International Journal of Medicine and Medical Sciences. Vol. 1 (8), pp. 306-317, August, 2009.
Available online at http://www.academicjournals.org/ijmms

Full Length Research Paper

Efficacy and safety of curative catheter ablation for atrial fibrillation

Carlo Bonanno*, Mariemma Paccanaro, Luigi La Vecchia, Renato Ometto and Alessandro Fontanelli

Cardiology, S. Bortolo Hospital, Viale Rodolfi, 37 36100 Vicenza, Italy

Accepted 02 July, 2009

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. Its treatment is still widely debated due to the large variety of therapeutic options. Radiofrequency catheter ablation (RFCA) around pulmonary vein ostia and in left atrium has been proposed as a curative technique to treat AF and is now performed with increasing success worldwide. However, few randomised controlled trials (RCTs) are available. Some of these have been recently published and not yet included in meta-analyses. To address the efficacy and safety of RFCA for curative treatment of AF, we perform a systematic review, in order to provide a more precise estimate of post-procedural atrial tachyarrhythmias (ATs) recurrence, adverse effects and complications. Using electronic databases, we searched for RCTs comparing RFCA with anti-arrhythmic drugs for the management of AF. The efficacy end-point was freedom from ATs (including atrial fibrillation, atrial flutter and atrial tachycardia), following the procedure. The safety end-point was the rate complications and adverse events. The results are reported as relative risk (RR) and 95% confidence interval (CI), calculated using the RevMan software (The Cochrane Collaboration, Copenhagen, 2008). A total of 8 RCTs were identified, including 844 patients. Overall, 98 (23.2%) of 421 patients in the treatment group and 324 (76.6%) of 423 patients in the control group had ATs recurrence. Catheter ablation decreased ATs recurrence by 71% (RR = 0.29, 95% CI 0.20 to 0.41, $p<0.00001$, with random effects model). Fewer complications and adverse events were reported in the ablation group compared with the control group (RR = 0.72, 95% CI 0.40 to 1.30, $p=0.28$, with random effects model). In selected patients with AF, RFCA is a relatively efficacious and safe procedure for the curative treatment of AF. Even though the results of this systematic review favoUr ablation therapy, large, well-designed, multicenter RCTs are needed to confirm the efficacy and safety of RFCA for AF.

Key words: Atrial fibrillation, randomised controlled trials, radiofrequency catheter ablation, anti-arrhythmic drugs, meta-analysis.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with significant morbidity and mortality (Fuster et al., 2006). There are several therapies for the management of AF. Currently available approaches include anti-thrombotic treatment, and pharmacological or non-pharmacological control of heart rhythm or rate.

Although a strategy aiming at rhythm control with the use of anti-arrhythmic drugs or electrical cardioversion offers no survival advantage over a rate control strategy, retrospective analyses of major trials show that maintenance of sinus rhythm may be associated with improved survival (Corley et al., 2004) and quality of life (Hagens et al., 2004). In the AF follow-up investigation of rhythm management (AFFIRM) trial (Steinberg et al., 2004), deaths in the rhythm control arm exceeded those in the rate control arm, suggesting that adverse effects of anti-arrhythmic drugs may obscure the benefits of maintaining sinus rhythm. These results suggest that the presence of sinus rhythm but not anti-arrhythmic drugs use is associated with a lower risk of death. If an effective method for maintaining sinus rhythm with fewer adverse effects was available, it might improve survival. At

*Corresponding author. E-mail: cbonanno64@yahoo.it. Tel.: 0039 0444 75 3644. Fax: 0039 0444 75 3250.

present, rhythm control of AF is receiving a resurgence of attention. This is due to curative radiofrequency catheter ablation (RFCA). Current ablation techniques target susceptible atrial substrate, electrical triggers, and autonomic tone, factors that are considered to be important for the initiation and maintenance of AF. There are a variety of approaches reported for performing ablation procedures. Although there has been some convergence in techniques that considered the isolation of the pulmonary veins (PVs) a cornerstone for RFCA or AF, the technology used, the end-points of ablation, and intensity of patient follow-up continues to differ. Moreover, the literature provides little data comparing RFCA with other therapies for rhythm control strategy in AF, and whether a better rhythm control translates into reduced morbidity and mortality remains to be demonstrated and should be the objective of future large scale trials. Nowadays, patients considering ablation must be willing to undergo a prolonged procedure with associated risks, and signify-cant likelihood of AF recurrences (Calkins et al., 2007), but large randomised controlled trials (RCTs) are lacking till date. Four meta-analyses of available RCTs have been published (Gjesdal et al., 2008; Noheria et al., 2008; Rodgers et al., 2008; Nair et al., 2009), corroborating the effects of RFCA upon the maintenance of sinus rhythm, adverse events and complications. We performed this systematic review of RCTs (published up to May 2009) as an update: 2 additional trials (Khan et al., 2008; Forleo et al., 2009) have now been reported and we obtained further details on a study (Jaïs et al., 2008) included as abstract in previous meta-analyses and now available as full-text.

METHODS

Search strategy

We searched the medical literature through the following electronic resources: EJS E-Journals, Health Business Full-text Elite, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, MEDLINE, CINAHL, using a Web-based search engines (EBSCOhost and DynaMed Research Databases). Additionally, relevant studies were identified through a manual references search of initially identified articles and reviews. We did not apply any language restriction. Medical subject heading (MeSH) keywords included one or more of the following: random, control, blind, clinical trial, comparative-study, randomised-study combined with one or more of the following: atrial fibrillation, catheter ablation, radio frequency, pulmonary vein, and their combinations.

