Hypertrophic Obstructive Cardiomyopathy – Symptoms, treatment and threats: A Systematic Review

Version 2

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Abstract

Introduction: Hypertrophic cardiomyopathy is characterized by left ventricular hypertrophy that cannot be explained by other clinical or pathological causes. In HOCM the stroke volume is reduced due to impaired diastolic filling, which results from the reduced chamber size and compliance of the hypertrophied left ventricle. HOCM can be treated both pharmacologically and invasively, aiming at reducing symptoms and extending longevity. Traditionally, the choice of treatment of severe HOCM has been ventricular septal myectomy. However, less invasive methods, such as septal alcohol ablation have become more popular during the past decades.

Objective: This systematic review describes different treatment options to relieve the symptoms and to prevent complications of hypertrophic obstructive cardiomyopathy. It will consider the alternatives of treating HOCM and describe the outcome and complications of the treatments.

Methods: Pubmed, Cochrane and Trip databases were searched for studies related to HOCM and its treatment. In total 585 articles were collected from these databases, 150 articles were screened and 26 full-text articles were assessed for eligibility. The final selection consisted of 11 articles.

Results: There was no difference in mortality, long-term survival and survival free from SCD between septal myectomy and SAA. Peri- and postoperative complications and NYHA scores did not differ between these two groups. Nevertheless, invasive treatment seemed to be more effective in relieving symptoms and extending longevity than conservative medical therapy.

Conclusion: Septal myectomy and septal alcohol ablation are both safe and effective options to treat HOCM. However, pharmacological treatment would benefit from new innovative agents targeted to treat HOCM.
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**Abbreviations**

AF – Atrial fibrillation  
CMR – Cardiac magnetic resonance imaging  
CT – Computed tomography  
DDD pacing – Dual pacing for both chambers, Dual chamber activity sensing, Dual response  
HCM – Hypertrophic cardiomyopathy  
HOCM – Hypertrophic obstructive cardiomyopathy  
LAD – Left anterior descending artery  
LV – Left ventricle  
LVOT – Left ventricular outflow tract  
LVOTO – Left ventricular outflow tract obstruction  
MRI – Magnetic resonance imaging  
MYBPC3 – myosin-binding protein C  
MYH7 – betamyosin heavy chain  
NYHA – New York Heart Association  
PTSMA – Percutaneous transluminal myocardial ablation  
SAA – Septal alcohol ablation  
SCD – Sudden cardiac death
1. Introduction

1.1. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a disease of the heart that reduces the heart’s ability to pump blood and makes the heart muscle work in an uncoordinated and ineffective way. It is characterized by left ventricular (LV) wall thickness and often associated with atrial fibrillation (AF). It can lead to heart failure and can be a major cause of sudden cardiac death [1]. Hypertrophic cardiomyopathy is a disease of both males and females and it is seen in all ages and ethnic backgrounds [2]. The prevalence of unexplained increase in LV thickness ranges from 0.02% to 0.23% in adults. Prevalence may be age-related, peaking after the age of 25 [33]. The most common form is autosomal dominant with variable expressivity and sporadic, although X-linked and mitochondrial inheritance can also be seen [2]. It is caused by mutations in more than 11 genes encoding thick and thin contractile myofilament protein components of the sarcomere, or adjacent Z-disc. Most patients have mutations in betamyosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) [3,13]. Individuals inheriting mutation that causes the disease show signs of left-ventricular hypertrophy by early adulthood, most often arising during adolescence due to accelerated growth. This hypertrophy is often complete by the age of 17; that is to say with physical maturity. The development of the phenotype is not related to symptom onset or disease progression [13].

The diagnosis of hypertrophic cardiomyopathy is set in an adult when the wall thickness of the left ventricle is ≥15 mm in one or more myocardial segments. It is
measured by echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography (CT). For the diagnosis, it is also needed that the thickening cannot be explained by loading conditions alone [33]. The abnormal hypertrophy is often located to the anterior septum although posterior septum and anterior wall can also be affected [6]. Voltage criteria often show left ventricular hypertrophy as a T wave inversion and magnetic resonance imaging (MRI) shows major hypertrophy. Echocardiogram can have features related to reduced left ventricular cavity dimensions, as well as hyperdynamic indices of systolic function and abnormal indices of diastolic function with atrial enlargement. The papillary muscles and the mitral valve can also be affected [2]. Hypertrophic obstructive cardiomyopathy then again is characterized by a severe obstruction at the left ventricular outflow tract (LVOT).

