Catheter Ablation for Atrial Fibrillation in Hypertrophic Cardiomyopathy: A Systematic Review and Meta-analysis

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Abstract

Objective: Atrial fibrillation (AF) is common in hypertrophic cardiomyopathy (HCM) and is associated with a high risk of stroke. The efficacy and safety of catheter ablation in this setting is poorly characterised. We aimed to systematically review the existing literature and to perform a meta-analysis to determine the efficacy and safety of catheter ablation of AF in patients with HCM.

Methods: Random-effects meta-analysis of studies comparing HCM vs. non-HCM controls. The outcomes of freedom from AF/atrial tachycardia, and acute procedure-related complications were assessed. Studies were searched on MEDLINE, EMBASE, COCHRANE and clinicaltrials.gov.

Results: Fourteen studies were considered eligible for the systematic review, of which five were included in the meta-analysis. Freedom from AF/atrial tachycardia relapse was higher in non-HCM patients (after a single procedure: 38.7% HCM vs. 49.8% controls, OR=2.25, 95%CI 1.09-4.64, P=0.03; after ≥1 procedure: 51.8% HCM vs. 71.2% controls, OR=2.62, 95%CI 1.52-4.51, P=0.0006; I^2=33% and 26%, respectively). Risk of procedural-related adverse events was low. Repeat procedures (mean difference=0.16, 95%CI 0.0-0.32, P=0.05, I^2=53%) and anti-arrhythmic drugs (OR=4.70, 95%CI 2.31-9.55, P<0.0001, I^2=0%) are more frequently needed in HCM patients to prevent arrhythmia relapse. Sensitivity analyses suggested that the outcome in HCM patients with less dilated atria and paroxysmal AF may be more comparable to the general population.

Conclusions*:* The observed complication rate of catheter ablation of AF in patients with HCM was low. Even though the risk of relapse is two-fold higher, catheter ablation can be effective in patients with HCM and AF, particularly in patients with paroxysmal AF and smaller atria.

Keywords: hypertrophy; left atrial dilation; fibrosis; pulmonary veins; sinus rhythm.

Background

Hypertrophic cardiomyopathy (HCM) is the most frequent monogenic cardiovascular disease affecting 1 out of every 500 individuals in the general population [1]. Atrial fibrillation (AF) is the most common arrhythmia in patients with HCM with a prevalence and annual incidence 22.5% and 3.1%, respectively [2]. New-onset AF is often associated with heart failure symptoms [3] and requires prompt treatment with direct current cardioversion in haemodynamically unstable patients or ventricular rate control with oral ß-blockers or non-dihydropyridine calcium channel antagonists followed by elective cardioversion [4]. There are no randomized controlled trials examining the effect of anti-arrhythmic drugs on long-term prevention of AF in patients with HCM and results in observational studies are conflicting [5-7]. Similarly, studies assessing the impact of catheter ablation of AF in patients with HCM are sparse and provide contradictory results. The joint *Heart Rhythm Society / European Heart Rhythm Association / European Cardiac Arrhythmia Society* expert consensus statement on catheter ablation suggests that registries could facilitate the collection of more robust information on the safety and efficacy of AF ablation in the setting of less common underlying conditions, such as HCM [8].

The aim of this study is to systematically review the existing literature and to perform a meta-analysis of observational studies to determine the efficacy and safety of catheter ablation of AF in patients with HCM.

Methods

I – Study Selection

We performed a search in the databases MEDLINE, EMBASE and COCHRANE (from inception to the 7th July 2015) using the following search string: “catheter ablation” AND “hypertrophic cardiomyopathy” AND “atrial fibrillation”. Reference lists of all accessed full-text articles were searched for sources of potentially relevant information. Ongoing studies assessing the outcomes of catheter ablation of AF in patients with HCM were searched on ClinicalTrials.gov, and experts in the field were contacted to ensure that all important studies had been included. Authors of full-text papers and congress abstract authors were also contacted by email to retrieve additional information.

The population, intervention, comparison and outcome (PICO) approach was used for conducting the meta-analysis [9]. The population of interest included patients with HCM and the intervention was catheter ablation of AF. Comparisons were performed between HCM and controls (patients without HCM undergoing catheter ablation of AF). The outcomes were midterm procedural success, need of anti-arrhythmic drugs after successful ablation, number of catheter ablation procedures, and procedural complications.

Procedural success was defined as freedom from AF or atrial tachycardia relapse, with ECG documentation, after a blanking period. Procedural complications included in the analysis were thromboembolic events (including stroke and transient ischemic attack), pericardial tamponade requiring pericardiocentesis or pericardial effusion causing hemodynamic imbalance and necessitating prolonged monitoring, pulmonary vein (PV) stenosis, atrio-esophageal fistula and procedure-related death occurring in the first 30 days post-procedure.

To meet inclusion criteria, studies were required to provide information on age, gender, and AF type (i.e. paroxysmal, persistent or permanent).

Studies providing no information regarding follow-up duration, and number of events in each group were excluded. Similarly, studies consisting of catheter ablation of the atrioventricular node or surgical ablation, and conference abstracts not published as full-text articles in the five years following to presentation were not examined. Studies presenting data in HCM patients

but not in controls were included in the systematic review, but excluded from the meta-analysis.

Search results were reviewed and consensus reached by three investigators (RP, KP, and GB) to ensure that all studies met the pre-specified inclusion criteria.

Study quality was formally evaluated using a modified Newcastle–Ottawa Quality Assessment Scale for Cohort Studies [10] by three reviewers (RP, KB and NS). An agreement between these three reviewers was mandatory for the final classification of studies.