Study selection and inclusion criteria

To address the efficacy and safety of RFCA, we limited our analysis to RCTs that compared RFCA with either anti-arrhythmic drug therapy alone or combined with other treatment (including devices) for the management of AF. Types of participants were patients with symptomatic paroxysmal, persistent or long-standing persistent AF. RFCA approaches included segmental ostial pulmonary vein ablation (SOA), circumferential antral pulmonary vein ablation (CPVA), superior vena cava isolation, LA posterior wall ablation, interatrial septum ablation and “ligament of Marshall”. We also include ablation techniques preventing propagation of electrical wave through the atrium as “substrate modification”. We selected studies that followed patients for more than 3 months and reported at least one outcome of interest: recurrence of atrial tachyarrhythmias (ATs) (including AF/atrial flutter/atrial tachycardia) during the follow-up; time-to-recurrence of ATs following RFCA; and major complications and adverse events related to intervention, defined as those that result in death or permanent injury, require intervention for treatment, or prolong or require hospitalization. Studies not meeting these criteria were excluded. We considered the primary publication reference for each trial of interest. When multiple studies from a research group were eligible for inclusion, only the most recent or comprehensive study was used. Abstracts, unpublished and ongoing RCTs with reported data were excluded. One of us (CB) reviewed the titles and abstracts of the articles from the initial search and excluded those that did not meet the inclusion criteria. A consensus was reached on which articles should be completely reviewed for inclusion in the study.

Data collection and analysis

Two review authors (CB, MP) independently assessed the trials for eligibility and methodological quality without consideration of the results. Any disagreement was resolved by discussion with a third reviewer (RO). Trials were not assessed blindly, as we knew the author's name, institution and the source of publication. First, we assessed allocation concealment for each included trial using the Cochrane approach (Higgins et al., 2008): adequate (A), unclear (B), inadequate (C), not used (D). We did not include studies rated D. Second, a five-point scoring system (Jadad et al., 1996) was used to assess randomisation, double blinding, and reporting of withdrawals and dropouts. We only included studies with a score ≥ 3. In addition, the funding source and whether authors reported the use of an intention-to-treat analysis were noted. Decision rules regarding the application of the tool were developed a priori and discrepancies were resolved through discussion between the two reviewers.

The review authors extracted the data, checked them for discrepancies and processed them. We resolved any disagreement until a consensus was reached. Extracted data included study characteristics, inclusion/exclusion criteria, drug use, characteristics of participants, procedural data, and outcomes. Efficacy outcomes included recurrence of ATs (either electrophysiological or clinical) during the follow-up, and time-to-recurrence of ATs after RFCA. Rhythm monitoring was assessed during routine clinical follow-up, with daily or weekly brief electrocardiogram monitoring or with repeated Holter monitoring. Trials using more accurate diagnostic criteria for recurrent ATs, based on daily or weekly brief event monitoring, were taken into consideration. Safety outcomes included death, cardiac tamponade or pericardial effusion, transient ischemic attack or stroke, symptomatic or > 50% PVs stenosis, atrio-oesophageal perforation, vascular complications, phrenic nerve injury or other major events related to RFCA.

Numerical results were primarily meta-analysed in Review Manager (RevMan), version 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). We calculated relative risks (RRs) and 95% confidence intervals (CIs) for dichotomous data. Due to the differences expected between studies, we decided a priori to combine results primarily using random effects model; fixed effects models were considered in sensitivity analyses. To check for statistical evidence of heterogeneity among trial-specific RRs, a Chi-square (χ^2) test was used and it was quantified using the I^2 statistic (a value of 0% indicates limited heterogeneity, and larger values demonstrate increasing heterogeneity). Time-to-event data (that is recurrence of ATs were summarized by

ATs) were summarized by the log hazards ratio; Kaplan Meier curves were generated. An individual patient dataset for this analysis was constructed using summary monthly mortality tables in the trial manuscripts. A blanking period, where data about recurrence of ATs were not censored, was accepted, according to the study protocol of the included trials. The log rank test assessed for treatment group differences across curves. All results were reported with 95% CI where reasonable. Quantitative analyses were performed on an intention-to-treat basis and were confined to data derived from randomised follow-up period. Sensitivity analyses were performed to assess the importance of different statistical methods, individual trials, and missing data. We also used meta-regression analyses to identify causes of heterogeneity among the trials.

Finally, safety results were meta-analysed in Comprehensive Meta Analysis, version 2.2.046 (Biostat, Englewood, NJ, USA). Procedural risks of RFCA were reported by event and not by patient. Weighted event rates were simply pooled and all results were reported with 95% CI. Statistical heterogeneity was assessed using the χ^2 test; $p<0.05$ was considered heterogeneous.

RESULTS

Qualitative findings

Eight parallel RCTs provided relevant data and were found eligible for our meta-analysis (Krittayaphong et al., 2003; Wazni et al., 2005; Stabile et al., 2006; Oral et al., 2006; Pappone et al., 2006; Khan et al., 2008; Jaïs et al., 2008; Forleo et al., 2009). Table 1 summarizes the description of design, study population, primary and secondary end-points of the selected studies. In 3 studies (Stabile et al., 2006; Oral et al., 2006; Pappone et al., 2006), the active arm included patients treated with CPVA; in 5 studies (Krittayaphong et al., 2003; Wazni et al., 2005; Khan et al., 2008; Jaïs et al., 2008; Forleo et al., 2009) the patients were treated with SOA of the PVs as the major ablation technique end-point. Adjunctive ablation lines in right and left atrium and/or ablation of complex fractionated electrograms in left atrium were performed per protocol in all studies, except one (Wazni et al., 2005). All studies, except one (Krittayaphong et al., 2003), considered a blanking period from 1.5 to 3 months after ablation when reporting outcomes. All trials, but one (Khan et al., 2008), had the rate of ATs recurrence as primary end-point. Baseline patient characteristics of all trials are summarized in Table 2. The inclusion criteria were symptomatic paroxysmal or persistent AF. Two studies (Oral et al., 2006; Khan et al., 2008) included patients with long-standing persistent AF. Seven studies included patients with AF who had failed al least one or two anti-arrhythmic drugs or who were intolerant of anti-arrhythmic medications. One study (Wazni et al., 2005) only randomised patients to RFCA as first-line therapy. The majority of patients in each trial had absence of structural heart disease or heart disease with normal left ventricular systolic function. One trial (Khan et al., 2008) specifically evaluated the effects of RFCA in patients with left ventricular systolic dysfunction and another (Forleo et al., 2009) included only patients with diabetes.

