ORIGINAL ARTICLE

Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis

Rui Providencia,[1] Perry Elliott,[1,2] Kiran Patel,[2] Jack McCready,[3] Girish Babu,[1] Neil Srinivasan,[1,2] Kostantinos Bronis,[1] Nikolaos Papageorgiou,[1,2] Anthony Chow,[1] Edward Rowland,[1] Martin Lowe,[1] Oliver R Segal,[1] Pier D Lambiase[1,2]

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[1]Barts Heart Centre, Barts Health NHS Trust, London, UK
[2]Institute of Cardiovascular Science, University College of London, London, United Kingdom
[3]Cardiology Department, Royal Sussex County Hospital, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK

Correspondence to
Dr Pier D Lambiase, Professor of Cardiology, Institute of Cardiovascular Science, University College of London, Barts Heart Centre, Barts Health NHS Trust, West Smithfield, London EC1A 7BE, UK; pierlambiase@hotmail.com

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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 versus 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 patients without HCM (after a single procedure: 38.7% HCM vs 49.8% controls, OR=2.25, 95% CI 1.09 to 4.64, p=0.03; after ≥1 procedure: 51.8% HCM vs 71.2% controls, OR=2.62, 95% CI 1.52 to 4.51, p=0.0006; I^2=33% and 26%, respectively). Risk of procedure-related adverse events was low. Repeat procedures (mean difference=0.16, 95% CI 0.0 to 0.32, p=0.05, I^2=53%) and antiarrhythmic drugs (OR=4.70, 95% CI 2.31 to 9.55, p<0.0001, I^2=0%) are more frequently needed in patients with HCM to prevent arrhythmia relapse. Sensitivity analyses suggested that the outcome in patients with HCM 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 twofold higher, catheter ablation can be effective in patients with HCM and AF, particularly in patients with paroxysmal AF and smaller atria.

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 randomised controlled trials examining the effect of antiarrhythmic drugs on long-term prevention of AF in patients with HCM and the encouraging results in observational studies which took place decades ago[5–7] are conflicting with our daily practice, as antiarrhythmic agents are frequently ineffective in eradicating arrhythmias. 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

Study selection

We performed a search in the databases MEDLINE, EMBASE and COCHRANE (from inception to 7 July 2015) using the following search string: 'catheter ablation' AND 'HCM' AND 'AF'. 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 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 mid-term procedural success, need of antiarrhythmic 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 ischaemic attack), pericardial tamponade requiring pericardiocentesis or pericardial effusion causing haemodynamic imbalance and necessitating prolonged monitoring, pulmonary vein (PV) stenosis, atrio-oesophageal 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 (ie, 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 5 years following presentation were not examined. Studies presenting data in patients with HCM 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 prespecified 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.

Data extraction

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (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, postprocedural monitoring, use of antiarrhythmic agents after blanking, predictors of relapse, mid-term outcomes and procedural complications.

Statistical analysis

Data were pooled using random-effects according to the Mantel–Haenszel model (Review Manager, RevMan, V.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 patients with HCM and patients without HCM were performed using OR, or mean difference when appropriate, and respective 95% CIs 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 antiarrhythmic 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

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.

Baseline data: patients with HCM undergoing catheter ablation of AF

The design of selected investigations and baseline data are summarised 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 non-randomised, and only five were prospective.[16 17 20 21 25] Four studies were multicentre.[14 15 18 21]

Quality assessment of the included studies is shown in 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 six 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,[34] the recent ACCF/American Heart Association guidelines,[29] or other preceding documents.[28 30–32] 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 patients with HCM, with a median prevalence of 30% (IQR 26%–33%). Persistent AF was the most common AF type in seven studies.[19 20 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 47 mm (IQR 46–51 mm) and median maximum left ventricular thickness was 18 mm (IQR 18–21 mm). Only