II – Data Extraction

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the PRISMA group [11]. From each study, we retrieved study design, study population characteristics (age range, gender and AF type, mitral regurgitation, left ventricular outflow tract obstruction, previous myectomy or septal ablation), follow-up duration, lesion set used in the ablation procedure, definition of relapse, post-procedural monitoring, use of anti-arrhythmic agents after blanking, predictors of relapse, midterm outcomes, and procedural complications

III - Statistical analysis

Data were pooled using random-effects according to the Mantel-Haenszel model (Review Manager, RevMan, Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). A random-effects model was chosen for more precisely addressing different effect sizes and non-uniform variation across studies.

Comparisons between HCM and non-HCM patients were performed using odds ratio (OR), or mean difference when appropriate, and respective 95% confidence intervals were shown. Outcomes were maintenance of sinus rhythm after one catheter ablation procedure, or after one or more catheter ablation procedures, number of ablation procedures, need of anti-arrhythmic drugs following a successful ablation, and procedural complications. Weights of each study in forest-plots were calculated using the inverse variance method. Sensitivity analyses were performed excluding data from studies published only as conference abstracts for left atrial size, prevalence of individuals with persistent AF and left atrial size (comparison of studies below vs. above median level for the last two scenarios).

Statistical heterogeneity on each outcome of interest was assessed and quantified using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance. Values below 25%, between 25% and 50% and higher than 50% are, by convention, classified as low, moderate, and high degrees of heterogeneity, respectively [12].

Funnel plots and meta-regression analyses were not performed as part of the assessment for the presence of publication bias, and possible association of baseline differences with modulator variables in procedural outcomes, respectively, as comparisons involved less than 10 studies, which is the minimum number for assuring the appropriateness of these methods [13].

Results

I. Search Results

A total of 209 entries were retrieved for analysis of titles and abstracts. Of these, 177 were excluded as they were either duplicates or deemed unsuitable for the purpose of the meta-analysis (editorials, letters, reviews or case reports). The remaining 32 studies were carefully

screened and after analysis of their abstracts and/or full-text only [14-27] (one was a conference abstract [22]) were considered adequate for inclusion in the systematic review (Figure 1). Of these, only six studies [16, 19, 22-25] provided enough details to be included in the meta-analysis. There was full agreement between investigators (RP, KP and GB) on the inclusion of the selected studies.

II. Baseline Data: Patients with HCM undergoing catheter ablation of AF

The design of selected investigations and baseline data are summarized in Tables 1 and 2. The final population of the systematic review included 403 patients with HCM; 139 patients with HCM and 393 controls were included in the meta-analysis. All included studies were observational and nonrandomised, and only 5 were prospective [16, 17, 20, 21, 25]. Four studies were multi-centre [14, 15, 18, 21].

Quality assessment of the included studies is shown on Table 3. Study quality was modest, with only two studies [16, 23] being assigned 7 out of 9 possible points with the Newcastle-Ottawa scale.

The median HCM cohort size was 27 patients (IQR 22-39.5). Only one observational study included more than 50 patients with HCM [18]. In the 6 studies included in the meta-analysis, treatment groups were balanced for all baseline variables (Tables 1 and 2). Diagnosis of HCM was mostly based on the *American College of Cardiology Foundation* (ACCF) and *European Society of Cardiology* consensus [28], the recent ACCF/*American Heart Association* guidelines [29], or other preceding documents [30-33]. One study had genotype information in 11 patients [18] and one provided no diagnostic criteria for diagnosing HCM [22].

Median age was 57 years (IQR 54-59). Women accounted for the minority of the HCM patients, with a median prevalence of 30% (interquartile range – IQR - 26-33%). Persistent AF was the

most common AF type in seven studies [19-21, 23-26]. The median prevalence of non-paroxysmal AF was 53% (IQR 37-69%) (Table 1).

In studies reporting time since AF diagnosis [14-18, 20,21, 23, 26, 27], the median duration was 5.9 years (IQR 4.0-6.9). Median left atrial size was 47mm (IQR 46-51mm) and median maximum left ventricular thickness was 18mm (IQR 18-21mm). Only 9 studies reported on mitral regurgitation, and this was reported as moderate in 7 to 36% of patients in 6 out of the 9 studies reporting on this variable. The presence of left ventricular outflow tract obstruction at baseline and previous myectomy or alcohol septal ablation were reported in 11 [14-20, 23-26] and 6 studies [14-16, 18, 19, 22, 24, 26] respectively, and had a median prevalence of 24% (IQR 20-37.5%) and 14.5% (IQR 1.8-28.8%) (Table 1).

III. Procedural data

All AF ablation procedures consisted of PV isolation and used radiofrequency as the energy source. In two studies [14, 15], the PVs were the only targeted structures, but in the remainder ablation lines were created in the left atrium and/or right atrium, or lesions deployed to terminate atrial tachycardias (Table 2). Ostial PV isolation was performed in two publications [17, 20], while in the remainder further ablation was performed in a more antral location. In three studies, complex atrial fractionated electrogram ablation was also performed [19-21].

IV. Procedural outcomes

The median follow-up was 1.8 years (IQR 1.05-3.30 years). Except for three studies [14, 15, 25], mean follow-up duration was greater than one year (Table 4). In two studies, mean/median follow-up was greater than 3 years [18, 21]. Definition of relapse and monitoring post-ablation across all studies are described in Table 5.