Quantitative findings

There were 421 patients included in the RFCA arm, of whom 98 (23.2%) had ATs recurrence, while 423 patients were included in the control arm, of whom 324 (76.6%) had ATs recurrence during the follow-up. The mean age of the population ranged between 51 and 62 years. There was a history of symptomatic paroxysmal AF in 567 patients, and persistent or long-standing persistent AF in 278 patients. The follow-up ranged from 6 months to 1 year, depending on the trial. Table 3 summarises the results reported in the selected studies. In each trial there was a statistically significant reduction of ATs recurrence. When data from the 8 studies were pooled using a random effects model, RFCA resulted in a significant 71% RR reduction of ATs recurrence (RR 0.29; 95% CI 0.20 to 0.41, $p<0.00001$) (Figure 1). To test the differences in the RRs, we performed a χ^2 test for heterogeneity. By this measure, we found evidence of quantitative heterogeneity ($p=0.002$, χ^2 test; $I^2=69\%$). Using meta-regression with mean age of trial participants, percentage of men in each trial, percentage of patients with paroxysmal AF included in the trials, and method used in the trials to detect AF as predictor variables, there was no statistical evidence for heterogeneity due to men percentage ($p=0.08$), or method used for AF detection ($p=0.21$); a statistically significant test for heterogeneity was found for mean age ($p=0.01$), and percentage of patients with paroxysmal AF ($p=0.02$).

We performed sensitivity analyses to determine the plausible changes in assumption on the association between RFCA and relapse of ATs. First, we compared fixed effects and random effects statistical model. The two types of models yielded similar results. Second, we assessed the influence of individual trials on the pooled RR. With exclusion of individual trials, the point estimates changed very little and ranged from 0.26 to 0.32. With cumulative analysis, adding sequentially each individual trial, the point estimates changed from 0.21 to 0.33, without statistically significant differences. Therefore, no single study had major impact on the point estimates of pooled RR. Finally, we performed a “worst case” analysis, in which withdrawals from the ablation group were assumed to have arrhythmia and those from the comparison group were assumed to be free of arrhythmia. There were only 10 patients lost to follow-up across the studies; assuming that data from these patients would be unfavourable to ablation had no influence on the pooled estimate.

Six studies (Krittayaphong et al., 2003; Wazni et al., 2005; Stabile et al., 2006; Pappone et al., 2006; Jaïs et al., 2008; Forleo et al., 2009) with 610 patients reported adequate data to define freedom from arrhythmia at several follow-up points. The survival analysis indicated a significantly lower rate of ATs recurrence in the ablation group on the log-rank test ($p<0.0001$), with a 78% [standard error (SE) 2.4%] event-free for the ablation

Table 1. Description of studies included in the review.

1st Author Year Trial name	Design Follow-up (Blanking Period)	Allocation generation ok? Allocation concealment ok? Blinding Simple size calculation Intention-to-treat analysis? Events committee? Founding source	PVs isolation technique	Concomitant AADs in ablation group	Primary control group AADs	Navigation tools	Authors' primary outcomes	Authors' secondary outcomes
Krittayaphong 2003 **NR**	RCT 12 months (NR)	NR NR NR NR Yes NR Foundation	SOA	Amiodarone for 3 months post-procedure	Amiodarone (100%)	CARTO	AF	QOL, complications, and adverse effects of amiodarone
Wazni 2005 **RAAFT**	RCT 12 months (8 weeks)	Yes NR NR Yes No NR Industry	SOA	Not allowed	Flecainide (77%) Sotalol (23%)	ICE	AF	Hospitalization, QOL
Stabile 2006 **CACAF**	RCT 12 months (4 weeks)	Yes NR Yes Yes Yes No Industry	CPVA	If needed	Amiodarone (62%) Flecainide (26%) Propafenone (10%) Disopyramide (1%) Sotalol (6%)	CARTO	AF, AFL, or ATach	NR
Oral 2006 **NR**	RCT 12 months (12 weeks)	Yes NR NR Yes NR Foundation	CPVA	Amiodarone for 3 months post-procedure; after if needed	Amiodarone and up 2 CVE within 3 months of randomisation; after if needed	CARTO	AF, AFL, or ATach	Complications, changes in LA diameter & LV EF, changes severity symptoms

Table 1. Description of studies included in the review (Continued).

Pappone 2006 **APAF**	RCT 12 months (6 weeks)	NR NR NR Yes Yes NR NR	CPVA	For 6 weeks post-procedure; after, if needed	Amiodarone (62%) Flecainide (33%) Sotalol (31%)	CARTO	AF, AFL ATach, or repeated procedure	Analysis according to mapping system & catheters, hospitalizations, complications
Khan 2008 **PABA-CHF**	RCT 6 months (8 weeks)	Yes NR NR Yes Yes NR Foundation	SOA	For 8 weeks post-procedure; after, if needed	AVNA + BVP, amiodarone (90%), other class III AAD (10%)	FLUORO	Composite of QOL, LV EF, and 6-minute walk	AF, LA size
Jaïs 2008 **4A**	RCT 12 months (12 weeks)	NR NR NR NR Yes Yes Industry	SOA	For 9 weeks post-procedure; after, if needed	Class I AAD (83%), class III AAD (76%)	FLUORO	AF	Time to recurrent AF, complications and adverse effects, changes in left heart dimensions and function, QOL, exercise capacity, AF burden, and efficacy of amiodarone when used for the first time during the study
Forleo 2009 **NR**	RCT 12 months (5 weeks)	NR NR NR NR Yes NR NR	SOA	For 4 to 9 weeks post-procedure; after, if needed	Class I AAD (77%), sotalol (9%), amiodarone (63%)	CARTO	AF	Trombo-embolic events, bleedings, hospitalization, QOL

Table 2. Baseline characteristics of patients in trials included in the review.

