I, Doolan A, Ingles J, et al. Long-term follow-up of implantable cardioverter defibrillator therapy for hypertrophic cardiomyopathy. Am J Cardiol 2004;93:1192-4.
6. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007;298:405-12.
7. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of Hypertrophic Cardiomyopathy-Related Death : Revisited in a Large Non-Referral-Based Patient Population. Circulation 2000;102:858-64.
8. Elliott PM, Gimeno JR, Thaman R, et al. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. Heart 2006;92:785-91.
9. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-6.
10. Sherrid MV, Daubert JP. Risks and challenges of implantable cardioverter-defibrillators in young adults. Prog Cardiovasc Dis 2008;51:237-63.
11. Begley DA, Mohiddin SA, Tripodi D, et al. Efficacy of implantable cardioverter defibrillator therapy for primary and secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Pacing Clin Electrophysiol 2003;26:1887-96.
12. McLeod CJ, Ommen SR, Ackerman MJ, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. Eur Heart J 2007;28:2583-8.
13. Lin G, Nishimura RA, Gersh BJ, et al. Device complications and inappropriate implantable cardioverter defibrillator shocks in patients with hypertrophic cardiomyopathy. Heart 2009;95:709-14.
14. Bos JM, Maron BJ, Ackerman MJ, et al. Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. Am J Cardiol 2010;106:1481-6.
15. Syska P, Przybylski A, Chojnowska L, et al. Implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy: efficacy and complications of the therapy in long-term follow-up. J Cardiovasc Electrophysiol 2010;21:883-9.
16. O'Mahony C, Lambiase PD, Quarta G, et al. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. Heart 2012;98:116-25.
17. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. Eur Heart J 2003;24:1965-91.
18. Schinkel AF, Vriesendorp PA, Sijbrands EJ, et al. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail 2012;5:552-9.
19. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of

Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. Circulation 2006;114:e385-484.

20. Maron BJ. Risk Stratification and Role of Implantable Defibrillators for Prevention of Sudden Death in Patients With Hypertrophic Cardiomyopathy. Circulation Journal 2010;74:2271-82.
21. Dickstein K, Vardas PE, Auricchio A, et al. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Eur Heart J 2010;31:2677-87.
22. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999;341:1882-90.
23. Nanthakumar K, Dorian P, Paquette M, et al. Is inappropriate implantable defibrillator shock therapy predictable? J Interv Card Electrophysiol 2003;8:215-20.
24. Woo A, Monakier D, Harris L, et al. Determinants of implantable defibrillator discharges in high-risk patients with hypertrophic cardiomyopathy. Heart 2007;93:1044-5.
25. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275-83.
26. Di Donna P, Olivotto I, Delcre SD, et al. Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. Europace 2010;12:347-55.
27. ten Cate FJ, Soliman OI, Michels M, et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. Circ Heart Fail 2010;3:362-9.
28. Green JJ, Berger JS, Kramer CM, et al. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging 2012;5:370-7.
29. Girolami F, Ho CY, Semsarian C, et al. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol 2010;55:1444-53.

IV – Clinical implications of sarcomeric mutations

Chapter 13

Value of genetic testing for the prediction of long-term outcome in patients with hypertrophic cardiomyopathy

Van Velzen HG, Vriesendorp PA, Oldenburg RA,
Van Slegtenhorst MA, Van der Velden J, Schinkel AFL,
Michels M

Am J Cardiol. 2016 Jun 27. [Epub ahead of print]

ABSTRACT

Pathogenic gene mutations are found in about 50 % of hypertrophic cardiomyopathy (HC) patients. Previous studies have shown an association between sarcomere mutations and medium-term outcome. The association with long-term outcome has not been described. The aim of this cohort study was to assess the long-term outcomes of genotype positive (G+) and genotype negative (G-) HC patients. The study population consisted of 626 HC patients (512 probands, and 114 relatives) who underwent phenotyping and genetic testing between 1985 and 2014. End points were: all-cause mortality, cardiovascular (CV) mortality, heart failure (HF) related mortality and sudden cardiac death/aborted sudden cardiac death (SCD/aborted SCD). Kaplan Meier and multivariate cox regression analyses were performed. A pathogenic mutation was detected in 327 (52%) patients. G+ probands were younger than G- probands (46±15 vs 55±15 years, p<0.001), had more non sustained ventricular tachycardia (34% vs 13%; p<0.001), more often a history of syncope (14% vs 7%; p=0.016), and more extreme hypertrophy (maximal wall thickness ≥ 30 mm 7% vs 1%; p<0.001). G- probands were more symptomatic (NYHA ≥ II 73% vs 53%, p<0.001) and had higher left ventricular outflow tract gradients (42±39 vs 29±33 mmHg, p=0.001). During 12±9 years follow-up, G+ status was an independent risk factor for all-cause mortality (HR 1.90; 95% CI 1.14 –3.15; p=0.014), CV mortality (HR 2.82; 95% CI 1.49–5.36; p=0.002), HF related mortality (HR 6.33; 95% CI 1.79–22.41; p=0.004), and SCD/aborted SCD (HR 2.88; 95% CI 1.23–6.71; p=0.015). In conclusion, during long-term follow-up, G+ HC patients are at increased risk of all-cause death, CV death, HF related death, and SCD/aborted SCD.

INTRODUCTION

Hypertrophic cardiomyopathy (HC) is the most common inherited myocardial disease, with an estimated prevalence of 1 in 500.[1] Although the majority of patients with HC have a good prognosis, a small minority may experience life-threatening complications, such as heart failure (HF), sudden cardiac death (SCD) and atrial fibrillation, leading to stroke.[2] The difficulty in determining the prognosis of HC patients lies in the genetic and clinical heterogeneity. More than 1500 pathogenic mutations in at least 11 genes encoding thick and thin myofilament protein components of the sarcomere have been identified.[1] A pathogenic mutation is found in about 50% of HC patients.[3] Current guidelines advise to genotype HC patients in order to facilitate family screening.[4] The prognostic significance of genetic test results in patients with HC is still under debate. Previous studies have shown an association between sarcomere mutations and clinical outcome.[5-8] The follow-up duration in these studies varied from 1[5] to 6.6[7] years. Information on the value of genetic testing for the prediction of the long-term outcome in patients with HC is currently not available. Therefore, the aim of this study was to investigate the association between G+ status and long-term clinical outcome.

METHODS

This prospective cohort study included 626 HC patients (probands: n=512, 82%; relatives: n=114, 18%), who attended the cardio-genetic outpatient clinic between May 1985 and August 2014. Probands were defined as patients with HC who presented with signs or symptoms of HC. Relatives were defined as patients with HC who were identified via family screening. Each patient had an established diagnosis of HC based on maximal wall thickness (MWT) ≥ 15 mm unexplained by loading conditions, or ≥ 13 mm for relatives of HC patients. Patients with HC linked to other causes were excluded. The study conforms to the principles of the Declaration of Helsinki. All patients gave informed consent, and review board approval was obtained.

All patients underwent genetic counselling. Before the year 2012, DNA analysis consisted of direct sequencing of all coding intro-exon boundaries of the following genes: myosin binding protein C (*MYBPC3*), myosin heavy chain 7 (*MYH7*), regulatory myosin light chain 2 (*MYL2*), regulatory myosin light chain 3 (*MYL3*), troponin T (*TNNT2*), troponin I (*TNNI3*), cysteine and glycine-rich protein 3 (*CSRP3*), titin-cap/telethonin (*TCAP*), α-tropomyosin 1 (*TPM1*), cardiac muscle alpha actin (*ACTC1*), cardiac troponin C (*TNNC1*), and teneurin C-terminal associated peptides (*TCAP*). From 2012, next-generation-sequencing was used, covering the following genes: *ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CALR3, CAV3, CRYAB, CSRP3, CTNNA3, DES, DSC2, DSG2, DSP, EMD, FHL1, GLA, JPH2, JUP,*

LAMA4, LAMP2, LDB3, LMNA, MIB1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEXN, PKP2, PLN, PRDM16, PRKAG2, RBM20, SCN5A, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR and *VCL*. Variants were classified into classes: (I) benign; (II) likely benign; (III) variant of unknown clinical significance; (IV) likely pathogenic; or (V) pathogenic, adapted from the classification proposed by Plon et al.[9] Patients were considered G+ when the mutation was classified as class IV or V.

Follow-up data were obtained in November 2014, and was complete for 99 % of patients. Mortality was retrieved from the civil register. An electrophysiologist evaluated ICD interventions. The study end points were: all-cause mortality, CV mortality, HF related mortality, and SCD/aborted SCD. Cardiac transplantation was considered HF related mortality. CV mortality consisted of HF related death, SCD/aborted SCD, postoperative death after a cardiac intervention and stroke related death. SCD/aborted SCD was defined as: (1) instantaneous and unexpected death in patients who were previously in a stable clinical condition, or nocturnal death with no history of worsening symptoms; (2) resuscitation after cardiac arrest; or (3) ICD intervention for ventricular fibrillation or for fast ventricular tachycardia (>200 beats/min). Syncope was defined according to the guidelines.[4]

Statistical analyses were performed using SPSS 21 (IBM, Armonk, New York) and Microsoft Access 2010 (version 14.0.7143.5000). Unpaired t-test or the chi-square test were used to compare variables. P values < 0.05 were considered significant. Multivariate analysis was performed with a model in which each variable with $p < 0.05$ (based on univariate analysis) was entered, with a maximum of 1 variable per 10 events. Survival curves were constructed according to the Kaplan Meier method, and compared using the log rank test. Due to a high prevalence of three *MYBPC3* founder mutations (c.2373dupG, c.2827C>T and c.2864_2865delCT)[10], we adjusted for the founder effect by including only the first enrolled proband with a founder mutation. Founder mutations were defined according to Alders et al.[11] All reported annual mortality rates are in 50-year survivors.

RESULTS

The baseline characteristics are presented in TABLE 1. A pathogenic mutation was detected in 234 (46%) probands, and in 93 (82%) relatives. G+ probands were younger than G- probands (46±15 vs 55±15 years, p<0.001), had more atrial fibrillation (26% vs 15%; p<0.001), and a higher MWT (20±5 mm vs 18±4 mm; p<0.001). The following risk factors for SCD were more common in G+ probands: family history of SCD, non-sustained ventricular tachycardia, syncope, and MWT ≥ 30 mm. G- probands were more symptomatic (NYHA ≥ II 73% vs 53%, p=<0.001) and had higher LVOT gradients (42±39 vs 29±33 mmHg, p=0.001). Relatives presented to clinic primarily through familial evaluation (n=66, 58%) and through positive genetic screening (n=48, 42%). Compared to probands, relatives were younger (46±15 vs

TABLE 1 – Baseline characteristics of probands and relatives with hypertrophic cardiomyopathy.

Variable	Entire cohort (n=626)	Probands (n=512)			Relatives (n=114)		
		Genotype + (n=234)	Genotype - (n=278)	p-value	Genotype + (n=93)	Genotype - (n=21)	p-value
Male	404 (65%)	159 (68%)	171 (62%)	0.130	61 (66%)	13 (62%)	0.749
Age (years)	51±15	46±15	55±15	<0.001	45±15	51±13	0.092
AF (by history)	115 (18%)	61 (26%)	41 (15%)	0.001	1 (12%)	2 (10%)	0.764
NYHA II or higher	216 (55%)	81 (53%)	121 (73%)	<0.001	11 (16%)	3 (25%)	0.473
Maximal wall thickness	18±5	20±5	18±4	<0.001	17±4	17±4	0.806
Left atrial size	44±8	45±8	45±7	0.996	43±8	41±7	0.340
LV end diastolic diameter	46±6	45±6	46±7	0.438	46±5	47±7	0.541
Apical morphology	31 (5%)	4 (2%)	22 (8%)	0.001	3 (3%)	2 (10%)	0.203
LVOT peak gradient	32±16	29±33	42±39	0.001	10±14	16±20	0.325
LVOT PG > 30 mmHg	178 (28%)	67 (29%)	106 (38%)	0.024	3 (3%)	2 (10%)	0.203
LV systolic dysfunction	70 (12%)	31 (15%)	31 (12%)	0.430	7 (8%)	1 (5%)	0.632
Family history of SCD	61 (12%)	46 (20%)	15 (6%)	<0.001	26 (30%)	5 (25%)	0.706
nsVT on Holter monitoring	111 (22%)	67 (34%)	26 (13%)	<0.001	14 (18%)	4 (22%)	0.675
Abnormal exercise BPR	79 (16%)	28 (14%)	41 (20%)	0.141	8 (10%)	2 (12%)	0.790
Syncope	52 (10%)	32 (14%)	20 (7%)	0.016	4 (4%)	1 (5%)	0.926
MWT ≥ 30 mm	18 (4%)	16 (7%)	2 (1%)	<0.001	0	0	-

All values are mean ± SD or number (%) AF = atrial fibrillation, BPR = blood pressure response, LV = left ventricle, LVOT = left ventricular outflow tract, MWT = maximal wall thickness, NYHA = New York Heart Association functional class, nsVT = non sustained ventricular tachycardia, PG = peak gradient, SCD = sudden cardiac death.

51±15 y, p=0.003), had fewer AF (11% vs 20%, p=0.034), were less symptomatic (NYHA ≥ II 18% vs 64%, p<0.001), had a lower MWT (17±4 vs 19±5 mm, p<0.001), smaller left atria (41±7 vs 45±8, p<0.001), and had lower LVOT peak gradients (11±15 vs 36±37, p<0.001). Relatives more often had a family history of SCD (28% vs 12%, p<0.001). There were no significant differences between G+ and G- relatives (TABLE 1).

The distribution of the affected genes is presented in FIGURE 1. Next-generation sequencing was performed in 161 (26%) patients. Most patients had *MYBPC3* mutations (n=240; 73%), followed by *MYH7* mutations (n=47; 14%) and thin filament mutations (n=19; 6%). FIGURE 2

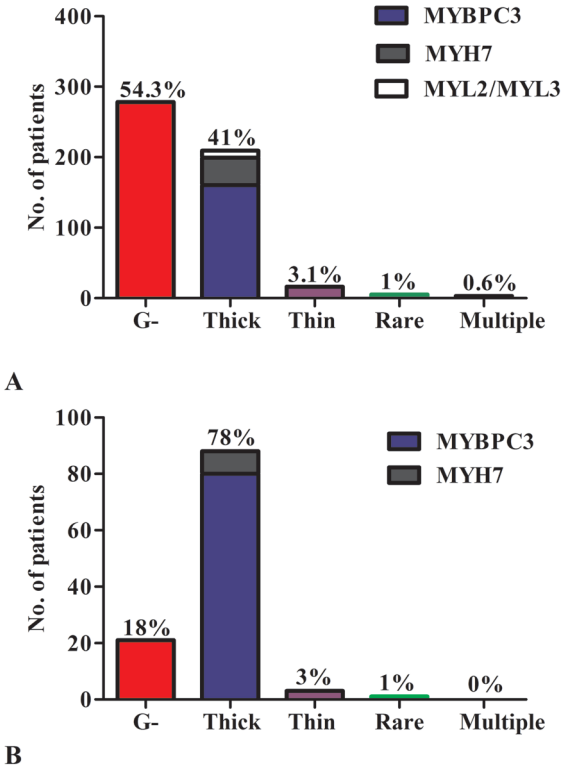


FIGURE 1 – The distribution of pathogenic gene mutations in 512 probands (A; top) and 114 relatives (B; bottom). G- = genotype-negative HC patients. Thick = patients with thick filament associated gene mutations: myosin binding protein C (MYBPC3), myosin heavy chain (MYH7), regulatory myosin light chain 2 (MYL2) and regulatory myosin light chain 3 (MYL3). Thin = patients with thin filament associated gene mutations: troponin I, troponin T and α-tropomyosin 1. Rare = patients with rare mutations: calreticulin 3, cysteine and glycine-rich protein 3, and myopalladin. Multiple = patients with multiple mutations.

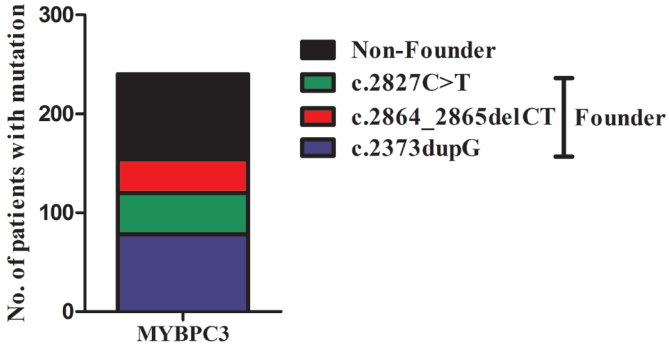


FIGURE 2 – The distribution of founder and non-founder mutations in the myosin binding protein C (MYBPC3) gene. MYBPC3 founder mutations include: c.2373dupG (purple); n=78 (33%), c.2827C>T (green); n=42 (18%) and c.2864_2865delCT (red); n=33 (14%). Non-founder MYBPC3 mutations (black): n=86 (36%).

TABLE 2 – Mortality and interventions during follow-up of probands and relatives

		Probands (n=512)			Relatives (n=114)		
Variable	**Entire cohort (n=626)**	**Genotype + (n=234)**	**Genotype – (n=278)**	**p-value**	**Genotype + (n=93)**	**Genotype – (n=21)**	**p-value**
All-cause mortality	81 (13%)	40 (17%)	30 (11%)	0.039	10 (11%)	1 (5%)	0.401
Age at death, y	62±14	62±16	64±11	0.488	58±14	49	0.550
Cardiovascular mortality	53 (9%)	32 (14%)	16 (6%)	0.002	4 (4%)	1 (5%)	0.926
Heart failure related mortality	20 (3%)	15 (6%)	3 (1%)	0.001	2 (2%)	0	0.498
Cardiac transplantation	7 (1%)	4 (2%)	2 (1%)	0.300	1 (1%)	0	0.633
SCD/aborted SCD	29 (5%)	17 (7%)	9 (3%)	0.039	2 (2%)	1 (5%)	0.500
True SCD	9 (1%)	7 (3%)	2 (1%)	0.051	0	0	
Aborted SCD	20 (3%)	10 (4%)	7 (3%)	0.269	2 (2%)	1(5%)	0.500
Stroke related death	2 (0.3%)	0	2 (0.7)	0.194	0	0	
Post procedural cardiac death	2 (0.3%)	0	2 (0.7)	0.194	0	0	
Septal reduction therapy	171 (27%)	73 (31%)	91 (33%)	0.710	7 (8%)	0	0.194
Alcohol septal ablation	53 (9%)	21 (9%)	32 (12%)	0.348	0	0	
Surgical myectomy	126 (20%)	53 (23%)	66 (24%)	0.771	7 (8%)	0	0.194
ICD	98 (16%)	49 (21%)	35 (13%)	0.011	10 (11%)	4 (19%)	0.296
For primary prevention	76 (12%)	38 (16%)	26 (9%)	0.019	8 (9%)	4 (19%)	0.159
For secondary prevention	22 (4%)	11 (5%)	9 (3%)	0.395	2 (2%)	0	0.498

All values are mean ± SD, median [Q1 – Q3] or number (%). ICD = implantable cardioverter defibrillator, SCD=sudden cardiac death

demonstrates the distribution of the *MYBPC3* founder mutations. *MYBPC3* founder mutations were present in 101 (47%) G+ probands and 53 (57%) G+ relatives. A detailed overview of the individual pathogenic mutations is presented in supplementary TABLE 1. Three patients (1%) had multiple mutations: one compound heterozygous *MYBPC3* mutation in trans and two double heterozygous (*MYBPC3*/*MYL2* and *MYH7*/*MIB1*) mutations. Most mutations were truncating mutations (n=184; 56%) followed by missense (n=101; 31%) and splice site mutations (n=34; 10%). SUPPLEMENTARY TABLE 2 illustrates the varying types of mutations in the patients who died from HF and SCD/aborted SCD. The gene most commonly affected

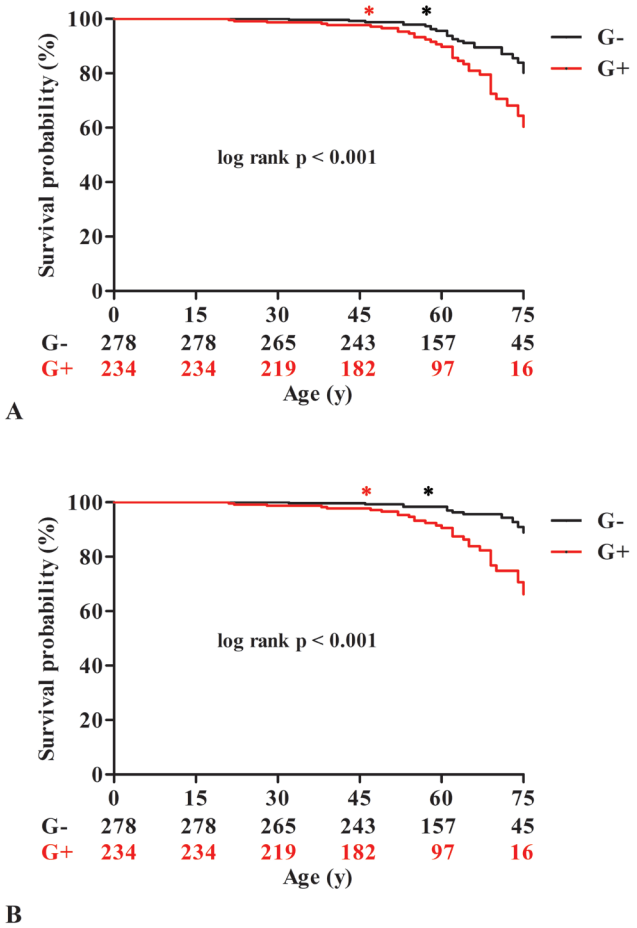
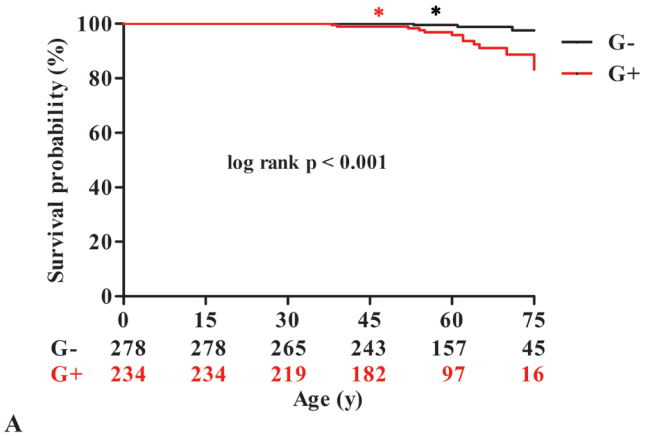


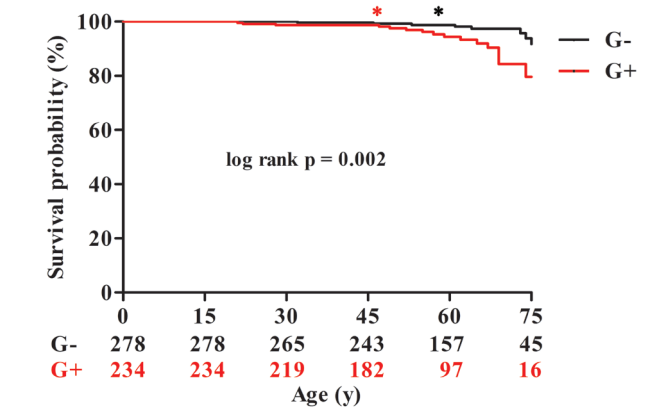
FIGURE 3 – Kaplan-Meier analysis comparing (A; top) all-cause mortality in G+ probands and G- probands and (B; bottom) cardiovascular mortality in G+ probands and G- probands. * = age at presentation (red for G+ and black for G-). G+ = genotype-positive. G- = genotype-negative. Cardiovascular mortality is defined as death related to heart failure or stroke, sudden cardiac death or postoperative death after a cardiac intervention.

in SCD/aborted SCD was *MYBPC3* (founder: n=10, non-founder: n=6), followed by *MYH7* (n=2), and a double mutation carrier. SCD/aborted SCD did not occur among *TNNT2* mutation carriers (n=10; mean age 61±9).

Mortality and interventions during follow-up are presented in TABLE 2. During the mean follow-up period of 12±9 years, G+ probands had a greater probability of all end points: all-cause mortality, HF related mortality, CV mortality, and SCD/aborted SCD (figures 3 and 4). Annual rates for G+ vs G- patients were as follows: (1) all-cause mortality: 2.4% vs 1.0%, log rank p<0.001; (2) HF related mortality: 0.9% vs 0.2%, log rank p<0.001; (3) CV mortality:



A



B

FIGURE 4 – Kaplan-Meier analysis comparing (A; top) heart failure related mortality in G+ probands and G- probands and (B; bottom) sudden cardiac death/aborted sudden cardiac death in G+ probands and G- probands. * = age at presentation (red for G+ and black for G-). G+ = genotype-positive. G- = genotype-negative.

1.8% vs 0.4%, log rank p<0.001; and (4) SCD/aborted SCD: 1.1% vs 0.15%, log rank p=0.002. After adjustment for the founder effect, all of these differences remained significant. ICDs for primary prevention were implanted more often in G+ probands (16% vs 9%; p=0.019). There was no significant difference in the number of septal reduction therapies (both ASA and surgical myectomy) between G+ and G- probands (31% vs 33%; p=0.710). All-cause mortality for relatives was comparable to probands (10% vs 14%, p=0.247), with an annual all-cause mortality rate of 1.3%. Compared to probands, cardiovascular death trended lower in relatives (4% vs 9%, p=0.084). There were no significant differences between G+ and G- relatives. Multivariate cox regression analyses of G+ status in probands for the end points are presented in TABLE 3. G+ status was an independent predictor of all-cause mortality (HR 1.90, p=0.014), CV mortality (HR 2.82, p=0.002) and HF related mortality (HR 6.33, p=0.004). G+ status was also a predictor of SCD/aborted SCD, after adjusting for established risk factors for SCD as described in the guidelines from 2003[12] and 2011[13].