In four studies, freedom from AF (no documentation of further AF episodes after ablation) at the end of follow-up and after ≥ 1 procedure was 70% or greater [14, 15, 21, 23]. In two studies, this figure was 60% [16, 18] and in all remaining studies success rate was lower, in spite of several repeat ablation procedures.

Figure 2 illustrates freedom from arrhythmia in patients with HCM and controls. Control patients had no structural heart disease, except for left ventricular hypertrophy secondary to systemic hypertension in *Müssigbrodt* et al. [25], and in *Gaita et al.* valvular heart disease was observed in 10 patients and dilated cardiomyopathy in 6 [16]. Both after a single procedure and after ≥ 1 procedure, sinus rhythm maintenance was lower in HCM patients: 38.7% (36/93) HCM vs. 49.8% (148/297) controls, OR=2.25, 95%CI 1.09-4.64, P=0.03; 51.8% (72/139) HCM vs. 71.2% (280/393) controls, OR=2.62, 95%CI 1.52-4.51, P=0.0006, respectively. Heterogeneity was moderate for both comparisons: I^2=33% and 26%, respectively).

The median number of procedures was 1.4 (IQR 1.2-1.5) in HCM patients and 1.2 (IQR 1.2-1.3) in controls. A second or third ablation procedure was required in 25% to 50% of HCM patients in ten studies [14, 15, 17-21, 23-25]. Figure 3 illustrates the comparison of total number of procedures in controlled studies, showing that HCM patients underwent repeat procedures more often: mean difference=0.16, 95%CI 0.0-0.32, P=0.05, I^2=53%.

In two studies, patients remained in sinus rhythm free from anti-arrhythmic drugs [21], or these were used in only a minority of patients [22]. However, in the remaining studies, anti-arrhythmic agents were needed for optimisation of the rhythm control strategy in more than 25 to 50% of HCM patients. In controlled studies, chances of remaining on anti-arrhythmic drugs following a successful ablation were five-fold higher in HCM patients: OR=4.70, 95%CI 2.31-9.55, P<0.0001, I^2=0% (Figure 3). Of note, in some HCM patients these drugs were used because of concomitant ventricular arrhythmias.

V. Predictors of Procedural Success

Left atrial size was the most frequently identified predictor of procedural success [17, 18, 24-27). In two studies, persistent AF was also associated with worse procedural outcomes (OR=7.7, 95%CI 1.13-50, P=0.02 [20] and OR=2.58, 95%CI 1.11-6.05, P=0.028 [21]). Other predictors of relapse were identified separately in single studies: age and NYHA class [18], left atrial pressure and left ventricle outflow tract obstruction [24], AF duration in months and E/E' [25], and QTc duration [27] (Table 4).

VI. Sensitivity Analyses

Sensitivity analysis after excluding results published as a conference abstract [22] confirmed that frequency of sinus rhythm maintenance after one or more catheter ablation procedures was two-fold higher in non-HCM patients: HCM 52.9% (63/119) vs. Controls 71.1% (248/349); OR=2.52, 95%CI 1.28-4.93, P=0.007, I^2=39% (Figure S-1 – Supplementary Material).

Pooling of studies including less than ≤53% (median % of persistent AF) of subjects with persistent AF displayed a higher relapse rate in HCM patients: HCM 61.9% (39/63) vs. Controls 76.2% (99/130); OR=2.05, 95%CI 1.05-4.01, P=0.04, I^2=0%. However, data from studies with >53% of patients with persistent AF showed a even higher relapse rate in HCM patients (HCM 43.4% (33/76) vs. Controls 76.7% (181/263); OR = 3.46, 95%CI 1.22-9.78, P=0.02, I^2=58%), suggesting that persistent AF is associated with a lack of procedural success (Figures S-2.A and S-2.B, Supplementary Material).

Similarly, a sensitivity analysis for left atrial size showed that studies with more severely dilated left atria (≥47mm, the median LA diameter in the HCM cohort) presented with higher relapse rate in HCM patients [HCM 45.0% (27/60) vs. Controls 64.5% (189/293); OR=3.52, 95%CI 1.16-10.67, P=0.03, I^2=62%], whereas pooling of studies with less pronounced degrees of left atrial dilation produced neutral results [HCM 66.7% (26/39) vs. Controls 78.6% (44/56);

OR=1.51, 95%CI 0.57-3.98, P=0.41, I^2=0%], suggesting comparable success rate in HCM patients to the normal population when the left atrium is not excessively dilated (Figures S-3.A and S-3.B, Supplementary Material).

Funnel-plots and meta-regression were not performed, as only 6 entries were eligible for the meta-analysis.

VII. Complications of AF ablation

While six studies reported no major complications, thromboembolic complications without permanent sequels occurred in two studies [17, 20] (Table 5). PV stenosis was reported in three entries, ranging from 3.0% [17] and 4.5% [25] to 4.8% [15]. *Contreras-Valdes* and colleagues reported that HCM patients may have longer post-ablation hospitalisation and higher readmission rate at 30 days, at the expense of heart failure and congestive symptoms [24].

Due to the low incidence of major complications, no forest-plots could be created as no comparisons were possible between HCM and controls.