1.2. Left ventricular outflow tract obstruction

Left ventricular outflow has been shown to be a great prognostic factor in patients with hypertrophic cardiomyopathy. Patients with outflow tract obstruction face increased risk of death and more congestive symptoms [5,6,33]. The obstruction is often located in the left ventricular outflow tract and is caused by systolic anterior motion of the mitral valve and mitral-septal contact. A dysfunctional papillary muscle can also cause obstruction by inserting directly into the base of the anterior mitral leaflet, without intervening chordae, that is to say, systolic apposition of the anterior papillary muscle and the septum is the reason for the obstruction [6]. It is still largely unknown why chronic subaortic obstruction causes symptoms of heart failure or even death in patients with hypertrophic cardiomyopathy. However, it can be assumed that obstruction elevates the left ventricular pressures, which in turn leads to increased wall stress, myocardial ischemia, and later on cell death and scarring. All in all, the left ventricle becomes stiff and noncompliant resulting in diastolic dysfunction, electrical instability and even death [5].

1.3. Atrial fibrillation

Atrial fibrillation is the most common arrhythmia in patients with hypertrophic cardiomyopathy [7,8,33]. The prevalence of atrial fibrillation has been reported to be 22.5% and the annual incidence of atrial fibrillation is 3.1%. The prevalence and annual incidence of thromboembolism in patients with atrial fibrillation were 27.1%
and 3.8% respectively. Factors predisposing for atrial fibrillation include increased left atrial pressure and size, due to diastolic dysfunction, left ventricular outflow tract obstruction (LVOTO) and mitral regurgitation [33]. Atrial fibrillation has been shown to convey a higher risk for all-cause death, cardiovascular death, severe heart failure and ischemic and embolic stroke [8,13]. It still remains unclear what the pathophysiological mechanism predisposing HCM patients to atrial arrhythmia is. Nonetheless, it is known that diastolic dysfunction and mitral regurgitation together with outflow obstruction increase atrial size and stretch [9]. Older patients and those with substantial left-atrial enlargement are more susceptible for atrial fibrillation [13].

1.4. Symptoms

Symptoms of hypertrophic cardiomyopathy are often related to the underlying pathological changes. Dyspnea and intolerance to exercise are caused by the left ventricular diastolic dysfunction and left ventricular outflow obstruction, if present. Angina pectoris is common in patients with HCM with and without obstruction [6]. During exercise, the diastolic dysfunction reduces stroke volume. The reason of diastolic dysfunction in hypertrophic cardiomyopathy may be abnormal compliance resulting from myocyte hypertrophy and fibrosis or failure of active relaxation because of ischemia [10]. The diastolic dysfunction leads to increased left ventricle end-diastolic and left atrial pressures, which causes increased pulmonary congestion and reduced exercise tolerance [14]. Ischemia can be seen on pacing-induced myocardial lactate production. To be able to provide the hypertrophied myocardium with enough blood, the epicardial coronary arteries become dilated, whereas arterioles have signs of intimal and medial hyperplasia, which leads to narrowing of the vessels [11]. Left ventricular outflow tract obstruction increases the left ventricle’s workload and aortic diastolic- and left ventricle perfusion pressure which can exacerbate the ischemia. Syncope can be related to ventricular arrhythmia or be neurally mediated. Fatigue is a common, although nonspecific, complaint that might be caused by β-blockers, as well as HCM [6].
1.5. Pharmacological treatment

1.5.1. β-Adrenoceptor blockers

β-Blockers have long been used in the treatment of HCM and are especially effective in patients with angina or dyspnoea on effort related to LVOTO. They are often used to reduce the prevalence of sustained ventricular arrhythmias. β-blockers mediate a sympathetic modulation of heart rate and ventricular contractility. This gives an improved ventricular relaxation, a longer time for diastolic filling and reduced excitability [4,30]. β-Blockers are effective in treating latent, exercise-related LVOT obstruction, but tend give a reduced response in case of a severe obstruction at rest [4,6,15,30].

1.5.2. Calcium channel blockers

Verapamil and diltiazem, which are non-dihydropiridine calcium-channel blockers, can be used to treat HCM [4]. Verapamil titrated to maximum tolerated dose is recommended for patients with resting or provoked LVOTO who cannot be treated with β-blockers due to intolerance or contraindications. Diltiazem titrated to maximum tolerated dose may be effective for patients with resting or provoked LVOTO and who are intolerant or have contraindications to β-blockers and verapamil [33]. However, because of their potentially adverse haemodynamic effects, verapamil and diltiazem should not be used in patients with significant LVOT obstruction. Due to their negative inotropic and chronotropic effects, calcium channel blockers give a prolonged left ventricular filling time and improve redistribution of flow towards the subendocardial layers of the left ventricle [4]. Verapamil improves left ventricular filling properties in patients with predominant diastolic dysfunction [15]. Verapamil is only recommended for patients with mild to moderate gradients because of the vasodilating effects of Verapamil, which can cause the gradient to rise and lead to pulmonary edema and death in patients with severe obstruction and severe symptoms [6,15,30].
1.5.3. **Disopyramide**

Disopyramide has negative inotropic properties, which may reduce the dynamic subaortic obstruction. Treatment with negative ionotropes prevents mitral-septal contact by reducing the hydrodynamic force on the protruding mitral leaflet and helps to reduce obstruction by decreasing left ventricular ejection acceleration. However, it has anticholinergic side effects and it prolongs QTc, which can in itself cause arrhythmia [4,30]. Disopyramide has not been shown to improve diastolic function in nonobstructed patients [6].