First Author Year Trial name	Gender (M/F)	Mean age (SD)	Mean AADs (SD)	Structural heart disease and hypertension	Mean duration of AF (SD)	AF pattern			Mean LA size (SD)	Mean LV EF (SD)
						Paroxysmal	Persistent	Permanent		
Krittayaphong 2003 **NR**	T = 11/4 C = 8/7	T = 55 (11) y C = 49 (15) y	NR	T = 2 (13%) & 7 (47%) C = 2 (13%) & 4 (27%)	T = 63 (58) m C = 48 (64) m	T = 11 (73%) C = 10 (67%)	T = 4 (27%) C = 6 (40%)	-	T = 40 (8) mm C = 39 (7) mm	T = 64 (10) % C = 62 (9) %
Wazni 2005 **RAAFT**	NR	T = 53 (8) y C = 54 (8) y	NR	T = 8 (25%) C = 10 (28%)	T = 5 (2) m C = 5 (3) m	T = 32 (97%) C = 35 (95%)	T = 1 (3%) C = 2 (5%)	-	T = 41 (8) mm C = 42 (7) mm	T = 53 (5) % C = 54 (6) %
Stabile 2006 **CACAF**	T = 42/26 C = 44/25	T = 62 (9) y C = 62 (10) y	NR	T = 43 (63%) & 36 (53%) C = 43 (62%) & 34 (49%)	T = 5 (4) y C = 7 (6) y	T = 42 (62%) C = 50 (72%)	T = 26 (38%) C = 19 (28%)	-	T = 46 (5) mm C = 45 (6) mm	T = 59 (7) % C = 58 (6) %
Oral 2006 **N/A**	T = 67/10 C = 62/7	T = 55 (9) y C = 58 (8) y	T = 2.(1.2) C = 2.1 (1.2)	T = 6 (8%) & NR C = 6 (9%) & NR	T= 60 (48) m C = 48 (48) m	-	-	T = 77 (100%) C = 69 (100%)	T = 45 (6) mm C = 45 (5) mm	T = 55 (7) % C = 56 (7) %
Pappone 2006 **APAF**	T = 69/30 C = 64/35	T = 55 (10) y C = 57 (10) y	T = 2 (1) C = 2 (1)	T = 7 (7%) & 55 (56%) C = 4 (4%) & 56 (57%)	T = 6 (4) y C = 6 (6) y	T = 99 (100%) C = 99 (100%)	-	-	T = 40 (6) mm C = 38 (6) mm	T = 60 (8) % C = 61 (6) %
Khan 2008 **PABA-CHF**	T = 39/2 C = 35/5	T = 60 (8) y C = 61 (8) y	NR	*T = 41 (100%) & NR *C = 40 (100%) & NR	T = 48 (29) m C = 47 (34) m	T = 20 (49%) C = 22 (54%)	T = 21 (51%) C = 18 (46%)		T = 50 (10) mm C = 50 (10) mm	T = 27 (8) % C = 29 (7) %
Jaïs 2008 **4A**	T = 45/8 C = 49/10	T = 50 (11) y C = 52 (11) y	NR	T = 10 (19%) & 11 (22%) C = 14 (24) & 18 (30)	NR	T = 53 (100%) C = 59 (100%)	-	-	T = 40 (6) mm C = 40 (6) mm	T = 63 (11) % C = 66 (7) %
Forleo 2009 **NR**	T = 20/15 C = 23/12	T = 63 (9) y C = 65 (6) y	T = 1.5 (0.4) C = 1.8 (0.5)	T = 16 (46%) & 22 (63%) C = 19 (54%) & 24 (69%)	^T = 41 (18-66) m ^C = 36 (17-55) m	T = 16 (46%) C = 13 (37%)	T = 19 (54%) C = 22 (63%)	-	T = 44 (6) mm C = 45 (5) mm	T = 55 (7) % C = 53 (9) %

T, treatment; C, control; M, male; F, female; y, years; m, months; mm, millimetres; NR, not reported; SD, standard deviation; LA, left atrial; LV EF, ejection fraction of left ventricle; AAD, anti-arrhythmic drugs; AF atrial fibrillation. *T, 30 (73%) and C, 27 (68%) had coronary artery disease; ^median (inter-quartile range).

Table 3. Results in RCTs included in the review.