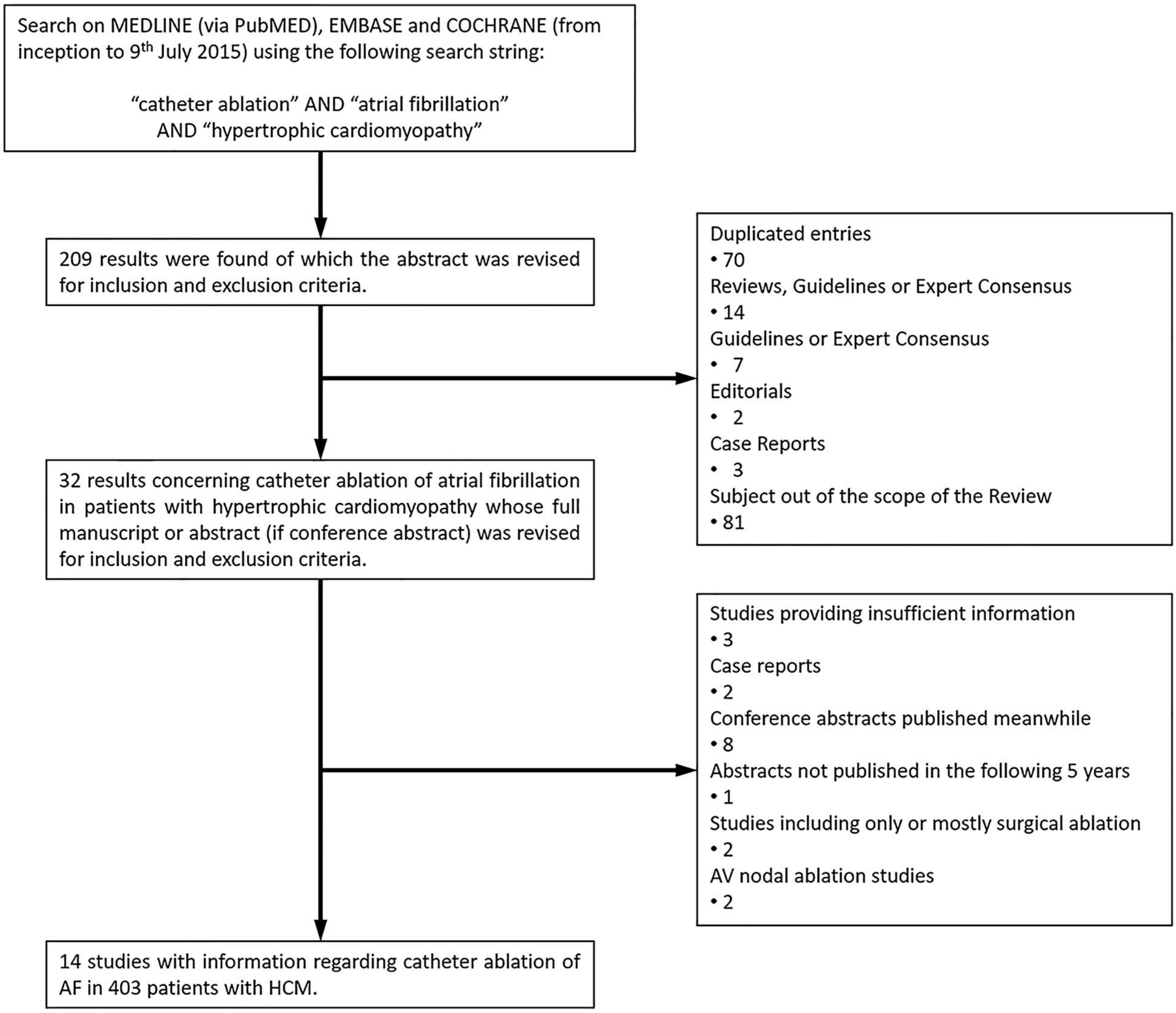

Figure 1 Study selection diagram. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy.

nine studies reported on mitral regurgitation, and this was reported as moderate in 7%–36% of patients in six out of the nine 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).