1.5.4. **Amiodarone**

Amiodarone is very effective in treating AF, which is common in HCM patients. However, its side effects limit long-term use. The start of atrial fibrillation often marks a change in the course of the disease and is related to mortality, symptomatic deterioration and risk of having a stroke [4].

1.6. **Surgical Septal Myectomy**

If medical management of the symptoms of hypertrophic obstructive cardiomyopathy fails, the patients have symptoms of advanced limiting heart failure and the symptoms are associated with an outflow gradient of 50 mm Hg or more, septal reduction therapy should be considered [13,33]. The most common surgical procedure used to treat left ventricular outflow tract obstruction is ventricular septal myectomy, also known as the Morrow procedure [33].

Heart failure related to hypertrophic cardiomyopathy can be reversed with the removal of left ventricular outflow tract obstruction, normalisation of intraventricular pressures and reduction in mitral regurgitation. The operation provides symptom relief with a substantially improved quality of life, as well as extended longevity with a survival rate post-operatively similar to that in normal population. With myectomy a small amount of muscle from the basal septum is removed [13]. The surgery is performed through an aortotomy and begins with two parallel, longitudinal incisions in the basal septum. These incisions extend distally, and are connected transversely beneath the aortic valve. The resection may continue beyond the level of mitral-septal contact and subaortic obstruction or at mid-ventricular level at the base of papillary muscles. To identify the level of obstruction and the distribution of septal
hypertrophy, trans-esophageal echocardiographic guidance is used. If there is a case of mitral regurgitation because of primary valvular disease, simultaneous mitral valve repair may be performed. Surgical mortality for septal myectomy and associated mitral intervention is 3-4% [33].

Septal myectomy may be a treatment option in case of heart failure symptoms, such as fatigue, orthopnea, paroxysmal nocturnal dyspnea or syncope. The symptoms must cause substantial lifestyle limitation equal to New York Heart association (NYHA) functional classes III or IV and LV outflow tract obstruction needs to be present [12]. Septal myectomy is recommended for patients who are in need of septal reduction therapy and who have other lesions, for example in the mitral valves or papillary muscles that require surgical intervention. Complications related to septal myectomy include AV nodal block, ventricular septal defect and aortic regurgitation. Although these symptoms are uncommon, they can be seen as possible threats for optimal treatment outcome. Orthotopic cardiac transplantation must be considered for patients with moderate or severe drug refractory symptoms, if the LVOTO does not meet standard eligibility criteria [33].

Figure 1. Picture (A) shows the classical left ventricular septal myectomy. (B) Extended left ventricular septal myectomy due to anomalous papillary muscle. Picture from Minakata et al. [36].
1.7. Septal Alcohol Ablation

Septal alcohol ablation (SAA) is another invasive option to treat hypertrophic cardiomyopathy, in which the first septal branch of the left anterior descending artery (LAD) is instilled with 96 % alcohol [14,15]. The amount of alcohol injected is highly dependent on the acute hemodynamic effect and the echocardiographically estimated size of the contrasted septal area [15]. In septal alcohol ablation, the infusion of absolute alcohol into the first major septal perforator artery causes a large artificial septal infarct, which is usually transmural and occupies about 10 % of the left ventricle [13,14]. This ideally widens the left ventricular outflow tract gradient, decreases mitral regurgitation, restricts septal excursion and gives global negative ventricular remodelling.

The morphological and functional changes related to SAA follow a triphasic pattern. The alcohol is injected into the target vessel and immediately after that well-demarcated coagulative necrosis of the myocardium and vascular epithelium occurs. At first, there is an immediate reduction in the gradient followed by a partial modest rise in the gradient, most likely due to recovery or to increasing myocardial edema. Eventually, the scarring and thinning of the basal septum leads to widening of the left ventricular outflow tract and reverse remodeling of the left ventricle. The decreased left ventricular outflow obstruction improves left atrial emptying and reduces left atrial systolic and diastolic dimensions [14].