Discussion

This systematic review demonstrates that the success rate of AF ablation is lower in patients with HCM than in patients without HCM with an overall efficacy of AF ablation in HCM at least 50% lower than in controls for ≥1 procedure. The need for repeat procedures and maintenance of anti-arrhythmic drugs are frequent. Left atrial size and AF type were the most frequently identified predictors of procedural success. HCM patients also underwent ablation late in the course of their disease (median of 5.9 years after the diagnosis of atrial arrhythmias) with non-paroxysmal AF being present in at least 50% of patients in half of the included studies. Therefore, by the time of the first procedure patients were likely to have a greater

degree of electrophysiological and structural remodelling which further increases the chances of failure. Furthermore, a significant proportion had mitral regurgitation and left ventricular outflow obstruction, promoting atrial stretching, which can shorten the effective atrial refractory period, increasing the dispersion of repolarisation thus potentiating the ability of ectopic triggers to maintain AF [34, 35]. Indeed, it is this diastolic dysfunction which results in the marked deterioration in clinical status with the transition to AF and loss of atrial transport contributing to the cardiac output [36].

Given these major factors limiting success, it is remarkable that after a median of 1.4 procedures, the success rate is 52%. These data would suggest that if AF can be treated earlier in the natural history of the disease before it becomes established, then the success rates may be higher but this has to be balanced against the degree of left atrial dilation on initial presentation and degree of mitral regurgitation and LV diastolic dysfunction affecting the likelihood of at least medium-term success. Indeed the challenge remains to identify those patients who are most likely to benefit from ablation in the context of their HCM status and disease course. The high use of long term anti-arrhythmic drugs highlights the fact that on-going remodelling limits the efficacy of ablation but should not be seen as a “failure” of the procedure since an combined treatment approach may be successful in these complex patients.

A number of structural and mechanistic factors further impact on the success rates of AF ablation in HCM. HCM patients have a high prevalence of atrial fibrosis, which may serve as a substrate for slow conduction and intra-atrial reentry, thereby playing a crucial role in the development and maintenance of AF [37, 38]. Sarcomeric gene mutations account for 60% of HCM cases. The β-MHC missense mutation Arg663His has been associated with an increased risk of AF in HCM patients with 47% Arg663His carriers developing AF over a seven-year follow-up period [39]. Polymorphisms in the angiotensin receptor gene have also been implicated in

the development of AF in HCM [40]. Anatomic variations in left atrial thickness have been suggested [24]. However, preliminary data from *Hayashi* et al using computed tomography to measure left atrial thickness in a small sample of patients indicate that left atrial wall in HCM is no thicker than in matched patients without structural heart disease [23].

Abnormal calcium handling is a recognized pathophysiological mechanism in HCM and could account for triggered activity (from delayed after depolarisations) precipitating AF in the pro-arrhythmic myocardial tissue architecture [41].

Myocardial ischemia [42] and autonomic dysfunction [43] are two other factors that have been previously suggested as relevant triggers of AF, and may make AF ablation more difficult in the context of HCM.

Clearly, understanding the pathophysiology of AF in HCM and identifying predictors of relapse remain important to improve overall procedural outcomes. *Santangelli* et al. have suggested that these patients present with frequent non-PV triggers, which may be responsible for late recurrences [21]. These authors have favoured extensive ablation beyond PV isolation. However, as we demonstrate in this review a consensus on the optimal approach for AF ablation in HCM patients remains elusive. It is unclear if performing PV isolation and targeting sustained atrial tachycardias is superior to employing a more aggressive approach with extensive lesion sets including lines, targeting complex fractionated electrograms and non-PV triggers in both atria. This is particularly important as even the optimal strategy to identify these sites and their relevance in procedural outcomes is contentious [44]. Furthermore, the optimal energy source to utilise is also not clear as all studies in this review have been performed using radiofrequency ablation. A randomized controlled trial to address this matter would be of interest.

Although the incidence of major complications was low and comparable to the general population, cases of PV stenosis, most of them asymptomatic, have been noted (ranging from 3 to 4.8%). In two reports these occurred in the setting of non-ostial PV isolation [15, 25]. As pulmonary venogram was not routinely performed in all cases we cannot report on the prevalence of this complication and this reflects the Registry data in the general AF ablation populations as asymptomatic PV stenosis is not reported routinely [45].

Given the small numbers of patients in all included studies, it is unclear if the apparently high rate of PV stenosis truly reflects a higher risk in this population or if it is a product of small sample sizes in the reporting studies [15]. It has been suggested by *Killicaslan* et al. that patients with HCM might be prone to more exaggerated hypertrophic tissue responses leading to tissue stenosis [15]. This is yet to be confirmed, but it may also be a contributory factor for more frequent gap formation and PV reconnection in the HCM population. The possible increase in PV stenosis in this subset of patients warrants clarification, and the electrophysiologist performing cases in these patients should be aware of this potential complication and try to deliver lesions as far away as possible from the PVs.

Two systematic reviews on the role of catheter ablation of AF in HCM patients have been recently published [46, 47]. However, unlike these, where the overall success rate of the procedure is reported, ours is the first meta-analysis with a case-control design. This is of importance, as it is the first paper allowing comparisons between HCM patients vs. other patients undergoing AF ablation, providing a better understanding of the true effectiveness of the catheter ablation in this setting. As included studies in the aforementioned systematic reviews [46, 47] span for almost a decade, simply pooling the success rates in those cohorts of HCM patients without having any control group/comparator, makes the pooled odds ratio impossible to interpret.