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 (LA) 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]

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 >1 year (table 4). In two studies, mean/median follow-up was >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%.[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*[16] valvular heart disease was observed in 10 patients and dilated cardiomyopathy in 6. Both after a single procedure and after ≥1 procedure, sinus rhythm maintenance was lower in patients with HCM: 38.7% (36/93) HCM vs 49.8% (148/297) controls, OR=2.25, 95% CI 1.09 to 4.64, p=0.03; 51.8% (72/139) HCM vs 71.2% (280/393) controls, OR=2.62, 95% CI 1.52 to 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 patients with HCM and 1.2 (IQR 1.2–1.3) in controls. A second or third ablation procedure was required in 25%–50% of patients with HCM in 10 studies.[14 15 17–21 23 25] Figure 3 illustrates the comparison of the total number of procedures in

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 (two centres)	4 patients with HOCM based on echocardiographic criteria[28]	58±8	50% (2)	0% (0)	8±8.5	46±9 mm	27±5	N.A.	100% (4)	0% (0)
Kilicaslan *et al* (2006)[15]	Retrospective Multicentre (four centres)	27 patients with primary HCM according to ACCF/ESC consensus[29]	55±10	30% (8)	48% (13)	5.4±3.6	50±9 mm 170±48 mL	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 patients with HCM based on TTE (LV ≥13 to 15 mm) ±family history and absence of other cardiac or systemic disease Controls: 52 patients	58±11	31% (8)	50% (13)	7.3±6.2	52±6 mm 70±26 mL/m^2	23±4	Mild: 69% (18) Moderate: 12% (3)	At rest—23% (6)	19% (5)
Bunch *et al* (2008)[17]	Prospective Single-centre	33 patients with HCM Diagnosis criteria—guidelines/specialised clinic (Mayo)	51±11	24% (8)	36% (12)	6.2±5.2	51±7 mm 140 mL (125–180)	N.A.	Mild–moderate: 21% (7)	At rest—24% (8)	N.A.
Di Donna *et al* (2010)[18]	Retrospective Multicentre (two centres)	61 patients with HCM based on TTE (LV ≥13 to 15 mm) and absence of other cardiac or systemic disease Genotype available in 11 patients	54±13	28% (17)	43% (26)	5.7±5.5	52±5 mm 180±40 mL	20±5	Mild: 50% (28) Moderate: 36% (22)	At rest—20% (12)	10% (6)
McCready *et al* (2011)[19]	Retrospective Cohort Single-centre	14 patients with HCM—according to ACCF/ESC consensus[29] 177 controls	58±13	21% (40)	100% (191)	N.A.	47±7 mm	17±4	Mild: 14.3% (2) Moderate: 7.1% (1)	28.6% (4)	N.A.
Derejko *et al* (2013)[20]	Prospective observational	30 patients with HCM according to ACCF/ESC consensus[29]	49±11	33% (10)	53% (16)	6±4.2	51±7 mm	21±6	N.A.	20% (6)	7% (2)
Santangeli *et al* (2013)[21]	Prospective Multicentre (eight centres)	43 patients with HCM according to ACCF/ESC consensus[29]	59±8	33% (14)	72% (31)	Median 3.0, IQR 4.3	47±8 mm	20±4	N.A.	N.A.	N.A.
Yan *et al* (2013)[22]	Retrospective Cohort Single-centre	25 patients with HCM Diagnosis criteria—N.A. 50 controls	53±8 54±8	24% (6) 24% (12)	36% (9) 40% (20)	N.A.	47±8 mm	N.A.	N.A.	N.A.	N.A.
Hayashi *et al* (2014)[23]	Retrospective Cohort Single-centre	17 patients with HCM based on TTE (LV ≥15 mm) and absence of other cardiac or systemic disease[30 31] 34 controls	63±12 66±9	29% (5)	53% (9)	3.5±3.5 4.1±3.7	46±7 mm	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 patients with HCM according to the ACCF/AHA guidelines[32] 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 patients with HCM based on TTE (LV ≥15mm) ± LVOT obstruction and absence of other cardiac or systemic disease[33] 22 patients with secondary cardiac hypertrophy	57±8 63±10	32% (7) 36% (8)	55% (12) 55% (12)	N.A.	46±8 mm	19±4	Significant: 14% (3) 0% (0)	36% (8)	32% (7)
Okamatsu *et al* (2015)[26]	Retrospective Single-centre	22 patients with HCM 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±6 mm 98±38 mL	13±4	Greater than or equal to moderate: 23% (5)	14% (3)	N.A.