The septal scar caused by alcohol ablation can in some cases lead to life-threatening ventricular tachyarrhythmias and sudden death, although the risk of this happening is relatively small. Mortality associated with SAA is most often related to complete heart block and arrhythmias such as ST-segment elevation, ventricular fibrillation, tachycardia and sinus bradycardia [14]. However, the procedural mortality is similar to that of isolated myectomy [33]. LAD dissection, cardiogenic shock, pulmonary embolia, and cardiac tamponade are some of the complications that threat the best possible treatment outcome [14]. Alcohol ablation is also sometimes associated with a permanent pacemaker implantation for heart block. Alcohol ablation can be considered as a treatment option for older patients, those with comorbidities or if the patient is very reluctant towards surgery [13].
Figure 2. Septal alcohol ablation demonstrated by angiography. Picture (A) shows the optimal positioning of the balloon catheter in the proximal part of the septal artery. (B) The injection of the angiographic contrast dye through the central lumen of the balloon catheter. (C) The stump of the septal artery. (D) Occlusion induced by alcohol. Picture courtesy of Leal et al. [35].

2. Objective

The primary objective for this systematic review is to summarize different treatment options to relieve the symptoms and to prevent complications of hypertrophic obstructive cardiomyopathy. This will be achieved by comparing therapy options and their outcomes with each other, based on current literature. The study will provide insight of indications, alternatives, outcomes and complications of treating HOCM.
3. Methods

The layout and presentation of this systematic review is based on recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [34].

3.1. Electronic Search Methods and Study Selection

Pubmed, Cochrane and Trip databases were used in this study. The collection of studies took place from the 10\textsuperscript{th} of November 2014 until the 2\textsuperscript{nd} of December 2014. Pubmed was searched for the MeSH terms “cardiomyopathy, hypertrophic” and “hypertrophic obstructive cardiomyopathy” combined with “therapy”, “drug therapy”, “surgery”, “septal myectomy”, “alcohol ablation”, “atrial fibrillation”, “left outflow tract obstruction”, “mortality”, “prognosis”, “long-term outcome” and “treatment outcome”. Free text search using “septal myectomy versus alcohol ablation” and “invasive versus conventional treatment” was also used. Free text search was used to find new, lately published articles still lacking MeSH terms. Duplicates were eliminated. The term “hypertrophic cardiomyopathy” combined with “long-term outcome and treatment outcome” or “survival and mortality” was used to search in Cochrane. First, the selection of articles was dependent on abstracts, but the final selection was based on reading full articles. The studies selected were in English and dealt with studies with humans. Most of them were retrospective cohort studies because randomized trials are difficult to execute in the field of HOCM [27].

3.2. Inclusion and Exclusion Criteria

The articles chosen for this review all described survival, mortality, long-term outcome and treatment outcome in HOCM. Articles about asymptomatic and non-obstructive HCM were excluded. The effect of a specific treatment method on an exact symptom related to HOCM was not of interest. That is why studies outlining the effects of septal alcohol ablation, septal myectomy and drug treatment on left ventricular diastolic or systolic function, acute reduction in left ventricular outflow tract pressure gradient obstruction or in reducing atrial fibrillation or the recurrence of syncope were excluded.

One study was excluded because it described the predictors of long-term outcome in septal myectomy instead of the long-term outcome itself, whereas another article
was not included because of conflict of interest. In the institution where the study took part, the treatment of choice was DDD pacing and indeed the results for DDD pacing were very positive, against all other studies. Patients taking part in the selected studies were adults, basically from the same age group, so studies describing children or pre-term infants were excluded. Studies with small study populations were also excluded as well as case-reports. The studies included were published between 2001 and 2014 (see Appendix for Table 1).

3.3. The Quality of Studies

The quality of the articles included in this systematic review was assessed and the studies were ranked as of high, medium or low quality (see Appendix for Table 1). For the study to be of high quality it had to have equal treatment and control groups before treatment, the number of the smallest treatment group had to be of significance, and the outcome had to be valid as well as the treatment outcome measured had to be reliable. There also needed to be a proper follow-up. The size of the study population also affected the ranking of the articles; studies with small study populations were ranked medium or low. As most of the studies included were retrospective cohort studies, randomization between the treatment and control groups was not assessed. The quality of the studies forms by Forsberg and Wengström [37] were used as an assessment tool.

3.4. Ethics

Considering that this study is a systematic review of literature, no ethical problems related to this study can be reported. Nevertheless, the authors of only one of the articles included reported that their study was approved by the Research Ethics Board of their institution [19].