TABLE 3 – Cox regression analysis of genotype-positive status for the clinical endpoints of 512 probands

End point	Predictor	HR (95% CI)	P-value
All-cause mortality	Genotype-positive status	1.90 (1.14-3.15)	0.014
	Atrial fibrillation	2.15 (1.30-3.56)	0.003
	Systolic left ventricular dysfunction	1.92 (1.07-3.47)	0.030
	Extreme hypertrophy (MWT ≥ 30 mm)	6.22 (2.33-16.60)	<0.001
Cardiovascular mortality	Genotype-positive status	2.82 (1.49-5.36)	0.002
	Atrial fibrillation	3.31 (1.81-6.06)	<0.001
	Systolic left ventricular dysfunction	2.33 (1.18-4.60)	0.015
	Extreme hypertrophy (MWT ≥ 30 mm)	10.23 (3.64-28.73)	<0.001
Heart failure related mortality	Genotype-positive status	6.33 (1.79-22.41)	0.004
	Atrial fibrillation	12.66 (3.63-44.20)	<0.001
SCD/aborted SCD analysis 1	Genotype-positive status	2.88 (1.23-6.71)	0.015
	≥ 2 established risk factors (2003 guidelines)	2.44 (0.99-6.01)	0.052
SCD/aborted SCD analysis 2	Genotype-positive status	2.88 (1.24-6.67)	0.014
	≥1 established risk factors (2011 guidelines)	2.32 (1.04-5.16)	0.039

Multivariate Cox proportional-hazards analysis was used. MWT = maximal wall thickness. SCD = sudden cardiac death. Established risk factors for sudden cardiac death according to the 2003 guidelines included: extreme hypertrophy (maximal wall thickness ≥ 30 mm), unexplained syncope, abnormal exercise blood pressure, non-sustained ventricular tachycardia, family history of sudden cardiac death. Established risk factors for sudden cardiac death according to the 2011 guidelines included: extreme hypertrophy (maximal wall thickness ≥ 30 mm), unexplained syncope and a family history of sudden cardiac death.

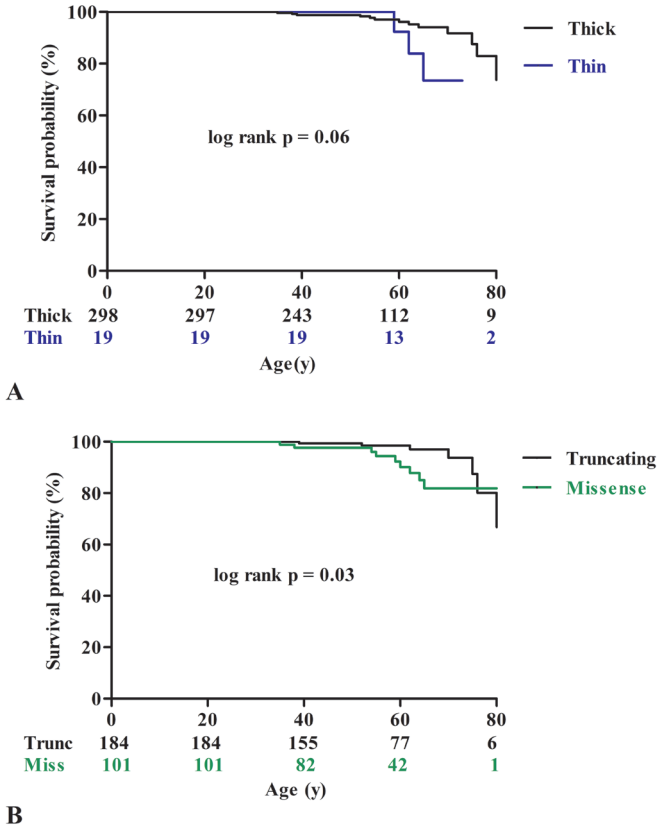


FIGURE 5 – Kaplan-Meier analysis comparing heart failure related death in (A; top) HC patients with thick filament associated gene mutations and HC patients with thin filament associated gene mutations, and (B; bottom) HC patients with truncating gene mutations and HC patients with missense gene mutations.

Kaplan Meier curves for HF related mortality in carriers of different types of mutations are presented in FIGURE 5. Thin filament mutation carriers had a greater probability of HF related death than thick filament mutation carriers (16% vs 5%, log rank p=0.06), and missense mutation carriers had a greater probability of HF related death than truncating mutation carriers (7% vs 4%, log rank p=0.03).

DISCUSSION

This study compared the clinical outcome of G+ and G- patients with HC. During 12±9 years follow-up, multivariate analysis demonstrated that G+ status was an independent risk factor for all-cause mortality, CV mortality, HF related mortality, and SCD/aborted SCD.

Several previous studies have evaluated the impact of sarcomere mutations on clinical outcome. Olivotto et al[8] studied 203 patients (G+: 62%), and found a greater probability of severe left ventricular systolic and diastolic dysfunction (HR 2.1; 95% CI 1.1-4.0;p=0.02), during a median follow up of 4.5 years. Li. et al[7] studied 558 patients (G+: 35%), and demonstrated that G+ status was an independent predictor of HF events (HR 4.5; 95% CI 2.1-9.3; p<0.001), during a mean follow up of 6.6±6.3 years. Fujita et al.[5] studied 193 patients (G+: 47%), and reported more CV events in G+ HC, during 1 year follow up. Lopes et al.[6] studied 874 patients (G+: 44%), and reported a higher proportion of CV deaths and SCD events in G+ patients, during a mean follow up of 4.8±3.5 years. The mean follow-up period in these previous studies varied from 1 to 6.6 years. The present long-term follow-up study confirms and extends the findings from these previous studies.

G+ status in HC patients was an independent predictor of HF related mortality. The precise pathways through which sarcomere mutations lead to HF are unclear. In this study, 47% of G+ HC was caused by *MYBPC3* founder mutations. These mutations are responsible for ~35% of HC cases in the Netherlands.[10] The pathophysiological consequences of *MYBPC3* founder mutations have been investigated by van Dijk et al.[14] They reported a reduction of 33% in full-length cardiac MyBP-C protein, suggesting haploinsufficiency is part of the pathophysiology. In addition, the force generating capacity of cardiomyocytes was lower than myocardium from donor samples. This ''hypocontractile sarcomere phenotype'' seemed to be a common feature of HC patients, suggesting it is rather part of the remodeling process.[14,15] This was investigated by correcting for a decrease in myofibril density.[16] After correction, values returned to normal for *MYBPC3* mutations, but not for *MYH7* mutations[16]. And so, *MYH7* mutations seem to cause hypocontractile sarcomeres directly. Other pathophysiological mechanisms may be a reduced phosphorylation of sarcomeric proteins, and enhanced Ca^{2+}-sensitivity of the sarcomeres. Possibly, these early pathways involved in disease progression can be targets for future therapies.[3,17]

This study demonstrates a significant relationship between G+ status and SCD/aborted SCD. The risk of SCD/aborted SCD was low in G- probands and relatives. Lopes et al.[6] similarly reported an increased incidence of SCD/aborted SCD in G+ HC. However, other studies[7,8] did not show a relationship between G+ status and SCD, probably related to the low number of events, or relatively short follow-up duration. Ho et al.[18] demonstrated that myocardial collagen synthesis was increased in G+ individuals compared to control subjects. This suggests that sarcomere mutations lead to myocardial fibrosis, which is a substrate for SCD. Since myocardial fibrosis is believed to be visualized by cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE), it was shown that the extent of LGE on CMR was associated with an increased risk of SCD events.[19,20] Furthermore, an independent association between LGE and HF was reported.[21]

In this cohort, G- probands were older, more symptomatic, and had higher LVOT gradients. During follow-up, 33% of G- probands underwent septal reduction therapy. Previous

data have shown excellent long-term outcomes after septal reduction therapy in symptomatic patients with HC and severe LVOT obstruction.[22] The survival disadvantage associated with LVOT obstruction can be substantially decreased by appropriate invasive therapy.[22] The G+ probands in this study had a more advanced cardiomyopathy, which is indicated by a higher MWT, higher incidence of AF, higher incidence of non-sustained ventricular tachycardia, and more often a family history of SCD (TABLE 1). Therefore, the G+ probands were at an increased risk of SCD and HF related death. Part of G- HC patients may have undiscovered pathogenic mutations. However, the additive genetic yield of next generation sequencing in HC seems limited.[23,24] Possibly, whole-exome and whole-genome sequencing will add more value to the discovery of new mutations.[3] However, such massive sequencing also generates many variants of unknown significance.[3,23] Determining of the clinical significance of these variants is a major challenge.[23]

In this study, relatives with HC were younger and had a more benign phenotype than probands. This can be explained by the way of presentation. It seems that family screening leads to the detection of disease in an earlier phase.[25] Although this was not reflected in a significantly better clinical outcome, a trend was found for fewer cardiovascular deaths among relatives. The lack of difference between G+ and G- relatives can be explained by the small number of G- relatives.

The current findings demonstrate that G+ HC patients are at increased risk of progression towards HF and SCD/aborted SCD. Previous studies have demonstrated that genetic test results are predictive of medium-term outcome, and the current study demonstrates that this also holds for the long-term outcome of patients with HC. Due to the heterogeneous nature of HC, the therapeutic implications of a G+ status are currently limited. Phenotypic characterization is currently still the most important factor for determining prognosis in HC patients. The clinical challenge is to incorporate genetic test results in contemporary risk prediction models. Fundamental research on the pathophysiological consequences of sarcomere mutations is crucial to develop genotype-specific risk-assessment and targeted therapies.

This study has several limitations. Patients who died and never presented to the clinic were missed in the analysis. Due to significant advances in DNA-sequencing methodology during the past decade, there was no homogenous genotyping over the whole period. The rate of complex genotype (1%) could be an underestimation of the real rate of complex genotype. Previous literature reported a rate of 5-7%[3].

REFERENCES

1. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol 2014;64:83-99.
2. Lopes LR, Rahman MS, Elliott PM. A systematic review and meta-analysis of genotype-phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations. Heart 2013;99:1800-1811.
3. Ho CY, Charron P, Richard P, Girolami F, Van Spaendonck-Zwarts KY, Pinto Y. Genetic advances in sarcomeric cardiomyopathies: state of the art. Cardiovasc Res 2015;105:397-408.
4. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-2779.
5. Fujita T, Fujino N, Anan R, Tei C, Kubo T, Doi Y, Kinugawa S, Tsutsui H, Kobayashi S, Yano M, Asakura M, Kitakaze M, Komuro I, Konno T, Hayashi K, Kawashiri MA, Ino H, Yamagishi M. Sarcomere gene mutations are associated with increased cardiovascular events in left ventricular hypertrophy: results from multicenter registration in Japan. JACC Heart Fail 2013;1:459-466.
6. Lopes LR, Syrris P, Guttmann OP, O'Mahony C, Tang HC, Dalageorgou C, Jenkins S, Hubank M, Monserrat L, McKenna WJ, Plagnol V, Elliott PM. Novel genotype-phenotype associations demonstrated by high-throughput sequencing in patients with hypertrophic cardiomyopathy. Heart 2015;101:294-301.
7. Li Q, Gruner C, Chan RH, Care M, Siminovitch K, Williams L, Woo A, Rakowski H. Genotype-positive status in patients with hypertrophic cardiomyopathy is associated with higher rates of heart failure events. Circ Cardiovasc Genet 2014;7:416-422.
8. Olivotto I, Girolami F, Ackerman MJ, Nistri S, Bos JM, Zachara E, Ommen SR, Theis JL, Vaubel RA, Re F, Armentano C, Poggesi C, Torricelli F, Cecchi F. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clin Proc 2008;83:630-638.
9. Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS, Hogervorst FB, Hoogerbrugge N, Spurdle AB, Tavtigian SV, Group IUGVW. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. Hum Mutat 2008;29:1282-1291.
10. Christiaans I, Nannenberg EA, Dooijes D, Jongbloed RJ, Michels M, Postema PG, Majoor-Krakauer D, van den Wijngaard A, Mannens MM, van Tintelen JP, van Langen IM, Wilde AA. Founder mutations in hypertrophic cardiomyopathy patients in the Netherlands. Neth Heart J 2010;18:248-254.
11. Alders M, Jongbloed R, Deelen W, van den Wijngaard A, Doevendans P, Ten Cate F, Regitz-Zagrosek V, Vosberg HP, van Langen I, Wilde A, Dooijes D, Mannens M. The 2373insG mutation in the MYBPC3 gene is a founder mutation, which accounts for nearly one-fourth of the HCM cases in the Netherlands. Eur Heart J 2003;24:1848-1853.
12. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, 3rd, Spirito P, Ten Cate FJ, Wigle ED, Task Force on Clinical Expert Consensus Documents. American College of C, Committee for Practice Guidelines. European Society of C. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687-1713.
13. American College of Cardiology Foundation/American Heart Association Task Force on P, American Association for Thoracic S, American Society of E, American Society of Nuclear C, Heart Failure Society of A, Heart Rhythm S, Society for Cardiovascular A, Interventions, Society of Thoracic S, Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seid-

man CE, Towbin JA, Udelson JE, Yancy CW. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 2011;142:e153-203.

14. van Dijk SJ, Dooijes D, dos Remedios C, Michels M, Lamers JM, Winegrad S, Schlossarek S, Carrier L, ten Cate FJ, Stienen GJ, van der Velden J. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation 2009;119:1473-1483.
15. van Dijk SJ, Bezold KL, Harris SP. Earning stripes: myosin binding protein-C interactions with actin. Pflugers Arch 2014;466:445-450.
16. Witjas-Paalberends ER, Piroddi N, Stam K, van Dijk SJ, Oliviera VS, Ferrara C, Scellini B, Hazebroek M, ten Cate FJ, van Slegtenhorst M, dos Remedios C, Niessen HW, Tesi C, Stienen GJ, Heymans S, Michels M, Poggesi C, van der Velden J. Mutations in MYH7 reduce the force generating capacity of sarcomeres in human familial hypertrophic cardiomyopathy. Cardiovasc Res 2013;99:432-441.
17. Tardiff JC, Carrier L, Bers DM, Poggesi C, Ferrantini C, Coppini R, Maier LS, Ashrafian H, Huke S, van der Velden J. Targets for therapy in sarcomeric cardiomyopathies. Cardiovasc Res 2015;105:457-470.
18. Ho CY, Lopez B, Coelho-Filho OR, Lakdawala NK, Cirino AL, Jarolim P, Kwong R, Gonzalez A, Colan SD, Seidman JG, Diez J, Seidman CE. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. N Engl J Med 2010;363:552-563.
19. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484-495.
20. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, Das B, Khwaja J, Alpendurada FD, Wage R, Roughton M, McKenna WJ, Moon JC, Varnava A, Shakespeare C, Cowie MR, Cook SA, Elliott P, O'Hanlon R, Pennell DJ, Prasad SK. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. Heart 2014;100:1851-1858.
21. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulaibeekh L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ, Prasad SK. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:867-874.
22. Vriesendorp PA, Liebregts M, Steggerda RC, Schinkel AF, Willems R, Ten Cate FJ, van Cleemput J, Ten Berg JM, Michels M. Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. JACC Heart Fail 2014;2:630-636.
23. Mogensen J, van Tintelen JP, Fokstuen S, Elliott P, van Langen IM, Meder B, Richard P, Syrris P, Caforio AL, Adler Y, Anastasakis A, Gimeno JR, Klingel K, Linhart A, Imazio M, Pinto Y, Newbery R, Schmidtke J, Charron P. The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions: a viewpoint paper of the European Society of Cardiology working group on myocardial and pericardial diseases and members of the European Society of Human Genetics. Eur Heart J 2015;36:1367-1370.
24. Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, Shen J, McLaughlin HM, Clark EH, Babb LJ, Cox SW, DePalma SR, Ho CY, Seidman JG, Seidman CE, Rehm HL. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. Genet Med 2015.
25. Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 2012;5:535-546.

SUPPLEMENTARY TABLE 1 – Gene mutations associated with Hypertrophic Cardiomyopathy in 327 genotype-positive patients with hypertrophic cardiomyopathy

Nucleotide change	Protein change	Mutation type	No. of patients with mutation	Nucleotide change	Protein change	Mutation type	No. of patients with mutation
MYBPC3 Gene (n=240)				**MYH7 Gene (n=47)**			
c.2373dupG	p.Trp792fs	frameshift	78	c.4130C>T	p.Thr1377Met	missense	4
c.2827C>T	p.Arg943*	nonsense	42	c.1816G>A	p.Val606Met	missense	4
c.2864_2865delCT	p.Pro955fs	frameshift	34	c.1207C>T	p.Arg403Trp	missense	3
c.1458-1G>C	p.?	splicesite	8	c.976G>C	p.Ala326Pro	missense	3
c.3776delA	p.Gln1259Argfs	frameshift	8	c.2156A>G	p.Arg719Gln	missense	3
c.481C>T	p.Pro161Ser	missense	8	c.1727A>G	p.His576Arg	missense	2
c.1624+1G>A	p.?	splicesite	5	c.1063G>A	p.Ala355Thr	missense	2
c.2149-2delA	p.?	splicesite	5	c.1987C>T	p.Arg663Cys	missense	2
c.927-2A>G	p.?	splicesite	5	c.2080C>T	p.Arg694Cys	missense	2
c.654+1G>A	p.?	splicesite	3	c.2783A>T	p.Asp928Val	missense	2
c.1831G>A	p.Glu611Lys	missense	4	c.2081G>A	p.Arg694His	missense	1
c.2308G>A	p.Asp770Asn	missense	2	c.1988G>A	p.Arg663His	missense	1
c.2391C>A	p.Tyr797*	nonsense	2	c.2104A>G	p.Arg719Gln	missense	1
c.688delC	p.Gln230fs	frameshift	2	c.2167C>T	p.Arg723Cys	missense	1
c.1484G>A	p.Arg495Gln	missense	2	c.2945T>C	p.Met982Thr	missense	1
c.772G>A	p.Glu258Lys	missense	3	c.2221G>C	p.Gly741Arg	missense	1
c.1696T>C	p.Cys566Arg	missense	2	c.3133C>T	p.Arg1045Cys	missense	1
c.897delG	p.Lys301fs	frameshift	2	c.3100-2A>C	p.?	splicesite	1
c.913_914delTT	p.Phe305fs	frameshift	1	c.3169G>A	p.Gly1057Ser	missense	1

SUPPLEMENTARY TABLE 1 – continued

Nucleotide change	Protein change	Mutation type	No. of patients with mutation	Nucleotide change	Protein change	Mutation type	No. of patients with mutation
c.1766G>A	p.Arg589His	missense	1	c.1357C>T	p.Arg453Cys	missense	1
c.1548-1G>A	p.?	splicesite	1	c.727C>T	p.Arg243Cys	missense	1
c.2543_2544dupCG	p.Val849fs	frameshift	1	c.728G>A	p.Arg243His	missense	1
c.2432A>G	p.Lys811Arg	missense	1	c.1532T>C	p.Ile511Thr	missense	1
c.3029delA	p.Glu1010fs	frameshift	1	c.5135G>A	p.Arg1712Gln	missense	3
c.2893C>T	p.Gln965*	nonsense	1	c.2146G>A	p.Gly716Arg	missense	1
c.3181C>T	p.Gln1061*	nonsense	1	c.5786C>T	p.Thr1929Met	missense	1
c.3640T>C	p.Trp1214Arg	missense	1	c.2306T>C c.2788G>A	p.Leu769Pro p.Glu930Lys	missense missense	1 1
c.3332_3335dup	p.Trp1112*	nonsense	1	**MYL2 gene (n=8)**			
c.3331-2A>G	p.?	splicesite	1	c.64G>A	p.Glu22Lys	missense	6
c.3392T>C	p.Ile1131Thr	missense	1	c.403-1G>C	p.?	splicesite	1
c.3814+1G>A	p.?	splicesite	1	c.286G>A	p.Glu96Lys	missense	1
c.442G>A	p.Gly148Arg	missense	1	**MYL3 gene (n=3)**			
c.1800delA	p.Lys600Asnfs	frameshift	1	c.452C>T	p.Ala151Val	missense	3
c.1404delG	p.Gln469fs	frameshift	1	**MYPN gene (n=1)**			
c.701ins26	unknown	frameshift	1	c.59A>G	p.Tyr20Cys	missense	1
c.208delG	p.Glu70fs	frameshift	1	**TNNI3 gene (n=7)**			
c.1053_1054delGCinsTT	p.Arg351_ Leu352delinsSerPhe	complex	1	c.433C>T	p.Arg145Trp	missense	4
c.7191-1G>A	p.?	splicesite	1	c.497C>T	p.Ser166Phe	missense	1

SUPPLEMENTARY TABLE 1 – continued

Nucleotide change	Protein change	Mutation type	No. of patients with mutation	Nucleotide change	Protein change	Mutation type	No. of patients with mutation
c.821+1G>A	p.?	splicesite	1	c.114dupA	p.Ser39fs	frameshift	1
c.932C>A	p.Ser311*	nonsense	1	c.470C>T	p.Ala157Val	missense	1
del exon 23-26	p.?	splicesite	1		**TNNT2 gene (n=10)**		
c.1000G>T	p.Glu334*	nonsense	1	c.832C>T	p.Arg278Cys	missense	3
c.3490+1G>T	p.?	splicesite	1	c.856C>T	p.Arg286Cys	missense	3
				c.274C>T	p.Arg92Trp	missense	1
	Double mutations (n=3)			c.421delC	p.Arg141fs	frameshift	1
c.1000G>T (*MYBPC3*) & c.64G>A (*MYBPC3*)	p.Glu334* & p.Glu22Lys		1	c.874C>T	p.Arg292Trp	missense	1
c.913_914delT (*MYBPC3*) & c.1468G>A (*MYL2*)	p.Phe305fs & p.Gly490Arg		1	c.853C>T	p.Arg285Cys	missense	1
c.5135G>A (*MYH7*) & c.2530_2532delTCTinsC (*MIB1*)	p.Arg1712Gln & p.Ser844fs		1	c.184G>C	**TPM1 (n=2)** p.Glu62Gln	missense	2
	CSRP3 gene (n=2)				**CALR3 (n=4)**		
c.131T>C	p.Leu44Pro	missense	2	c.564delT	p.Gly189fs	frameshift	4

CSRP3 = cysteine and glycine-rich protein 3, *CALR3* = calreticulin 3, *MYBPC3* = myosin binding protein C, *MYH7* = myosin heavy chain 7, *MYL2* = regulatory myosin light chain 2, *MYL3* = regulatory myosin light chain 3, *MYPN* = myopalladin, *TNNT2* = troponin T, *TNNI3* = troponin I, *TPM1* = α-tropomyosin 1.

SUPPLEMENTARY TABLE 2 – Patients with hypertrophic cardiomyopathy that died from heart failure or sudden cardiac death, presented per gene affected and type of mutation.

Gene	Mutation type	No. of patients with mutation	Heart failure related death	Sudden cardiac death
Total		327	17 (5%)	19 (6%)
MYBPC3	Truncating	179	7 (4%)	12 (7%)
	Missense	27	2 (7%)	2 (7%)
	Splicesite	33	1 (3%)	2 (6%)
	Complex	1	0	0
MYH7	Missense	46	3 (7%)	2 (4%)
	Splicesite	1	0	0
MYL2	missense	7	1 (14%)	0
	splicesite	1	0	0
MYL3	missense	3	0	0
MYPN	missense	1	0	0
TNNI3	truncating	1	0	0
	missense	6	0	0
TNNT2	truncating	1		
	missense	9	1 (11%)	0
TPM1	missense	2	2 (100%)	0
CALR3	truncating	4	0	0
CSRP3	missense	2	0	0
Complex genotype		3	0	1 (33%)

All values are in number (%). *CSRP3* = cysteine and glycine-rich protein 3, *CALR3* = calreticulin 3, *MYBPC3* = myosin binding protein C, *MYH7* = myosin heavy chain 7, *MYL2* = regulatory myosin light chain 2, *MYL3* = regulatory myosin light chain 3, *MYPN* = myopalladin, *TNNT2* = troponin T, *TNNI3* = troponin I, *TPM1* = α-tropomyosin 1.

Chapter 14

Follow-up of patients with preclinical hypertrophic cardiomyopathy

Vriesendorp PA, Van Velzen HG, Oldenburg RA,
Van Slegtenhorst MA, Schinkel AFL, Michels M

submitted

ABSTRACT

Purpose

Preclinical hypertrophic cardiomyopathy (HCM) is defined as the presence of a pathogenic mutation without left ventricular hypertrophy (LVH). The aim of this study was to assess the natural course of subjects with preclinical hypertrophic cardiomyopathy and to determine if there are predictors of disease occurrence.

Methods

In this single center cohort of 136 subjects with preclinical HCM, 86 had > 1 echocardiographic evaluation > 1 year apart, and were included in this study. At baseline and last follow-up, structural characteristics, systolic function and diastolic function were assessed by 2-D echocardiography. In addition speckle tracking echocardiography was performed to determine peak systolic longitudinal strain and strain rate. The endpoints of the study were the development of manifest HCM (LVH ≥ 15mm) and major adverse cardiac events.