Continued

Table 1 Continued

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
Wen *et al* (2015)[27]	Retrospective Single-centre	39 patients with HCM according to ACCF/AHA guidelines[32] and ESC[29]	54±10	26% (10)	31% (12)	5.8±5.6	46±7 mm	20±4	Mild: 26% (10)	N.A.	0% (0)
Total or median (quartiles)		Systematic review—403 patients with HCM Meta-analysis—139 patients with HCM 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)	47 mm (46–51)	20 (18–21)	N.A.	24% (20%–37.5%)	14.5% (1.8%–28.8%)

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

controlled studies, showing that patients with HCM underwent repeat procedures more often: mean difference=0.16, 95% CI 0.0 to 0.32, p=0.05, I^2=53%.

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

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 to 50, p=0.02[20] and OR=2.58, 95% CI 1.11 to 6.05, p=0.028[21]). Other predictors of relapse were identified separately in single studies: age and New York Heart Association (NYHA) class,[18] left atrial pressure and left ventricle (LV) outflow tract obstruction,[24] AF duration in months and E/E′,[25] and corrected QT interval (QTc) duration[27] (table 4).

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 twofold higher in patients without HCM: HCM 52.9% (63/119) versus controls 71.1% (248/349); OR=2.52, 95% CI 1.28 to 4.93, p=0.007, I^2=39% (see online supplementary figure S1).

Pooling of studies including ≤53% (median % of persistent AF) of subjects with persistent AF displayed a higher relapse rate in patients with HCM: HCM 61.9% (39/63) versus controls 76.2% (99/130); OR=2.05, 95% CI 1.05 to 4.01, p=0.04, I^2=0%. However, data from studies with >53% of patients with persistent AF showed an even higher relapse rate in patients with HCM (HCM 43.4% (33/76) versus controls 76.7% (181/263); OR=3.46, 95% CI 1.22 to 9.78, p=0.02, I^2=58%), suggesting that persistent AF is associated with a lack of procedural success (see online supplementary figures S2A and S2B).

Similarly, a sensitivity analysis for left atrial size showed that studies with more severely dilated left atria (≥47 mm, the median LA diameter in the HCM cohort) presented with higher relapse rate in patients with HCM (HCM 45.0% (27/60) versus controls 64.5% (189/293); OR=3.52, 95% CI 1.16 to 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) versus controls 78.6% (44/56); OR=1.51, 95% CI 0.57 to 3.98, p=0.41, I^2=0%), suggesting comparable success rate in patients with HCM to the normal population when the LA is not excessively dilated (see online supplementary figures S3A and S3B).

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

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 *et al* reported that patients with HCM may have longer postablation hospitalisation and higher readmission