1st Author Year Trial Name	Patients randomised	Dropouts	Crossover to RFCA	RE-DO	ATs recurrence	*Rhythm monitoring
Krittayaphong 2003 **NR**	30 (T = 15; C = 15)	-	-	-	T = 3 (20%) C = 9 (60%)	Periodic Holter monitoring (1, 3, 6, 12 months)
Wazni 2005 **RAAFT**	70 (T = 33; C = 37)	3 (T = 1; C = 2)	-	-	T = 4 (12%) C = 22 (59%)	Daily brief event monitoring during first and third months; event monitoring for symptomatic episodes after the third month; periodic Holter monitoring (pre-discharge, 3, 6, and 12 months)
Stabile 2006 **CACAF**	137 (T = 68; C = 69)	3 (T = 1; C = 2)	36 (52%)	-	T = 30 (44%) C = 63 (91%)	Daily brief event monitoring during first three months, also if symptomatic, and periodic Holter monitoring (1, 4, 7, 10, and 13 months)
Oral 2006 **NR**	146 (T = 77; C = 69)	-	53 (77%)	25	T = 25 (32%) C = 53 (77%)	Daily brief event monitoring (5 days/week); additional event monitoring for symptomatic episodes
Pappone 2006 **APAF**	198 (T = 99; C = 99)	-	42 (42%)	9	T = 14 (14%) C = 75 (76)	Daily brief event monitoring and for symptomatic events; periodic Holter monitoring (pre-discharge, 3, 6, and 12 months)
Khan 2008 **PABA-CHF**	81 (T = 41; C = 40)	-	-	3	T = 8 (20%) C = 40 (100%)	Weekly brief event monitoring and for symptomatic events during second and sixth months
Jaïs 2008 **4A**	112 (T = 53; C = 59)	4 (T & C = NR)	37 (63%)	23	T = 7 (13%) C = 42 (71%)	Periodic Holter monitoring (3, 6, 12 months)
Forleo 2009 **NR**	70 (T = 35; C = 35)	-	-	-	T = 7 (20%) C = 20 (57%)	Patients instructed to regularly assess their pulse and to confirm on ECG any suspected recurrence of arrhythmia

NR, not reported; T, treatment; C, control; RCT, randomised controlled trial; RFCA, radiofrequency catheter ablation; AT, atrial tachyarrhythmia; RE-DO, repeated ablation procedure. *Includes assessment at routine clinic appointments.

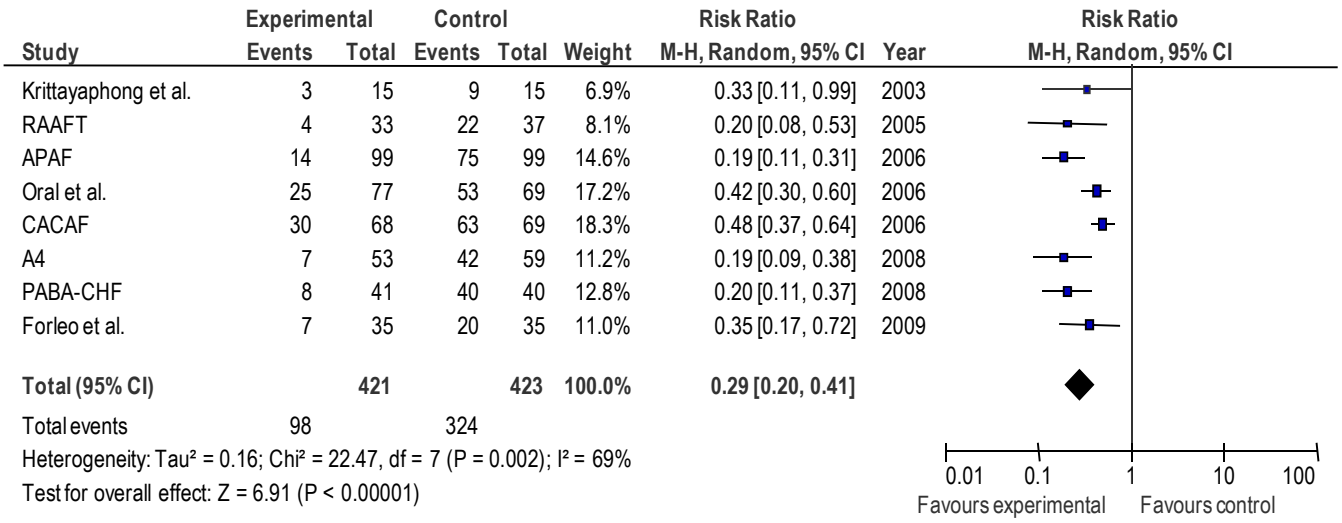

Figure 1. Effects of radiofrequency catheter ablation on proportion of patients with recurrence of atrial tachycardias.

group and 25% (SE 2.5%) for the control group (Figure 2). Since data were integrated from 6 studies, we used a Cox proportional hazards model, using studies as a covariate. The hazard ratio was 5.08 (95% CI 3.85 to 6.07) at AT recurrence.

There were 38 (9%) patients in the ablation group and 57 patients (13.4%) in the control group with complications and adverse events. Table 4 summarises the complications and adverse events reported in the selected studies. Pooled data from the 8 studies did not demonstrate any significant differences (RR 0.72; 95% CI 0.40 to 1.30, p=0.28, using random effects model). There was no statistical evidence of heterogeneity (p=0.06, χ^2 test; I^2=48%) among the studies (Figure 3). A sensitivity analysis, using fixed effects model, showed significant differences in favour of RFCA (RR 0.67; 95% CI 0.46 to 0.99, p=0.04). However, some of the complications and adverse events in the RFCA group were much more severe than those in the control group. Overall, in 8 RCTs of RFCA there were 687 ablation procedures. The weighted frequency of major complication and adverse effects in patients who underwent RCFA was 6.2% (95% CI 3.6% to 10.5%). Fatal and non-fatal embolic complications (including stroke, transient ischemic attack and thromboembolic events) occurred in 1.7% (95% CI 0.4% to 6.8%); PVs stenosis was 3.1% (95% CI 0.9% to 9.9%); bleeding (including pericardial effusion, tamponade and peripheral vascular hematoma) was 3.8% (95% CI 1.9% to 7.4%). A patient who had a stroke during ablation died of a brain haemorrhage 9 months later.