Results

During 4.5 ± 1.9 years (range 6.8 years) of follow-up, 1 patient developed manifest HCM(15 mm, after 6.6y) and no cardiac events occurred. Maximal left ventricular wall thickness did not increase during follow-up. In subjects with progressive diastolic dysfunction during follow-up there was an increase of LV mass (+9g ±36 vs. -9g ± 28, p=0.04) and reduction of septal strain (-3.5% ±6 vs. -0.5% ± 6, p=0.08) and strain rate (-0.4 ± 0.5 vs. -0.1 ±0.4, p=0.03), compared with subjects with stable diastolic function.

Conclusion

During 4.5 year follow-up, manifest HCM occurred in one patient and there were no cardiac events. This suggests that preclinical HCM in adults is a relatively benign condition. We propose a 5-year interval between clinical evaluations in asymptomatic subjects with preclinical HCM unless a change in clinical status occurs.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common inheritable myocardial disease, with a prevalence of 1:500 in the general population. In 1989 the first pathogenic mutation was identified in the myosin heavy chain gene by Seidman et al.[1] Subsequent research had led to the discovery of >1300 mutations in > 20 genes and has increased the understanding of the disease.[2] After identification of a pathogenic mutation in a HCM patient, presymptomatic DNA testing can be offered to relatives, which is currently recommended by both the 2011 ACCF/AHA guidelines and the 2014 ESC guidelines.[3, 4]

The use of presymptomatic DNA testing in family screening introduced a new patient category to the field of HCM; namely genotype positive (G+) subjects without left ventricular hypertrophy (LVH). The natural course of these subjects with preclinical HCM remains unclear. But the reported risk of adverse cardiac events is low, and in a large multicenter registry no sudden cardiac death occurred.[5] Another problem is the difficulty to determine which of these subjects will develop manifest HCM (LVH ≥ 15mm), as currently no predictors are known. It has been suggested that the presence of diastolic dysfunction may preclude to manifest HCM. [6, 7] Other potential predictors are subclinical abnormalities of systolic function which can be assessed by strain and strain rate echocardiography. The purpose of this study was to assess the natural course of subjects with preclinical HCM, and to determine if there are clinical or echocardiographic predictors for development to manifest HCM.

METHODS

Study population

This single-center cohort study consists of 136 subjects with a pathogenic mutation without left ventricular hypertrophy (LVH), who were identified through family screening at cardio-genetic outpatient clinic of the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands between 2005-2014. Genetic testing was performed in family members after identification of the mutation in the index-patient. Subjects were included for further analysis if: (1) there was a confirmed pathogenic mutation; (2) LVH < 15mm; (3) there was >1 echocardiographic evaluation >1 year apart. Subjects with an unclassified genetic variant were excluded. Genetic testing was performed from 2006-2012 with classic Sanger technique for the following genes: *cardiac myosin binding protein C* (MYBPC3) and *ß-cardiac myosin heavy chain* (MYH7), *cardiac myosin regulatory light polypeptide 2* (MYL2*), cardiac troponin T* (TNNT2), *cardiac troponin I type 3* (TNNI3), *cysteine and glycine-rich protein 3* (CSRP3), *titin-cap/telethonin* (TCAP) and *α-tropomyosin 1* (TPM1). From 2012 onwards, next-generation-sequencing was performed, where a total of 48 genes were screened for mutations.

The study conforms to the principles of the Helsinki Declaration. All subjects gave informed consent and local institutional review board approval was obtained.

Echocardiographic evaluation

Structural characteristics, systolic function and diastolic function were assessed by 2-D echocardiography at baseline and follow-up. The following data were acquired: LV septal and posterior wall thickness, LV end-diastolic and end-systolic diameters, left atrial dimensions, LV systolic function, and maximal LV outflow tract gradient. Doppler imaging was used to acquire early (E) and late (A) filling velocities, E/A ratio and E-velocity deceleration time. Tissue Doppler imaging (TDI) was used to acquire medial and lateral mitral annular systolic (S'), and early (E') and late (A') diastolic velocities. LA volume and LV mass were calculated and diastolic function was graded all according to current guidelines.[8, 9]

In addition, speckle tracking echocardiography (STE) was performed as previously described, [10, 11] to measure peak systolic longitudinal strain, and peak systolic longitudinal strain rate (SR), in apical 4-chamber, 2-chamber and 3-chamber views (TomTEC Imaging Systems, Unterschleissheim, Germany). After manual tracing of the endocardial borders at end-systole, tracking was done automatically by the software. When necessary, manual readjustment of the tracking was performed. For each segment longitudinal strain and SR curves were generated and peak values were documented. This data was analyzed by an observer, who was blinded for the clinical data.

Follow-up

Follow-up vital status and cause of death, if applicable, was obtained by reviewing the hospital records, from general practitioners and civil registries. Follow-up data were complete for all subjects. The primary endpoint of this study was the development of manifest HCM (LVH $\geq$ 15mm). Secondary endpoints were major cardiac adverse events: including HCM-related death, sudden cardiac death or successful resuscitation after cardiac arrest, and hospital admissions related to HCM.

Statistical Analysis

All statistics were performed using the SPSS 21 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median (interquartile range). To compare continuous variables Student t test, Wilcoxon Signed Rank test or Mann-Whitney U-test were used, and to compare categorical variables the χ2-test was used. All tests were 2-sided and a p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The entire cohort consisted of 136 subjects with preclinical HCM, and 86 (56% female, age at baseline was 41 ±13 years) of those had >1 echocardiographic evaluation >1 year apart. Echocardiographic data at baseline are listed in TABLE 1. The distribution of pathogenic mutations is shown in FIGURE 1. The majority of subjects (57%) had 1 of the 3 Dutch founder mutations in MYBPC3: c.2827C>T (n=20, 23%), c.2373dupG (n=18, 21%) and c.2864delCT (n=11, 13%). In none of the subjects, >1 mutation was identified.

Follow-up

Follow-up (4.5 ±1.9 years, range 6.8, 384 patient-years) was complete in all subjects. During follow-up one patient (female, age 51y, MYBPC3 c.2864_2865delCT) developed manifest HCM (from 13mm to 15mm) after 6.6 years. There were no major adverse cardiac events. There was no increase in maximal LV wall thickness or LV mass. Ejection fraction was stable

TABLE 1 – Echocardiographic characteristics at baseline and at last follow-up of 86 subjects with preclinical HCM.

	Baseline	**Follow-up**	*P*
Structural characteristics			
- Ventricular septum, mm	10 ± 2	10 ± 2	**0.002**
- LV posterior wall, mm	9 ± 2	9 ± 1	**0.02**
- LV end diastolic diameter, mm	47 ± 5	46 ± 4	**0.05**
- LV end systolic diameter, mm	28 ± 5	27 ± 5	**0.02**
- LV mass, g	157 ± 45	152 ± 45	0.2
- Left atrial volume, ml	41 ± 18	41 ± 21	0.3
- LV outflow tract gradient, mmHg	6 ± 2	6 ± 6	0.5
Functional characteristics			
- Ejection fraction, %	59 ± 8	58 ± 7	0.3
- Fractional shortening, %	40 ± 8	42 ± 8	0.1
- E/A ratio	1.3 ± 0.7	1.2 ± 0.8	**0.02**
- Deceleration time, ms	180 ± 53	209 ± 74	**< 0.001**
- TDI s' velocity, cm/s	9.2 ± 2.8	8.4 ± 3.1	0.9
- TDI e' velocity, cm/s	9.5 ± 2.6	8.2 ± 3.3	**0.02**
- TDI a' velocity, cm/s	7.4 ± 1.9	10.0 ± 2.4	**< 0.001**
- E/e' ratio	11.7 ± 3.8	8.5 ± 2.6	**< 0.001**

Data are displayed as mean ± SD or median ± IQR. LV: left ventricular; TDI: tissue Doppler imaging.

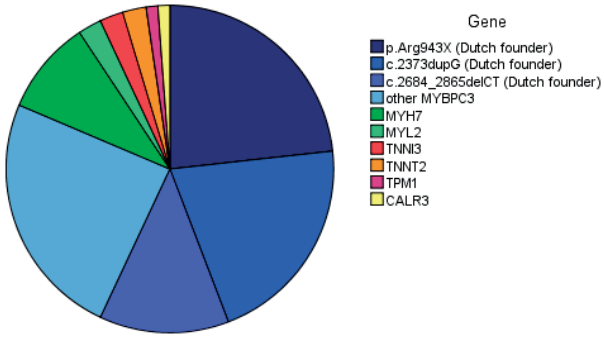


FIGURE 1 – Distribution of pathogenic mutations.

during follow-up (59% ± 8 at baseline and 58% ± 7 at last visit, p=0.3). In 67 subjects (78%) diastolic function was stable, and 16 subjects (19%) had progressive diastolic dysfunction during follow-up. In 3 subjects this could not be assessed. Other echocardiographic characteristics at follow-up are listed in TABLE 1.

TABLE 2 – Global and regional systolic function in subjects with preclinical HCM, with stable diastolic function, and progressive diastolic dysfunction during follow-up. In 3 subjects diastolic function could not be determined.

	Stable diastolic LVF			**Decrease in diastolic LVF**		
n =	67			16		
	Baseline	Follow-up	P	Baseline	Follow-up	P
Ejection fraction, %	59 ± 8	58 ± 7	0.4	62 ± 7	61 ± 7	0.5
Systolic strain, %	-20.1 ± 3.7	-19.8 ± 3.3	0.5	-21.3 ± 2.5	-19.7 ± 4.0	0.2
Septal strain, %	-18.7 ± 5.0	-18.0 ± 4.2	0.5	-20.5 ± 4.3	-16.8 ± 4.7	**0.04**
Lateral strain, %	-20.6 ± 6.0	-20.2 ± 5.2	0.7	-20.6 ± 3.9	-19.2 ± 5.3	0.5
Apical strain, %	-21.2 ± 5.1	-21.2 ± 4.9	0.8	-23.5 ± 5.3	-23 .2 ± 5.0	0.9
Systolic strain rate,1/s	-1.29 ± 0.35	-1.17 ± 0.18	**0.02**	-1.39 ± 0.30	-1.15 ± 0.21	**0.04**
Septal strain rate, 1/s	-1.20 ± 0.47	-1.07 ± 0.24	0.05	-1.41 ± 0.41	-1.01 ± 0.34	**0.02**
Lateral strain rate, 1/s	-1.39 ± 0.52	-1.19 ± 0.30	**0.01**	-1.32 ± 0.40	-1.12 ±0.28	0.3
Apical strain rate. 1/s	-1.34 ± 0.37	-1.27 ± 0.30	0.2	-1.53 ± 0.37	-1.38 ± 0.34	0.2

LVF: left ventricular function

Structural and functional characteristics

Subjects with progressive diastolic dysfunction during follow-up were older at last visit (51 ±12 y) than subjects with stable diastolic LV function (44 ± 13y, p=0.07). Although no significant increase of maximal LV wall thickness was observed during follow-up in both groups (p=0.7), subjects with progressive diastolic dysfunction had an increase of LV mass (+9g ± 36), in contrast to subjects with stable diastolic LV function (-9g ± 28, p=0.04).

Regional systolic strain and peak systolic strain rate were assessed by STE. Global systolic strain was -20.3% ± 3.5 at baseline and -19.8% ± 3.3 at last visit (p=0.3), global systolic strain rate was -1.29 ± 0.3 and -1.17 ± 0.2 respectively (p=0.002). There were no regional differences in strain values at baseline or during follow-up; the only exception is the significant reduction of septal strain in subjects with progressive diastolic dysfunction (from -21% ± 4 to -17% ± 5, p=0.04). Global strain rate was reduced during follow-up, and in subjects with progressive diastolic dysfunction, there was also a reduction of septal strain rate (from -1.4 ± 0.4 to -1.0 ± 0.3, p= 0.02; TABLE 2).

Dutch founder mutations were present in 49 subjects. Subjects with the c.2827C>T and c.2373dupG mutations had a significant reduction in septal strain rate during follow-up.

TABLE 3 – Septal systolic function in subjects with Dutch founder mutations

	Septal systolic strain (%)		
	Baseline	Follow-up	P
Dutch founder mutations (MYBPC3)			
- c.2827C>T (n=20)	-18.4 ± 4.5	-15.9 ± 4.3	0.08
- c.2373dupG (n=18)	-19.1 ± 4.6	-18.3 ± 5.1	0.5
- c.2864_2865delCT (n=11)	-16.5 ± 5.5	-17.9 ± 4.3	0.5
Other mutations			
- MYBPC3 (n=21)	-20.3 ± 4.9	-18.5 ± 3.4	0.2
- Other genes (n=16)	-19.0 ± 3.7	-18.9 ± 3.6	0.9
	Septal systolic strain rate (1/s)		
	Baseline	Follow-up	P
Dutch founder mutations (MYBPC3)			
- c.2827C>T (n=20)	-1.15 ± 0.30	-0.96 ± 0.21	**0.03**
- c.2373dupG (n=18)	-1.31 ± 0.37	-1.06 ± 0.28	**0.03**
- c.2864_2865delCT (n=11)	-1.02 ± 0.39	-1.05 ± 0.35	0.9
Other mutations			
- MYBPC3 (n=21)	-1.31 ± 0.42	-1.15 ± 0.18	0.2
- Other genes (n=16)	-1.18 ± 0.32	-1.07 ± 0.27	0.2

However regional strain or strain rate values could not be used to discriminate between the different mutations (TABLE 3).

DISCUSSION

The key finding of this study is that even a 4.5-year follow-up appears to be insufficient to determine which subjects with a pathogenic mutation will develop manifest HCM. Only one patient developed LVH of 15mm, and there were no adverse events during the study. This suggests that preclinical HCM in adults is a relatively benign condition, and this has several important implications.

Clinical recommendations

The 2014 ESC guidelines recommend a 1 or 2 yearly follow up for unaffected family members without known pathogenic mutation, but lacks practical recommendations of the follow-up of subjects with preclinical HCM.

Our study showed zero events in 384 patient years of follow-up, and this confirms the preliminary findings by Gray et al. They found that in a small cohort of adult preclinical HCM subjects (n=16, follow-up of ±4 years), none of these developed manifest HCM.[12] Also, the rate of SCD in subjects with preclinical HCM is very low; only incidental case reports have been published [13], but both in this study and the study by Christiaans et al.[5] there were no reported SCD or cardiac resuscitations in subjects with preclinical HCM. Furthermore, combined with the very low event rate in patients > 60 years of age with overt HCM[14], one could wonder if follow-up is necessary in asymptomatic subjects with preclinical HCM that are older than 60 years.

All considered, we conclude that (bi-)annual evaluation is not necessary in the majority of the subjects, and we propose a 5-year interval between clinical evaluations in these subjects, unless a change in clinical status occurs. Several signs of potential disease progression could lead to increased frequency of follow-up: most importantly, the presence of symptoms. If during follow-up a progressive diastolic dysfunction or maximal LV wall thickness of 13-14mm is detected, more frequent evaluation is justifiable. In addition, in subjects without LVH but with apparent ECG abnormalities (such as the McKenna criteria [15]) further analysis with cardiac magnetic resonance imaging (CMR) is warranted; to determine the presence of myocardial scarring or fibrosis, which increases the risk of life-threatening ventricular arrhythmias in these subjects.[13, 16]

Whether or not subjects with preclinical HCM should be excluded from sports is subject to debate, and current guidelines are ambiguous: "Mutation carriers without disease expression on ECG or echocardiography, who wish to participate in competitive sports, should be

advised on an individual basis, taking into account the local legal framework, the underlying mutation and the type of sporting activity."[3]

Older European recommendations[17] advice to exclude these subject from sports activities, but the Bethesda Conference no. 36 consensus recommendations do not exclude preclinical HCM subjects from sports. Based on the findings of this study and the current literature describing the virtual absence of any cardiovascular events in subjects with preclinical HCM, our HCM program usually allows them to enroll in competitive sport activities, but keeps them under close clinical surveillance with cardiac evaluations every year, as long as they participate in competitive sport. In addition, CMR can be used to fully exclude the phenotype.

It is important to note that these findings only consider the development of HCM in adults. In this study the minimum age was 17 years old at baseline. The progression of disease in children and adolescents needs to be investigated separately. Recently, Jensen et al. have demonstrated after 12 years of follow-up, a low (6%) penetrance of HCM in childhood and early adulthood. Also no cardiac events were seen in child relatives. The authors further state that: "this low penetrance challenges the general perception that HCM develops predominantly during the growth spurt in childhood or adolescence."[18]

Identifying predictors of disease progression

The mechanisms of progression from preclinical to manifest HCM remain unclear. In a subset of these patients, cardiomyocytes start to remodel and this remodeling may lead to compensatory hypertrophy –locally at first – and more regional as disease progresses.[6, 7, 19-22] But the slow progression of preclinical HCM limits the ability to identify potential predictors of disease progression. With only one patient that developed LVH ≥ 15mm, no further analysis could be performed to determine which subjects are at risk to develop HCM.

Progressive diastolic dysfunction could be a potential predictor for disease progression; but the relevance of it is unclear in this study. Only 16 subjects had progressive diastolic dysfunction, and the majority (9, 64%) was older than 50 years at the end of the study, and it is known that diastolic function also decreases with age.

On the other hand, in subjects with progressive diastolic dysfunction there was a significant decrease in septal systolic strain and strain rate, which was not present in subjects with stable diastolic function.

Earlier studies have demonstrated that this regional systolic dysfunction, especially at the basal septum, is present in patients with manifest HCM.[23, 24] Although there was no clear reduction in systolic strain in subjects with preclinical HCM, compared with healthy controls,[6] our findings show that the reduced regional contractility is only present in subjects with progressive diastolic dysfunction over time. Thus the remodeling of the cardiomyocytes could present itself as early local systolic and diastolic abnormalities, and progresses later towards manifest HCM with asymmetrical hypertrophy and systolic and diastolic dysfunction

(FIGURE 2). The finding that subjects with progressive diastolic dysfunction also appear to have impaired regional systolic function and increased LV mass may support this hypothesis. The favorable response to treatment with diltiazem in a recent study performed by Ho et al., which improves calcium handling, and removes one of the extrinsic factors that could trigger the remodeling of the cardiomyocyte, also supports this.[25]

Preventive strategies

Several strategies to prevent the development of LVH have been proposed. As mentioned above, Ho et al. randomized subjects with preclinical HCM between daily treatment with diltiazem or placebo. After ± 2 years of treatment there was no difference in the low number of patients who were diagnosed with HCM (2 in each group, all aged < 18y), but diltiazem was associated with improved diastolic function and LV wall thickness in MYBPC3 mutation carriers.[25] This potential beneficial effect of diltiazem could be contributed to the improved calcium regulation on sarcomere level, observed in several preclinical studies.[26, 27] Sarcomeric mutations are known to disturb calcium sensitivity, which is one of the factors that could lead to impairment of cardiomyocyte contractility and relaxation, and may lead to remodeling of the cardiomyocyte.[21, 28, 29]

Transgenic HCM models showed that angiotensin receptor blockers, such as losartan, may be effective in preventing of development of a clinical phenotype, and causing regression of disease,[30] but the results of recently published INHERIT trial did not demonstrate any disease regression in patients with manifest HCM.[31] The ongoing VANISH trial (ClinicalTrials.gov Identifier: NCT01912534) is designed to determine whether losartan can reduce or halt disease progression. Future research could also focus on the possibility of preventing the disease by allele-specific silencing.[32]

The very limited occurrence of LVH in subjects with preclinical HCM could hamper the findings of these studies; especially because it is unclear which subjects with preclinical HCM are more prone to develop manifest HCM.

Limitations

The findings of this study are limited by the small sample size. STE is limited by the quality of echocardiographic images and in 3 subjects diastolic function could also not be assessed properly due to poor image quality. Genetic analysis was performed initially using classic Sanger technique. Next generation sequencing screening was not performed until and could lead to the identification of subjects with >1 mutation, and determine if this is a potential predictor for disease progression. Another important limitation is the distribution of the mutations in the study population; the majority of the subjects had a mutation in the MYBPC3 gene, due to the presence of three Dutch founder mutations. It is uncertain if the benign course of preclinical HCM that was described in this study can be generalized to other populations. However

mutations in MYBPC3 gene are one of the most frequent causes of HCM, accounting for ± 30% of the identified mutations worldwide.[33]

CONCLUSION

During 4.5 year follow-up, manifest HCM occurred in one patient and there were no cardiac events. This suggests that preclinical HCM in adults is a relatively benign condition. We propose a 5-year interval between clinical evaluations in asymptomatic subjects with preclinical HCM unless a change in clinical status occurs. It is unclear what the mechanisms of progression from preclinical to manifest HCM are, and the very limited occurrence of LVH in subjects with preclinical HCM could hamper the identification of preventive strategies.

REFERENCES

1. Jarcho JA, McKenna W, Pare JA, et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. N Engl J Med 1989;321:1372-8.
2. Ho CY. Genetic considerations in hypertrophic cardiomyopathy. Prog Cardiovasc Dis 2012;54:456-60.
3. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.
4. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
5. Christiaans I, Birnie E, Bonsel GJ, et al. Manifest disease, risk factors for sudden cardiac death, and cardiac events in a large nationwide cohort of predictively tested hypertrophic cardiomyopathy mutation carriers: determining the best cardiological screening strategy. Eur Heart J 2011;32:1161-70.
6. Ho CY, Carlsen C, Thune JJ, et al. Echocardiographic strain imaging to assess early and late consequences of sarcomere mutations in hypertrophic cardiomyopathy. Circ Cardiovasc Genet 2009;2:314-21.
7. Michels M, Soliman OI, Kofflard MJ, et al. Diastolic abnormalities as the first feature of hypertrophic cardiomyopathy in Dutch myosin-binding protein C founder mutations. JACC Cardiovasc Imaging 2009;2:58-64.
8. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
9. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.
10. Carasso S, Yang H, Woo A, et al. Systolic myocardial mechanics in hypertrophic cardiomyopathy: novel concepts and implications for clinical status. J Am Soc Echocardiogr 2008;21:675-83.
11. Risum N, Ali S, Olsen NT, et al. Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults. J Am Soc Echocardiogr 2012;25:1195-203.
12. Gray B, Ingles J, Semsarian C. Natural history of genotype positive-phenotype negative patients with hypertrophic cardiomyopathy. Int J Cardiol 2011;152:258-9.
13. Pasquale F, Syrris P, Kaski JP, et al. Long-term outcomes in hypertrophic cardiomyopathy caused by mutations in the cardiac troponin T gene. Circ Cardiovasc Genet 2012;5:10-7.
14. Maron BJ, Rowin EJ, Casey SA, et al. Risk stratification and outcome of patients with hypertrophic cardiomyopathy >=60 years of age. Circulation 2013;127:585-93.
15. McKenna WJ, Spirito P, Desnos M, et al. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. Heart 1997;77:130-2.
16. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484-95.
17. Pelliccia A, Corrado D, Bjornstad HH, et al. Recommendations for participation in competitive sport and leisure-time physical activity in individuals with cardiomyopathies, myocarditis and pericarditis. Eur J Cardiovasc Prev Rehabil 2006;13:876-85.
18. Jensen MK, Havndrup O, Christiansen M, et al. Penetrance of hypertrophic cardiomyopathy in children and adolescents: a 12-year follow-up study of clinical screening and predictive genetic testing. Circulation 2013;127:48-54.

19. van Dijk SJ, Dooijes D, dos Remedios C, et al. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation 2009;119:1473-83.
20. Hoskins AC, Jacques A, Bardswell SC, et al. Normal passive viscoelasticity but abnormal myofibrillar force generation in human hypertrophic cardiomyopathy. J Mol Cell Cardiol 2010;49:737-45.
21. Witjas-Paalberends ER, Piroddi N, Stam K, et al. Mutations in MYH7 reduce the force generating capacity of sarcomeres in human familial hypertrophic cardiomyopathy. Cardiovasc Res 2013;99:432-41.
22. Kraft T, Witjas-Paalberends ER, Boontje NM, et al. Familial hypertrophic cardiomyopathy: functional effects of myosin mutation R723G in cardiomyocytes. J Mol Cell Cardiol 2013;57:13-22.
23. Geske JB, Bos JM, Gersh BJ, et al. Deformation patterns in genotyped patients with hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging 2014;15:456-65.
24. Kobayashi T, Popovic Z, Bhonsale A, et al. Association between septal strain rate and histopathology in symptomatic hypertrophic cardiomyopathy patients undergoing septal myectomy. Am Heart J 2013;166:503-11.
25. Ho CY, Lakdawala NK, Cirino AL, et al. Diltiazem treatment for pre-clinical hypertrophic cardiomyopathy sarcomere mutation carriers: a pilot randomized trial to modify disease expression. JACC Heart Fail 2015;3:180-8.
26. Westermann D, Knollmann BC, Steendijk P, et al. Diltiazem treatment prevents diastolic heart failure in mice with familial hypertrophic cardiomyopathy. Eur J Heart Fail 2006;8:115-21.
27. Semsarian C, Ahmad I, Giewat M, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. J Clin Invest 2002;109:1013-20.
28. van Dijk SJ, Paalberends ER, Najafi A, et al. Contractile dysfunction irrespective of the mutant protein in human hypertrophic cardiomyopathy with normal systolic function. Circ Heart Fail 2012;5:36-46.
29. Hamdani N, Kooij V, van Dijk S, et al. Sarcomeric dysfunction in heart failure. Cardiovasc Res 2008;77:649-58.
30. van der Velden J, Ho CY, Tardiff JC, et al. Research priorities in sarcomeric cardiomyopathies. Cardiovasc Res 2015;105:449-56.
31. Axelsson A, Iversen K, Vejlstrup N, et al. Efficacy and safety of the angiotensin II receptor blocker losartan for hypertrophic cardiomyopathy: the INHERIT randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2015;3:123-31.
32. Jiang J, Wakimoto H, Seidman JG, et al. Allele-specific silencing of mutant Myh6 transcripts in mice suppresses hypertrophic cardiomyopathy. Science 2013;342:111-4.
33. Bos JM, Towbin JA, Ackerman MJ. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol 2009;54:201-11.