Table 2 Procedural aspects and use of AADs

Author (year)	Ablation procedure	Number of procedures	Use of AADs after blanking
Liu *et al* (2005)[14]	PVI	1.3 Second procedure: 25% (1)	Oral amiodarone in one patient (25%) to prevent AT relapses after second procedure
Kilicaslan *et al* (2006)[15]	PVI	1.3 Second procedure: 25.9% (7)	5 of 13 patients (38.5%) with relapse after the first procedure remained in SR on AADs 1 out of 2 patients with relapse after the second procedure remained in SR on AADs
Gaita *et al* (2007)[16]	PVI+roof line+mitral isthmus	1.2 Second procedure: 19.2% (5)	10 of 16 patients (62.5%) in SR were off AADs
Bunch *et al* (2008)[17]	Ostial PVI in 15 patients+roof line and mitral isthmus in seven patients WACA+roof line and mitral isthmus in 18 patients	1.4 Second procedure: 39% (13)	Of the 78% patients in SR at 1 year, 14% were under AADs Of the 74% patients 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 patients)	1.5 Second procedure: 52%	11 of 17 patients (64.7%) in SR after the first procedure were on AADs 11 of 24 patients (45.8%) in SR after the second 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 Second procedure: 71.4% (10) HCM Third procedure: 14.3% (2) HCM Fourth procedure: 7.1% (1) HCM	The two patients with HCM 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 Second procedure: 43% (13)	16 patients with no AF/AT relapse at 12 months were under AADs and these were stopped in five patients
Santangeli *et al* (2013)[21]	All patients: 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 Second procedure: 58% (25) (All patients with recurrence)	91% of patients 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	Eight of nine patients with HCM (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 Second procedure: 47% (8) HCM, 35% (12) controls (p=0.87)	AADs used more frequently in patients with HCM (47% vs 12%, p=0.008)
Contreras-Valdes *et al* (2015)[24]	PVI Ablation of sustained organised 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 Second procedure: five patients with HCM vs three controls Third procedure: three patients with HCM (p=0.045)	6 of 22 (27%) patients with HCM treated with AADs vs none in non-HCM group (p=0.008)
Okamatsu *et al* (2015)[26]	PVI±CTI	1.1 Second procedure: three patients with HCM	15 (68%) patients 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.

AADs, antiarrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; CFAE, complex fractionated atrial electrograms; CS, coronary sinus; CTI, cavotricuspid isthmus; HCM, hypertrophic cardiomyopathy; LA, left atrium; N.A., not available; PVI, to be interpreted as wide antral circumferential ablation, unless stated ostial PVI; PV, pulmonary vein; SVC, superior vena cava; SR, sinus rhythm; WACA, wide antral circumferential ablation.

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 patients with 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 antiarrhythmic drugs is frequent. Left atrial size and AF type were the most frequently identified

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

Article (year)	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

*From 0 to 9 points.

Table 4 Mid-term procedural results and predictors of procedural failure

Author (year)	FUP duration (years) Mean±SD or median (IQR)	Predictors of relapse	Mid-term 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 patients with HCM remained in SR after the first procedure; this rose to 62% (16/26) after ≥1 procedure vs 65% (17/26) of patients with secondary LVH and 77% (20/26) with idiopathic AF
Bunch *et al* (2008)[17]	1.5±1.2	***Uni:*** LA dilation	Maintenance of SR free from AADs was 64% (95% CI 58% to 72%) at 1 year and 47% (36% to 58%) at 3 years
Di Donna *et al* (2010)[18]	Total FUP: 3.3±0.7 Post last procedure: 2.4±1.3	***Uni***: older age (>50 years), atrial size >130 mL and NYHA ≥III ***Multi***: LA volume (HR=1.009, 95% CI 1.001 to 1.018, p=0.037) NYHA (HR=2.24, 95% CI 1.16 to 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 patients with HCM were free from recurrence, one after one procedure 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 to 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 procedure: 1.3(0.7–1.6)	***Uni***: long-standing persistent AF (OR=2.58, 95% CI 1.11 to 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 one 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 ≥12 mm Hg (HR=3.1, 95% CI 1.4 to 7.1, p=0.005) and dilated LA (HR=1.06, 95%1.003 to 1.11 per mm; p=0.04) ***Multi***: LVOT obstruction (HR=4.3, 95% CI 1.6 to 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 >45 mm in patients with HCM (p=0.041) but not in controls	After first 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 to 1.145, p=0.038), longer QTc (HR=1.02, 1.004 to 1.036, p=0.013); every 10 min (HR 1.227, 95% CI 1.053 to 1.431, p=0.009)	41% (16/39) remained in SR

AADs, antiarrhythmic drugs; AF, atrial fibrillation; E/E′, The ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; FUP, follow-up; HCM, hypertrophic cardiomyopathy; LA, left atrium; LVH, left ventricular hypertrophy; LVOT, left ventricle outflow tract; Multi, multivariate analysis; N.A., not available; NS, non-significant; SD, standard deviation; SR, sinus rhythm; Uni, univariate analysis.

predictors of procedural success. Patients with HCM 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.[33 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.[3]

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 antiarrhythmic drugs highlights the fact that ongoing remodelling limits the efficacy of ablation but should not be seen as a 'failure' of the procedure since a combined treatment approach may be successful in these complex patients.

