Summary, Discussion and Future Perspectives

Abbreviations

AHA = American Heart Association

ASA = alcohol septal ablation

ACC = American College of Cardiology

CK = creatine kinase

CMRI = contrast cardiac magnetic resonance imaging

HCM = hypertrophic cardiomyopathy

ESC = European Society of Cardiology

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LVOT = left ventricular outflow tract

LVWT = left ventricular wall thickness

MCE = myocardial contrast echocardiography

NSVT = non-sustained ventricular tachycardia

NYHA = New York Heart Association

SCD = sudden cardiac death

Alcohol septal ablation (ASA) for the treatment of obstructive hypertrophic cardiomyopathy (HCM) was introduced as a percutaneous alternative to surgical myectomy in 1995 (1). Initial performance of ASA was shrouded in safety concerns, due to the intracoronary injection of ethanol, creating a potentially arrhythmogenic ablation scar. In the polarizing debate concerning the role of ASA in the treatment of obstructive HCM, most arguments were based on short-term follow-up studies. In the present thesis we set out to provide long-term results following ASA to 1) decide on its role in the treatment of obstructive HCM, as compared to myectomy; 2) seek ways to improve the outcome of ASA; 3) investigate which patients can benefit from ASA, outside of current expert opinion guidelines; 4) engage ASA patients in current sudden cardiac death (SCD) risk prediction models.

Needle vs knife

Alcohol septal ablation and surgical myectomy are, apart from having the same objective, two completely different procedures, making comparisons difficult. Ideally, a randomised controlled trial were to be set up to end the discussion about which procedure is “best". This would require 1200 patients eligible and willing to be randomised to ASA or surgical myectomy. Seen as the prevalence of HCM is 1 in 500 and <10% of these patients require septal reduction therapy, such a trial is practically impossible, as Olivotto et al. clearly demonstrated (2). Hence, the only way to compare the two procedures at this time is by retrospective analyses.

We started by comparing the two procedures in a single-center study, focusing on peri-procedural complications and clinical efficacy **(3)**. A total of 161 patients after ASA and 102 patients after myectomy were compared during a maximal follow-up period of 11 years. The rate of periprocedural severe complications (death, CVA, and ventricular arrhythmias) after ASA and myectomy was not significantly different. Tamponade and urgent (repeat) thoracotomy were more frequent following myectomy, however all repeat thoracotomies were performed successfully and were not associated with a worse long-term outcome. Other peri-procedural complications, including permanent pacemaker implantation, were comparable between ASA and myectomy. The median length of hospital stay following myectomy was 9 days, compared to 5 days following ASA. At late follow-up the gradient over the left ventricular outflow tract (LVOT) was slightly higher following ASA, and reintervention following ASA was more frequent compared to myectomy. Questionnaires were send to all patients at late follow-up and showed no differences in symptomatic status following ASA and myectomy.

In **CHAPTER 3** we combined data from multiple hospitals and emphasised on long-term outcomes. With 1,047 HCM patients from the St. Antonius Hospital Nieuwegein, Erasmus MC Rotterdam and University Hospital Leuven, it is the largest study comparing ASA and myectomy to date. Of the 690 patients (66%) with a LVOT gradient >30 mmHg, 124 (12%) were treated medically, 316 (30%) underwent ASA, and 250 (24%) underwent myectomy. Long-term outcomes were compared to 349 (34%) nonobstructive HCM patients during a mean follow-up of 7.6 years. After ASA and myectomy, both mortality and SCD risk were found to be similarly low, and comparable to patients with nonobstructive HCM.