Chapter 15

Positive correlation between contractile dysfunction of the sarcomere and impaired regional systolic strain in hypertrophic cardiomyopathy.

Vriesendop PA, Witjas-Paalberends ER, Schinkel AFL, Nijenkamp L, Soliman OII, Van Slegtenhorst MA, Ten Cate FJ, Van der Velden J, Michels M

submitted

ABSTRACT

Aims

Recent studies showed reduced maximal force generating capacity of cardiomyocytes from hypertrophic cardiomyopathy (HCM) patients with normal systolic function. In the present study we investigated if reduced maximal force at cellular level is associated with local systolic dysfunction in HCM patients.

Methods and Results

A total of 46 HCM patients (age 51 ±10 years, 64% male) underwent pre-operative transthoracic echocardiography, and additionally, segmental systolic strain and strain-rate were measured from apical 4-, 2-, and 3-chamber views). Echocardiographic data were compared with age- and sex-matched controls. Maximal force development was measured in membrane-permeabilized cardiomyocytes isolated from tissue obtained via surgical myectomy from 30 of these patients. Non-failing donors (n=10) served as control group. Ejection fraction of HCM patients was in the normal range. Peak systolic strain and strain rate were markedly lower in the septal wall of HCM patients compared with controls. A significantly lower maximal force generating capacity was found in cells from the HCM patients compared to non-failing donor hearts, and correlated with the reduction in systolic strain. In addition, systolic strain correlated negatively with septal thickness.

Conclusion

Systolic function in HCM patients is reduced at a regional level despite normal ejection fraction. Impairment of regional systolic function, demonstrated by strain and strain rate analysis, may be explained by a reduction in force generating capacity at the level of sarcomeres. This could result in the development of asymmetric hypertrophy.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most prevalent inheritable myocardial disease, and is defined by the presence of left ventricular hypertrophy (LVH) of ≥15 mm, in absence of abnormal loading conditions.[1] Genotyping studies have identified a pathogenic mutation in ± 70% of all patients with HCM.[2, 3] In total, >1300 mutations have been found in 13 genes, mostly coding for the sarcomeric proteins.[2] There is both genetic and clinical heterogeneity in HCM[4]: even when patients harbor the same mutation, the phenotype varies widely. The complex genotype-phenotype relationship remains unclear.

Recent studies [5-8] showed that, regardless of the disease-causing mutation, the force-generating capacity of the cardiomyocyte was reduced. Interestingly, this reduced force-generating capacity was found in patients with normal global systolic function.[7, 9] On the other hand, there is increasing evidence that regional myocardial dysfunction is present in HCM patients based on systolic strain analysis.[10-13] However it is unclear if there is a correlation between this regional myocardial dysfunction and the reduced force-generating capacity at sarcomere level of HCM cardiomyocytes.

In the present study we investigated whether reduced maximal force generating capacity at single cardiomyocyte level is associated with regional systolic dysfunction in HCM patients with and without sarcomeric gene mutations. *In vitro* force measurements were performed in single cardiomyocytes isolated from septal tissue obtained during myectomy surgery from HCM patients. These measurements were combined with the *in vivo* systolic function of these patients, which was assessed before surgery.

METHODS

Study design and patient population

The initial study population consisted of 46 HCM patients who underwent surgical myectomy at the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. Each patient had an established diagnosis of HCM, based on unexplained LVH of ≥15 mm, assessed by echocardiography. Patients with HCM linked to Noonan's syndrome, Fabry's disease, mitochondrial disease or congenital heart defects were excluded. All patients were accepted for surgical myectomy or alcohol septal ablation (ASA) based on the presence of symptoms despite maximal medical therapy and LVOT gradients > 50 mmHg. In these patients tissue from the interventricular (IVS) septum was obtained directly during surgery, or as IVS biopsy, prior to the ablation procedure.

Genetic testing was performed in all patients; the following genes were screened: cardiac myosin binding protein C (*MYBPC3*), β-cardiac myosin heavy chain (*MYH7*), myosin regulatory light chain (*MYL2*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), cardiac

troponin C (*TNNC1*), α-actin (*ACTC1*), and α-tropomyosin (*TPM1*). Next-generation sequencing was not systematically performed in all patients. Patients were divided in 2 groups: sarcomere mutation-positive HCM (HCM_{MUT}), sarcomere mutation-negative HCM (HCM_{SMN}), and controls.

Echocardiographic controls were obtained from age- and gender matched healthy subjects. Donors (n = 10, age 36 ± 5, 80% male) with no history of cardiac abnormalities, normal ECG and normal ventricular function on echocardiography within 24 hours of heart transplantation served as controls for the myocardial samples. The study conforms to the principles of the Helsinki Declaration. Informed consent of each patient was obtained in addition to local institutional review board approval.

Cardiomyocyte measurements

The septal tissue obtained during myectomy was used for single cardiomyocyte force measurements using a previously described method [7, 14]. In short, single cardiomyocytes were mechanically isolated and treated with 0.5% Triton X-100 to permeabilize the membranes providing us with the opportunity to asses force generating capacity of the sarcomeres without interference of Ca^{2+}-handling proteins. A single cardiomyocyte was mounted between a force transducer and a piezoelectric motor and stretched to a sarcomere length of 2.2 μm. In an activating solution with a calcium concentration of 31.62 μmol/L (pCa 4.5), the myocyte started to generate force. After reaching the steady state force level the cardiomyocyte was mechanically shortened by 30% to determine total force development (F_{total}). Subsequently, the cardiomyocyte was transferred to relaxing solution with a calcium concentration of 10^{-6} μmol/L (pCa 9.0) to measure passive force development (F_{pas}). Maximal force generating capacity (F_{max}) was calculated by subtracting F_{pas} from F_{total}. (FIGURE 1A).

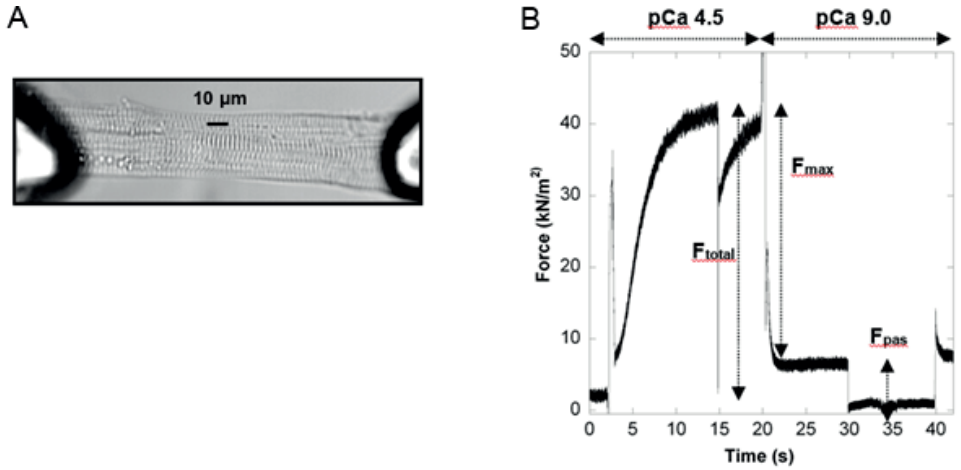


FIGURE 1 – Functional measurements of single cardiomyocytes. Single cardiomyocyte at a sarcomere length of 2.2μm in the experimental setup (A). Force recording of the cardiomyocyte (B).

Force values were normalized to cross-sectional area (CSA), to obtain the tension, of the preparations calculated on the basis of cardiomyocyte/myofibril width and depth determined in the experimental set-ups (i.e. CSA = width x depth x ϖ/4). Force signals were analyzed using Labview version 9.0 (National Instruments Corporation, Austin, TX).

Echocardiography

All patients underwent comprehensive echocardiography using commercially available ultrasound machines (Philips Healthcare, Eindhoven, the Netherlands and Siemens Healthcare, Erlangen, Germany). All echocardiographic analyses were blinded from clinical characteristics. The following data were acquired: end-diastolic IVS and posterior wall thickness, end-diastolic and end-systolic diameters, left atrial dimensions, and LV ejection fraction, all according to current guidelines.[15] The severity of the mitral valve regurgitation (MR) was graded on a 0 to 4 scale by color flow Doppler echocardiography [16]. The severity of the SAM of the anterior mitral valve leaflet was determined from the 2D images and was graded on a scale from 0 to 3 depending on the mitral-septal distance (grade 0 indicating no SAM and grade 3 indicating prolonged contact between mitral valve and septum) [17]. Peak LVOT gradient was estimated with continuous wave Doppler echocardiography by the modified Bernoulli equation ($P = 4v^2$), where P is the pressure gradient and v is Doppler-determined blood velocity. LVOT gradient was measured at rest and during provocative maneuvers (such as Valsalva maneuver), and the highest gradient was considered the peak LVOT gradient.

Speckle tracking echocardiography (STE) was performed as previously described.[12, 18] Peak systolic longitudinal strain, peak systolic longitudinal strain rate (SR), and early diastolic SR in apical 4-chamber, 2-chamber and 3-chamber views were measured and calculated.(TomTEC Imaging Systems, Unterschleissheim, Germany). After manual tracing of the endocardial borders at end-systole, tracking was done automatically by the software. When necessary, manual readjustment of the tracking was performed. For each segment longitudinal strain and SR curves were generated and peak values were documented.

Statistical Analysis

Regarding the clinical data SPSS version 20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) were used for statistical analyses. Categorical variables were summarized as percentages. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median (interquartile range). To compare continuous variables (such as EF, LV wall thickness, LVOT gradient, segmental SS values) Student *t* test, ANOVA-tests or Mann-Whitney U-test were used, and to compare categorical variables the χ^2-test was used. Correlation was determined using Spearman's ρ.

Regarding the cardiomyocyte force measurements data analysis and statistics were performed using Prism version 4.0 (Graphpad Software, Inc., La Jolla, CA). A one-way ANOVA

was used to gain insight in the differences in force development of the cardiomyocytes among the patient groups (HCM_{mut}, HCM_{smn} and donor). All tests were 2-sided and a p-value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Cardiomyocyte force measurements could not be performed in 13 of 46 patients due to tissue availability and lack of genetic data, and these were excluded from further analysis. The clinical and echocardiographic characteristics of the remaining 33 patients (51 ± 13 years old, 12 (36%) female) are listed in TABLE 1. Myectomy was performed in 27 patients (81%), and ASA in 6 (18%). In 21 patients a pathogenic mutation was found: MYBPC3 in 15 (71%), MYH7 in 3 (14%), TNNI3 in 2 (10%) and TMP1 in 1 patient (5%). The *MYBPC3* mutations are all truncating mutations and the mutations in the other genes are missense mutations. In 12 patients genetic screening revealed no pathogenic mutation. These patients were older (57 ± 9.7 years) than patients with a mutation (48 ± 14.7, p=0.05). Other clinical and echocardiographic characteristics did not differ significantly between the two groups: septal wall thickness was 23 ± 5 mm in HCM_{MUT} and 21±3 in HCM_{SMN} (p=0.2); maximal LVOT gradient (either resting or after provocation) was 83 ± 25 mmHg in HCM_{MUT} and 96 ±33 in HCM_{SMN}(p=0.7); and LVEF was 63 ± 6 % in HCM_{MUT} and 65 ± 8 % in HCM_{SMN} (p=0.5, FIGURE 2A).

TABLE 1 – Clinical and echocardiographic characteristics of 33 HCM patients at the time of surgery.

	Mutation	Age (y)	Sex	NYHA	LVWT (mm)	LVOTG (mmHg)	LVEF (%)
Truncating mutations							
MYBPC3							
1	c.2373dupG	69	M	3	19	60	61
2	c.2373dupG	32	M	2	23	85	69
3	c.2373dupG	60	M	3	26	77	70
4	c.2827C>T	24	F	3	24	80	58
5	c.2827C>T	34	M	3	39	60	67
6	c.2827C>T	50	M	3	20	80	56
7	c.2864_2865delCT	62	F	3	19	110	61
8	c.927-2A>G	37	M	3	20	60	66
9	c.927-2A>G	58	F	3	25	75	63
10	c.927-2A>G	21	M	3	32	70	49

TABLE 1 – continued

	Mutation	Age (y)	Sex	NYHA	LVWT (mm)	LVOTG (mmHg)	LVEF (%)
11	c.1790G>A	47	F	2	20	85	55
12	c.2783C>T	71	M	3	22	75	66
13	c.3029delA	45	F	3	23	125	56
14	c.3407_3409del	55	M	3	19	95	68
15	c.772G>A	36	M	2	30	10	63
		47±16			24±6	76±26	62±6
Missense mutations							
MYH7							
1	c.1291G>C	35	M	3	20	93	65
2	c.1816G>A	48	F	3	25	80	71
3	c.4130C>T	43	M	3	24	120	53
TNNI3							
1	c.433C>T	46	M	2	20	100	74
2	c.433C>T	66	M	2	20	100	65
TMP1							
1	c.850A>T	65	M	3	20	100	60
		51±12			22±2	99±13	65±8
HCM_{smn}							
1	-	74	F	3	21	137	61
2	-	58	M	3	26	115	51
3	-	73	F	3	24	90	62
4	-	49	M	3	18	60	63
5	-	65	F	2	17	85	78
6	-	52	M	3	22	170	72
7	-	44	M	2	20	85	64
8	-	60	M	2	20	100	64
9	-	46	F	3	20	90	66
10	-	56	F	2	15	75	76
11	-	52	M	3	17	45	55
12	-	60	F	2	17	100	59
		57±10			20±3	96±33	64±8

LVEF: left ventricular ejection fraction; LVOTG: maximal left ventricular outflow tract gradient; LVWT: maximal left ventricular wall thickness; NYHA: New York Heart Association functional class;

Force measurements

Single cardiomyocyte force measurements were performed at sarcomere length of 2.2μm to gain insight in F_{max}. FIGURE 1A shows a representative image of a single cardiomyocyte mounted in the experimental set-up. An example force recording is provided in FIGURE 1B of an HCM_{MUT} cardiomyocyte. F_{max} was significantly lower (p=0.002) in the HCM_{MUT} compared to donor cardiomyocytes (FIGURE 2D).

There was no significant difference in tension between cardiomyocytes with truncating (MYBPC3) and missense (MYH7, TNNI3 and TPM1) mutations. However, cardiomyocytes with missense mutations showed clearly a lower tension compared with cardiomyocytes from HCM_{SMN} patients (TABLE 2).

Regional function and wall thickness

Ejection fraction was in the normal range in both the HCM_{MUT} (63 ± 6%) and HCM_{SMN} patients (65 ± 8%), and was similar to controls (63 ± 4%, p=1.0 and p=0.9 respectively, FIGURE 2A). An

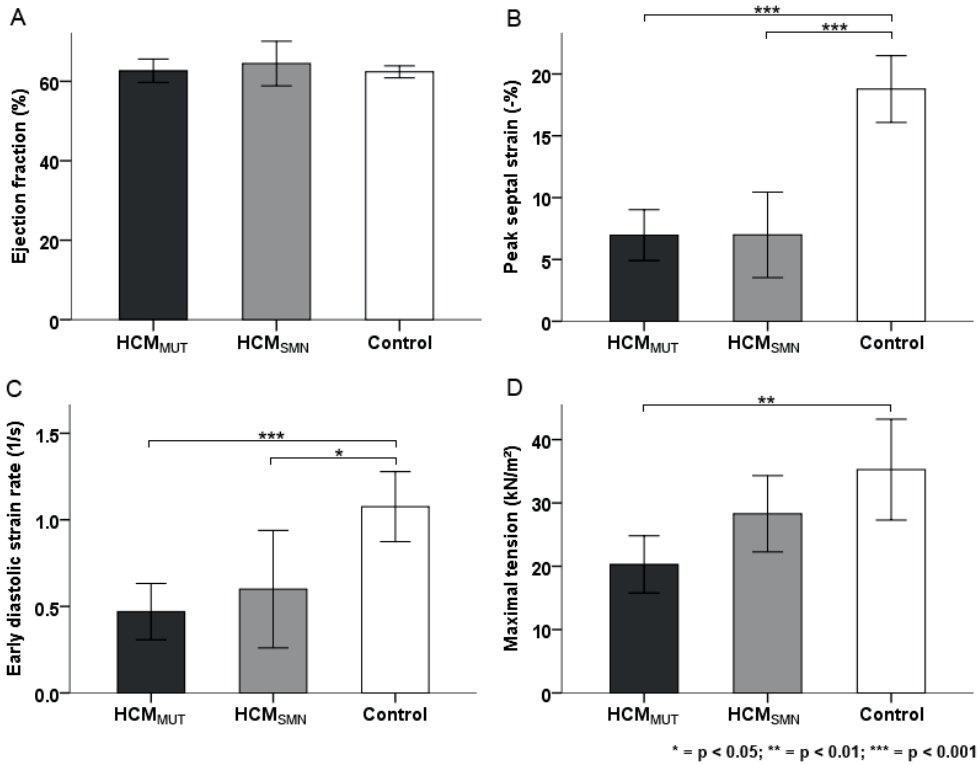


FIGURE 2 – *In vivo* and *in vitro contractile dysfunction*. Despite a normal ejection fraction (A) in the 3 groups (control, HCM_{mut}, HCM_{smn}) there is reduced peak systolic septal strain (B), reduced early diastolic septal strain rate (C) and reduced maximal tension development at long (2.2 μm) sarcomere length (D) in HCM patients.

TABLE 2 – Myocardial and cardiac mechanics of the basal septum in HCM patients with truncating and missense mutations.

	HCM_{MYBPC3}		**$HCM_{Missense}$**		**HCM_{SMN}**	
		P SMN		*P MYBPC3*		*P missense*
Fmax at 2.2μm, kN/m²	22.9 ± 10.4	0.4	13.7 ± 4.1	0.1	28.3 ± 9.5	**0.01**
Septal systolic strain, %	-7.5 ± 3.8	1.0	-5.7 ± 5.4	1.0	-7.0 ± 4.8	1.0
Septal systolic SR, 1/s	-0.60 ± 0.29	1.0	-0.73 ± 1.01	1.0	-0.62 ± 0.39	1.0
Septal early diastolic SR, 1/s	0.56 ± 0.30	1.0	0.29 ± 0.32	0.5	0.60 ± 0.48	0.4

SR: longitudinal strain rate. P values calculated with One-way ANOVA

overview of segmental strain per group is shown in FIGURE 3. Global strain was reduced in both HCM_{MUT} (-16.0 ± 3.2%) and HCM_{SMN} (-15.1 ± 3.1%) compared with controls (-21.0 ± 3.2%, p<0.001 and p<0.001 respectively). The biggest reduction in regional strain, compared with controls, was at basal segments of the anterior and inferior septum, both in HCM_{MUT} and HCM_{SMN} patients (TABLE 3 and FIGURE 2, 3). Decrease in septal strain was similar in HCM_{MUT} and HCM_{SMN}, and no differences were found between truncating and missense mutations (TABLE 2, 3). Apical levels of strain were normal or slightly increased compared with controls. Peak septal systolic SR and early diastolic SR were clearly decreased compared with controls (FIGURE 2C), but no difference was found between truncating and missense mutations (TABLE 2, 3)

Although the maximal wall thickness was similar between the groups (see above), basal anterior wall thickness was increased in HCM_{MUT} patients (22 ± 5 mm) compared with HCM_{SMN} patients (18 ± 6 mm; p=0.02). Hypertrophy was most pronounced in the septal wall, with exception from the apical area (FIGURE 4).

TABLE 3 – Myocardial and cardiac mechanics of the basal septum in HCM_{MUT} patients, HCM_{SMN} patients and healthy controls.

	HCM_{MUT}		**HCM_{SMN}**		**Control**	
		P control		*P MUT*		*P SMN*
Fmax at 2.2μm, kN/m²	20.3 ± 9.9	**0.002**	28.3 ± 9.5	0.09	35.3 ± 10.4	0.4
Septal systolic strain, %	-7.0 ± 4.3	**<0.001**	-7.0 ± 4.8	1.0	-18.8 ± 7.4	**<0.001**
Septal systolic SR, 1/s	-0.64 ± 0.58	**0.007**	-0.62 ± 0.39	1.0	-1.19 ± 0.64	**0.03**
Septal early diastolic SR, 1/s	0.47 ± 0.33	**<0.001**	0.60 ± 0.48	1.0	1.08 ± 0.54	**0.02**

SR: longitudinal strain rate. P values calculated with One-way ANOVA

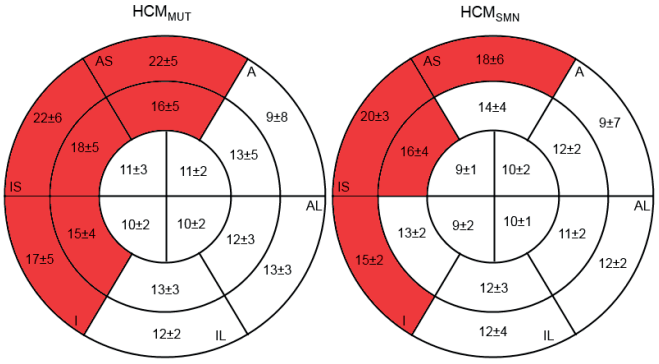


FIGURE 3 – Peak systolic longitudinal strain per segment. Measurements in HCMMUT group, HCMSMN group, and control group. A: anterior; AL: anterolateral; AS: anteroseptal; I: inferior; IL: inferolateral; IS: inferoseptal. Red segments have peak systolic strain < -15%.

Basal septal peak longitudinal strain was plotted as a function of F_{max} (FIGURE 5A) and septal wall thickness (FIGURE 5B) revealing a modest correlation with maximal force development (Spearman's ρ 0.46, p = 0.01) and a negative correlation with hypertrophy (Spearman's ρ -0.38; p = 0.04).

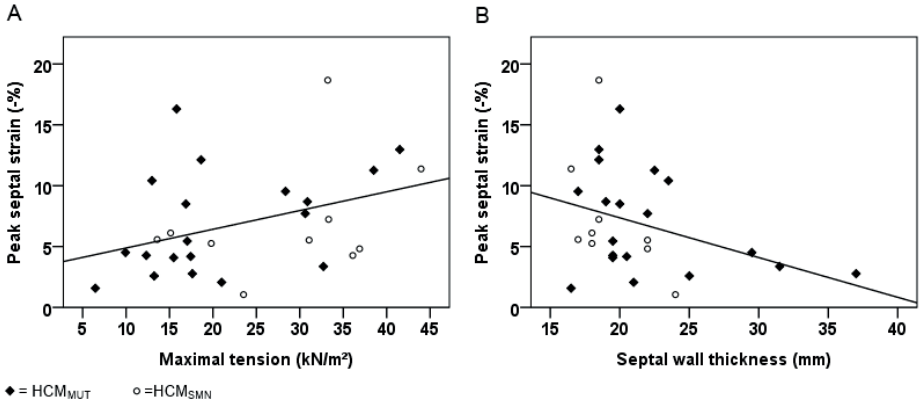


FIGURE 4 – Maximal wall thickness per segment. Measurements in HCMMUT and HCMSMN groups. A: anterior; AL: anterolateral; AS: anteroseptal; I: inferior; IL: inferolateral; IS: inferoseptal. Red segments have wall thickness ≥ 15 mm.

DISCUSSION

This is the first study to compare myocardial function on a regional and cellular level. The most important finding of this study is that there is an association between the reduced maximal force development of the cardiomyocyte and impaired regional systolic function, especially of the septal wall, in patients with HCM.

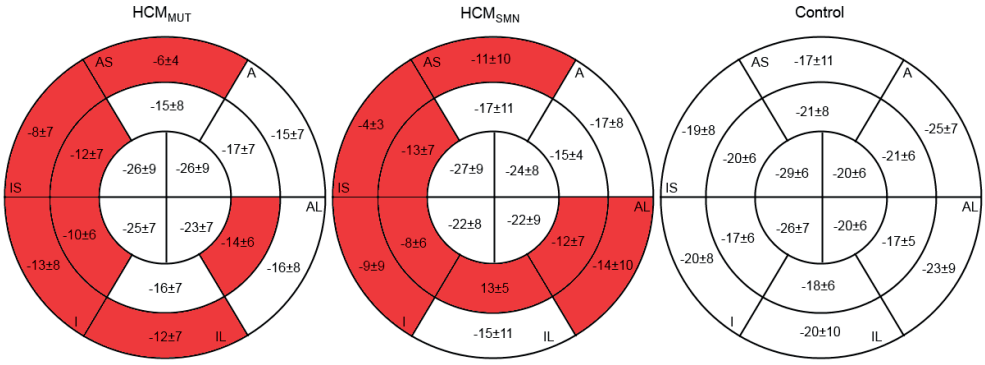


FIGURE 5 – Correlations. Correlation between septal peak longitudinal strain and maximal tension development at long (2.2μm) sarcomere length (A) and septal peak longitudinal strain and maximal segmental wall thickness (B).

Reduced force generating capacity at single cardiomyocyte level

A lower maximal force generating capacity was measured in HCM cardiomyocytes compared with non-failing donor cardiomyocytes (FIGURE 2C), and this was in line with previous studies [5-8]. This drop in cellular performance can be can be explained by a combination of structural cellular remodeling and mutation-induced intrinsic sarcomeric defects.