Limitations

There are some limitations to this meta-analysis. First, there is a paucity of data and studies allowing the comparison of HCM and non-HCM patients. As a result of the included small number of studies and patients this analysis has low power. However, these data are able to demonstrate differences in outcomes of catheter ablation of AF in HCM and non-HCM patients. Second, the rate of HCM patients to controls differs across studies. Third, moderate to high heterogeneity was observed across the included studies. A careful analysis of Figures 2 and 3, shows that the rate of relapse and number of redo procedures in HCM patients stands out as higher in the cohort published by McCready et al. [19]. This can be attributable to the fact that all patients in that study had persistent AF, and in most circumstances this was longstanding persistent. Lastly, data quality was modest, with no data derived from randomised controlled trials or large registries. The abovementioned factors suggest that the reliability of the estimated effect sizes may be sub-optimal.

Conclusions

Data regarding catheter ablation of AF in the HCM population is scarce and of modest quality. The observed complication rate was low. Although outcomes seem less favourable than for the general population, with a two-fold higher risk of relapse, more frequent need of repeat procedures and concomitant use of anti-arrhythmic drugs, ablation can be a valuable option for symptomatic drug-refractory HCM patients, particularly in those with paroxysmal AF and smaller atria.

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Figure 1 – Study selection diagram

Legend: HCM – hypertrophic cardiomyopathy.

Figure 2 – Forest plots comparing procedural outcomes (freedom from AF/AT relapse) of catheter ablation of atrial fibrillation in patients with and without hypertrophic cardiomyopathy.

Legend: AF – atrial fibrillation, AT – atrial tachycardia, HCM – hypertrophic cardiomyopathy.

Figure 3 – Forest plots comparing number of ablation procedures (upper panel) and need of AADs following a successful ablation procedure in HCM patients vs. controls.

Legend: AADs – anti-arrhythmic drugs; HCM – hypertrophic cardiomyopathy.

Table 1 – Study design and sample characteristics.

Author, Year	Study Design	Number of HCM and control patients Diagnosis of HCM	Age (years)	♀	Non-paroxysmal AF	AF duration (years)	LA size	LVT (mm)	% mitral regurgitation	LVOT obstruction	Previous myectomy or septal ablation
Liu et al 2005 [14]	Retrospective Multicentre (2 Centr.)	4 HOCM pts based on echocardiographic criteria [31]	58±8	50% (2)	0% (0)	8±8.5	46±9mm	27±5	N.A.	100% (4)	0% (0)
Kilicaslan et al 2006 [15]	Retrospective Multicentre (4 Centr.)	27 primary HCM pts according to ACCF/ESC Consensus [29]	55±10	30% (8)	48% (13)	5.4±3.6	50±9mm 170±48ml	17±5	Grade 1-2: 67% (18) Grade 3-4: 7% (2)	At rest – 44.4% (12) Provoked – 37.0% (10)	19% (5)
Gaita et al 2007 [16]	Prospective Cohort Single-centre	26 pts with HCM based on TTE (LV ≥13 to 15mm) ±family history and absence of other cardiac or systemic disease Controls: 52 pts	58±11	31% (8)	50% (13)	7.3±6.2	52±6mm 70±26ml/m²	23±4	mild: 69% (18) moderate: 12% (3)	At rest – 23% (6)	19% (5)
Bunch et al 2008 [17]	Prospective Single-centre	33 HCM pts Diagnosis criteria – Guidelines / specialised clinic (Mayo)	51±11	24% (8)	36% (12)	6.2±5.2	51±7mm 140ml (125-180)	N.A.	Mild-moderate: 21%(7)	At rest – 24% (8)	N.A.
Di Donna et al 2010 [18]	Retrospective Multicentre (2 Centr.)	61 pts with HCM based on TTE (LV ≥13 to 15mm) and absence of other cardiac or systemic disease. Genotype available in 11 pts	54±13	28% (17)	43% (26)	5.7±5.5	52±5mm 180±40ml	20±5	Mild: 50% (28) Moderate: 36% (22)	At rest – 20% (12)	10% (6)
McCready et al 2011 [19]	Retrospective Cohort Single-centre	14 HCM pts - according to ACCF/ESC Consensus [29] 177 controls	58±13	21% (40)	100% (191)	N.A.	47±7mm	17±4	Mild: 14.3% (2) Moderate: 7.1% (1)	28.6% (4)	N.A.
Derejko et al 2013 [20]	Prospective observational	30 HCM pts according to ACCF/ESC Consensus [29]	49±11	33% (10)	53% (16)	6±4.2	51±7mm	21±6	N.A.	20% (6)	7% (2)
Santangeli et al 2013 [21]	Prospective Multicentre (8 Centr.)	43 HCM pts according to ACCF/ESC Consensus [29]	59±8	33% (14)	72% (31)	Median 3.0, IQR 4.3	47±8mm	20±4	N.A.	N.A.	N.A.
Yan et al 2013 [22]	Retrospective Cohort Single-centre	25 HCM pts Diagnosis criteria – N.A. 50 controls	53±8 54±8	24% (6) 24% (12)	36% (9) 40% (20)	N.A.	47±8mm	N.A.	N.A.	N.A.	N.A.
Hayashi et al 2014 [23]	Retrospective Cohort Single-centre	17 HCM pts based on TTE (LV ≥15mm) and absence of other cardiac or systemic disease [32, 33] 34 controls	63±12 66±9	29% (5)	53% (9)	3.5±3.5 4.1±3.7	46±7mm	19±4	Moderate or severe 18% (3) 9% (3)	23.5% (4)	41% (7)
Contreras-Valdes et al 2015 [24]	Retrospective Cohort Single-centre	40 HCM pts according to the ACCF/AHA guidelines [30] 64 controls	54±7	30% (12)	68% (27) 70% (45)	N.A.	N.A.	18±3	N.A.	37.5% (15)	N.A.
Müssigbrodt et al 2015 [25]	Prospective Cohort Single-centre	22 HCM based on TTE (LV ≥15mm) ± LVOT obstruction and absence of other cardiac or systemic disease [34] 22 pts with secondary cardiac hypertrophy	57±8 63±10	32% (7) 36% (8)	55% (12) 55% (12)	N.A.	46±8mm	19±4	Significant: 14% (3) 0% (0)	36% (8)	32% (7)
Okamatsu et al 2015 [26]	Retrospective Single-centre	22 HCM pts based on the presence of myocardial hypertrophy and absence of local or systemic aetiology	65±11	55% (12)	77%(17)	6.7±4.4	48±6mm 98±38ml	13±4	≥moderate: 23% (5)	14% (3)	N.A.
Wen et al 2015 [27]	Retrospective Single-centre	39 HCM pts according to ACCF/AHA guidelines [30] and ESC [29]	54±10	26% (10)	31% (12)	5.8±5.6	46±7mm	20±4	Mild: 26% (10)	N.A.	0% (0)
Total or Median (Quartiles)		Systematic Review – 403 HCM pts Meta-analysis – 139 HCM pts vs. 393 controls Median HCM cohort size 27 (22-39.5)	57 (54-59)	30% (26-33%)	53% (37-69%)	5.9 (4.0-6.9)	47mm (46-51)	20 (18-21)	N.A.	24% (20-37.5%)	14.5% (1.8-28.8%)