4. Results

In total, 26 articles went through to the final selection based on their abstracts and full text, out of which 11 fulfilled all the inclusion criteria. These studies covered 4422 patients in total. 1177 patients went through septal myectomy and 1548 patients got septal alcohol ablation. 403 were treated invasively either with septal myectomy,
alcohol septal ablation or DDD pacing and 246 were managed medically. One of the studies also included patients, who were not operated, with left ventricular outflow tract obstruction (n=228), and patients with HCM without obstruction (n=820), in the study population. Only three of the studies specified the male or female proportion. In total, these studies had 289 men and 547 women. The age of the participants ranged from 26 to 89 years, mean age being 66,8 years. Five of the studies did not report the age of the participants. Two of the studies took place in the Netherlands, two in Scandinavia and the rest in the USA. The articles in this study are described in Table 1. (see Appendix).

Figure 3. The selection process and the excluded articles. Flow Chart modified from the Prisma 2009 Flow Diagram [34].
4.1. Effects of Interventions Based on Study Endpoints

4.1.1. Mortality

Mortality in total ranged from 0.3% to 5.9% in the studies included. Procedural mortality and in-hospital mortality varied from 0.3% to 0.8% [21,22]. According to Sorajja et al [17], the mortality of septal alcohol ablation did not differ from the expected survival of background population or from the age- and sex-matched patients undergoing isolated surgical myectomy over a follow-up period of 5.7 years and the 8-year survival estimate was 79% in both groups. This is confirmed by Steggerda et al [18] who constated that the annual cardiac mortality after SAA and myectomy are comparable, annual cardiac mortality being 0.7% for SAA and 1.4% for septal myectomy. However, the propensity score adjustment by Ralph-Edwards et al [23] state that mortality after an alcohol ablation is statistically higher compared to that of isolated myectomy or myectomy with concomitant procedures. In the study of Panaich et al [24], the post-procedural mortality of septal myectomy was 5.9%, which is substantially higher than the procedural mortality and in-hospital mortality described by Jensen et al [21] and Ommen et al [22]. The latter article described 25 deaths in total after septal myectomy, out of which two were operative deaths (procedural mortality 0.8%), seven caused by hypertrophic cardiomyopathy and 16 noncardiac deaths. In this study the mean age at death was 64 ± 12 years (range 22 to 82 years), occurring 6.8 ± 5 years (range 0.2 to 17 years) after myectomy.

4.1.2. Peri- and Postoperative Complications

In the study of Panaich et al [24] cardiac complications after a septal myectomy were the most common, followed by iatrogenic cardiac complications and complete heart block requiring a pacemaker. Less common complications related to septal myectomy were vascular and respiratory. A small amount of patients also had renal or metabolic complications. The rate of postprocedural complications was 30.2%. Age at the time of the procedure predicted severity and occurrence of these postoperative complications. Steggerda et al [18] found no difference in complications, such as death, cerebrovascular accident and ventricular fibrillation, between SAA and septal
myectomy. There was no difference between the groups in the need of pacemaker implantation, which is partly explained by the fact that in this actual study age at baseline was comparable for both treatments. Nonetheless, this study stated that the frequency of periprocedural complications was lower in the SAA group, which is something that other studies have not stated. This difference can mostly be explained with the need for repeat sternotomy after myectomy due to bleeding or tamponade. Septal alcohol ablation conveys a higher risk of AV block that requires a permanent pacemaker implantation and residual LV outflow tract gradients are more common [33].

4.1.3. Long-term survival

Survival of septal alcohol ablation after one year was 97%, whereas after five years it ranged from 87% to 94% and after 10 years from 67% to 94% based on the studies included. Jensen et al [21] found that survival of SAA was comparable to that of general population age being the only predictor of survival, whereas baseline comorbidities strongly affected the symptomatic long-term outcome. Survival of septal alcohol ablation at 1, 5 and 10 years was 97%, 87% and 67% respectively in all patients. Veselka et al [25] found that survival of alcohol septal ablation 1, 5, and 10 years after the treatment was 97%, 94% and 94% respectively. During that time four patients died. Ball et al [19] compared the long-term survival of patients suffering from HOCM and were treated invasively (septal myectomy, alcohol septal ablation or DDD pacing), versus conservatively. According to the results of Ball et al [19] the survival in the invasive group was 99.5% after one year, 96.3% after five years and 90.2% after 10 years of treatment. In the conservative group, the respective percentages were 97.8% after the first year, 94.6% after five years and 86.9% after 10 years. Ommen et al [22] describe the annual survival rate of septal myectomy at 1, 5, and 10 years as 98%, 96% and 83%, which is basically the same as the mortality of general age- and sex-matched U.S. population. This survival rate did not differ from that of patients with nonobstructive HCM.
4.1.4. Survival Free from Sudden Cardiac Death (SCD)

Survival free from sudden cardiac death during the first year for septal alcohol ablation was 96%-100%. Survival free of SCD one year after septal myectomy was 100% and 96%-99% after five years. According to ten Cate et al [20], survival free from SCD for patients who underwent alcohol septal ablation was 96% during the first year, 86% after five years and 67% after eight years, whereas Jensen et al [26] states that 95% of patients were free from SCD 10 years after SAA. Ommen et al [22] described survival free of sudden cardiac death after septal myectomy as 100% during the first year, 99% after five years and 99% after 10 years. However, ten Cate et al [20] also found that 100% of patients operated for septal myectomy were free of SCD during the first year, 96% after five years and 96% at 6.6±2.7 years.