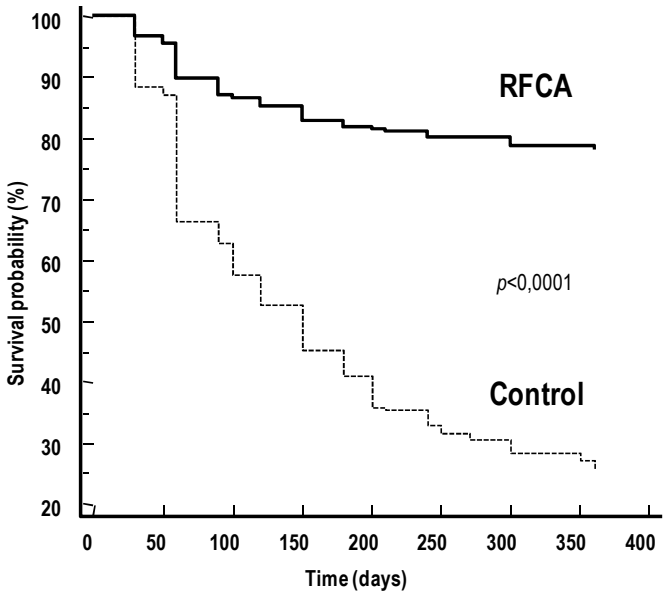

Figure 2. Kaplan-Meier curve of survival free from atrial tachycardias.

DISCUSSION

In this meta-analysis we showed that RFCA for the curative treatment for AF conferred a 71% RR reduction in recurrence of ATs (RR 0.29; 95% CI 0.20 to 0.41). Ablation strategy resulted in ATs event-free survival at 1 year of 78%, whereas only 25% of patients in the control group remained free from ATs recurrence. The primary finding of our analysis is the high efficacy of RFCA in maintaining sinus rhythm. Efficacy of RFCA may even be higher than estimated, because Kaplan-Meier analysis includes isolated recurrences of ATs. These sporadic recurrences are commonly observed and may determine

Table 4. Complications and adverse events in RCTs included in the review.

1st Author Year Trial name	Krittayaphong[8] 2003 NR	Wazni[9] 2005 RAAFT	Oral[10] 2006 NR	Stabile[11] 2006 CACAF	Pappone[12] 2006 APAF	Khan[13] 2008 PABA-CHF	Jais[14] 2008 A4	Forleo[15] 2009 NR
Stroke/CVA	T = 1 (7%)	–	–	T = 1 (2%)	–	–	–	–
Tamponade/ pericardial effusion	–	–	–	T = 1 (2%)	T = 1 (1%)	T = 1 (2%)	T = 1 (2%) C = 1 (2%)	–
PV stenosis	–	T = 2 (6%)	–	–	–	T = 2 (5%)	C = 1 (2%)	–
Death	–	–	T = 1 (1%)	T = 1 (2%) C = 2 (1%)	–	–	–	–
Tyroid dysfunction	C = 4 (27%)	–	–	–	C = 7 (7%)	–	C = 1 (2%)	–
Liver dysfunction	C = 2 (13%)	–	–	–	–	–	–	–
Sinus node dysfunction	T = 1 (7%) T = 1 (7%)	–	–	–	–	–	–	–
Atypical atrial flutter	–	–	T = 5 (7%)	–	–	–	–	–
Groin hematoma	T = 1 (7%)	–	–	–	–	–	T = 1 (2%) C = 1(2%)	–
Pro-arrhythmia	–	–	–	–	C = 3 (3%)	–	–	–
Sexual impairment	–	–	–	–	C = 11 (11%)	–	–	–
GI adverse events	T = 2 (13%) C = 6 (40%)	–	–	–	–	–	–	–
Bradycardia	–	C = 3 (8%)	–	–	–	–	–	–
Tachycardia	–	–	–	–	T = 3 (3%)	–	–	–
Bleeding	–	T = 2 (6%) C = 1 (3%)	–	–	–	T = 3 (7%) C = 2 (5%)	–	T = 2 (6%) C = 2 (6%)
Transient phenic paralysis	–	–	–	T = 1 (2%)	–	–	–	–
Transient ischaemic attack	–	–	–	C = 1 (1%)	T = 1 (1%)	–	–	–
Pulmonary edema	–	–	–	–	–	T = 1 (2%)	–	–
Myocardial ischaemia	–	–	–	T = 1 (2%)	–	–	–	–
Peripheral embolism	–	–	–	–	–	–	–	–
Corneal microdeposit	C = 2 (13%)	–	–	–	–	–	–	–
AADs adverse events	–	–	–	T = 2 (3%)	–	–	–	T = 1 (3%) C = 6 (17%)
Cancer	–	–	–	C = 2 (1%)	–	–	–	–
Lead problems	–	–	–	–	–	C = 4 (10%)	–	–
Pneumotorax	–	–	–	–	–	C = 1 (2%)	–	–
Total	**T = 5 (33%)** **C = 7 (47%)**	**T = 4 (12%)** **C = 4 (11%)**	**T = 6 (10%)** **C = 0 (0%)**	**T = 6 (9%)** **C = 4 (6%)**	**T = 5 (5%)** **C = 23 (23%)**	**T = 7 (17%)** **C = 7 (17%)**	**T = 2 (4%)** **C = 4 (7%)**	**T = 3 (9%)** **C = 8 (23%)**

GI, gastrointestinal; AAD, anti-arrhythmic drugs.

