Long-term outcome after catheter ablation for atrial fibrillation: safety, efficacy and impact on prognosis

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Accepted 4 May 2010

ABSTRACT

Catheter ablation of atrial fibrillation (AF) continues to expand and evolve. Large registries like the worldwide survey have provided insight into methods, safety and efficacy of catheter ablation for AF in the short term, and how these are changing. Long-term follow-up data are also emerging answering important questions about safety and efficacy over subsequent years. A small number of studies have attempted to examine whether catheter ablation of AF impacts on hard end points such as stroke and death and hence improve prognosis. This article reviews the current literature providing insight into these rapidly changing areas.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting 1% of the general population, and rising to 17% in those aged ≥84 years.[1] Two-thirds of patients with AF are troubled by symptoms and the course is far from benign with incidence of stroke being increased sixfold and mortality double that of age-matched controls.[2] AF is already an enormous financial burden, accounting for around 1% of the UK's NHS budget, and with the demographic change its prevalence is expected to double over the next 25 years.[3]

The association between AF and stroke is well recognised, and early risk stratification to decide the need for anticoagulation is universally accepted. However, other aspects of management such as rate control versus rhythm control, which antiarrhythmic drugs (AADs) to use, the place of cardioversion and catheter ablation are all still controversial. The AFFIRM study and others initially showed no benefit in pursuing a rhythm control strategy over rate control for symptoms or mortality.[4] Treatment was predominantly pharmacological and was not very successful. At the end of the AFFIRM study one-third of the rate control group were in sinus rhythm compared with two-thirds in the rhythm control group, leading some to conclude this was a test of a treatment strategy rather than comparing the effect of sinus rhythm restoration with continued AF.

Subsequent reanalysis of the AFFIRM study has shown that in those achieving sinus rhythm mortality was halved, although this effect was effectively negated if antiarrhythmic treatment continued to be used.[5] As a post hoc finding this association between sinus rhythm and improved mortality must be interpreted with caution. This relationship has been demonstrated subsequently in some studies,[6 7] but not others.[8] The potential for AADs to increase mortality has been documented in several high-profile trials such as CAST and SWORD,[9 10] but has also been shown in other cohorts of patients taking AADs for AF such as in the Stroke Prevention in AF (SPAF) study.[11] The toxicity of AADs combined with their limited efficacy in the treatment of AF may be obscuring a possible symptomatic or prognostic advantage in pursuing sinus rhythm.

Several randomised controlled trials have demonstrated the superiority of catheter ablation (CA) over medical treatment for AF in terms of maintenance of sinus rhythm and improved symptoms.[12–17] This has prompted the question: if CA of AF can restore sinus rhythm without the need for lifelong AADs, could it improve hard outcomes such as stroke, cardiovascular events or mortality? To answer this question we should consider the efficacy of CA, the safety profile of the procedure and the emerging evidence of its prognostic benefit.

EFFICACY OF CATHETER ABLATION

CA is now successful in restoring sinus rhythm long term for both paroxysmal and persistent AF. The first worldwide survey conducted by Cappato reported registry data from 100 centres between 1995 and 2002 for a mixed cohort of 8745 patients with paroxysmal and persistent AF.[18] Freedom from AF or other atrial tachyarrhythmias (ATs) was reported in 52% of patients not receiving AADs, rising to 76% after reintroduction of previously ineffective AAD treatment at almost 1 year. However, techniques have evolved significantly in a short space of time.

Early catheter-based techniques tried to replicate the surgical maze procedure with very limited success.[19] Targeting of initiating pulmonary vein (PV) foci was not reported until 1998,[20] and only in 2000 was it realised that all PVs must be targeted to avoid later emergence of ectopy not apparent at the index procedure.[21] High rates of PV stenosis with ostial isolation prompted lesion placement in the left atrium 1–2 cm outside the vein ostia, forming continuous rings of scar around them (usually with the use of three-dimensional mapping systems).[22] It remains controversial as to whether isolation of the PVs at their ostia or at a distance in pairs is more effective, and data from randomised controlled trials are conflicting.[23 24] Many groups have used the technically challenging procedural end point of PV electrical isolation, although firm evidence of incremental benefit from randomised trials has been lacking until recently.[25]

PV isolation (PVI) alone is successful for 70–90% of patients with paroxysmal AF.[23 26] This now forms the cornerstone of CA for AF and is recommended in current guidelines.[27] However, PVI alone

maintains sinus rhythm in only 10–30% of patients with persistent AF.[23 26 28] Efforts to improve outcomes, particularly for persistent AF, has led to investigation of alternative and adjunctive targets such as ganglionic plexi,[29] fractionated electrograms,[28 30] linear lesions,[31 32] isolation of the posterior wall between the PVs,[28 33] or extensive modification of the posterior and inferior wall.[34] CA of persistent AF now usually involves a hybrid strategy, incorporating PVI with further ablation, typically in the form of linear lesions and/or complex fractionated electrograms.[31 32]