Cellular remodeling exists of cardiomyocyte hypertrophy and a reduction in myofibrillar density. Previously we revealed a negative correlation between myofibrillar density and cardiomyocyte area. Interestingly, cellular remodeling and dysfunction was more evident in patients with a sarcomeric gene mutation compared to HCM patients without an identified mutation, suggesting a clear difference in genotype-positive and genotype-negative HCM disease [7]. Also in the present study maximal force generating capacity was less decreased in HCM$_{SMN}$ patients (FIGURE 2C).

Depending on the type of mutation, the reduced force generating capacity is caused by the mutant protein itself or results from cellular remodeling. Most included patients harbored a truncating mutation in MYBPC3 (n=15) and the remainder missense mutations in MYH7, TNNI3 and TPM1 (n=6). Truncated proteins are not incorporated in the sarcomere and will be degraded, hence only the healthy protein is incorporated, albeit to a lesser extent. [5, 19, 20]

Missense mutations, however, potentially lead to poison peptides incorporated in the sarcomere [21, 22]. Previously, when maximal tension was corrected for myofibrillar density [7], maximal force generating capacity was normalized to donor level in absence of a mutation or in presence of a truncating mutation in MYBPC3 or missense mutation in TNNI3. This was not the case when a missense mutation in MYH7 or TPM1 was present. Indeed, the present results confirm this previous observation as cardiomyocytes harboring missense mutations revealed even a lower tension compared with HCM$_{SMN}$ cardiomyocytes (TABLE 2). This suggests a clear mutation-induced sarcomere defect leading to the reduction in tension, in addition to the cellular remodeling.

Regional systolic impairment and hypertrophy

Leaving the specific type sarcomeric gene mutation out of the equation, the observed reduction in maximal force generating capacity is typical for HCM, as in patients with idiopathic dilated cardiomyopathy and ischemic cardiomyopathy this reduction is not present[23]. This suggests the possibility that underlying HCM mutations trigger a common pathway of impaired contraction of the cardiomyocytes, and that this hypocontractility leads to regional dysfunction and asymmetrical hypertrophy. Classic echocardiographic assessment of HCM patients usually describes a hypercontractile heart, with normal or increased ejection fraction. However using deformation and strain analysis, it has become clear that there is regional systolic and diastolic dysfunction in HCM, especially in the basal septal wall.[11, 13] Indeed, in the present study the lower force generating capacity of the cardiomyocytes in HCM patients is accompanied with regional systolic and diastolic dysfunction, demonstrated by strain and SR analysis, and regional hypertrophy (FIGURE 3 and 4, TABLE 3).

Impaired cardiac mechanics appear to be an expression of the HCM phenotype: apical and classic HCM have different strain patterns [24]. Recently, it was demonstrated that strain was similarly reduced in HCM patients with and without pathogenic mutations.[11] In our study likewise no significant differences in regional strain values were found between HCM_{MUT} and HCM_{SMN} patients (FIGURE 3 and TABLE 3). On the other hand, there was a relationship between wall thickness and impaired regional function.

The reduced strain and SR (both systolic and diastolic) can be ascribed to several aspects of the myocardium of HCM patients. First, the presence of fibrosis is associated with reduced strain. Using cardiac magnetic resonance (CMR) imaging, Popovic et al. [25] demonstrated that the presence of myocardial fibrosis on CMR was correlated with reduced systolic strain, and Kobayashi et al.[13] showed that both systolic and diastolic septal SR were more decreased if more interstitial fibrosis was present on a cellular level. But both studies also demonstrated that the presence of hypertrophy itself was an independent predictor of reduced strain and strain rate. This is also confirmed by the negative correlation found in this study between wall thickness and septal strain (FIGURE 5B).

Not only in patients with HCM is strain reduced. In patients with LVH caused by severe valvular aortic stenosis, longitudinal systolic strain was also reduced. However, after aortic valve replacement, strain would improve to normal values [26-28]. Strain analysis after surgical myectomy [29] and septal ablation [30] showed that despite improved NYHA class and reduced LVOT gradient and septal wall thickness, longitudinal strain remained impaired. This may suggest that the impaired cardiac mechanics in HCM also appear to be related to the intrinsic myocardial dysfunction, and not only to the loading conditions and LVH.

Disease progression in HCM

The mechanisms of progression from preclinical HCM to the classic phenotype are largely unknown, and it has been suggested that diastolic dysfunction precedes the development of

hypertrophy. The findings in this study combined with other literature may hint at an alternative hypothesis for the development of HCM.

Patients with preclinical HCM appear to have a normal heart, but at a certain point remodeling of the cardiomyocyte starts. Several intrinsic and external factors could lead to the remodeling of the cardiomyocyte: impaired contractility (related to structural cellular remodeling and mutation-induced intrinsic sarcomeric defects, see above), microvascular dysfunction and energy depletion. Coronary microvascular dysfunction may lead to local ischemia, replacement fibrosis [31], and together with increased energetic costs of contraction,[32] possibly increased oxidative stress of the cardiomyocyte. In combination with a reduction in myofilament protein phosphorylation and higher Ca^{2+} -sensitivity, contractility might be further hampered leading to impairment of cardiomyocyte relaxation.[5] The remodeling of the hypocontractile cardiomyocyte may then lead to compensatory hypertrophy of the myocardium – initially locally – and more regional as disease progresses. This might present itself as initial diastolic dysfunction and later also clear (regional) systolic impairment.

Further studies that focus on the development of hypertrophy and the regression of systolic and diastolic function during follow-up of preclinical HCM patients could improve this hypothesis.

Clinical implications and limitations

The number of included patients with both STE and myocardial tissue analysis was relatively small. In addition, the study was performed in a referral center for patients with HCM, therefore selection and referral bias may have influenced the study results. All patients included were severely symptomatic due to important LVOT obstruction requiring septal reduction therapy. This is only a subset of the disease-spectrum of HCM. Nevertheless, to improve our understanding of the development of HCM, a longitudinal prospective study assessing strain and SR in a large cohort of HCM mutation carriers and overt HCM patients would be of interest to investigate the development of the HCM phenotype over time. In addition, further research is required to reveal possible therapy targets at cellular contractile level to possibly delay or even reverse the progression from pre-hypertrophic HCM to manifest HCM disease.

In conclusion, despite the preserved ejection fraction of HCM patients, regional systolic strain and SR was reduced. This correlated with the reduction in maximal force generating capacity at the cellular level and with septal wall thickness. Therefore, contractile dysfunction at the sarcomere might lead to regional systolic dysfunction, and eventually to asymmetrical hypertrophy.

REFERENCES

1. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
2. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. J Cardiovasc Electrophysiol 2008;19:104-10.
3. Van Driest SL, Ommen SR, Tajik AJ, et al. Sarcomeric genotyping in hypertrophic cardiomyopathy. Mayo Clin Proc 2005;80:463-9.
4. Cannan CR, Reeder GS, Bailey KR, et al. Natural history of hypertrophic cardiomyopathy. A population-based study, 1976 through 1990. Circulation 1995;92:2488-95.
5. van Dijk SJ, Dooijes D, dos Remedios C, et al. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation 2009;119:1473-83.
6. Hoskins AC, Jacques A, Bardswell SC, et al. Normal passive viscoelasticity but abnormal myofibrillar force generation in human hypertrophic cardiomyopathy. J Mol Cell Cardiol 2010;49:737-45.
7. Witjas-Paalberends ER, Piroddi N, Stam K, et al. Mutations in MYH7 reduce the force generating capacity of sarcomeres in human familial hypertrophic cardiomyopathy. Cardiovasc Res 2013;99:432-41.
8. Kraft T, Witjas-Paalberends ER, Boontje NM, et al. Familial hypertrophic cardiomyopathy: functional effects of myosin mutation R723G in cardiomyocytes. J Mol Cell Cardiol 2013;57:13-22.
9. van Dijk SJ, Paalberends ER, Najafi A, et al. Contractile dysfunction irrespective of the mutant protein in human hypertrophic cardiomyopathy with normal systolic function. Circ Heart Fail 2012;5:36-46.
10. Ho CY, Carlsen C, Thune JJ, et al. Echocardiographic strain imaging to assess early and late consequences of sarcomere mutations in hypertrophic cardiomyopathy. Circ Cardiovasc Genet 2009;2:314-21.
11. Geske JB, Bos JM, Gersh BJ, et al. Deformation patterns in genotyped patients with hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging 2014;15:456-65.
12. Carasso S, Yang H, Woo A, et al. Systolic myocardial mechanics in hypertrophic cardiomyopathy: novel concepts and implications for clinical status. J Am Soc Echocardiogr 2008;21:675-83.
13. Kobayashi T, Popovic Z, Bhonsale A, et al. Association between septal strain rate and histopathology in symptomatic hypertrophic cardiomyopathy patients undergoing septal myectomy. Am Heart J 2013;166:503-11.
14. van der Velden J, Moorman AF, Stienen GJ. Age-dependent changes in myosin composition correlate with enhanced economy of contraction in guinea-pig hearts. J Physiol 1998;507 (Pt 2):497-510.
15. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
16. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777-802.
17. Gilbert BW, Pollick C, Adelman AG, et al. Hypertrophic cardiomyopathy: subclassification by m mode echocardiography. Am J Cardiol 1980;45:861-72.
18. Risum N, Ali S, Olsen NT, et al. Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults. J Am Soc Echocardiogr 2012;25:1195-203.
19. Schlossarek S, Frey N, Carrier L. Ubiquitin-proteasome system and hereditary cardiomyopathies. J Mol Cell Cardiol 2013.

20. Marston S, Copeland O, Jacques A, et al. Evidence from human myectomy samples that MYBPC3 mutations cause hypertrophic cardiomyopathy through haploinsufficiency. Circ Res 2009;105:219-22.
21. Becker KD, Gottshall KR, Hickey R, et al. Point mutations in human beta cardiac myosin heavy chain have differential effects on sarcomeric structure and assembly: an ATP binding site change disrupts both thick and thin filaments, whereas hypertrophic cardiomyopathy mutations display normal assembly. J Cell Biol 1997;137:131-40.
22. Vybiral T, Deitiker PR, Roberts R, et al. Accumulation and assembly of myosin in hypertrophic cardiomyopathy with the 403 Arg to Gln beta-myosin heavy chain mutation. Circ Res 1992;71:1404-9.
23. Hamdani N, Borbely A, Veenstra SP, et al. More severe cellular phenotype in human idiopathic dilated cardiomyopathy compared to ischemic heart disease. J Muscle Res Cell Motil 2010;31:289-301.
24. Yang H, Carasso S, Woo A, et al. Hypertrophy pattern and regional myocardial mechanics are related in septal and apical hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2010;23:1081-9.
25. Popovic ZB, Kwon DH, Mishra M, et al. Association between regional ventricular function and myocardial fibrosis in hypertrophic cardiomyopathy assessed by speckle tracking echocardiography and delayed hyperenhancement magnetic resonance imaging. J Am Soc Echocardiogr 2008;21:1299-305.
26. Poulsen SH, Sogaard P, Nielsen-Kudsk JE, et al. Recovery of left ventricular systolic longitudinal strain after valve replacement in aortic stenosis and relation to natriuretic peptides. J Am Soc Echocardiogr 2007;20:877-84.
27. Delgado V, Tops LF, van Bommel RJ, et al. Strain analysis in patients with severe aortic stenosis and preserved left ventricular ejection fraction undergoing surgical valve replacement. Eur Heart J 2009;30:3037-47.
28. Schattke S, Baldenhofer G, Prauka I, et al. Acute regional improvement of myocardial function after interventional transfemoral aortic valve replacement in aortic stenosis: a speckle tracking echocardiography study. Cardiovasc Ultrasound 2012;10:15.
29. Moravsky G, Bruchal-Garbicz B, Jamorski M, et al. Myocardial mechanical remodeling after septal myectomy for severe obstructive hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2013;26:893-900.
30. Sommer A, Poulsen SH, Mogensen J, et al. Left ventricular longitudinal systolic function after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a long-term follow-up study focused on speckle tracking echocardiography. Eur J Echocardiogr 2010;11:883-8.
31. Olivotto I, Girolami F, Sciagra R, et al. Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations. J Am Coll Cardiol 2011;58:839-48.
32. Witjas-Paalberends ER, Guclu A, Germans T, et al. Gene-specific increase in energetic cost of contraction in hypertrophic cardiomyopathy caused by thick filament mutations. Cardiovasc Res 2014.

V – Discussion

This thesis, as outlined in the introduction, seeks to approach the overall pathophysiology of hypertrophic cardiomyopathy (HCM) in a similar manner as we approach a patient with HCM (FIGURE 1).

When a patient with HCM presents, the initial approach is threefold. Often patients will present with (invalidating) symptoms, the majority of which is related to left ventricular outflow tract (LVOT) obstruction. If medical therapy fails, an invasive approach is indicated. This invasive treatment of symptomatic LVOT obstruction is discussed in PART II. Second, a subset of these patients is at increased risk of sudden cardiac death (SCD). In PART III we discussed the prediction and prevention of SCD in patients with HCM. The final step is to realize that behind every HCM patient is a potential HCM family; clinical and genetic screening can be used to distinguish family members at risk. The clinical implications of sarcomeric mutations are discussed in PART IV.

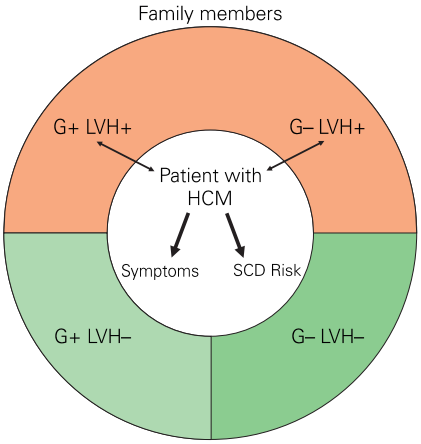


FIGURE 1 – Assessment of the patient with hypertrophic cardiomyopathy (HCM). G: Genotype; LVH: left ventricular hypertrophy; SCD: sudden cardiac death.

INVASIVE TREATMENT OF SYMPTOMATIC LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Septal myectomy versus alcohol septal ablation

Dynamic LVOT obstruction is present in the majority of the patients with HCM.[1] Not only is LVOT obstruction associated with symptoms such as dyspnea on exertion, fatigue, chest pain or syncope, but previous studies have also demonstrated that the presence of LVOT obstruction increases all-cause mortality and the occurrence of SCD in these patients.[2, 3] Substantial improvement in the quality-of-life of symptomatic patients with hypertrophic obstructive cardiomyopathy (HOCM) may be achieved by the use of a beta blocker, calci-

umantagonist or disopyramide. Medical therapy-resistant obstructive HCM can be treated surgically, by performing septal myectomy, and percutaneously with alcohol septal ablation. During the last years there is an intense and polarizing debate to define the best strategy.[4-8]

In this debate, and current guidelines, most arguments and recommendations are based on short-term follow-up results or expert opinion. The long-term outcomes remain unclear, and this could be solved by a randomized controlled trial; but as outlined by Olivotto et al., this is not feasible. As we have demonstrated in CHAPTER 1 and 2, event rates are relatively low, and this means that a very large cohort will be necessary; larger than all combined cohorts in North America, Asia and Europe. Alternatively a smaller study group could be used, but then we need a follow-up of 10-20 years, which is also not realistic.[9] The issue is further complicated by the specialization of the referral centers. Most hospitals that perform septal reduction therapy will do alcohol septal ablation or surgical myectomy; but only a minority is experienced in both [6, 10].

By combining data from multiple hospitals we could improve our current understanding. In CHAPTER 1 we focused on the long-term outcomes of both invasive procedures, and compared them with non-obstructive HCM patients. All procedures were performed in centers specialized in HCM care (Leuven, Nieuwegein, and Rotterdam). The most important finding was that after alcohol septal ablation and myectomy, both mortality and SCD risk were found to be similarly low, and comparable to patients with non-obstructive HCM (FIGURE 2). This demonstrates that the survival disadvantage associated with symptomatic LVOT obstruction can be effectively annulled by appropriate invasive therapy and management in referral

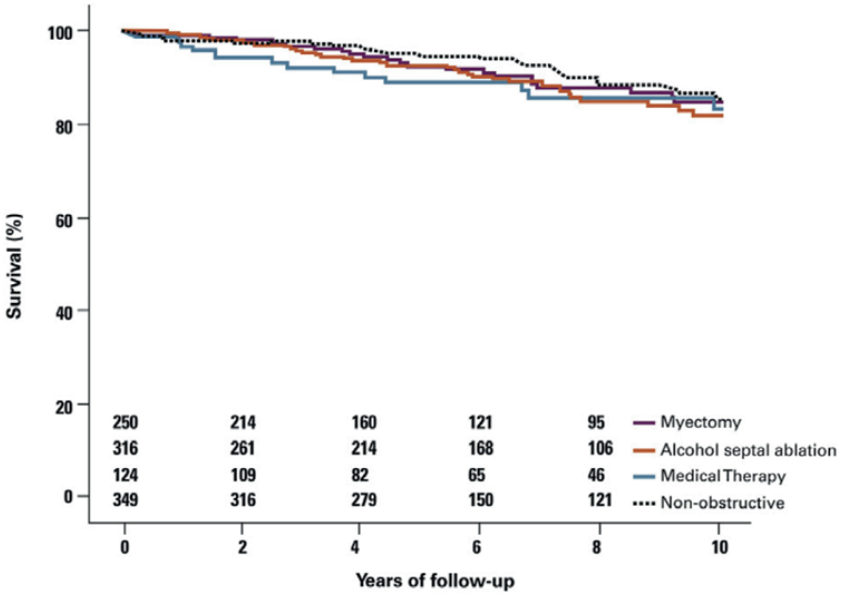


FIGURE 2 – Kaplan Meier survival graph of 1047 patients with hypertrophic cardiomyopathy.

centers for HCM care.[11] In the meta-analysis we performed in CHAPTER 2, the long-term follow-up of more than 4500 patients confirmed the similarly low mortality (1.4% per year after myectomy and 1.5% per year after alcohol septal ablation, p = 0.8) and SCD rates (0.5% per year after myectomy and 0.4% per year after alcohol septal ablation, p = 0.5). The main difference between the two interventions was found in procedure related complications: patients who undergo alcohol septal ablation are at increased risk of pacemaker implantation due to periprocedural damage of the atrioventricular conduction system (10% versus 4.4%, p < 0.001). There was also a higher need for additional septal reduction therapy in patients who underwent alcohol septal ablation (7.7% versus 1.6%, p = 0.001).

Improvement of individual approaches

Surgical septal myectomy was introduced in the 1960s by Morrow[12] and became the preferred approach for septal reduction therapy, with excellent results in the original and extended technique [13-17]. Abnormalities of papillary muscles (hypertrophy, anterior and internal displacement, direct insertion into the anterior mitral valve leaflet) or elongated mitral leaflets may contribute to LVOT obstruction, and these remain untouched when solely a myectomy is performed. Concomitant mitral valve surgery could be beneficial in these patients, especially if there is limited septal thickness, but marked mitral leaflet elongation or mitral regurgitation. The addition of anterior mitral leaflet extension, which stiffens the mid-segment of the anterior leaflet, to septal myectomy approaches these mitral valve abnormalities. Our results in CHAPTER 3 show that in selected HCM patients, myectomy combined with anterior mitral leaflet extension is an effective procedure to abolish LVOT obstruction, and can be performed at the cost of acceptable morbidity and very low operative mortality (0% vs 2.5% respectively, as described in the myectomy cohorts in CHAPTER 2).[18]

Periprocedural adverse arrhythmic events, such as sustained ventricular tachycardia or ventricular fibrillation, remain one of the potential concerns of alcohol septal ablation. The use of alcohol, with its inherent cardiotoxicity, and the risk of spillage in the left anterior descending coronary artery, has been blamed as the culprit of these life-threatening arrhythmias. In CHAPTER 6 we found that alcohol dosage did not predict the risk of arrhythmia. But in line with previous studies, infarct size – determined by CK-MB levels – did predict the risk of life-threatening ventricular arrhythmias. A higher dosage of alcohol was associated with a larger infarct size, as were a larger caliber of the septal perforator and LV wall thickness. Although infarct size may be hard to predict in the individual patient, the finding of high CK-MB levels post-procedure could warrant extended monitoring or even preventive ICD implantation, especially in the presence of other risk factors of SCD.

PREDICTION AND PREVENTION OF SUDDEN CARDIAC DEATH

SCD is a relatively rare but devastating clinical event in HCM with an incidence of 0.5-1%/year in patients with HCM.[13] Originally, in the older 2003 ACC/ESC guidelines and 2011 ACCF/AHA guidelines, the identification of high-risk patients was based on five clinical characteristics: a family history of SCD in first-degree relatives < 40 years of age, maximal left ventricular wall thickness (LVWT) of >30 mm, unexplainable syncope, non-sustained ventricular tachycardia (nsVT) and abnormal blood pressure response during exercise.[19, 20] Although it was clear that the risk of SCD increases with increasing number of risk factors, both 2003 and 2011 guidelines distinguish high and low risk patients with only limited power (FIGURE 3). [21]

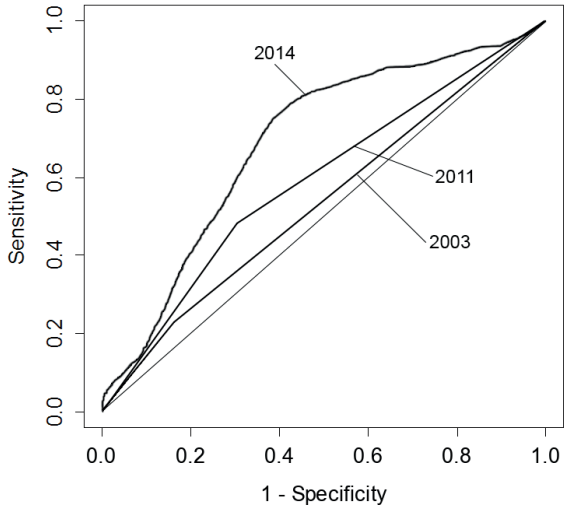


FIGURE 3 – Time-dependent receiver operating characteristic curves for the risk prediction models of the 2014 ESC guidelines (AUC=0.69), 2003 ACC/ESC guidelines (AUC=0.55), and 2011 ACCF/AHA guidelines (AUC=0.60), and the reference line (AUC=0.5). [24]

Identifying patients at high risk of SCD

In CHAPTER 9 we validated the new risk prediction model for SCD that was proposed in the 2014 ESC guidelines.[22] This model – the HCM Risk-SCD score – provides an individualized 5 year SCD risk, and is based on some of the aforementioned risk factors, (abnormal blood pressure response during exercise was excluded) combined with LVOT gradient, left atrial diameter and age at evaluation. The model classifies patients based on their 5-year risk: low (<4%), intermediate (4-6%), and high (>6%); and is the basis of the 2014 ESC guidelines recommendation on ICD implantation.[13, 23]

In an independent setting, we found that the HCM Risk-SCD score discriminates better between patients with a high or low SCD risk, than the older models based on the 5 classic

risk factors.[24] Probably this model is a better predictor of outcome because the effects of cardiac remodeling are now considered. CHAPTER 10 demonstrated that SCD risk increases significantly if factors of adverse LV remodeling are present.[25] Interestingly, an American examination of the prediction model found that the HCM Risk-SCD score is too insensitive to accurately identify high-risk patients. But these findings may be obscured by the inclusion of patients in the model that are not deemed eligible by the original authors, e.g. patients < 18 years old or with septal thickness > 34 mm. These contradicting findings confirm that the HCM Risk-SCD score is not a replacement of clinical judgment. Another issue not addressed by the new risk model is the role of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (MRI) as a possible predictor of SCD risk. The presence of LGE is associated with HCM-related mortality [26], but the relationship with SCD is ambiguous at best. [26-28] A recent meta-analysis did not show any relationship with SCD.[29] This may be related to the fact that LGE can detect large areas of scar tissue and myocardial fibrosis; but interstitial fibrosis or disarray may not be detected. Another issue is the method of quantification of LGE, and significant variation on LGE volume depending on the method.[30] Hopefully, these issues will be addressed in the HCMR study – in which we also participate – that is due for 2018. This NIH funded registry (clinicaltrials.gov identifier: NCT01915615) aims to identify novel risk predictors by using MRI.

ICD therapy in patients with HCM

If a patient is considered to be at increased risk of SCD, an ICD implantation should be considered. CHAPTER 11 and CHAPTER 12 demonstrate that this protection of death due to malignant ventricular arrhythmias comes at the price of inappropriate shocks (4.8% per year) and device related complications (3.4% per year).[31, 32] Because HCM patients are young at implantation the risks should not be underestimated, because of the long period that young patients will live with the implanted device and leads.