Legend: Legend: pts – patients; HCM – hypertrophic cardiomyopathy; HOCM – hypertrophic obstructive cardiomyopathy; AF – atrial fibrillation; ESC – European Society of Cardiology; ACC or ACCF – American College of Cardiology Foundation; American Heart Association; LV – left ventricle; LVT – left ventricle thickness; LA – left atrium; LVOT – left ventricle outflow tract; TTE – transthoracic echocardiogram; N.A. – not available.

Table 2 – Procedural aspects and use of anti-arrhythmic drugs.

Author, Year	Ablation Procedure	Number of Procedures	Use of AADs after blanking
Liu et al 2005 [14]	PVI	1.3 2nd procedure: 25% (1)	Oral amiodarone in one patient (25%) to prevent AT relapses after 2nd procedure.
Kilicaslan et al 2006 [15]	PVI	1.3 2ndprocedure: 25.9% (7)	5 of 13 pts (38.5%) with relapse after the 1st procedure remained in SR on AADs 1 out of 2 pts with relapse after the 2nd procedure remained in SR on AADs
Gaita et al 2007 [16]	PVI + roof line + mitral isthmus	1.2 2ndprocedure: 19.2% (5)	10 of 16 pts (62.5%) in SR were off AADs
Bunch et al 2008 [17]	Ostial PVI in 15 pts + roof line and mitral isthmus in 7 pts WACA + roof line and mitral isthmus in 18 pts	1.4 2nd procedure: 39% (13)	Of the 78% pts in SR at 1 year, 14% were under AADs Of the 74% pts in SR at 3 years, 27% were under AADs
Di Donna et al 2010 [18]	PVI + roof line + mitral isthmus + CTI (under fluoroscopic guidance in 15 pts)	1.5 2nd procedure: 52%	11 of 17 pts (64.7%) in SR after the 1st procedure were on AADs 11 of 24 pts (45.8%) in SR after the 2nd procedure were on AADs
McCready et al 2011 [19]	PVI ± roof line, mitral isthmus and CFAE ablation at the discretion of the operator	HCM 1.5; Controls 1.3 2nd procedure: 71.4% (10) HCM 3rd procedure: 14.3% (2) HCM 4th procedure: 7.1% (1) HCM	The 2 HCM pts in SR after catheter ablation were on AADs
Derejko et al 2013 [20]	Ostial PVI + CTI line ± mitral isthmus, roof line and CFAE ablation at the discretion of the operator	1.4 2nd procedure: 43% (13)	16 patients with no AF/AT relapse at 12 months were under AADs and these were stopped in 5 pts.
Santangeli et al 2013 [21]	All pts: PVI + posterior wall isolation between PVs. + SVC isolation Persistent AF: + all posterior wall (CS and left side of septum) + CFAE (LA and CS) Redo: + non-PV triggers	1.6±0.7 2nd procedure: 58% (25) (all pts with recurrence)	91% of pts in SR at 12 months, but only 76% off ADDs.
Yan et al 2013 [22]	PVI ± roof line, mitral isthmus or CTI line	1.1	8 of 9 HCM pts (88.9%) were free from AF recurrence without AADs
Hayashi et al 2014 [23]	PVI + roof line + posterior inferior line +CTI ± mitral isthmus, if persistent AF	HCM 1.5; Controls 1.4 2nd procedure: 47%(8)HCM 35%(12) controls (P=0.87)	AADs used more frequently in HCM patients (47% vs. 12%, P=0.008)
Contreras-Valdes et al 2015 [24]	PVI Ablation of sustained organized AT	HCM 1.3±0.5 Controls 1.2±0.4 (P=0.7)	Chronic AADs in 45% HCM vs. 18.8% controls (P=0.007)
Müssigbrodt et al 2015 [25]	PVI ± roof line, septal line and CTI line	HCM 1.4, Controls 1.1 2nd procedure: 5 HCM pts vs. 3 controls. 3rd procedure: 3 HCM pts (p=0.045)	6 of 22 (27%) HCM treated with AADs vs. none in non-HCM group (p=0.008)
Okamatsu et al 2015 [26]	PVI ± CTI	1.1 2nd procedure: 3 HCM pts	15 (68%) pts used concomitant AADs
Wen et al 2015 [27]	Paroxysmal AF: PVI + CTI (if documentation of typical flutter) Persistent AF: + roof line, mitral isthmus and CTI	1.0	N.A.