At the time, only 3 other studies comparing long-term outcomes after ASA and myectomy had been conducted (4-6). Because of some conflicting reports between these and the above studies a systematic review and meta-analysis on long-term outcomes after ASA and myectomy was conducted in **CHAPTER 4**. Twenty-four studies were selected for inclusion, containing 16 myectomy cohorts (n = 2,791; mean follow-up 7.4 years) and 11 ASA cohorts (n = 2,013; mean follow-up 6.2 years). Periprocedural mortality was found to be 1.3% after ASA and 2.5% after myectomy; permanent pacemaker implantation was more frequent following ASA compared to myectomy (10.0% vs 4.4%, P <0.001); periprocedural ventricular arrhythmia occurrence was comparable after ASA and myectomy; and the incidence of tamponade and stroke was also similar at <1% after both procedures. When studies from before 2000 were excluded in light of potentially less developed periprocedural care in the 20th century, the periprocedural mortality rate of myectomy further approximated that of ASA (1.1% vs 1.3%, respectively). Pooled all-cause mortality rates after myectomy and ASA were similar (1.4% per year vs 1.5% per year, respectively). The rate of (aborted) SCD during follow-up was 0.4% per year after ASA and 0.5% per year after myectomy. Improvement of functional status and LVOT gradient reduction at long-term follow-up were similar following both procedures. However, the number of reinterventions (either ASA or myectomy) was significantly higher after ASA (7.7%) compared with myectomy (1.6%, P = 0.001).

Alcohol and its effects

In the early days of ASA, relatively high volumes of alcohol were used. The first 3 cases described by Sigwart were treated with an average of 4.5 mL, for example (1). Over time, clinical experience combined with better strategies to identify the target septal branches (e.g. the use of myocardial contrast echocardiography [MCE]) has led to the use of lower volumes of alcohol during ASA. However, the effect of alcohol dosage on LVOT gradient reduction and complication rate is still not well understood. The amount of alcohol used

for ASA has been related to infarct size (7-9), and one of the main concerns of ASA is the possible arrhythmogenicity of the ablation scar.

In **CHAPTER 5** we sought to find out if there is a relationship between alcohol volume used for ASA and adverse events during long-term follow-up. During 6.3 years of follow-up, the 124 patients treated with >2 mL alcohol were found to have a similar all-cause mortality and adverse arrhythmic event (AAE) rate compared to the 143 patients treated with ≤2 mL. However, a larger infarct (maximum creatinine kinase [CK]-MB >240 IU/L) was found to be an independent predictor of AAEs during long-term follow-up (Hazard Ratio [HR] 3.3). Although no direct effect of alcohol dosage on AAE rate was observed, a higher amount of alcohol was associated with higher CK-MB levels. Furthermore, caliber of the target septal perforator(s) and left ventricular wall thickness (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. In **CHAPTER 9**, a maximum CK-MB level >240 IU/L was found to predict periprocedural (<30 days) AAEs in a cohort of 844 ASA patients (HR 7.5). After censoring of these patients, larger infarcts were not found to be predictive of long-term SCD risk however.

In **CHAPTER 6** we reported on the largest multinational ASA registry (Euro-ASA registry), which was conducted to determine predictors of long-term outcome following ASA. A total of 1275 patients were included who underwent ASA in one of 10 European tertiary centers between 1996 and 2015. The 30-day mortality was 1%, similar to the periprocedural mortality rates following ASA and myectomy in our meta-analysis. Survival estimates at 1, 5 and 10 years were 98%, 89%, and 77%, respectively. Remarkably, this means that the 10-year survival rates of the largest ASA and largest myectomy cohort to date are identical (Schaff et al.[10] reported a 10-year survival of 77% in 749 patients operated on at the Mayo Clinic). Baseline predictors of mortality were higher age, New York Heart Association (NYHA) class, and septal thickness. The volume of alcohol used for ASA was found to be a predictor of LVOT reduction, and was associated with a higher incidence of complete heart block. Reduction of the LVOT gradient was found to be of particular importance since it was an independent predictor of survival and symptom relief at last follow-up. On the other hand, a (transient) periprocedural complete heart block resulted in permanent pacemaker implantation in one-third of patients (12% of all patients). Based on these findings, ASA alcohol volumes ranging between 1.5 mL and 2.5 mL were deemed well balanced in terms of efficacy and safety for most patients.