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. Three patients had a telemetric ECG recorder for 6 months. Two patients had device interrogation.	**Major:** none.
Kilicaslan *et al* (2006)[15]	Recurrences were based on patient reporting and rhythm transmitter, Holter and/or ECG data.	Outpatient clinic at 3, 6, 12 months and 6 months thereafter. Rhythm transmitter used in the first 3 months (extra 3 months if early recurrence). Forty-eight-hour Holter recording at 3, 6 and 12 months.	**Major:** asymptomatic PV stenosis: <50% in two patients (7%) and 50%–69% in two patients (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 five patients (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:** two patients had a periprocedural TIA and one developed a symptomatic PV stenosis.
Di Donna *et al* (2010)[18]	Recurrence of AF, AT or atrial flutter lasting >3 min.	Patients 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. Five (8%) patients developed mild non-haemodynamic comprising pericardial effusion.
McCready *et al* (2011)[19]	Episode of AF or AT >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 one patient (7.1%).
Derejko *et al* (2013)[20]	Recurrence of AF, atrial flutter or AT lasting >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. Eight patients 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/AT lasting for ≥30 s 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 AT lasting for >30 s 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 30 s ×2 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 hospitalisation 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 (>30 s) AF or atrial flutter after a 3-month blanking period.	7-day Holter recordings during 6-month, 12-month and 24-month follow-up visits. Interrogation of implantable cardiac devices.	**Major:** PV stenosis requiring balloon dilation in one patient with HCM.
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 30 s after a 3-month blanking period.	ECG, 24 h Holter at 1, 3, 6 and 12 months and every 6 months thereafter. Phone interviews.	N.A.

AADs, antiarrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; EGM, intracavitary electrograms; HCM, hypertrophic cardiomyopathy; HF, heart failure; N.A., not available; PV, pulmonary vein; SR, sinus rhythm; TIA, transient ischaemic attack.

A number of structural and mechanistic factors further impact on the success rates of AF ablation in HCM. Patients with HCM have a high prevalence of atrial fibrosis, which may serve as a substrate for slow conduction and intra-atrial re-entry, thereby playing a crucial role in the development and maintenance of AF.[36 37] Sarcomeric gene mutations account for 60% of HCM cases. The β-myosin heavy chain (MHC) missense mutation Arg663His has been associated with an increased risk of AF in patients with HCM with 47% Arg663His carriers developing AF over a 7-year follow-up period.[38] Polymorphisms in the angiotensin receptor gene have also been implicated in the development of AF in HCM.[39] Anatomical variations in left atrial thickness have been suggested.[24] However, preliminary data from Hayashi *et al*[23] using CT 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.

Abnormal calcium handling is a recognised pathophysiological mechanism in HCM and could account for triggered activity (from delayed after depolarisations) precipitating AF in the proarrhythmic myocardial tissue architecture.[40]