4.1.5. New York Heart Association Functional Classification

Qin et al [16] found that the NYHA functional class improved after SAA (1.9 ± 0.7, p < 0.0001) as well as it did after a septal myectomy (1.5 ± 0.7, p < 0.0001). At follow-up the NYHA functional class did not differ in these two groups. Steggerda et al [18] described in their study that of the 102 patients in the myectomy group 5 % were in NYHA class I, 19 % in class II and 76 % either in class III or IV at baseline. However, after septal myectomy 52 % of these patients were in class I, 30 % in class II and 18 % in class III or class IV. At baseline, before septal alcohol ablation, out of the 161 patients, 1% was class I, 19% class II and 80% either class III or IV. After the procedure, the respective percentages for SAA were 53%, 31% and 16%. In conclusion, the proportion of patients suffering from severe symptoms significantly reduced both after SAA and septal myectomy and the NYHA functional class improved. Nonetheless, Ralph-Edwards et al [23] found that patients treated with SAA had a worse NYHA functional classification at most recent follow-up.

4.2. Risk of Bias

Most of the studies included are retrospective cohort studies due to the fact that a randomized trial examining HOCM and its treatment is difficult to execute because of the need of a very large study cohort. Acute complications, gradient reduction and relief of symptoms after SAA and septal myectomy may be resolved by observational
data, even though placebo effect can play a major role, whereas it would be necessary to make a randomized trial of long-term outcome. Nevertheless, this has proven difficult considering the low event rates after these two procedures [27]. Having noted this, it can be stated that there is selection bias in the studies included in this systematic review. All the studies published about HOCM are written by professionals involved in the field, such as surgeons, cardiologists and radiologists. This also poses selection bias, due to the fact that their point of view may not be objective as they work with HCM constantly. Patients with HOCM are indeed often treated in specific centers and hospitals. Patients in the SAA group were often older than the ones in the septal myectomy group, which also poses a selection bias. Only one study reported that the patients in both groups were the same age [18].

Studies with an unobjective outcome were excluded, so in that sense performance bias and detection bias were taken into consideration in the systematic review. However, all the finally selected studies reported both positive and negative, wanted and unwanted results so reporting bias may not be of great magnitude. Incomplete data was properly reported in all of the studies; the number of deaths and possible drop-outs were addressed so the risk for attrition bias was low. All studies described the limitations of the study clearly.

5. Discussion

The initial treatment of hypertrophic cardiomyopathy with obstruction consists of pharmacological therapy with β-blockers and verapamil and some selected patients may even benefit from adding disopyramide [28,30]. Nonetheless, β-blockers do not affect the rise in the gradient related to exercise, but the slowing heart rate may improve filling in the case of significant diastolic abnormalities [30]. Disopyramide can be useful for patients whose next option is septal reduction therapy. It effectively lowers outflow gradient and provides even patients with a substantial resting obstruction with symptomatic relief [28]. However, as the American College of Cardiology-European Society of Cardiology Expert Consensus Guidelines as well as almost five decades of experience in septal myectomy suggest, septal myectomy is considered as the gold standard treatment of obstructive hypertrophic cardiomyopathy with drug-refractory symptoms [29,31]. Nevertheless, septal myectomy is an invasive procedure that requires a relatively long stay in the hospital and that is why new, less
invasive approaches, such as septal alcohol ablation, have derived during the past few years [29].

According to this systematic review, there is no significant difference between alcohol septal ablation and septal myectomy in terms of mortality, long-term survival and survival free of SCD. There was no difference between the complications after a septal myectomy and septal alcohol ablation. Nonetheless, conservative therapy with medication showed worse long-term survival than the invasive ones. Mortality and postprocedural complications have been traditionally higher after septal alcohol ablation, but current methods, techniques, strategies and know-how have made it a safe option for the treatment of HOCM [17]. Nevertheless, if CMR shows extensive septal scarring or if the patient suffers from severe hypertrophy (≥30mm), septal alcohol ablation may be less effective [33]. Both septal alcohol ablation and septal myectomy provide patients with symptomatic relief and clinical improvement. However, the hemodynamic relief may be more substantial with septal myectomy [23]. In this study the term threat refers to the complications related to each treatment option. As mentioned earlier, septal alcohol ablation and septal myectomy both have potentially severe complications, which can be seen as threats for the treatment outcome and long-term survival.