Expanding the indication

One of the reasons why the updated guidelines on the management of HCM are not shared between America and Europe like they were in 2003 (11), is that the ASA versus myectomy debate is predominantly a trans-Atlantic one. The 2011 American College of Cardiology Foundation(ACCF)/American Heart Association (AHA) guidelines state that surgical myectomy is the gold standard for treatment of medical therapy resistant obstructive HCM, and that ASA should be reserved for elderly patients or patients with serious comorbidities, not suitable for surgery (12). The 2014 European Society of Cardiology (ESC) guidelines do not make this distinction (13).

In **CHAPTERS 7 & 8** we set out to describe outcomes of ASA in younger HCM patients in cohorts of 217 and 1197 patients, respectively, divided by age. Young patients (≤55 and ≤50 years, respectively) were found to have 1) a favourable long-term survival following ASA; 2) a similar AAE rate, as compared to non obstructive (CHAPTER 7), middle-aged and elderly HCM patients (CHAPTER 8); 3) excellent symptom improvement at short-term (CHAPTER 7) and long-term (CHAPTER 8) follow-up; and 4) a markedly lower risk of procedure related atrioventricular conduction disturbances as compared to older patients. We therefore propose that the indication for ASA can be broadened to younger patients, as agreed upon by dr. Fifer (Harvard Medical School, Boston, Massachusetts) in his editorial of CHAPTER 8.

Adverse arrhythmic events

From 2011 the American and European HCM guidelines differentiated in their approach to SCD risk stratification. The 2011 ACCF/AHA guidelines continued the path of the 2003 ACC/ESC guidelines in using 5 conventional risk factors for SCD (a family history of SCD, maximal LVWT ≥30mm, unexplained syncope, non-sustained ventricular tachycardia [NSVT], and abnormal blood pressure response to exercise)(11,12). In 2014 the HCM Outcomes Investigators presented a novel risk prediction model (HCM Risk-SCD), which provided a calculated 5-year SCD risk using 4 of the conventional (family history of SCD, NSVT, maximal LVWT, and unexplained syncope) and 3 additional risk factors: age, left atrial diameter, and LVOT gradient (14). The model was internally validated using bootstrapping and incorporated in the ESC guidelines that same year (13).

We started by conducting the first external validation of the HCM Risk-SCD model **(15)**. The study population consisted of a consecutive cohort of 706 HCM patients without prior SCD event, from 2 tertiary referral centers. The C-statistic of the HCM Risk-SCD model was 0.69 (P = 0.008), which performed significantly better than the conventional risk factor

models based on the 2003 ACC/ESC guidelines (C-statistic 0.55; P = 0.3), and 2011 ACCF/AHA guidelines (C-statistic 0.60; P = 0.07).

The HCM Risk-SCD model has not been validated in patients with obstructive HCM who have undergone septal reduction therapy, and application of the model in these patients is therefore not recommended (13). **CHAPTER 9** reports on the first validation of the HCM Risk-SCD model in patients undergoing ASA for obstructive HCM. A total of 844 ASA patients from 6 European tertiary invasive centers were included. Again, we found the HCM Risk-SCD model to discriminate better between patients with high or low risk of SCD, as compared to the models proposed by the 2003 ACC/ESC and 2011 ACCF/AHA guidelines.

Future perspectives

Twenty years after the introduction of ASA, the arrhythmogenicity of the ablation scar appears to be overemphasized. Instead, the focus should be shifted towards how to lower the rate of reinterventions and pacemaker implantations following ASA, since in this area ASA still appears to be inferior to myectomy.

Kim et al. recently showed that 67% of American ASA centers had performed <10 procedures during a 9 year study period (16). The first step in improving outcomes of ASA is to confine septal reduction therapy to centers of excellence with high operator volumes, which is also recommended by both ACCF/AHA and ESC guidelines (12,13). After a patient is referred to a HCM center of excellence, the choice between ASA and myectomy should be discussed in a multidisciplinary heart team, consisting of an imaging cardiologist, an interventional cardiologist experienced with ASA, and a surgeon experienced with myectomy. Here, patient factors such as co-morbidities, anatomical features (e.g. septal anatomy, mitral valve abnormalities), and patient preference can be taken into account.