Thus, the benefits and risk of ICD therapy in HCM patients should be carefully weighed. The improved discriminatory power of the new model implies that more high-risk patients are correctly identified and become eligible for ICD implantation, but also that unnecessary and potential harmful ICD implantations can be avoided in patients without increased SCD risk. However, the risk score is not a replacement of clinical judgment, but should be used as the authors state: "to complement clinical reasoning by providing objective individualized prognostic information."[23] This is in line with the American 2011 guidelines: "The decision for placement of primary prevention ICD in HCM often involves a large measure of individual clinical judgment, particularly when evidence for risk is ambiguous. The potential for SCD needs to be discussed with each fully informed HCM patient and family member in the context of their concerns and anxieties and should be balanced against the risks and benefits of proposed prophylactic ICD strategy."[20]

CLINICAL IMPLICATIONS OF SARCOMERIC MUTATIONS

When involved in the care of a patient with HCM, it is import to realize that behind this patient, there may be a family that consists of parents, siblings, and children. In all first-degree family members cardiologic evaluation should be offered. Genetic testing is recommended in the index patient, and if a pathogenic mutation is found, this can be used to further identify family members at risk.[13]

Identification of a pathogenic mutation not only helps to identify other family members. The results in chapter 13 demonstrated that patients with HCM and a pathogenic mutation have a greater probability of heart failure related death, compared with patients with HCM, without a mutation. This implies that patients with a pathogenic mutation should be followed up more closely to anticipate a change in clinical course. The adverse outcome associated with the presence of a pathogenic mutation is confirmed in a study that assessed the effect of triple mutations. These patients had marked adverse cardiac remodeling characterized by restrictive physiology, atrial dilation, and systolic dysfunction, and triple mutations were associated with a 14-fold higher risk to develop end-stage disease.[33] HCM patients with signs of adverse cardiac remodeling are considered at risk of further progression toward overt dysfunction and heart failure [34], and at increased risk of SCD as discussed in CHAPTER 10.[25] Aside from the clinical signs of adverse remodeling, our results favor incorporating genetic test results as a risk factor of adverse remodeling in patients with overt HCM.

The identification of a pathogenic mutation does not necessarily imply an adverse prognosis. Individuals with a pathogenic mutation without any overt signs of HCM (maximal left ventricular (LV) wall thickness < 13mm), appear to have a favorable outcome. In CHAPTER 14 we have demonstrated that after 4.5 years of follow-up there were no adverse events in the group of preclinical HCM subjects. Only one patient developed manifest HCM, over the course of 6.6 years. These findings have several important clinical implications. First, based hereupon, we propose a 5-yearly follow-up of adult preclinical HCM subjects, unless a change in clinical status occurs. Second, the slow development of LVH in subjects with preclinical HCM also hampers the identification of predictors of disease progression, and the identification of possible strategies to prevent the development of HCM in these subjects. For example, a recent study assessed the effect of diltiazem treatment in preclinical HCM subjects. After ± 2 years of treatment there was no difference in the low number of patients (11% in both treatment and placebo group) who were diagnosed with HCM in each group, all aged < 18y).[35] The NIH-funded VANISH trial (ClinicalTrials.gov Identifier: NCT01912534), in which we participate, is designed to determine whether losartan can reduce or halt disease progression. But both studies are limited by the slow disease progression and expected high number needed to treat.

Increasing the knowledge on the pathophysiology of how a specific mutation leads to HCM might increase the ability to prevent the development all together. In CHAPTER 15 we

uncovered a small segment of the black box of genotype-phenotype relations. We assessed myocardial function on a regional level and a cellular level. This showed that in patients with HCM, there is an association between the reduced maximal force development of the cardiomyocyte and impaired regional systolic function of the septal wall. This observed reduction in maximal force generating capacity is typical for HCM, and the impaired cardiac mechanics appears to be related to the intrinsic myocardial dysfunction, and not only to the altered loading conditions and LVH.

These findings, combined with the results of CHAPTER 14 and other literature may hint at a possible hypothesis for the disease progression of HCM in preclinical HCM subjects. Several intrinsic and extrinsic factors (e.g. haploinsufficiency or poison peptides caused by pathogenic mutations) could lead to remodeling of cardiomyocytes in an otherwise structurally normal heart.[36-40] The remodeling hampers both maximal force generating capacity and cardiomyocyte relaxation, and may lead to compensatory hypertrophy of the myocardium – initially locally – and more regional as disease progresses. This could present itself as initial diastolic and regional systolic dysfunction, and eventually to the typical asymmetrical hypertrophy (FIGURE 4).

In conclusion, the presence of a pathogenic sarcomeric mutation does imply a greater risk of adverse outcome, especially heart failure related events. However, in preclinical HCM subjects, it remains a benign condition. Finally, the association of regional and myocardial dysfunction could advance our understanding of disease progression, in both preclinical HCM and overt HCM patients.

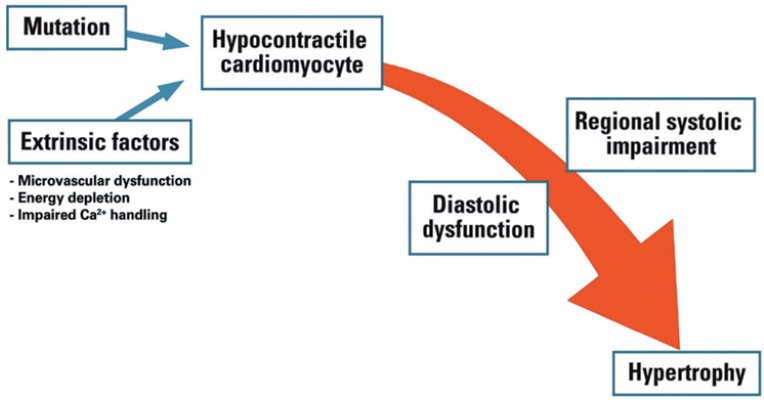


FIGURE 4 – Intrinsic effects (of the pathogenic mutation) and extrinsic factors lead to remodeling of the sarcomere and a hypocontractile cardiomyocyte. Regional systolic and diastolic impairment may lead to overt HCM.[41]

FUTURE DIRECTIONS

Both surgical myectomy and alcohol septal ablation are now established in the armamentarium of invasive therapies to reduce the symptoms related to symptomatic LVOT obstruction. An individual approach is required to determine the preferred method of septal reduction therapy. This decision should be based on patient co-morbidities, anatomical features (e.g. mitral valve abnormalities, septal anatomy), and patient preference. The first step is to discuss the symptomatic patient in an experienced multidisciplinary heart team (consisting of at least one cardiothoracic surgeon, an interventional cardiologist, and a cardiologist specializing in the care of patients with HCM). Preferably, and as stated in current guidelines, both the surgeon and the interventional cardiologist should be experienced in respectively myectomy and alcohol septal ablation. Therefore, we recommend early referral of patients with symptomatic LVOT obstruction to centers with substantial and specific expertise in HCM care.[13]

Future research in percutaneous septal reduction therapy may need to focus on reduction of procedural related atrioventricular disturbances and life-threatening arrhythmias. Current guidelines state that alcohol septal ablation should be reserved for elderly patients, but as demonstrated in CHAPTER 7, these patients are at increased risk for atrioventricular disturbances post-procedure. In younger patients (± 43 years) the risk for pacemaker implantation (5%) is comparable with patients in a similar age group post-myectomy (1-6%), but the very long-term follow-up (> 20 years) is still unclear, and a relevant issue in younger patients. Secondly, the use of an alternative for alcohol could also reduce the risk of procedure related arrhythmias. Septal microsphere embolization uses microspheres instead of alcohol to create a more controlled infarction. CHAPTER 8 describes the first clinical experience in the Netherlands using septal microsphere embolization as an alternative for alcohol septal ablation. Although in both cases it resulted in immediate improvement in hemodynamics, without any procedure-related arrhythmic events, future research, with a substantial cohort and longer follow-up will have to demonstrate whether septal microsphere embolization will be a viable alternative to alcohol septal ablation.[42]

The aforementioned multidisciplinary approach should also be considered in the prevention of SCD. Implantation of an ICD protects against SCD, but this protection comes at the price of potential inappropriate shocks and device-related complications. These risks are particularly relevant when the device is implanted in a younger population, as is the case in HCM. In this group it is important to implant a device as simple as sufficient, such as a single ventricular lead, or even a total subcutaneous device. The drawback of the latter is the dependency on screening vectors, and especially high-risk HCM patients are not eligible for subcutaneous ICD implantation.[43] This also means we should continue to strive for improved risk stratification. Aside from quantification of LGE on cardiac MRI (as discussed above), genetic information might contribute to further improvement of the risk stratification and identification of high-risk patients. Our current understanding of genetics and its role in

SCD is limited. The rise of referral centers for HCM and the participation of these centers in large international registries, such as HCMR and SHARE (www.theshareregistry.org), could clarify this relationship.

Finally, these large international collaborations could also improve our further understanding of the development of the disease, and the progression from a pathogenic mutation towards overt HCM. Currently, a pathogenic mutation is not a separate criterion for disease, but it raises the chance to obtain the disease. If we understand the progression of disease on a cellular level, targeting these mechanisms might also provide a strategy to halt disease progression. Gramlich et al.[44] demonstrated that the disruption of the titin reading frame due to truncating DCM mutation can be restored by exon skipping in both human and mouse models. This antisense mediated exon-skipping leads to improved cardiomyocyte function and normalized sarcomeric protein expression in vitro.[44] If, and when, these novel strategies will be available for HCM patients remains very uncertain, and we need to expand our knowledge on genotype-phenotype relations.

CONCLUSIONS

This thesis demonstrated with the excellent long-term results of myectomy and alcohol septal ablation, that both are safe and effective procedures to reduce symptoms in therapy refractory LVOT obstruction, but that for each patient an individual and multidisciplinary approach should be pursued. Also, by further improving the SCD risk prediction models and the indications of ICD implantation, we found that the prognosis of patients with HCM is now almost comparable to the general population. Finally, improving our understanding of phenotype-genotype relations could be the pathway to preventive strategies. The road ahead could lead to an effective curative therapy for HCM, and this road ahead is going to be bumpy. At least it will be an exciting ride.

REFERENCES

1. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-9.
2. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303.
3. Elliott PM, Gimeno JR, Tome MT, Shah J, Ward D, Thaman R, Mogensen J, McKenna WJ. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J 2006;27:1933-41.
4. Maron BJ. Controversies in cardiovascular medicine. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. Circulation 2007;116:196-206; discussion
5. Fifer MA. Controversies in cardiovascular medicine. Most fully informed patients choose septal ablation over septal myectomy. Circulation 2007;116:207-16; discussion 16.
6. Maron BJ, Yacoub M, Dearani JA. Controversies in cardiovascular medicine. Benefits of surgery in obstructive hypertrophic cardiomyopathy: bring septal myectomy back for European patients. Eur Heart J 2011;32:1055-8.
7. Fifer MA, Sigwart U. Controversies in cardiovascular medicine. Hypertrophic obstructive cardiomyopathy: alcohol septal ablation. Eur Heart J 2011;32:1059-64.
8. Ten Cate FJ, Soliman OII, Michels M, Theuns DAMJ, De Jong PL, Geleijnse ML, Serruys PW. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: A word of caution. Circ Heart Fail 2010;3:362-9.
9. Olivotto I, Ommen SR, Maron MS, Cecchi F, Maron BJ. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Will there ever be a randomized trial? J Am Coll Cardiol 2007;50:831-4.
10. Maron BJ, Rastegar H, Udelson JE, Dearani JA, Maron MS. Contemporary surgical management of hypertrophic cardiomyopathy, the need for more myectomy surgeons and disease-specific centers, and the tufts initiative. Am J Cardiol 2013;112:1512-5.
11. Vriesendorp PA, Liebregts M, Steggerda RC, Schinkel AF, Willems R, Ten Cate FJ, van Cleemput J, Ten Berg JM, Michels M. Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. JACC Heart Fail 2014;2:630-6.
12. Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, Itscoitz SB, Redwood DR. Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. Circulation 1975;52:88-102.
13. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.
14. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ, Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470-6.
15. Ten Berg JM, Suttorp MJ, Knaepen PJ, Ernst SMPG, Vermeulen FEE, Jaarsma W. Hypertrophic obstructive cardiomyopathy: Initial results and long-term follow-up after morrow septal myectomy. Circulation 1994;90:1781-5.

16. Maron BJ, Epstein SE, Morrow AG. Symptomatic status and prognosis of patients after operation for hypertrophic obstructive cardiomyopathy: Efficacy of ventricular septal myotomy and myectomy. Eur Heart J 1983;4:175-85.
17. Messmer BJ. Extended myectomy for hypertrophic obstructive cardiomyopathy. Ann Thorac Surg 1994;58:575-7.
18. Vriesendorp PA, Schinkel AF, Soliman OI, Kofflard MJ, de Jong PL, van Herwerden LA, Ten Cate FJ, Michels M. Long-term benefit of myectomy and anterior mitral leaflet extension in obstructive hypertrophic cardiomyopathy. Am J Cardiol 2015;115:670-5.
19. Maron BJ, McKenna WJ, Danielson GK, Kappenberger JKB, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, Spirito P, Cate FJT, Wigle ED. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy - A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. Eur Heart J 2003;24:1965-91.
20. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice G, American Association for Thoracic S, American Society of E, American Society of Nuclear C, Heart Failure Society of A, Heart Rhythm S, Society for Cardiovascular A, Interventions, Society of Thoracic S. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
21. O'Mahony C, Tome-Esteban M, Lambiase PD, Pantazis A, Dickie S, McKenna WJ, Elliott PM. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. Heart 2013;99:534-41.
22. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM, Ortiz-Genga M, Fernandez X, Vlagouli V, Stefanadis C, Coccolo F, Sandoval MJO, Pacileo G, Masarone D, Pantazis A, Tome-Esteban M, Dickie S, Lambiase PD, Rahman S. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). Eur Heart J 2014;35:2010-20.
23. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM, Hypertrophic Cardiomyopathy Outcomes I. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010-20.
24. Vriesendorp PA, Schinkel AF, Liebregts M, Theuns DA, van Cleemput J, Ten Cate FJ, Willems R, Michels M. Validation of the 2014 ESC Guidelines Risk Prediction Model for the Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy. Circ Arrhythm Electrophysiol 2015.
25. Vriesendorp PA, Schinkel AF, de Groot NM, van Domburg RT, Ten Cate FJ, Michels M. Impact of adverse left ventricular remodeling on sudden cardiac death in patients with hypertrophic cardiomyopathy. Clin Cardiol 2014;37:493-8.
26. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, Das B, Khwaja J, Alpendurada FD, Wage R, Roughton M, McKenna WJ, Moon JC, Varnava A, Shakespeare C, Cowie MR, Cook SA, Elliott P, O'Hanlon R, Pennell DJ, Prasad SK. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. Heart 2014;100:1851-8.
27. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic

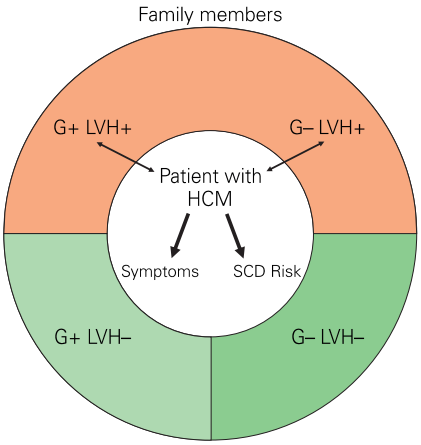
value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484-95.

28. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, Lesser JR, Hanna CA, Udelson JE, Manning WJ, Maron MS. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol 2008;51:1369-74.
29. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging 2012;5:370-7.
30. Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, Muthurangu V, Moon JC. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. JACC Cardiovasc Imaging 2011;4:150-6.
31. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, Ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail 2012;5:552-9.
32. Vriesendorp PA, Schinkel AF, Van Cleemput J, Willems R, Jordaens LJ, Theuns DA, van Slegtenhorst MA, de Ravel TJ, ten Cate FJ, Michels M. Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications. Am Heart J 2013;166:496-502.
33. Girolami F, Ho CY, Semsarian C, Baldi M, Will ML, Baldini K, Torricelli F, Yeates L, Cecchi F, Ackerman MJ, Olivotto I. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol 2010;55:1444-53.
34. Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 2012;5:535-46.
35. Ho CY, Lakdawala NK, Cirino AL, Lipshultz SE, Sparks E, Abbasi SA, Kwong RY, Antman EM, Semsarian C, Gonzalez A, Lopez B, Diez J, Orav EJ, Colan SD, Seidman CE. Diltiazem treatment for pre-clinical hypertrophic cardiomyopathy sarcomere mutation carriers: a pilot randomized trial to modify disease expression. JACC Heart Fail 2015;3:180-8.
36. van Dijk SJ, Dooijes D, dos Remedios C, Michels M, Lamers JM, Winegrad S, Schlossarek S, Carrier L, ten Cate FJ, Stienen GJ, van der Velden J. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation 2009;119:1473-83.
37. Witjas-Paalberends ER, Piroddi N, Stam K, van Dijk SJ, Oliviera VS, Ferrara C, Scellini B, Hazebroek M, ten Cate FJ, van Slegtenhorst M, dos Remedios C, Niessen HW, Tesi C, Stienen GJ, Heymans S, Michels M, Poggesi C, van der Velden J. Mutations in MYH7 reduce the force generating capacity of sarcomeres in human familial hypertrophic cardiomyopathy. Cardiovasc Res 2013;99:432-41.
38. Kraft T, Witjas-Paalberends ER, Boontje NM, Tripathi S, Brandis A, Montag J, Hodgkinson JL, Francino A, Navarro-Lopez F, Brenner B, Stienen GJ, van der Velden J. Familial hypertrophic cardiomyopathy: functional effects of myosin mutation R723G in cardiomyocytes. J Mol Cell Cardiol 2013;57:13-22.
39. Olivotto I, Girolami F, Sciagra R, Ackerman MJ, Sotgia B, Bos JM, Nistri S, Sgalambro A, Grifoni C, Torricelli F, Camici PG, Cecchi F. Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations. J Am Coll Cardiol 2011;58:839-48.
40. Witjas-Paalberends ER, Guclu A, Germans T, Knaapen P, Harms HJ, Vermeer AM, Christiaans I, Wilde AA, Remedios CD, Lammertsma AA, van Rossum AC, Stienen GJ, van Slegtenhorst M, Schinkel AF, Michels M, Ho CY, Poggesi C, van der Velden J. Gene-specific increase in energetic cost of contraction in hypertrophic cardiomyopathy caused by thick filament mutations. Cardiovasc Res 2014.

41. Vriesendorp P, Schinkel A, Soliman O, Van Slegtenhorst M, Ten Cate F, Michels M. Early detection of diastolic and systolic dysfunction with speckle-tracking echocardiography in carriers of hypertrophic cardiomyopathy mutations. Eur Heart J 2014:1088.
42. Vriesendorp PA, Van Mieghem NM, Vletter WB, Ten Cate FJ, de Jong PL, Schinkel AF, Michels M. Microsphere embolisation as an alternative for alcohol in percutaneous transluminal septal myocardial ablation. Neth Heart J 2013;21:245-8.
43. Maurizi N, Olivotto I, Olde Nordkamp LR, Baldini K, Fumagalli C, Brouwer TF, Knops RE, Cecchi F. Prevalence of Subcutaneous Implantable Defibrillator Candidacy Based on Template ECG Screening In Patients With Hypertrophic Cardiomyopathy. Heart Rhythm 2015.
44. Gramlich M, Pane LS, Zhou Q, Chen Z, Murgia M, Schotterl S, Goedel A, Metzger K, Brade T, Parrotta E, Schaller M, Gerull B, Thierfelder L, Aartsma-Rus A, Labeit S, Atherton JJ, McGaughran J, Harvey RP, Sinnecker D, Mann M, Laugwitz KL, Gawaz MP, Moretti A. Antisense-mediated exon skipping: a therapeutic strategy for titin-based dilated cardiomyopathy. EMBO Mol Med 2015;7:562-76.

Nederlandse samenvatting

Dit proefschrift streeft ernaar om de pathofysiologie van hypertrofische cardiomyopathie (HCM) op dezelfde manier te benaderen zoals wij naar een patiënt met HCM kijken (FIGUUR 1). Als een patiënt met HCM zich presenteert op de polikliniek, bestaat deze initiële benadering uit 3 aspecten. Vaak is het zo dat een patiënt komt met symptomen zoals dyspnoe d'effort, of thoracale pijnklachten. Het overgrote deel hiervan is gerelateerd aan obstructie van de uitstroombaan van de linker ventrikel. De eerste stap in de behandeling van deze klachten is middels medicatie, maar als maximaal medicamenteus beleid niet toereikend is, moet invasieve behandeling overwogen worden. Deze invasieve benadering wordt besproken in DEEL II. Ten tweede is het zo dat een deel van de patiënten met HCM een verhoogd risico heeft op plotse dood. DEEL III bespreekt dan ook het voorspellen en voorkomen van plotse dood in patiënten met HCM. Tenslotte moeten we niet vergeten dat bij elke patiënt met HCM er ook een potentiele HCM-familie hoort; klinische en genetische screening kunnen dan gebruikt worden om familieleden die de ziekte hebben of een verhoogd risico erop op te sporen. De klinische implicaties van een positieve gen mutatie worden besproken in DEEL IV.



FIGUUR 1 – Benadering van de patient met hypertrofische cardiomyopathie (HCM). G: genotype; LVH: linker ventrikel hypertrofie; SCD: plotse dood.

INVASIEVE BEHANDELING VAN OBSTRUCTIEVE HCM

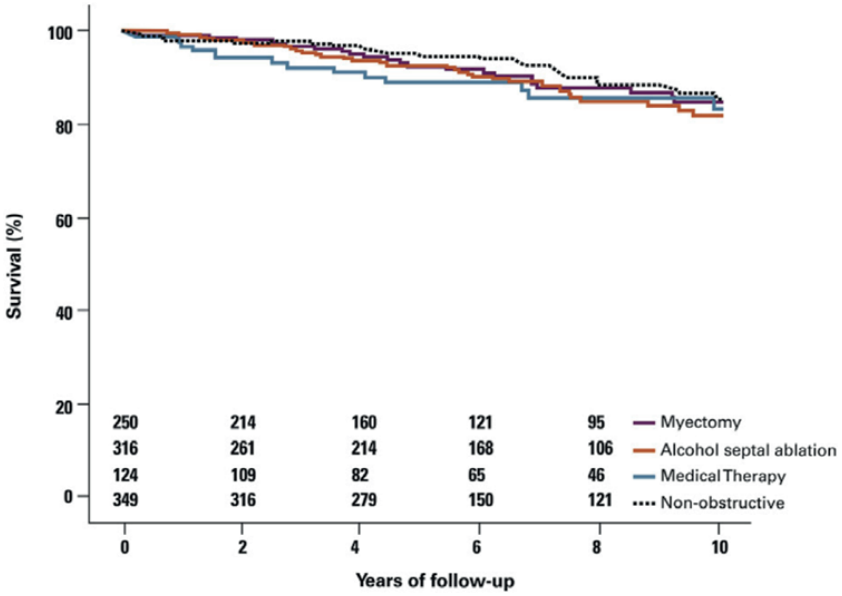
Septale myectomie versus alcohol septum ablatie

In de meerderheid van patiënten met HCM is dynamische linker ventrikel (LV)-uitstroombaan obstructie aanwezig. [1] Deze obstructie is niet alleen geassocieerd met symptomen zoals dyspnoe d'effort, vermoeidheid, thoracale pijnklachten of syncope, maar diverse studies hebben ook aangetoond dat de aanwezigheid van een significante LV-uitstroombaan obstructie de kans verhoogd op overlijden, en ook het optreden van levensgevaarlijke ritmestoornissen en

plotse dood. [2,3] In een deel van de patiënten kan aanzienlijke verbetering van kwaliteit van leven bereikt worden met medicamenteuze therapie. Hierin spelen bètablokkers, calciumantagonisten en disopyramide de belangrijkste rol. In patiënten met obstructieve HCM, die klachten blijven houden ondanks optimale medicamenteuze therapie, kan invasief ingegrepen worden. Dit kan chirurgisch door middel van septale myectomie, of percutaan door middel van alcohol septum ablatie. Zeker in de laatste jaren is er een intense en polariserend debat gaande in internationale literatuur om de beste behandelstrategie te omschrijven. [4-8]

Het probleem van dit debat, en ook de huidige richtlijnen, is dat de meeste argumenten en aanbevelingen gebaseerd zijn op de korte termijn uitkomsten, of op basis van de zogenaamde 'expert opinion'. Langetermijnresultaten zijn minder duidelijk, en een gerandomiseerde studie zou helderheid kunnen bieden. Echter, Olivotto et al. hebben aangetoond dat dit niet mogelijk is. In hoofdstuk 1 en 2 tonen we aan dat de event rates zeldzaam zijn, en dit betekent dat een zeer groot cohort nodig is – groter dan een combinatie van Europese, Amerikaanse en Aziatische cohorten - om uitspraken over de 2 interventies te kunnen doen. Indien we een kleinere studiepopulatie nemen, moet de follow-up meer dan 10-20 jaar lang zijn, wat eveneens niet realistisch is. [9] Een losstaand probleem is dat de verwijzingscentra meestal gespecialiseerd zijn in slechts een van de interventies: of alcohol septum ablatie of chirurgische myectomie, maar slechts een minderheid heeft ervaring met beide technieken. [6,10]

Omdat een gerandomiseerde studie dus niet realistisch is hebben wij besloten de gegevens van meerdere centra te combineren. In hoofdstuk 1 hebben we de langetermijnresultaten van beide invasieve procedures naast elkaar gelegd, en dit vergeleken met niet-obstructieve HCM-patiënten. Alle ingrepen zijn verricht in tertiaire verwijzingscentra (UZ Leuven, St. Antonius Ziekenhuis Nieuwegein en Erasmus MC Rotterdam), gespecialiseerd in de behandeling van HCM-patiënten. De belangrijkste bevinding was dat zowel na alcohol septum ablatie als myectomie, de gehele mortaliteit en het risico op plotse dood, zeer laag waren; vergelijkbaar met patiënten zonder LV-uitstroombaan obstructie (FIGUUR 2). Dit toont dan ook aan dat de verhoogde kans op overlijden, geassocieerd met obstructieve HCM, weggenomen kan worden na geïndiceerde invasief ingrijpen en behandeling door een team gespecialiseerd in de behandeling van HCM. [11] In hoofdstuk 2 hebben we een meta-analyse verricht die in meer dan 4500 patiënten naar de langetermijnresultaten kijkt, en hierin werden eveneens de lage gehele mortaliteit (1,4% na myectomie en 1,5% na alcohol septum ablatie, p=0.8) en het lage risico op plotse dood (0,5% na myectomie en 0,4% na alcohol septum ablatie, p=0.5). Het belangrijkste verschil tussen beide procedures was met name terug te vinden in de complicaties gerelateerd aan de ingreep: na alcohol septum ablatie was het risico op permanente pacemakerimplantatie duidelijk verhoogd (10% versus 4,4% na myectomie, p<0,001). Bovendien was er na alcohol septum ablatie vaker een 2^{e} ingreep nodig om gewenst effect te bereiken (7,7% versus 1,6%, p=0,001).