SAA is a less invasive method compared with septal myectomy and has a shorter in-hospital stay, but does not provide patients with immediate relief because the reduction of the gradient might require several months [16,32]. In short, the choice of treatment must be made based on the individual needs and characteristics of the patient. Septal alcohol ablation might, for example, be better for older patients, patients who are very reluctant for septal myectomy and for patients with several co-morbidities due to its less invasive nature [26,17,18,13]. It must also be considered that the risk of ventriculoseptal defect after septal alcohol ablation or septal myectomy is higher in patients with mild hypertrophy (≥16mm) at the point of the mitral leaflet-septal contact [33]. It can be assumed that less invasive procedures will probably become more and more common in the future, and there might be less open-heart surgery due to the longer in-hospital stay and psychological and physical side-effects.

This study was a systematic review that consisted of 11 articles. The small amount of articles can be considered as a limitation. For the study to be even more valid and accurate, more articles should be retrieved from databases. Only one person chose the
articles included, so it is possible that the selection was quite subjective. For a more objective outcome it would be better to have several authors going through the databases. The quality of the studies was also assessed by the same sole person, so the assessment of the quality was not purely objective either. In an ideal situation there would have been a group of authors discussing the articles and their quality.

6. Conclusion

When choosing the best treatment option for patients with HOCM, the choice must be based on systematic assessment of the mitral valve and septal anatomy that includes exclusion of the other left ventricular outflow tract and mitral valve abnormalities requiring surgical treatment [33]. The choice is made individually. Alcohol septal ablation may be a better option for older patients with several co-morbidities, whereas septal myectomy is effective in treating obstruction in patients who are good candidates for surgery. There is no significant difference in mortality, long-term survival or survival free from sudden cardiac death between septal alcohol ablation and septal myectomy. Both treatment options also improve the NYHA functional classification score. However, medical treatment does not provide the patients with substantial symptomatic relief in the long run and an invasive treatment option must be considered eventually. New and effective options for treating HOCM invasively have derived during the past eras, however little progress has been made in the field of pharmalogical therapy to control the symptoms of HCM. Indeed pharmacological therapy needs novel agents modified to fit the treatment of HCM.

7. Acknowledgements

I would like to thank my supervisor Anders Ahlsson for his support and ideas for this study. I also want to thank the Medical Library of The University of Örebro, and especially Liz Holmgren for her help with search methods.
References


27. Olivotto I, Ommen SR, Maron MS, Cecchi F, Maron BJ. Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy.
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Will there ever be a randomized trial? J Am Coll Cardiol 2007 Aug 28;50(9):831-834.