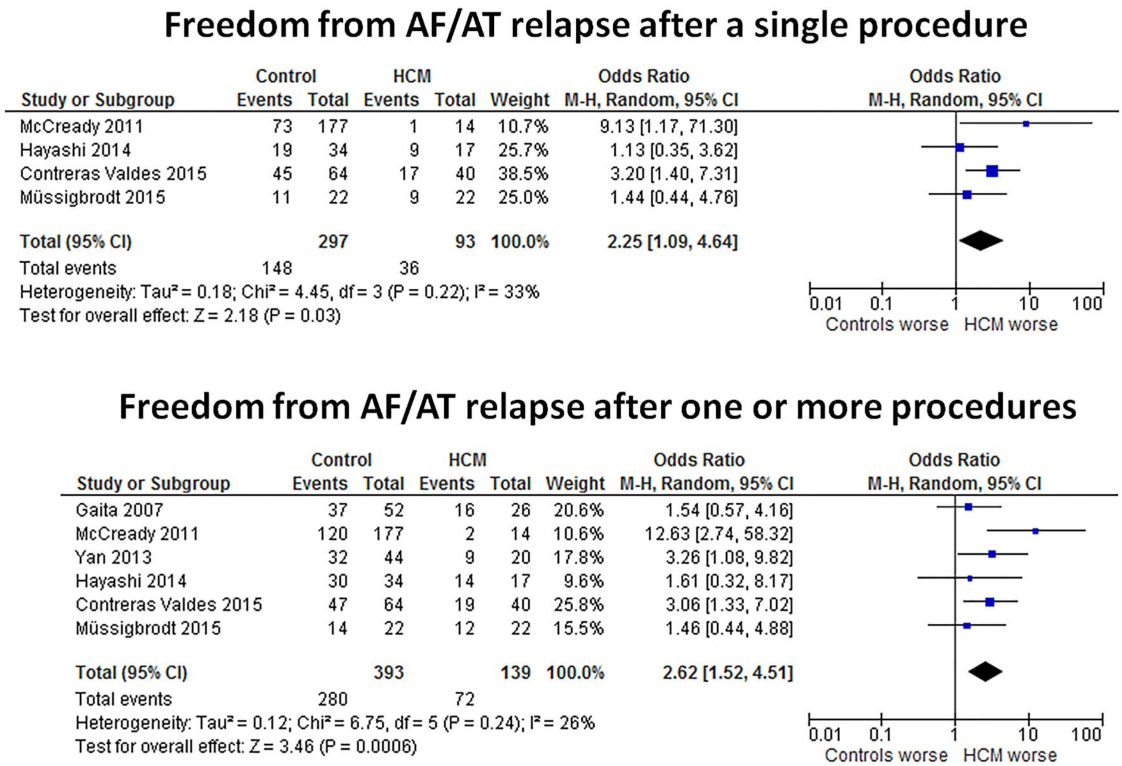

Figure 2 Forest plots comparing procedural outcomes (freedom from AF/AT relapse) of catheter ablation of AF in patients with and without HCM. AF, atrial fibrillation; AT, atrial tachycardia; HCM, hypertrophic cardiomyopathy.

Myocardial ischaemia[41] and autonomic dysfunction[42] 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. Santangeli *et al*[21] have suggested that these patients present with frequent non-PV