FIGUUR 2 – Kaplan Meier grafiek die de overleving toont van 1047 patiënten met hypertrofische cardiomyopathie.

Individuele verbeteringen van beide technieken

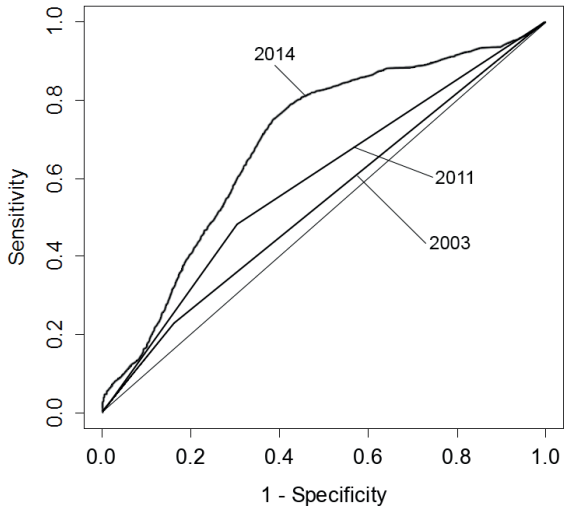
Chirurgische septale myectomie is in de jaren zestig geïntroduceerd door Morrow [12] en is snel de gouden standaard geworden, met goede resultaten bij de originele en de gemodificeerde (verlengde myectomie) techniek. [13-17]. Een beperking van deze techniek is dat afwijkingen van het papillair spieren (hypertrofie, malpositie en directe insertie op het voorste mitralisklepblad) of van de mitraalklepbladen zelf niet behandeld worden, als er enkel een myectomie verricht wordt. Gelijktijdige mitraalklepchirurgie kan dan ook van toegevoegde waarde zijn in bepaalde patiënten, zeker als er beperkte septale hypertrofie aanwezig is, maar wel verlengde klepbladen of ernstige mitralisklepinsufficiëntie. De combinatie van myectomie met anterieur klepblad extensie zorgt voor versteviging van dit klepblad, en behandeld dus ook de mitraalklep problematiek. Onze resultaten in hoofdstuk 3 laten zien dat in geselecteerde patiënten met obstructieve HCM de combinatie van myectomy en mitraalklepblad extensie een effectieve ingreep is die de gradiënt over LV-uitstroombaan doet verdwijnen en dit met zeer lage mortaliteit (0% in ons cohort versus 2,5% in de myectomie cohorten in hoofdstuk 2). [18]

In patiënten die alcohol septum ablatie ondergaan, is het optreden van procedure-gerelateerde aritmieën, met name ventriculaire tachycardie of fibrillatie, een punt van bezorgdheid. Alcohol, dat inherent cardiotoxisch is, wordt vaak als de schuldige geduid van deze levensbedreigende ritmestoornissen. In hoofdstuk 6 tonen we aan dat alcohol dosering op zich geen invloed had op het risico op ritmestoornissen. Wel was het zo, vergelijkbaar

met eerdere studies, dat een groot infarct – bepaald door serum concentratie van CK-MB, een voorspeller was van optreden van ritmestoornissen. Factoren die leiden tot een grotere infarcering waren LV-septum dikte, diameter van de septaaltak en alcoholdosering. Het is dus duidelijk dat in de individuele patiënt het van tevoren moeilijk te voorspellen is wie een verhoogde kans op levensbedreigende ritmestoornissen heeft. Wel is het zo dat patiënten met fors verhoogde cardiale enzymen na de ingreep zeker recht hebben op monitoring, of dat zelfs preventieve ICD-implantatie overwegen kan worden, zeker als patiënt nog andere risicofactoren voor plotse dood heeft.

VOORSPELLEN EN VOORKOMEN VAN PLOTSE DOOD

Plotse dood is relatieve zeldzaam maar natuurlijk zeer ernstige complicatie van HCM, met een gemiddelde incidentie van 0,5-1,0% per jaar. [13] Om te bepalen welke patiënten een verhoogd risico hebben op plotse dood werd in de 2003 ACC/ESC en 2011 ACCF/AHA richtlijnen gebruikt gemaakt van 5 klinische kenmerken: positieve familie anamnese voor plotse dood in 1^{e} graad familieleden < 40 jaar oud, maximale LV wanddikte van > 30mm, onverklaarde syncope, non-sustained ventriculaire tachycardie en abnormale bloeddruk response tijdens inspannig(stest). [19,20] Hoewel er wel een verband was tussen het aantal aanwezige risicofactoren en de kans op plotse dood, kon het verschil tussen hoog en laag risico patiënten maar beperkt gemaakt worden (FIGUUR 3). [21]



FIGUUR 3 – Tijdsafhankelijke ROC-curve voor de risico predictie modellen van de 2014 ESC richtlijn (AUC=0.69), 2003 ACC/ESC richtlijn (AUC=0.55), en 2011 ACCF/AHA richtlijn (AUC=0.60), en de referentielijn (AUC=0.50). [24]

Identificatie van hoog risico patiënten

In hoofdstuk 9 hebben wij als eerste het nieuwe risico voorspellend model van de in 2014 geïntroduceerde ESC-richtlijnen gevalideerd. Dit model dat gebaseerd is op de HCM Risk-SCD score, maakt gebruikt van een individuele 5-jaars risico, en is gebaseerd op enkele van de bovengenoemde risicofactoren (maar abnormale bloeddruk respons was hier buiten gelaten), in combinatie met LV uitstroombaan gradiënt, linker atrium diameter en leeftijd. Het model maakt vervolgens onderscheid op basis van het 5-jaars risico: laag (<4%), gemiddeld (4-6%) en hoog (>6%). Dit onderscheid is ook de basis voor de aanbevelingen voor ICD-implantatie in de Europese richtlijnen. [13,23]

Hoewel het model wel intern gevalideerd is geweest, hebben wij als eerste in een onafhankelijk cohort gevonden dat het HCM Risk-SCD model beter onderscheid kan maken tussen patiënten met een hoog en een laag risico op plotse dood, dan oudere modellen gebaseerd op de vijf klassieke risicofactoren. [24] Een mogelijke verklaring hiervoor is dat het effect van cardiale remodelleren betrokken wordt. Hoofdstuk 10 laat zien dat indien er sprake is van ongunstige remodeling, het risico op plotse dood significant verhoogd is. [25] Interessant is dat een Amerikaanse analyse het HCM Risk-SCD model als inaccuraat bestempeld, en als onvoldoende gevoelig om onderscheid te maken tussen patiënten met hoog en laag risico. Wel is het zo dat deze bevindingen vertroebeld worden door inclusie van patiënten die niet in aanmerking komen volgens de auteurs van de originele HCM Risk studie, bijvoorbeeld patiënten < 18 jaar, of met LV wanddikte van > 35mm. In ieder geval laten deze tegenstrijdige bevindingen wel zien dat het gebruik van een risico model geen vervanging moet zijn van het klinische oordeel van de specialist. Een ander probleem dat niet aan de orde komt in het nieuwe model is de rol van late gadolinium aankleuring op MRI in het voorspellen van plotse dood. Hoewel de aanwezigheid van deze late aankleuring geassocieerd is met HCM-gerelateerde mortaliteit, is de relatie met plotse dood dubbelzinnig op z'n best. [26-28] Een recente meta-analyse liet eveneens geen verband zien tussen plotse dood en aanwezigheid van late aankleuring. [29] Dit kan te maken hebben met het feit dat deze aankleuring wel myocardiale fibrose en verlittekening kan aantonen, maar geen interstitiële fibrose of myocardiale disarray. Bovendien is het zo dat de kwantificatie van deze aankleuring erg methodiek afhankelijk is. [30] Momenteel loopt de HCMR studie (clinicaltrials.gov nummer: NCT01915615), waar wij ook aan meedoen, die deze problemen en beperkingen in de rol van MRI in het voorspellen van plotse dood systematisch benadert, en hopelijk meer helderheid kan scheppen.

Gebruik van ICD's in patiënten met HCM

Indien een patiënt met HCM als een hoog risico patiënt voor plotse dood beschouwd wordt, moet ICD implantatie overwogen worden. In hoofdstuk 11 en 12 tonen wij aan dat de effectieve bescherming tegen plotse dood, wel ten koste gaat van onjuist toegediende schokken (4.8%/jaar)en complicaties gerelateerd aan het apparaat zelf (3.4%/jaar). Omdat de gemiddelde

HCM patiënt jong is als de ICD geplaatst wordt, kunnen deze risico's niet genegeerd worden, juist omdat deze patiënten veel langer met geplaatste elektroden en batterij moeten doen.

Al met al moeten de voor- en nadelen van ICD behandeling zorgvuldig afgewogen worden. Het gebruik van het nieuwe risico model, met een verbeterd onderscheidend vermogen tussen hoog en laag risicopatiënten, impliceert dat niet alleen meer hoog risico patiënten juist geïdentificeerd worden, maar ook minder patiënten met laag risico voor plotse dood onnodig behandeld worden met een ICD, en alle nadelen van dien. Zoals eerder beschreven is, is een risico score geen vervanging van het klinisch oordeel, maar moet gebruikt worden "als aanvulling op de kliniek door objectieve individuele prognostische informatie te bieden." [23] Dit sluit mooi aan bij de opmerking in de Amerikaanse richtlijnen uit 2011: "de beslissing om een ICD te implanteren in het kader van primaire preventie in patiënten met HCM is vaak gebaseerd op individuele klinische inschatting, zeker als het risico op plotse dood dubbelzinnig is. Dit risico moet met de volledig geïnformeerde patiënt besproken worden, en uiteindelijk een afweging zijn van de risico's en voordelen van preventieve ICD implantatie." [20]

KLINISCHE IMPLICATIES VAN SARCOMEER MUTATIES

Bij het behandelen van een patiënt met HCM is het belangrijk om niet uit het oog te verliezen dat achter deze patiënt ook een familie staat, bestaande uit ouders, broers en zussen, en kinderen. Bij alle nieuw gediagnosticeerde patiënten met HCM moeten alle 1^{e} graad familieleden ook geëvalueerd worden. Genetisch onderzoek wordt in de index-patiënt aangeraden, en indien een pathogene mutatie gevonden wordt kan dit gebruikt worden om andere familieleden te identificeren die het risico hebben op het ontwikkelen van HCM. [13]

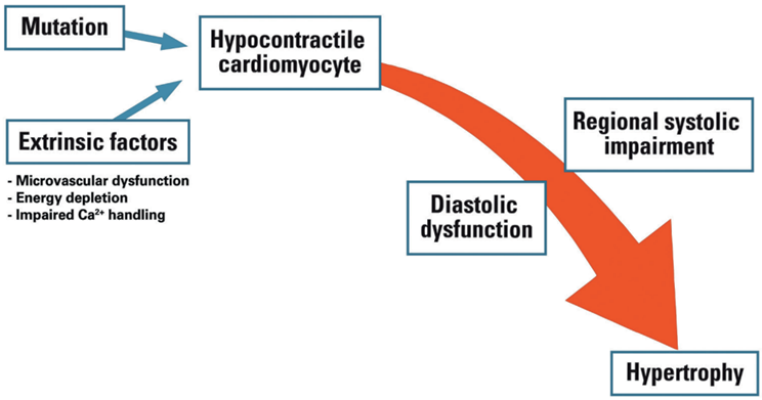
Maar het vinden van een pathogene mutatie zegt ook iets over de individuele patiënt. In hoofdstuk 13 hebben we aangetoond dat patiënten met HCM en de aanwezigheid van een pathogene mutatie een groter risico hebben om te overlijden als gevolg van hartfalen, dan patiënten zonder een mutatie. Dit impliceert dat patiënten met een mutatie recht hebben op striktere follow-up, zodat makkelijker op een verandering in klinisch beloop gereageerd kan worden. Dat de aanwezigheid van een sarcomeer mutatie een negatieve invloed heeft blijkt uit ook uit een eerdere studie waarin gekeken wordt naar het effect van dubbele en triple mutaties. Want deze patiënten hadden duidelijk meer cardiale remodeling, met restrictieve fysiologie, atriale dilatatie en systolische dysfunctie. De aanwezigheid van drievoudige mutaties was zelfs geassocieerd met een 14-voudig verhoogd risico op eindstadium ziekte te ontwikkelen. [33] HCM-patiënten met aanwijzingen voor negatieve cardiale remodeling hebben dus een verhoogd risico op hartfalen en, zoals aangetoond in hoofdstuk 10 ook een hoger risico op plotse dood. [25] Wij adviseren dan ook naar aanleiding van onze resultaten om genetisch onderzoek mee te laten wegen, naast de klinische tekens, om in te schatten welke patiënten een hoger risico op negatieve remodeling hebben.

Maar de aanwezigheid van een pathogene mutatie is niet altijd een teken van slechte prognose. Volwassenen met een pathogene mutatie, maar zonder aanwijzingen voor HCM, dus met een LV-wanddikte < 13mm, lijken hier geen beperkingen van te ondervinden. In hoofdstuk 14 hebben wij aangetoond dat er in een groep van deze 'patiënten' er in 4,5 geen ongunstige voorvallen plaatsvinden. Bovendien was er maar 1 patiënt die echte HCM ontwikkelde, en dat na 6,6 jaar. Deze bevindingen hebben enkele belangrijke klinische consequenties. Ten eerste, gebaseerd op bovenstaande resultaten, adviseren wij deze volwassen personen niet 1- of 2-jaarlijks maar om de 5 jaar te evalueren, tenzij er klinische veranderingen zijn. Ten tweede is deze trage ziekteprogressie en ontwikkeling tot echte HCM een belangrijke beperking in onderzoek naar voorspellers van ziekteprogressie, en beperkt het ook de identificatie van potentiele behandelstrategieën om ziekteprogressie te voorkomen. Bijvoorbeeld is er recent een studie gepubliceerd die het effect van diltiazem op personen met pathogene mutatie onderzocht heeft. Na +-2 jaar behandeling was er geen verschil tussen het (lage) aantal patiënten dat HCM ontwikkelde in de placebogroep en behandelgroep. Bovendien waren alle patiënten die HCM ontwikkelden < 18 jaar. Momenteel doen wij mee met de NIH-gesponsorde VANISH-studie, en hierin wordt bekeken of losartan ziekteprogressie kan vertragen of tot stilstaan brengen. Dat de ziekte uit zichzelf een trage progressie heeft blijft een beperking, en zal naar verwachting leiden tot een hoog 'number needed to treat'.

Wel kan het zo zijn dat een beter begrip van hoe een specifieke mutatie in het contractiel apparaat kan leiden tot de (asymmetrische) hypertrofie, kan bijdragen om mogelijkheden deze progressie tegen te houden. In hoofdstuk 15 hebben een tipje van de sluier gelicht, die over de genotype-fenotype relatie ligt. We beoordeelden de myocardfunctie op regionaal niveau en op cellulair niveau. Hieruit bleek dat bij patiënten met HCM, er een verband tussen de verminderde maximale krachtontwikkeling van de cardiomyocyt is en verminderde regionale systolische functie van de septale wand. Deze verlaging van maximale krachtontwikkeling is typisch voor HCM, en de verminderde cardiale mechanica blijkt gerelateerd aan de intrinsieke myocardiale disfunctie, en niet alleen aan de gewijzigde belasting en linker ventrikel hypertrofie.

Deze bevindingen, in combinatie met de resultaten van hoofdstuk 14 en andere literatuur kunnen wijzen op een mogelijke hypothese voor de progressie van de ziekte van HCM in gezonde mutatiedragers. Verschillende intrinsieke en extrinsieke factoren (bv haploinsufficientie of zogenaamde poison-peptides, veroorzaakt door pathogene mutaties) zouden kunnen leiden tot remodeling van hartspiercellen in een verder structureel normaal hart. [36-40] De remodeling belemmert zowel maximale kracht genererende capaciteit en relaxatie van de cardiomyocyten, en kan leiden tot compenserende hypertrofie van de hartspier - eerst lokaal - en later ook regionaal als de ziekte vordert. Dit kan zich uiten als eerst regionale diastolische en systolische disfunctie en uiteindelijk als de typische asymmetrische hypertrofie (FIGUUR 4).

Concluderend impliceert de aanwezigheid van een pathogene sarcomeer mutatie een groter risico op negatieve uitkomst, vooral hartfalen gerelateerde gebeurtenissen. In gezonde



FIGUUR 4 – Intrinsieke effecten (van de pathogene mutatie) en extrinsieke factoren leiden tot remodelleren van de sarcomeer en tot een hypocontractiele cardiomyocyt. Regionale systolische en diastolische dysfunctie kunnen uiteindelijk leiden tot manifeste HCM. [41]

mutatiedragers blijft het een goedaardige aandoening. Ten slotte zou de associatie van regionale functie en myocarddysfunctie ons begrip van de progressie van de ziekte kunnen bevorderen, zowel in mutatiedragers als echte HCM-patiënten.

TOEKOMSTPERSPECTIEVEN

Zowel chirurgische myectomie als alcohol septum ablatie zijn nu gevestigd in het arsenaal van invasieve behandelingen om symptomen die verband houden met symptomatische LV-uitstroombaan obstructie te verminderen. Een individuele aanpak is nodig om de optimale therapie te bepalen. Deze beslissing moet worden toegespitst worden op de patiënt: comorbiditeiten, anatomische kenmerken (bijv. mitralisklepafwijkingen, vasculaire anatomie van het septum), en de voorkeur van de patiënt zelf. De eerste stap is dat de symptomatische patiënt door een ervaren multidisciplinair hartteam (idealiter bestaande uit ten minste één cardiothoracale chirurg, een interventiecardioloog en een cardioloog gespecialiseerd in de behandeling van patiënten met HCM). Bij voorkeur, en zoals vermeld in de huidige richtlijnen, moeten zowel de chirurg als de interventiecardioloog ervaren zijn in respectievelijk myectomie en alcohol septum ablatie. Daarom adviseren wij vroegtijdige verwijzing van patiënten met symptomatische obstructieve HCM naar centra met specifieke expertise op het vlak van HCM. [13]

Toekomstig onderzoek in percutane septum reductie therapie zal zich moeten concentreren op de vermindering van de procedure-gerelateerde complicaties: atrioventriculaire geleidingsstoornissen en levensbedreigende hartritmestoornissen. In de huidige richtlijnen staat dat alcohol septum ablatie moet worden gereserveerd voor oudere patiënten, maar zoals aangetoond in hoofdstuk 7, hebben juist deze patiënten een verhoogd risico voor

atrioventriculaire geleidingsstoornissen na de procedure. Bij jongere patiënten (± 43 jaar) is het risico voor de implantatie van een pacemaker (5%) conform met patiënten in een vergelijkbare leeftijdsgroep post-myectomy (1-6%). De zeer lange termijn follow-up (> 20 jaar) is nog onduidelijk, en wel een relevante kwestie bij jongere patiënten. Ten tweede kan het gebruik van een alternatief voor alcohol ook het risico van procedure gerelateerde aritmieën verminderen. Septale embolisatie dat microsferen gebruikt in plaats van alcohol zou een meer gecontroleerde infarct kunnen maken. Hoofdstuk 8 beschrijft de eerste klinische ervaringen in Nederland met septale microsfeer embolisatie als alternatief voor alcohol septum ablatie. Hoewel beide gevallen resulteerde in onmiddellijke verbetering in de hemodynamica, zonder procedure gerelateerde aritmische gebeurtenissen, zal toekomstig onderzoek met een groter cohort en langere follow-up moeten aantonen of septale microsfeer embolisatie een levensvatbaar alternatief voor alcohol septum ablatie is. [42]

De bovengenoemde multidisciplinaire aanpak moet ook worden overwogen in de preventie van SCD. Implantatie van een ICD beschermt tegen plotse dood, maar deze bescherming heeft een prijs van onterechte schokken en apparaat-gerelateerde complicaties. Deze risico's zijn met name belangrijk wanneer in een jongere patiëntengroep geïmplanteerd wordt, zoals het geval is in HCM. In deze groep is het belangrijk om een zo eenvoudig mogelijk apparaat te implanteren, zoals een enkele ventriculaire elektrode, of zelfs een volledig subcutaan apparaat. Het nadeel van dit laatste alternatief is de afhankelijkheid van de juiste elektrische vectoren, en er is reeds aangetoond dat de hoog-risico patiënten met HCM niet in aanmerking komen voor subcutane ICD implantatie. [43] Dit betekent ook dat we moeten blijven streven naar een betere risicoanalyse. Naast kwantificering van late aankleuring op cardiale MRI (zoals hierboven besproken), kan de genetische informatie ook leiden tot een verdere verbetering van de risicostratificatie en identificatie van risicopatiënten. Onze huidige kennis van de genetica en haar rol in plotse dood is beperkt. De opkomst van tertiaire referentiecentra voor HCM en de deelname van deze centra in grote internationale registers, zoals HCMR en SHARE (www.thesharegistry.org), kan deze relatie verduidelijken.

Tenslotte kunnen deze grote internationale samenwerkingsverbanden ook leiden tot een verbetering van ons begrip van de ontwikkeling van de ziekte, en de overgang van mutatiedrager naar echte HCM-patiënt. Momenteel beschouwen wij een pathogene mutatie niet als afzonderlijk criterium voor de ziekte, maar een factor die de kans verhoogt om de ziekte te krijgen. Als we de progressie van de ziekte kunnen begrijpen op cellulair niveau, is het stoppen van deze mechanismen ook een strategie om de ziekteprogressie te stoppen, zoals bijvoorbeeld gerichte gentherapie. [44] Wanneer deze nieuwe strategieën beschikbaar zijn voor HCM-patiënten blijft erg onzeker, en we moeten dan ook onze kennis over genotype-fenotype relaties blijven uitbreiden.

CONCLUSIE

Dit proefschrift toonde aan dat myectomie en alcohol septum ablatie veilige en effectieve procedures zijn in de behandeling van obstructieve HCM, met uitstekende resultaten op lange termijn, maar dat voor elke individuele patiënt een multidisciplinaire aanpak moet worden ingezet. Ook de verbetering van de risicoanalyse voor plotse dood en indicatiestelling voor ICD-implantatie, heeft geleid dat de prognose van patiënten met HCM nu bijna vergelijkbaar met de algemene bevolking is. Tot slot, het verbeteren van ons begrip van fenotype-genotype relaties kan de weg vrijmaken voor preventieve strategieën. Dit zou kunnen leiden tot een effectieve curatieve therapie voor HCM, maar voor het zover is, is er nog een lange en hobbelige weg te gaan. Het zal in ieder geval een spannende rit worden.

REFERENTIES

1. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-9.
2. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303.
3. Elliott PM, Gimeno JR, Tome MT, Shah J, Ward D, Thaman R, Mogensen J, McKenna WJ. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J 2006;27:1933-41.
4. Maron BJ. Controversies in cardiovascular medicine. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. Circulation 2007;116:196-206; discussion
5. Fifer MA. Controversies in cardiovascular medicine. Most fully informed patients choose septal ablation over septal myectomy. Circulation 2007;116:207-16; discussion 16.
6. Maron BJ, Yacoub M, Dearani JA. Controversies in cardiovascular medicine. Benefits of surgery in obstructive hypertrophic cardiomyopathy: bring septal myectomy back for European patients. Eur Heart J 2011;32:1055-8.
7. Fifer MA, Sigwart U. Controversies in cardiovascular medicine. Hypertrophic obstructive cardiomyopathy: alcohol septal ablation. Eur Heart J 2011;32:1059-64.
8. Ten Cate FJ, Soliman OII, Michels M, Theuns DAMJ, De Jong PL, Geleijnse ML, Serruys PW. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: A word of caution. Circ Heart Fail 2010;3:362-9.
9. Olivotto I, Ommen SR, Maron MS, Cecchi F, Maron BJ. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Will there ever be a randomized trial? J Am Coll Cardiol 2007;50:831-4.
10. Maron BJ, Rastegar H, Udelson JE, Dearani JA, Maron MS. Contemporary surgical management of hypertrophic cardiomyopathy, the need for more myectomy surgeons and disease-specific centers, and the tufts initiative. Am J Cardiol 2013;112:1512-5.
11. Vriesendorp PA, Liebregts M, Steggerda RC, Schinkel AF, Willems R, Ten Cate FJ, van Cleemput J, Ten Berg JM, Michels M. Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. JACC Heart Fail 2014;2:630-6.
12. Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, Itscoitz SB, Redwood DR. Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. Circulation 1975;52:88-102.
13. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-79.
14. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ, Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470-6.
15. Ten Berg JM, Suttorp MJ, Knaepen PJ, Ernst SMPG, Vermeulen FEE, Jaarsma W. Hypertrophic obstructive cardiomyopathy: Initial results and long-term follow-up after morrow septal myectomy. Circulation 1994;90:1781-5.