## Appendix

Table 1. Articles included in this systematic review. Study characteristics and results.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study type</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Compared with</th>
<th>Study endpoints</th>
<th>Results</th>
<th>Quality of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qin JX, 2001, [16]</td>
<td>Retrospective cohort study</td>
<td>51 patients who underwent septal myectomy (n = 26, mean age 48 ± 13 years, men = 16) or PTSMA (n = 25, mean age 63 ± 14 years, men = 7)</td>
<td>PTSMA</td>
<td>Septal Myectomy</td>
<td>Two dimensional echocardiograms, NYHA functional class</td>
<td>Interventricular septal thickness diminished at follow-up in both groups. PG across LVOT reduced after the procedures in both groups. The NYHA functional class improved in both groups.</td>
<td>Medium</td>
</tr>
<tr>
<td>Soraja P, 2012, [17]</td>
<td>Retrospective cohort study</td>
<td>177 patients (mean age, 64 years; range 26-89 years, 68% women)</td>
<td>Alcohol Septal Ablation</td>
<td>Septal Myectomy, background population</td>
<td>Mortality</td>
<td>Over a follow-up of 5.7 years, survival free of all mortality did not differ from the expected survival of a comparable general population, and similar to that of age- and sex-matched patients who were operated for surgical myectomy (8-year survival estimate, 79% versus 79%; P=0.64).</td>
<td>High</td>
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<tr>
<td>Steggerda RC, 2014, [18]</td>
<td>Retrospective cohort study</td>
<td>161 patients for ASA, 102 patients for septal myectomy</td>
<td>Alcohol Septal Ablation</td>
<td>Septal Myectomy</td>
<td>Mortality, annual cardiac death rate, NYHA functional class, rehospitalization due to heart failure, myocardial infarction, cerebrovascular incident, reintervention</td>
<td>The periprocedural (30-day) complication frequency after ASA lower compared with myectomy. Median duration of in-hospital stay shorter. After ASA, provoked gradients were higher than with myectomy. Annual cardiac mortality after ASA and myectomy was comparable.</td>
<td>High</td>
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<tr>
<td>Ball W, 2011, [19]</td>
<td>Retrospective cohort study</td>
<td>649 patients, 246 patients conservatively managed, 403 invasively managed</td>
<td>Septal myectomy, alcohol septal ablation, DDD pacing</td>
<td>Conservative treatment</td>
<td>Long-term survival</td>
<td>Survival 99.5% (1 year), 96.3% (5 years), and 90.2% (10 years) in the invasive cohort, and 97.8% (1 year), 94.6% (5 years), and 86.9% (10 years) in the conservative cohort (p = 0.3).</td>
<td>High</td>
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<tr>
<td>ten Cate FJ, 2010, [20]</td>
<td>Retrospective cohort study</td>
<td>91 patients (aged 54±15 years)</td>
<td>Alcohol Septal Ablation</td>
<td>Septal Myectomy</td>
<td>Primary endpoint: cardiac death, aborted SCD. Secondary endpoint: noncardiac death, nonfatal complications.</td>
<td>The 1-, 5-, and 8-year survival-free from the primary end point was 96%, 86%, and 67%, respectively in ASA patients versus 100%, 96%, and 96%, respectively in myectomy patients during 6.6±2.7 years.</td>
<td>Medium</td>
</tr>
<tr>
<td>Publication</td>
<td>Study type</td>
<td>Patient characteristics</td>
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<tr>
<td>Jensen MK, 2011</td>
<td>Retrospective cohort study</td>
<td>279 patients aged 59±14 years</td>
<td>PTSM A</td>
<td>Background population</td>
<td>Long-term survival, in-hospital mortality, hemodynamic and symptomatic effects</td>
<td>Sustained hemodynamic and symptomatic effects. Survival comparable to that of the background population, age being the only predictor of survival. The in-hospital mortality low. Long-term symptomatic outcome affected by baseline comorbidities.</td>
<td>High</td>
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<tr>
<td>Ommen SR, 2005</td>
<td>Retrospective cohort study</td>
<td>1337 patients, surgical myectomy n = 289, LV outflow obstruction without operation n = 228, and nonobstructive n = 820</td>
<td>Septal myectomy</td>
<td>LV outflow obstruction without operation, non obstructive HCM</td>
<td>Mortality</td>
<td>Two operative deaths (procedural mortality, 0.8%), 1-, 5-, and 10-year overall survival after myectomy 98%, 96%, and 83%. Not different from that of the general U.S. population matched for age and gender (p = 0.2) or from patients with nonobstructive HCM (p = 0.8).</td>
<td>High</td>
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<tr>
<td>Ralph-Edwars A,</td>
<td>Propensity adjustment</td>
<td>150 patients, 60 alcohol ablation out of 5 crossed over to surgery, 95 septal myectomy</td>
<td>Alcohol Septal Ablation</td>
<td>Septal Myectomy</td>
<td>Mortality</td>
<td>ASA higher post-procedural resting and provokable outflow tract gradient. Worse NYHA classification at most recent follow-up. ASA group had longer postprocedural length of stay. Mortality was statistically higher in ASA than with that of isolated myectomy (or myectomy with concomitant procedures).</td>
<td>Medium</td>
</tr>
<tr>
<td>Panaich SS, 2014</td>
<td>Retrospective cohort study</td>
<td>665 patients, mean age 56.9 ± 0.6 years. Men constituted 40% of the cohort, with 52.8% being white.</td>
<td>Septal myectomy</td>
<td>Background population</td>
<td>Mortality, postoperative complications</td>
<td>The overall postprocedural mortality was 5.9%, while the rate of postprocedural complications was 30.2%.</td>
<td>High</td>
</tr>
<tr>
<td>Veselka J, 2014</td>
<td>Retrospective cohort study</td>
<td>290 patients, 75 of them younger than 50 years old</td>
<td>Alcohol Septal Ablation</td>
<td>Background population</td>
<td>Survival, annual mortality rate</td>
<td>Survival free of all-cause mortality at 1.5, and 10 years was 97 %, 94 %, and 94 %. During the study period four patients died.</td>
<td>High</td>
</tr>
<tr>
<td>Jensen MK, 2013</td>
<td>Observational cohort study</td>
<td>470 patients (age 56 ± 14 years)</td>
<td>Alcohol Septal Ablation</td>
<td>Background population</td>
<td>All-cause mortality, SCD and RFs for SCD before and after ASA.</td>
<td>Survival at 10 years 88%. Survival free of SCD at 10 years 95 %. The proportion of patients with two or more RFs reduced from 25 % to 8%.</td>
<td>High</td>
</tr>
</tbody>
</table>