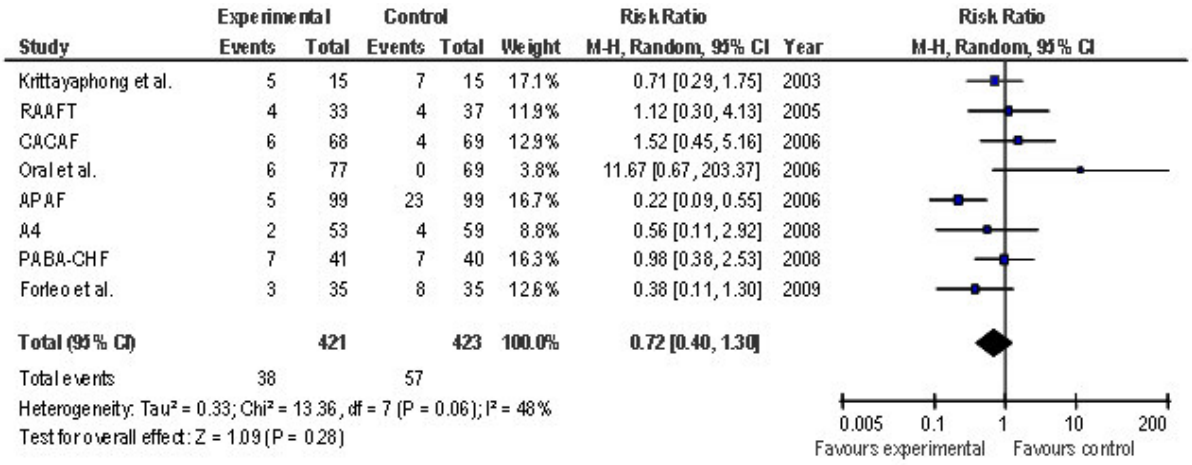

Figure 3. Effects of radiofrequency catheter ablation on proportion of patients with complications and adverse events.

minimal or no clinical consequences for the patients. Thus, it would be more clinically meaningful to report the results at the end of the follow-up. Unfortunately, only 4 studies (Wazni et al., 2005; Oral et al., 2006; Pappone et al., 2006; Khan et al., 2008) reported the number of patients in sinus rhythm at the end of follow-up. Because of the small number of studies and the crossover rate, this analysis could not be performed.

In addition, the complications and adverse events of the ablation group were not statistically different from the control group, with a RR of 0.72 (95% CI 0.40 to 1.30), indicating that RFCA is a relatively safe approach.

There are several problems in analyzing these results. First, the efficacy of RFCA for AF is not, at the present time, easy to establish. In order to define the success of the ablation strategy, all the trials included in this meta-analysis, except one (Khan et al., 2008), used recurrence of atrial arrhythmias as primary end-point. Unfortunately, the definition remains equivocal, since 3 studies (Stabile et al., 2006; Oral et al., 2006; Pappone et al., 2006) required freedom from AF, atrial flutter and other regular atrial tachycardias, while 5 studies (Krittayaphong et al., 2003; Wazni et al., 2005; Khan et al., 2008; Jaïs et al., 2008; Forleo et al., 2009) focused on freedom from AF alone. Moreover, the outcome of RFCA for AF compared with anti-arrhythmic drugs was limited by the concomitant use of anti-arrhythmic drug therapy (ADT) in the treatment group. A single study (Wazni et al., 2005) do use of anti-arrhythmic drug therapy (ADT) in the treatment group. A single study (Wazni et al., 2005) do not allow ADT in the ablation group; whereas in 6 studies (Krittayaphong et al., 2003; Oral et al., 2006; Pappone et al., 2006; Khan et al., 2008; Jaïs et al., 2008, Forleo et al., 2009) the intervention group received ADT for 3 to 9 weeks after RFCA, according to the study protocol. Finally, one trial (Stabile et al., 2006) evaluated the ablation therapy, combined with ADT or not, over ADT alone. Duration and time of occurrence of recurrent atrial arrhythmias varied among studies. A trial (Jaïs et al., 2008) did not count very brief AF recurrences (< 3 min), and all studies, except one (Krittayaphong et al., 2003), considered a post-ablation blanking period of several weeks to several months, where data were not censored. Finally, different methods for surveillance of rhythm were used, such as 12 lead electrocardiography, Holter monitoring, or event monitoring as prompted or not by symptoms. These methods have varying diagnostic accuracy for detecting occult arrhythmias. As few studies (Stabile et al., 2006; Oral et al., 2006; Pappone et al., 2006) reported the incidence of recurrent asymptomatic AF after ablation, in our analysis the predicted results by meta-regression according to daily or weekly event monitoring compared to patient reporting and routine electrocardiograms are remarkably consistent, confuting the hypothesis that the benefits may have been over-estimated. It is also important to clearly define the clinical characteristics of the patients enrolled in the trials. In general, the success rates of RFCA for AF are lower in cases of long-lasting AF than in those of paroxysmal or persistent AF. About this topic, our meta-analysis included most patients with paroxysmal/persistent AF. Using the meta-regression method, enrolled patients with paroxysmal AF showed a better outcome in our analysis. Lower success rates have also been seen in patients with significant structural heart disease (Fuster et al., 2006). Most of the patients included in the trials used in this meta-analysis had minimal structural heart disease, normal left ventricular systolic function and left atrial dimension < 50 mm. Because of the small number of patients with relevant underlying heart disease, subgroup analysis was not performed. All the trials used PVI as end-point of the ablation procedure, as suggested by a recent consensus document (Calkins et al., 2007). However, there were differences, including the approach to PVI, the adjunctive ablation strategies (linear lines, sources of complex fractionated electrograms), the

catheter technology (4-mm, 8-mm and cooled-tip catheters), and the use on non-fluoroscopic imaging tools. All these fields will impact the results of ablation therapy, but has not been systematically evaluated because of the small number of patients included in the analysis. Only one trial (Wazni et al, 2005) of this meta-analysis used RFCA as first-line approach to treat AF, although the results were favourable. Most of the patients included in the analyses had failed at least one anti-arrhythmic drug (class 1 or 3 agents) or were intolerant to medications.

Taking in account all these considerations and according to the current recommendations (Calkins et al., 2007), the results of our meta-analysis are in agreement with the hypothesis that RFCA is more efficacious in patients with symptomatic paroxysmal/persistent AF and minimal structural heart disease, refractory or intolerant to at least one anti-arrhythmic agent; the use as first-line therapy should be limited in rare clinical situations.