The ASA procedure should be guided using MCE. The use of this technique has proved to be useful by influencing the interventional strategy in 15-20% of cases, by either changing the target vessel or prompting the procedure to be aborted when remote parts of the myocardium light up. Also, it has improved the success rate of ASA despite lower infarct sizes (17,18). The latest innovation in ASA is three-dimensional MCE-guided ASA (19). With added accuracy and the ability to quantify the expected size of myocardial tissue affected by the ablation, this new technique has the potential to further improve the safety and effectivity of ASA. However, outcome studies on the use of three-dimensional MCE have yet to be conducted. Finally, use of the appropriate amount of alcohol for ASA is of importance, which may reduce the rate of pacemaker implantations following ASA. Also, reducing the amount of alcohol for ASA results in smaller infarcts,

which in turn may reduce periprocedural AAEs. Since most dedicated ASA centers show a trend of decreasing amounts of alcohol over the years, future studies may show improved outcomes following ASA.

We reported on favourable outcomes following ASA in younger patients with obstructive HCM and proposed to broaden the ACCF/AHA indication for ASA to younger patients. In the future, we might consider to take it another step further. Since the outcome of ASA in mildly symptomatic patients is not known, current guidelines recommend ASA only in highly symptomatic patients (NYHA III/IV)(12,13). However, recent data has suggested a significant impact of LVOT obstruction on long-term outcome in patients with HCM, independent of symptoms (20). This finding is important, especially in light of the ≤1% ASA-related mortality reported in CHAPTERS 4 & 6, with an enduring effect on LVOT obstruction and associated symptoms following the procedure. In a recent study **(21)**, we found that carefully selected, mildly symptomatic HCM patients (NYHA II) with severe LVOT obstruction treated with ASA in dedicated centers have long-term prognosis comparable with that of the age- and sex- matched general population. Furthermore, these patients were at minimal risk for developing severe heart failure and most of them achieve long-term functional class NYHA I and LVOT gradient ≤30 mmHg. Although the cohort was relatively small (n = 161), these results challenge the established clinical standard of treating only highly symptomatic obstructive HCM patients with ASA.

We validated the HCM Risk-SCD model for the prediction of SCD in patients with HCM and patients with obstructive HCM undergoing ASA. The HCM Risk-SCD model is far from perfect, however. To improve the performance of the model it is conceivable that additional risk factors may be added in the future. The use of contrast cardiac magnetic resonance imaging (CMRI) with late gadolinium enhancement (LGE) for quantification of myocardial fibrosis has received considerable attention in recent years, but was not independently linked to SCD until recently. Around the time that the 2014 ESC guidelines were published, a large multicenter study of 1293 HCM patients reported LGE to be an independent predictor for SCD with a continuous relationship between the extent of LGE and risk of SCD (a 40% increase in SCD risk per 10% increase in LGE)(22). A subsequent meta-analysis which included 5 additional studies confirmed a correlation between the presence of LGE and risk of SCD but not between the extent of LGE and SCD (23). Although LGE is a good tool for detecting focal myocardial fibrosis, detection of diffuse fibrosis remains challenging, since normal myocardium is required as a reference. A promising new CMRI technique is T1 mapping, which unlike LGE, does not rely upon nulling techniques and allows for fibrosis identification even in the absence of gadolinium

administration. Several investigators have begun to look at T1 mapping within HCM (24,25). However, no prognostic studies with T1 mapping have been conducted yet. Genetics is another domain with the potential to enter SCD risk stratification. Patients with multiple sarcomere gene mutations have been shown to be at an increased risk of end-stage progression and SCD (26,27). With next-generation sequencing it will be possible to screen for a larger number of culprit genes, which may lead to identification of more patients carrying mutations that can be useful for SCD risk stratification. Finally, as the SCD event rate is low in these patients, multicenter collaborations at a larger scale will likely be mandatory to optimize future SCD risk prediction models.

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