Legend: pts – patients; HCM – hypertrophic cardiomyopathy; AF – atrial fibrillation; PV – pulmonary vein; CS – coronary sinus; LA – left atrium; CTI – cavotricuspid isthmus; AADs – anti-arrhythmic drugs; PVI – to be interpreted as wide antral circumferential ablation, unless stated ostial PVI; WACA – wide antral circumferential ablation; CFAE – complex fractionated atrial electrograms; SR – sinus rhythm; N.A. – not available.

Table 3 – Study classification: Newcastle-Ottawa scale for cohort studies.

Article	Newcastle-Ottawa Quality Assessment*
Gaita et al 2007 [16]	7
McCready et al 2011 [19]	6
Yan et al 2013 [24]	6
Hayashi et al 2014 [23]	7
Contreras-Valdes et al 2015 [24]	5
Müssigbrodt et al 2015 [25]	5

Legend: * from 0 to 9 points.

Table 4 – Midterm procedural results and predictors of procedural failure

Author, Year	FUP Duration (years) mean±SD or median (IQR)	Predictors of Relapse	Midterm Procedural Results
Liu et al 2005 [14]	0.5±0.2	N.A.	All patients (4/4) were free from recurrence.
Kilicaslan et al 2006 [15]	0.9±0.6	N.A.	52% (14/27) remained in SR after the first procedure; after ≥ 1 procedure this rose to 70% (19/27).
Gaita et al 2007 [16]	1.6±0.8	N.A.	58% (15/26) of HCM pts remained in SR after the first procedure; this rose to 62% (16/26) after ≥1 procedure vs. 65% (17/26) of secondary LVH and 77% (20/26) of idiopathic AF pts.
Bunch et al 2008 [17]	1.5±1.2	***Uni:*** LA dilation	Maintenance of SR free from AADs was 64% (95%CI 58-72%) at 1 year and 47% (36-58%) at 3 years.
Di Donna et al 2010 [18]	Total FUP: 3.3±0.7 Post-last proced: 2.4±1.3	***Uni***: Older age (>50 years), atrial size >130mL and NYHA ≥III ***Multi***: LA volume (HR=1.009, 95%CI 1.001-1.018, P=0.037) NYHA (HR=2.24, 95%CI 1.16-4.35, P=0.016)	67% (41/61) were in SR following ≥1 procedure.
McCready et al 2011 [19]	1.1+0.7	N.A.	Only 14% (2/14) of HCM patients were free from recurrence, one after one procedures and the other requiring two ablation procedures.
Derejko et al 2013 [20]	1.9±1.2	***Uni***: non-paroxysmal AF ***Multi***: non-paroxysmal (OR=7.7, 95%CI 1.13-50, P=0.02)	First procedure success rate was 33% (10/30), and increased to 53% (16/30) after ≥1 procedure.
Santangeli et al 2013 [21]	3.5 (3.2-4.0) Post-last proced: 1.3(0.7-1.6)	***Uni***: longstanding persistent AF (OR=2.58, 95%CI 1.11-6.05, P=0.028)	Long-term success rate after a single procedure was 49% and after ≥1 procedure 94%.
Yan et al 2013 [22]	3.3±1.2	N.A.	SR in 45% (9/20) HCM vs. 72% (32/44) controls after ≥ 1 procedure (P=0.032)
Hayashi et al 2014 [23]	2.2±1.2	N.A.	SR in 53% (9/17) HCM vs. 56% (19/34) controls after 1 procedure (log rank P=0.78) and SR in 82% (14/17) HCM vs. 88% (30/34) controls after ≥1 procedure (log rank P=0.35).
Contreras-Valdes et al 2015 [24]	Median: 4.5 HCM 1.8-2.3 Controls 2.9-5.6	***Uni***: LA pressure ≥12mmHg (HR=3.1, 95%CI 1.4-7.1, P=0.005) and dilated LA (HR=1.06, 95%1.003/1.11 per mm; P=0.04) ***Multi***: LVOT obstruction (HR=4.3, 95%CI 1.6-11.4, P=0.0007)	42.5% HCM vs. 70.3% controls remained in SR at 1-year after a single procedure (P=0.005); after a redo procedure this changed to 45% HCM vs. 75% controls (P=0.001). At the end of FUP 35% of HCM vs. 67.2% of controls (P=0.001) remained in SR after a single procedure; after a redo procedure this increased to 47.5% vs. 73.4% (P=0.005).
Müssigbrodt et al 2015 [25]	HCM: 0.9±1.3 Controls: 1.4±0.6	LA > 45mm in HCM pts (p=0.041) but not in controls.	After 1st procedure: SR in 41% (9/22) HCM vs. 50% (11/22) controls (NS), but earlier relapses in HCM (Mantel Cox P=0.015). After the last procedure, 54% (12/22) HCM vs. 64% (14/22) controls (NS and Mantel Cox P=0.121).
Okamatsu et al 2015 [26]	1.8±1.0	***Uni***: duration of AF in months, E/E', LA volume and LA diameter. ***Multi***: E/E' (HR=1.16, 95%1.01-1.37, P=0.03)	SR in 59% (13/22).
Wen et al 2015 [27]	Mean: 1.2	***Uni***: LA diameter, QTc ***Multi***: LA diameter (HR =1.072, 95%CI 1.004-1.145, P=0.038), longer QTc (HR=1.02, 1.004-1.036,P=0.013); every 10ms (HR 1.227, 95%CI 1.053/1.431, P=0.009)	41% (16/39) remained in SR.