Four recent meta-analyses (Gjesdal et al., 2008; Noheria et al., 2008; Rodgers et al., 2008; Nair et al., 2009) of RCTs have shown results in agreement to ours. However, our systematic review included patients from 2 additional trials (Khan et al., 2008; Forleo et al., 2009) and added data from a trial (Jaïs et al., 2008) currently published as full-text. Performing this meta-analysis, we increase the power to see a difference in the effects that were evaluated. It also allows having a more precise estimation of these effects.

Our analysis bears some of the limitations inherent in meta-analysis of RCTs. First, patients enrolled in these trials may not be representative of those routinely seen in clinical practice. However, because randomisation accounts for both known and unknown confounders across treatment groups, this is the study design least vulnerable to biases. Second, our results may be influenced by a publication bias favouring RFCA procedures. Although this risk was minimized through an exhaustive search of the available literature, there is clearly limited power to detect such bias, given the small number of studies available. Third, the pooled RCTs estimates for AF are dominated by the APAF trial (Pappone et al., 2006), which was conducted by one of the world's leading catheter ablation centres. Consequently, the pooled effect estimates from the RCTs may overestimate the level of success that could be achieved by less experienced grown-ups. Although one large non-randomised study (Pappone et al, 2003) suggests that the effects of RFCA observed at 12 months remain fairly stable at 2 – 3 years post procedure, there is no evidence from RCTs that the favour-able effects of RFCA persist beyond one year. Only one trial (Khan et al., 2008) compared RFCA with ADT and atrioventricular-node ablation with biventricular pacing in patients with heart failure; therefore, there is insufficient evidence to assess the efficacy of RFCA relative to treat-ment strategies different from ADT alone. Finally, RCTs provide little evidence on mortality, adverse events and complications. The available controlled trials suggest the possibility of a relatively small risk of complications associated with RFCA (e.g. cardiac tamponade, PV stenosis) and adverse events associated with mid-term use of certain anti-arrhythmic agents (e.g. thyroid dysfunction associated with amiodarone). The evidence does not suggest that RFCA is associated with increased mortality related to the procedure itself.

Conclusions

The published data suggest that RFCA in a selected group of patients with AF is an effective intervention, with the majority of patients remaining free from arrhythmia at 12 months post-procedure. Complications and adverse events associated with RFCA are few, but not negligible. The currently available evidence does not show a significant relationship between RFCA and mortality, although existing RCTs were not been powered to assess this issue.

REFERENCES

Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, PapponeC, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ (2007). HRS/EHRA/ECAS Expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 4:816-61.

Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG; AFFIRM Investigators (2004). Relationships between sinus rhythm, treatment, and survival in the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. Circulat. 109:1509-13.

Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, De Sanctis V, Pappalardo A, Laurenzi F, Avella A, Casella M, Dello Russo A, Romeo F, Pelargonio G, Tondo C (2009). Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. J. Cardiovasc. Electrophysiol. 20(1):22-8.

Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL (2006). ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulat. 114:e257-354.

Gjesdal K, Vist GE, Bugge E, Rossvoll O, Johansen M, Norderhaug I, Ohm OJ (2008). Curative ablation for atrial fibrillation: a systematic rev. Scand. Cardiovasc. J. 42(1):3-8.

Hagens VE, Ranchor AV, van Sonderen E, Bosker HA, Kamp O, Tijssen JG, Kingma JH, Crijns HJ, Van Gelder IC; RACE Study Group

(2004). Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the rate control versus electrical cardioversion (RACE) study. J. Am. Coll. Cardiol. 43:241-7.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008] (2008). The Cochrane Collaboration. Available from www.cochrane-handbook.org.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996). Assessing the quality of reports of randomized clinical trials: is bliding necessary? Control Clin. Trials. 17:1-12

Jaïs P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clémenty J, Haïssaguerre M (2008). Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. Circulat. 118(24):2498-505.

Khan MN, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haïssaguerre M, Natale A; PABA-CHF Investigators (2008). Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N. Engl. J. Med. 359(17):1778-85.

Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, Kangkagate C (2003). A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. J. Med. Assoc. Thai. 86 Suppl 1:S8-16.

Nair GM, Nery PB, Diwakaramenon S, Healey JS, Connolly SJ, Morillo CA (2009). A systematic review of randomized trials comparing radiofrequency ablation with antiarrhythmic medications in patients with atrial fibrillation. J. Cardiovasc. Electrophysiol. 20(2):138-44.

Noheria A, Kumar A, Wylie JV Jr, Josephson ME (2008). Catheter ablation vs. antiarrhythmic drug therapy for atrial fibrillation: a systematic review. Arch. Intern. Med. 168(6):581-6.

Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F Jr, Bates ER, Lehmann MH, Vicedomini G, Augello G, Agricola E, Sala S, Santinelli V, Morady F (2006). Circumferential pulmonary-vein ablation for chronic atrial fibrillation. N. Engl. J. Med. 354(9):934-41.

Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benussi S, Alfieri O (2003). Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J. Am. Coll. Cardiol. 42(2):185-97

Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V (2006). A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J. Am. Coll. Cardiol. 48(11):2340-7.

Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, Pepper C, Todd D, Woolacott N (2008). Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. Health Technol. Assess. 12(34): 3-198.

Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF (2006). Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). Eur. Heart J. 27(2):216-21.

Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, Campbell WB, Havranek E, Murray K, Olshansky B, O'Neill G, Sami M, Schmidt S, Storm R, Zabalgoitia M, Miller J, Chandler M, Nasco EM, Greene HL (2004). Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Circulat. 109:1973-80.

Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A (2005). Radiofrequency ablation vs. antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA. 293(21):2634-40.