16. Maron BJ, Epstein SE, Morrow AG. Symptomatic status and prognosis of patients after operation for hypertrophic obstructive cardiomyopathy: Efficacy of ventricular septal myotomy and myectomy. Eur Heart J 1983;4:175-85.
17. Messmer BJ. Extended myectomy for hypertrophic obstructive cardiomyopathy. Ann Thorac Surg 1994;58:575-7.
18. Vriesendorp PA, Schinkel AF, Soliman OI, Kofflard MJ, de Jong PL, van Herwerden LA, Ten Cate FJ, Michels M. Long-term benefit of myectomy and anterior mitral leaflet extension in obstructive hypertrophic cardiomyopathy. Am J Cardiol 2015;115:670-5.
19. Maron BJ, McKenna WJ, Danielson GK, Kappenberger JKB, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, Spirito P, Cate FJT, Wigle ED. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy - A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. Eur Heart J 2003;24:1965-91.
20. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice G, American Association for Thoracic S, American Society of E, American Society of Nuclear C, Heart Failure Society of A, Heart Rhythm S, Society for Cardiovascular A, Interventions, Society of Thoracic S. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:2761-96.
21. O'Mahony C, Tome-Esteban M, Lambiase PD, Pantazis A, Dickie S, McKenna WJ, Elliott PM. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. Heart 2013;99:534-41.
22. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM, Ortiz-Genga M, Fernandez X, Vlagouli V, Stefanadis C, Coccolo F, Sandoval MJO, Pacileo G, Masarone D, Pantazis A, Tome-Esteban M, Dickie S, Lambiase PD, Rahman S. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). Eur Heart J 2014;35:2010-20.
23. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM, Hypertrophic Cardiomyopathy Outcomes I. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010-20.
24. Vriesendorp PA, Schinkel AF, Liebregts M, Theuns DA, van Cleemput J, Ten Cate FJ, Willems R, Michels M. Validation of the 2014 ESC Guidelines Risk Prediction Model for the Primary Prevention of Sudden Cardiac Death in Hypertrophic Cardiomyopathy. Circ Arrhythm Electrophysiol 2015.
25. Vriesendorp PA, Schinkel AF, de Groot NM, van Domburg RT, Ten Cate FJ, Michels M. Impact of adverse left ventricular remodeling on sudden cardiac death in patients with hypertrophic cardiomyopathy. Clin Cardiol 2014;37:493-8.
26. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, Das B, Khwaja J, Alpendurada FD, Wage R, Roughton M, McKenna WJ, Moon JC, Varnava A, Shakespeare C, Cowie MR, Cook SA, Elliott P, O'Hanlon R, Pennell DJ, Prasad SK. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. Heart 2014;100:1851-8.
27. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic

value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484-95.

28. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, Lesser JR, Hanna CA, Udelson JE, Manning WJ, Maron MS. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol 2008;51:1369-74.
29. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging 2012;5:370-7.
30. Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, Muthurangu V, Moon JC. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. JACC Cardiovasc Imaging 2011;4:150-6.
31. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, Ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail 2012;5:552-9.
32. Vriesendorp PA, Schinkel AF, Van Cleemput J, Willems R, Jordaens LJ, Theuns DA, van Slegtenhorst MA, de Ravel TJ, ten Cate FJ, Michels M. Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications. Am Heart J 2013;166:496-502.
33. Girolami F, Ho CY, Semsarian C, Baldi M, Will ML, Baldini K, Torricelli F, Yeates L, Cecchi F, Ackerman MJ, Olivotto I. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol 2010;55:1444-53.
34. Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 2012;5:535-46.
35. Ho CY, Lakdawala NK, Cirino AL, Lipshultz SE, Sparks E, Abbasi SA, Kwong RY, Antman EM, Semsarian C, Gonzalez A, Lopez B, Diez J, Orav EJ, Colan SD, Seidman CE. Diltiazem treatment for pre-clinical hypertrophic cardiomyopathy sarcomere mutation carriers: a pilot randomized trial to modify disease expression. JACC Heart Fail 2015;3:180-8.
36. van Dijk SJ, Dooijes D, dos Remedios C, Michels M, Lamers JM, Winegrad S, Schlossarek S, Carrier L, ten Cate FJ, Stienen GJ, van der Velden J. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation 2009;119:1473-83.
37. Witjas-Paalberends ER, Piroddi N, Stam K, van Dijk SJ, Oliviera VS, Ferrara C, Scellini B, Hazebroek M, ten Cate FJ, van Slegtenhorst M, dos Remedios C, Niessen HW, Tesi C, Stienen GJ, Heymans S, Michels M, Poggesi C, van der Velden J. Mutations in MYH7 reduce the force generating capacity of sarcomeres in human familial hypertrophic cardiomyopathy. Cardiovasc Res 2013;99:432-41.
38. Kraft T, Witjas-Paalberends ER, Boontje NM, Tripathi S, Brandis A, Montag J, Hodgkinson JL, Francino A, Navarro-Lopez F, Brenner B, Stienen GJ, van der Velden J. Familial hypertrophic cardiomyopathy: functional effects of myosin mutation R723G in cardiomyocytes. J Mol Cell Cardiol 2013;57:13-22.
39. Olivotto I, Girolami F, Sciagra R, Ackerman MJ, Sotgia B, Bos JM, Nistri S, Sgalambro A, Grifoni C, Torricelli F, Camici PG, Cecchi F. Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations. J Am Coll Cardiol 2011;58:839-48.
40. Witjas-Paalberends ER, Guclu A, Germans T, Knaapen P, Harms HJ, Vermeer AM, Christiaans I, Wilde AA, Remedios CD, Lammertsma AA, van Rossum AC, Stienen GJ, van Slegtenhorst M, Schinkel AF, Michels M, Ho CY, Poggesi C, van der Velden J. Gene-specific increase in energetic cost of contraction in hypertrophic cardiomyopathy caused by thick filament mutations. Cardiovasc Res 2014.

41. Vriesendorp P, Schinkel A, Soliman O, Van Slegtenhorst M, Ten Cate F, Michels M. Early detection of diastolic and systolic dysfunction with speckle-tracking echocardiography in carriers of hypertrophic cardiomyopathy mutations. Eur Heart J 2014:1088.
42. Vriesendorp PA, Van Mieghem NM, Vletter WB, Ten Cate FJ, de Jong PL, Schinkel AF, Michels M. Microsphere embolisation as an alternative for alcohol in percutaneous transluminal septal myocardial ablation. Neth Heart J 2013;21:245-8.
43. Maurizi N, Olivotto I, Olde Nordkamp LR, Baldini K, Fumagalli C, Brouwer TF, Knops RE, Cecchi F. Prevalence of Subcutaneous Implantable Defibrillator Candidacy Based on Template ECG Screening In Patients With Hypertrophic Cardiomyopathy. Heart Rhythm 2015.
44. Gramlich M, Pane LS, Zhou Q, Chen Z, Murgia M, Schotterl S, Goedel A, Metzger K, Brade T, Parrotta E, Schaller M, Gerull B, Thierfelder L, Aartsma-Rus A, Labeit S, Atherton JJ, McGaughran J, Harvey RP, Sinnecker D, Mann M, Laugwitz KL, Gawaz MP, Moretti A. Antisense-mediated exon skipping: a therapeutic strategy for titin-based dilated cardiomyopathy. EMBO Mol Med 2015;7:562-76.

VI – Epilogue

LIST OF PUBLICATIONS

Van Velzen HG, **Vriesendorp PA**, Oldenburg RA, Van Slegtenhorst MA, Van der Velden J, Schinkel AF, Michels M
Value of genetic testing for the prediction of long-term outcome in patients with hypertrophic cardiomyopathy
Am J Cardiol. 2016 Jun 27. [Epub ahead of print]

Liebregts M, **Vriesendorp PA**, Steggerda RC, Schinkel AF, Balt JC, Ten Cate FJ, Michels M, Ten Berg JM.
Effect of alcohol dosage on long-term outcomes after alcohol septal ablation in patients with hypertrophic cardiomyopathy.
Catheter Cardiovasc Interv. 2016 Mar 4 [Epub ahead of print]

Liebregts M, Steggerda RC, **Vriesendorp PA**, van Velzen HG, Schinkel AF, Willems R, van Cleemput J, van den Berg MP, Michels M, Ten Berg JM.
Long-term Outcome of Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy in the Young and the Elderly.
JACC Cardiovasc Interv. 2016 Mar 14;9(5):463-9

Liebregts M, **Vriesendorp PA**, Mahmoodi BK, Schinkel AF, Michels M, ten Berg JM.
A Systematic Review and Meta-Analysis of Long-Term Outcomes After Septal Reduction Therapy in Patients With Hypertrophic Cardiomyopathy.
JACC Heart Fail. 2015 Nov;3(11):896-905

Vriesendorp PA, Schinkel AF, Liebregts M, Theuns DA, van Cleemput J, Ten Cate FJ, Willems R, Michels M.
Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy.
Circ Arrhythm Electrophysiol. 2015 Aug;8(4):829-35

Vriesendorp PA, Schinkel AF, Soliman OI, Kofflard MJ, de Jong PL, van Herwerden LA, Ten Cate FJ, Michels M.
Long-term benefit of myectomy and anterior mitral leaflet extension in obstructive hypertrophic cardiomyopathy.
Am J Cardiol. 2015 Mar 1;115(5):670-5

Vriesendorp PA, Liebregts M, Steggerda RC, Schinkel AF, Willems R, Ten Cate FJ, van Cleemput J, Ten Berg JM, Michels M.
Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy.
JACC Heart Fail. 2014 Dec;2(6):630-6

Bergoli LC, **Vriesendorp PA**, Rodríguez-Olivares R, Van Mieghem NM.
Completely percutaneous repair of a failing surgical mitral valve repair.
Eur Heart J. 2015 Feb 14;36(7):433.

Vriesendorp PA, Schinkel AF, de Groot NM, van Domburg RT, Ten Cate FJ, Michels M.
Impact of adverse left ventricular remodeling on sudden cardiac death in patients with hypertrophic cardiomyopathy.
Clin Cardiol. 2014 Aug;37(8):493-8

Vriesendorp PA, Schinkel AF, Van Cleemput J, Willems R, Jordaens LJ, Theuns DA, van Slegtenhorst MA, de Ravel TJ, ten Cate FJ, Michels M.
Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications.
Am Heart J. 2013 Sep;166(3):496-502

Vriesendorp PA, Van Mieghem NM, Vletter WB, Ten Cate FJ, de Jong PL, Schinkel AF, Michels M.
Microsphere embolisation as an alternative for alcohol in percutaneous transluminal septal myocardial ablation.
Neth Heart J. 2013 May;21(5):245-8

Schinkel AF, **Vriesendorp PA**, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M.
Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis.
Circ Heart Fail. 2012 Sep 1;5(5):552-9

Mulier T, de Haan J, **Vriesendorp PA**, Reynders P.
The Treatment of Lisfranc Injuries: Review of Current Literature.
Eur J Trauma Emerg Surg. 2010 Jun;36(3):206-16

DANKWOORD

Bij het schrijven van het dankwoord begrijp je opeens hoe tegenstrijdig de term ‘mijn proefschrift’ is. Want als je iets niet alleen doet dan is het een proefschrift schrijven. Zonder de hulp en steun van jullie was dit er niet gekomen. Toch wil ik graag een aantal mensen in het bijzonder bedanken. Ik ben mij ervan bewust dat dit een risico is, omdat je altijd mensen kan vergeten; hiervoor bied ik alvast mijn excuses aan.

Ten eerste wil ik mijn promotor, prof.dr. Felix Zijlstra bedanken. Beste Felix, niet alleen wist je alles van een afstand in goede banen te leiden, maar ik weet nog goed hoe ik, vers uit de schoolbanken, een gesprek met je had over het wel of niet ingaan van een promotietraject. Een advies dat je me toen gaf was het volgende: “je moet alleen maar gaan promoveren als het onderwerp je kan boeien en je bereid bent je er helemaal op te storten. Je moet het niet doen voor een opleidingsplek, je ego, of druk van anderen, want dan worden het lange jaren.” Ik ben blij dat ik dat advies ter harte genomen heb, want lang hebben deze jaren nooit gevoeld, ze zijn eerder voorbij gevlogen.

Dan natuurlijk mij co-promotoren: dr. Michelle Michels en dr. Arend Schinkel. Beste Michelle, dank je wel om, samen met Arend mijn co-promotoren te zijn. Ik bewonder enorm hoe jij alles weet te combineren: een drukke HCM-poli, het instandhouden en verder uitbouwen van het (inter)nationaal onderzoeksnetwerk, onderwijs, supervisie, een actief gezinsleven, en nog veel meer. Dat ik ook nog eens altijd bij je terecht kon voor vragen, adviezen, tips en strategieën is voor mij heel waardevol geweest. Dank je wel voor het vertrouwen om je eerste promovendus te mogen zijn, ik had geen betere supervisor kunnen wensen. Beste Arend, doordat jij in de kamer naast mij zat was het ideaal om even binnen te schieten en te overleggen. Jouw feedback op de manuscripten waren voor mij heel belangrijk, en ik heb daar heel veel van geleerd. Jouw rust en pragmatisme waren een belangrijke steun als ik het na de zoveelste afwijzing even niet meer zag zitten. Jij en Michelle waren een ideaal team om mijn enthousiasme in goede banen te leiden, en de juiste richting op te sturen als ik mezelf voorbijschoot.

Dr. Folkert ten Cate, beste Folkert, zonder jou was ik hier waarschijnlijk niet terecht gekomen. Jouw gedrevenheid om Rotterdam op de HCM-kaart te zetten kan alleen maar geevenaard worden door jouw enthousiasme. Ik ben blij dat je mij een kans gegeven hebt in het Thoraxcenter, eerst als ANIOS, en enkele maanden later door mij het onderzoek in te duwen. Bovendien zag je altijd heel goed waar de controversiële onderwerpen en lacunes in de HCM-literatuur zaten, en die ideeën hebben een belangrijke bijdrage aan de totstandkoming van dit proefschrift geleverd.

Prof.dr. Robert-jan van Geuns, en prof.dr. Ad Bogers, dank voor het willen plaatsnemen in de kleine commissie. Prof.dr. Jolanda van der Velden, beste Jolanda, eveneens dank voor het

plaats willen nemen in de kleine commissie, maar vooral ook inde goede samenwerking, en het voor mij inzichtelijker maken van HCM op een cellulair niveau.

Prof.dr. Rik Willems en prof.dr. Johan van Cleemput, beste Rik, dank je wel voor de zeer goede samenwerking. Ik ben blij dat jij mij destijds geadviseerd hebt om mijn horizon naar Rotterdam te verleggen, want zie alle goeds dat het gebracht heeft. Beste Johan, vanaf het begin van mijn co-schappen in UZL heb je mij kunnen overtuigen van dat ik met cardiologie goed gekozen had. Ik weet nog dat je mij een lijst met onderwerpen voor mijn stagewerk gaf, en daar stond toen bij: alternatieven voor alcohol ablatie. Ik wist niet dat ik er 6 jaar later nog steeds mee bezig zou zijn.

Mijn paranimfen, Admir Dedic en Max Liebregts; Admir, vanaf het begin in Rotterdam heb ik veel aan je gehad. Samen de congressen afstruinen was natuurlijk fantastisch, maar weet dat jij mij als een van de eerste de voordelen van het promoveren hebt laten zien. Ik kijk al uit naar jouw eigen promotie binnenkort. Max, dat we vanuit Leuven al een hechte vriendschap hebben, maakt het alleen maar mooier dat je destijds geprikkeld genoeg was om mee te helpen met het eerste project. Door jou is de samenwerking Rotterdam-Leuven uitgebreid met Nieuwegein, en dat heeft ons zeker geen windeieren gelegd, zoals de oplettende lezer wel gemerkt heeft. Mooi dat jouw proefschrift ook bijna klaar is.

Mijn kamergenoten: Jackie, Rene, Lotte, Claire en Stijn. Twee jaar lang hebben jullie mij goed geholpen, of het nu met echobeelden maken of importeren was, de eerste stappen in speckle tracking en onderzoek in het algemeen. Bedankt voor de fijne samenwerking. Later kwam Hannah daar ook bij, jij hebt het vaandel overgenomen van mij in Rotterdam, en dat doe je met verve. Heel veel succes!

Dank aan al mijn (oud-)collega's in het Erasmus MC. In het bijzonder: Sing, je hebt mijn in het prille begin onder je hoede genomen en wegwijs gemaakt in de wereld van klinische wetenschap. Dank je wel. Nicolas, met dezelfde alma mater en muzieksmaak moest onze samenwerking wel goed gaan. Ik heb veel van je geleerd en jouw drive en ambitie is besmettelijk. Verder nog Ken, Sakir, Marcel, Olivier, Jannet, Tamas, Maarten, Joost, Anne Mijn, Floris, Crista, Joella, Jonathan, Julio, Jin, Osama, Lara, Matthijs: thank you for your support and the good conversations we had! Ron van Domburg, bedankt voor alle hulp met de statistische problematiek, geniet van je pensioen binnenkort. Prof.dr. Jaap Deckers, dank je wel om deel te nemen aan de grote commissie, en dank je wel om mijn jaar in het MCL mogelijk te maken.

Onderzoek is ook samenwerken met andere centra; Jur ten Berg en Marcel Kofflard, dank je wel hiervoor. Jur, bedankt om ook deel te nemen aan de grote commissie.

Mijn collega's van de interne geneeskunde, intensive care en cardiologie in het Maasstad ziekenhuis, dank voor de goede samenwerking en flexibiliteit als ik wat meer aandacht aan het afronden van mijn onderzoek wilde geven. Ik heb er twee mooie jaren gehad, en veel geleerd.

Mijn vrienden: Bram, Gijs, Guus, Huib, Max, Kristof, Roeland, Steven, Steven en Wout, mannen van idefix, jullie zijn me heel dierbaar. We zien elkaar minder dan in Leuven, maar de kwaliteit van die momenten neemt enkel toe. Gijs, koffiepartner in crime; binnenkort jij ook in deze schoenen?

Een hele hele belangrijke rol in alle ondersteuning is natuurlijk weggelegd voor mijn familie, en dan in de eerste plek voor mijn ouders: Papa, Mama en Nen, jullie steun kan ik ècht niet in een dankwoord uitdrukken, want dat doet het sowieso te kort. Dankzij jullie heb ik altijd de mogelijkheid en vertrouwen gekregen om te doen wat ik wilde; maar af en toe was het heerlijk om naar Tilburg of Amersfoort te vluchten, of juist samen te sparren over van alles. Wij boffen maar met zulke ouders! Jorijn, ik ben trots op jou, heel veel plezier voor jou en Daan met kleine Willem. Steven, jij blijft mijn maatje in Rotterdam, ook al ben je ondertussen naar de hoofdstad uitgeweken. Michiel, ik vind het heel leuk dat je mede-auteur bent in dit boekje. Ik hoop dat je hier ook een keer mag staan. Maus, je gaat als een trein in Delft, en dat vind ik knap, zeker zoals je het combineert. Jij hebt ook al je eerste stappen in het onderzoek gezet, dus wie weet? Ann, Nikolas, Pof en Herman, ik heb me vanaf het begin welkom gevoeld bij jullie in de familie, dank je wel voor jullie steun. Opa Haard, dank je wel voor je interesse, meeleven en emails.

Lieve Opa, Vriend! Beste collega, wat ben ik blij dat ik jou dit boekje mag overhandigen, maar ik ben nog blijer met de bijzondere band die ik als TKZ met je heb.

Oddi, dank je wel om mijn rug warm te houden tijdens de vele uren die wij achter de computer doorbrachten. Wandelingen met jou hebben vaak tot hele goede ingevingen geleid.

Lieve Valerie, jij bent degene die mij echt boven mezelf kan doen uitstijgen. Jij weet me altijd te prikkelen, stimuleren en verleiden om meer te geven, en je onvoorwaardelijke steun is immens belangrijk voor mij. Je volgde mij zonder twijfel naar een nieuw land en nieuwe stad, waar je ook je eigen dromen waar wist te maken. Ik ben zo trots, en gek, op jou, jij bent echt het beste wat mij overkomen is.

ABOUT THE AUTHOR

Pieter Adriaan Vriesendorp was born on June 20th, 1985 in Groningen, the Netherlands. After graduation from secondary school (Gymnasium, Theresialyceum, Tilburg) in 2003, he was a teacher for one year at the Wauna Primary School, in the jungle town Wauna in Guyana; close to the Venezuelan border. In 2004 he started medical school at the Katholieke Universiteit Leuven, and graduated cum laude in 2011. During the last years of his study, he became interested in cardiology, and in 2011 he started his first clinical job as a junior doctor at the cardiology department of the Erasmus Medical Center, Rotterdam, the Netherlands. In 2012 he started with his doctoral studies on hypertrophic cardiomyopathy under supervision of dr. Michelle Michels and dr. Arend Schinkel. After two years, in 2014, he combined this with his cardiology training. Currently, he is in the last months of his internal medicine residency at the Maasstad hospital in Rotterdam.

Pieter is engaged to Valerie Stockbroekx, and they live in Rotterdam and Groningen, with their dog Oddi.

COEUR PhD PORTFOLIO

Name:	P.A. Vriesendorp
Erasmus MC department:	Cardiology
Research school:	COEUR
Title thesis:	Improving Outcomes in Hypertrophic Cardiomyopathy
Promotor:	prof.dr. F. Zijlstra
Co-promotors:	dr. M. Michels and dr. A.F.L. Schinkel

Year	*Title/Name*	*ECTS*	*Location*
PhD Training		**37.0**	
In-depth courses		**8.5**	
COEUR courses			
2014	COEUR Debate on Cardiovascular Controversies	0.3	Rotterdam, the Netherlands
2013	Cardiovascular Imaging and diagnostics	1.5	Rotterdam, the Netherlands
Erasmus MC courses			
2013	Introduction to Regulations & Organization for Clinical Researchers (BROK)	1.8	Rotterdam, the Netherlands
2013	Functional and Applied Clinical Anatomy of the Heart (ERCATHAN)	0.3	Rotterdam, the Netherlands
2013	English Biomedical Writing and Communication	4	Rotterdam, the Netherlands
CVOI courses			
2014	The Heart-team: valvular disease and indications for surgery	0.6	Utrecht, the Netherlands
Teaching		**4.8**	
2014	Supervising Junior Med School, Erasmus MC	0.6	Rotterdam, the Netherlands
2014	Lecture: "Association between contractile dysfunction of the sarcomere and impaired regional function in HCM" at Cardiogenetics meeting, Erasmus MC	0.6	Rotterdam, the Netherlands
2014	Lecture: "Interventional therapy in obstructive hypertrophic cardiomyopathy" at Continuing Nursing Education (CNE), NVHVV	0.6	Utrecht, the Netherlands

2013	Lecture: "Follow-up of patients with genotype positive-phenotype negative hypertrophic cardiomyopathy" at Cardiogenetics meeting, Erasmus MC	0.6	Rotterdam, the Netherlands
2013	Lecture: "Hypertrophic cardiomyopathy" at *COEUR* Course Congenital Heart Disease and the Left Side, Erasmus MC	0.6	Rotterdam, the Netherlands
2013	Lecture: "Invasive Treatment of Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy" at Cardiology Research Meeting, Erasmus MC	0.6	Rotterdam, the Netherlands
2012	Lecture: "Genotype and prognosis in hypertrophic cardiomyopathy." at Cardiology Club Rijnmond meeting	0.6	Rotterdam, the Netherlands
2012	Lecture: "Sudden death in HOCM: medical vs. invasive treatment" at Cardiogenetics meeting, Erasmus MC	0.6	Rotterdam, the Netherlands

Symposia and congresses **23.7**

Oral presentations

2014	European Society of Cardiology (ESC) Congress	2.1	Barcelona, Spain
2014	ICIN working group of hereditary cardiac diseases	0.6	Utrecht, the Netherlands
2014	American College of Cardiology (ACC) Congress	1.8	Washington D.C., USA
2013	AAV Erasmus MC Science meeting (Wetenschapsmiddag)	0.6	Rotterdam, the Netherlands
2013	Dutch Society of Cardiology (NVVC) Spring Congress	0.9	Noordwijkerhout, the Netherlands
2013	American College of Cardiology (ACC) Congress	1.8	San Francisco, CA, USA
2012	Dutch Society of Cardiology (NVVC) Autumn Congress	1.2	Arnhem, the Netherlands
2012	Dutch Society of Cardiology (NVVC) Spring Congress	1.2	Noordwijkerhout, the Netherlands

Poster presentations

2016	European Society of Cardiology (ESC) Congress	0.6	Rome, Italy
2014	European Society of Cardiology (ESC) Congress	0.6	Barcelona, Spain
2014	American Society of Echocardiograhpy (ASE) Congress	1.5	Portland, OR, USA
2014	American College of Cardiology (ACC) Congress	0.6	Washington D.C., USA

2014	American College of Cardiology (ACC) Congress	0.6	Washington D.C., USA
2014	American College of Cardiology (ACC) Congress	0.6	Washington D.C., USA
2014	American College of Cardiology (ACC) Congress	0.6	Washington D.C., USA
2013	European Society of Cardiology (ESC) Congress	2.1	Amsterdam, the Netherlands
2012	European Society of Cardiology (ESC) Congress	2.1	Munich, Germany

Attended

2013	EuroEcho-Imaging Congress	1.2	Istanbul, Turkey
2013	Dutch Society of Cardiology (NVVC) Autumn Congress	0.6	Arnhem, the Netherlands
2013	Hypertrophic Cardiomyopathy International Summit V	0.9	Minneapolis, MN, USA
2013	Veerstichting Symposium	0.6	Leiden, the Netherlands
2012	International Symposium on Advances in Cardiomyopathies II	0.9	Florence, Italy