Legend: pts – patients; HCM – hypertrophic cardiomyopathy; AF – atrial fibrillation; proced. – procedure; Uni – univariate analysis; multi – multivariate analysis; LA – left atrium; SR – sinus rhythm; N.A. – not available.

Table 5 – complications and monitoring

Author, Year	Definition of relapse	Monitoring for AF/AT relapse	Procedural-related complications
Liu et al 2005 [14]	Any episode of AF, regardless of duration, was considered as arrhythmia recurrence.	ECG, 24-h Holter and echocardiography 1, 3, 6 and 9 months after ablation. Monthly telephone interviews. 3 pts had a telemetric ECG recorder for 6 months. 2 patients had device interrogation.	**Major:** None
Kilicaslan et al 2006 [15]	Recurrences were based upon patient reporting and rhythm transmitter, Holter and/or ECG data.	Outpatients clinic at 3, 6, 12 months and 6 months thereafter. Rhythm transmitter used in the first 3 months (extra 3 months if early recurrence). 48-h Holter recording at 3, 6 and 12 months.	**Major:** Asymptomatic PV stenosis: < 50% in 2 pts (7%) and 50-69% in 2 pts (7%)
Gaita et al 2007 [16]	Any documented recurrence of AF based on ECG recordings after 4 weeks of blanking.	Clinical evaluation, 12-lead ECG, echocardiogram and 24-h Holter monitor at 1, 3, 6, 12 months and every 6 months thereafter.	**Major:** none Mild pericardial effusion in 5 pts (21.7%).
Bunch et al 2008 [17]	AF elimination if no documented AF episodes in the absence of AADs. AF control if remaining in SR without relapse while on AADs.	Telephone contact, clinic follow-up visits and/or communication with referring physician. ECGs and 24-h Holter in subsequent clinical visits.	**Major:** 2 pts had a periprocedural TIA and 1 pt developed a symptomatic PV stenosis.
Di Donna et al 2010 [18]	Recurrence of AF, atrial tachycardia or atrial flutter lasting more than 3 min.	Pts followed at 1, 3, 6, and 12 months with ECG, echocardiography and 24-h Holter and every 6 months thereafter through telephone contact, clinic follow-up visits and communication with the referring physician.	**Major:** none 5 (8%) pts developed mild non-haemodynamic comprising pericardial effusion.
McCready et al 2011 [19]	Episode of AF or atrial tachycardia >30 s documented on Holter monitoring or any 12-lead ECG documentation after initial 3 months blanking (on or off AADs)	12-lead ECGs, Holter monitoring for 1–7 days, and pacemaker/implantable cardioverter-defibrillator interrogation (where available)	**Major:** cardiac tamponade in 1 pt (7.1%)
Derejko et al 2013 [20]	Recurrence of AF, atrial flutter or atrial tachycardia lasting more than 3 min, after the initial 3 months documented on ECG or EGM.	Clinical appointment, ECG and Holter at 4 weeks and then every 3-6 months. 8 pts underwent 2 weeks of continuous ECG monitoring.	**Major:** Stroke resolving without sequel after a redo procedure.
Santangeli et al 2013 [21]	Any episode of AF/atrial tachycardia lasting for ≥30s after initial 3 months blanking.	Physical examination, ECG and 7-day Holter monitoring at 3, 6, 9 and 12 months. Event recorder in the first 5 months.	**Major:** none
Yan et al 2013 [22]	N.A.	N.A.	**Major:** none
Hayashi et al 2014 [23]	Episode of AF or atrial tachycardia lasting for more than 30 seconds after the 3-month blanking period.	Outpatient clinic with ECG every month for the first 12 months and every 2-3 months thereafter. Cardiac event recorder used twice a day for 30s x2 during the first 4 months. A 24-h Holter monitor 3 months after the procedure and every 12 months thereafter.	**Major:** none
Contreras-Valdes et al 2015 [24]	Recurrent arrhythmia (AF or AT) after initial 3-month blanking	N.A.	**Complications:** Rare Median hospitalization was longer in HCM 2 (1-6) vs. 1 (1-3), P<0.0001. Longer readmission rate at 30 days in HCM 25% vs. 1.6%, P<0.0003 (HF and congestive symptoms)
Müssigbrodt et al 2015 [25]	Documented episodes of sustained (>30s) AF or atrial flutter after a 3-month blanking period.	7-day Holter recordings during 6, 12 and 24 month follow-up visits. Interrogation of implantable cardiac devices.	**Major**: PV stenosis requiring balloon dilation in 1 HCM pt.
Okamatsu et al 2015 [26]	Recurrence of AF lasting > 1 min, following a 2-month blanking period.	Clinical review, ECG and 24-h Holter every 1-3 months.	N.A.
Wen et al 2015 [27]	Episode of documented atrial tachyarrhythmia lasting at least 30s after 3-month blanking period.	ECG, 24-h Holter at 1, 3, 6 and 12 months and every 6 months thereafter. Phone interviews.	N.A.

Legend: pts – patients; HCM – hypertrophic cardiomyopathy; AF – atrial fibrillation; AT – atrial tachycardia; Uni – univariate analysis; multi – multivariate analysis; LA – left atrium; SR – sinus rhythm; N.A. – not available.