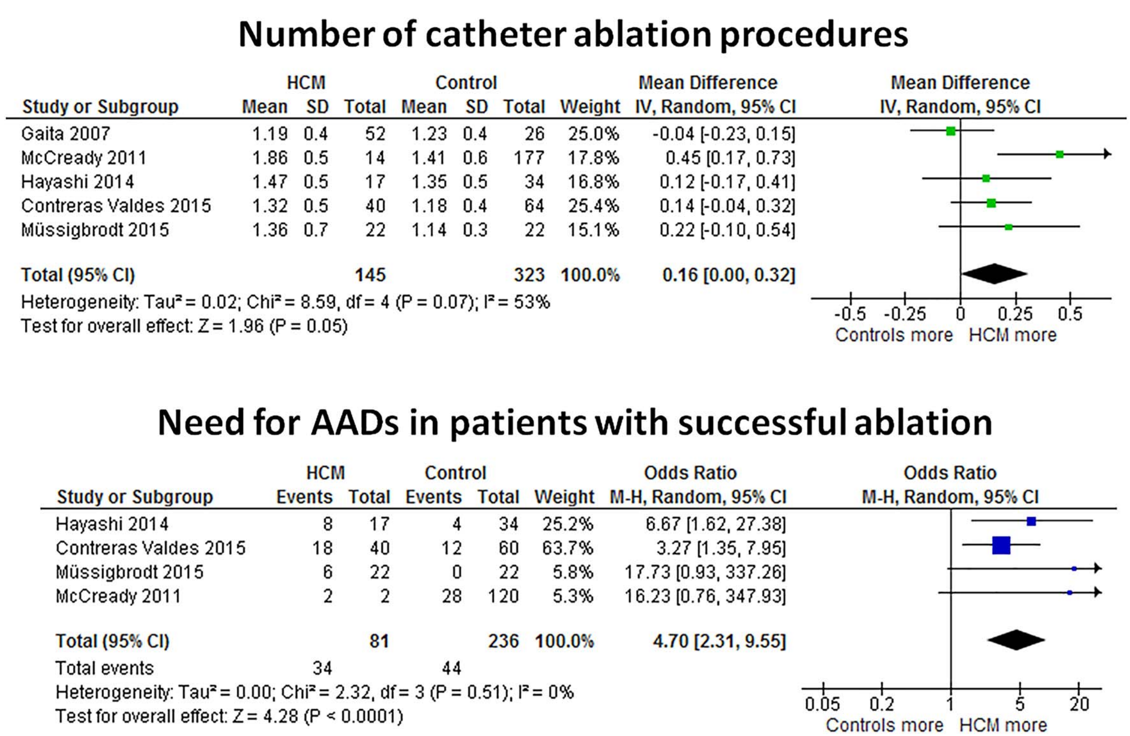

Figure 3 Forest plots comparing number of ablation procedures (upper panel) and need of AADs following a successful ablation procedure in patients with HCM versus controls. AADs, antiarrhythmic drugs; HCM, hypertrophic cardiomyopathy.

triggers, which may be responsible for late recurrences. 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 patients with HCM 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.[43] Furthermore, the optimal energy source to use is also not clear as all studies in this review have been performed using radiofrequency ablation. A randomised 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.[44]

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 Kilicaslan *et al*[15] that patients with HCM might be prone to more exaggerated hypertrophic tissue responses leading to tissue stenosis. 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 patients with HCM have been recently published.[45 46] 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 patients with HCM versus 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[45 46] span for almost a decade, simply pooling the success rates in those cohorts of patients with HCM without having any control group/comparator, makes the pooled OR 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 patients with HCM and patients without HCM. As a result of this (small number of included studies and patients) this analysis has low power. However, these data are able to demonstrate differences in outcomes of catheter ablation of AF in patients with HCM and patients without HCM. Second, the ratio of patients with HCM 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 patients with HCM 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 long-standing persistent. Lastly, data quality was modest, with no data derived from randomised controlled trials or large registries. The above-mentioned factors suggest that the reliability of the estimated effect sizes may be suboptimal.

CONCLUSIONS

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

Key messages

What is already known about this subject?

- Atrial fibrillation is a common finding in patients with hypertrophic cardiomyopathy, and anti-arrhythmic drugs are frequently not effective enough for a rhythm control strategy.

What does this study add?

- This meta-analysis confirms that catheter ablation can be a valuable option in patients with hypertrophic cardiomyopathy and atrial fibrillation.
- However, the overall success rate of an atrial fibrillation ablation procedure in patients with hypertrophic cardiomyopathy is worse than for the general population. Best candidates are patients with small atria and paroxysmal AF.

How might this impact on clinical practice?

- These results reinforce the role of appropriate patient selection and ideal timing of the procedure. Referral in early states of disease progression may optimize the chances of an effective rhythm control strategy.

Contributors RP and PDL planned this meta-analysis population, intervention, comparison and outcome (PICO) approach. RP and KP were responsible for data collection. GB, NS, KB and NP confirmed data collection, study selection criteria and performed study quality assessment. JM provided patient level data for one of the studies. RP performed the statistical analysis and wrote the first draft of the paper, which was thoroughly revised by PDL and PE, who provided important critical input. A new and revised version of the paper was prepared and sent to all authors, who provided suggestions and approval after the final version of the paper was written.

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