The worldwide survey reflected this progression in techniques, with the most common technique being right atrial maze from 1995 to 1997, targeting of PV foci from 1998 to 1999, and PVI from 2000 onwards. The second 'updated' worldwide survey reported registry data from 85 centres for 16 309 patients undergoing CA of AF from 2003 to 2008.[35] Freedom from AF had risen to 70% without the need for AADs (80% including those still taking AADs) at 18 months. The proportion of patients with persistent AF and longlasting persistent AF (ie, continuous for >1 year) had also risen markedly. Techniques almost always incorporated PVI for this cohort.

Studies now typically report long-term freedom from AF/AT in 70–90% of patients without the need for AADs, with some studies reporting data up to 7 years.[30 32 34 36–41] Table 1 summarises studies reporting more than 2 years of follow-up for more than 100 patients. There was initially a question as to whether sinus rhythm would be maintained long term, or whether CA was a palliative procedure delaying the inevitable. With the long-term data becoming available, it is apparent that most recurrences of AF/AT occur within a year of the procedure. The AF-free survival curve flattens between 2 and 3 years, with approximately 3% per year recurring after this.[30 34 38 41]

Success can be difficult to gauge for the reader, as results are reported differently in different studies. Guidelines now suggest that trials use frequent monitoring to look for asymptomatic AF, and that use of AADs or the capture of more than 30 s of any atrial tachyarrhythmia (regardless of symptoms) is regarded as failure.[27] This level of monitoring can be difficult to achieve outside clinical trials, and such harsh definitions of success may be seen as artificial and arbitrary. A patient with a short run of asymptomatic AF may well regard their procedure as a success and decline a repeat procedure. In the world of coronary intervention looking for asymptomatic ischaemia, with this or the use of anti-anginal medication counting as failure might be seen as excessive.

Hence, 'real-world' registry data typically involve less monitoring of asymptomatic patients, recognising that further monitoring of asymptomatic patients may show an increment in recurrent AF. Nademanee's group report monitoring patients only if they have recurrent symptoms,[30] and although Pappone's group have reported monitoring patients, they defined failure as symptomatic recurrence lasting longer than 10 min on ambulatory monitoring and confirmed on ECG.[38] The reader is then left with the difficult task of comparing results between studies reporting different techniques. This is now becoming easier as there is more uniformity in reporting, with the majority of studies now complying with the strict criteria in guidelines.[27] Therefore, although these harsh definitions of success typically under-represent the benefit some patients derive, they do form an essential bench mark for comparing trials using different techniques or technologies.

Not all patients stand equal chances of success after CA of AF. Although freedom from AF has been reported in approximately 70–90% of patients after ablation for paroxysmal AF for some time,[23 26 34] results for persistent AF had lagged behind. However, results are improving with many studies documenting long-term freedom from AF in excess of 70%[30 31 38] and some centres managing 80–90% without the need for AADs.[32 34] Many patients require more than one procedure to maintain freedom from AF, particularly for persistent AF, with studies typically reporting a mean of 1.2–1.5 procedures per patient. Figure 1 shows success rates for CA of paroxysmal and persistent AF in the longest follow-up series to date.

Other factors identified on multivariate analysis as predictors of recurrent arrhythmia (although none uniformly in all studies) include time spent in persistent AF, structural heart disease, left ventricular impairment, hypertension, female gender and, perhaps most consistently, left atrial diameter.[32 34] Many operators are reluctant to consider patients with a left atrial diameter >5 cm, although the thresholds of operators are continually decreasing as experience increases. Interestingly, there appears not to be an effect of age or ischaemic heart disease, and the impact of structural heart disease and left ventricular impairment appears small.

Table 1 Studies reporting long-term efficacy of catheter ablation for atrial fibrillation (AF)

Authors	Year	Patients (n)	Follow-up (years)	PAF (%)	AF free from drugs (%)
Bhargava[34]	2009	1404	4.7	52	88
O'Neill[32]	2009	153	2.8	0	89
Hunter[31]	2010	285	2.7	53	70
Pappone[38]	2003	589	2.5	69	79
Lee[41]	2004	207	2.5	100	72*
Nademanee[30]	2008	635	2.3	28	81
Zado[40]	2008	781	2.2	64	64
Oral[36]	2006	755	2.1	65	71
Cheema[37]	2006	200	2.1	46	41

Studies reporting follow-up for > 2 years following catheter ablation of AF for more than 100 patients are included.
*Results are from studies not specifying how many patients were still taking antiarrhythmic drugs.
PAF, paroxysmal AF.

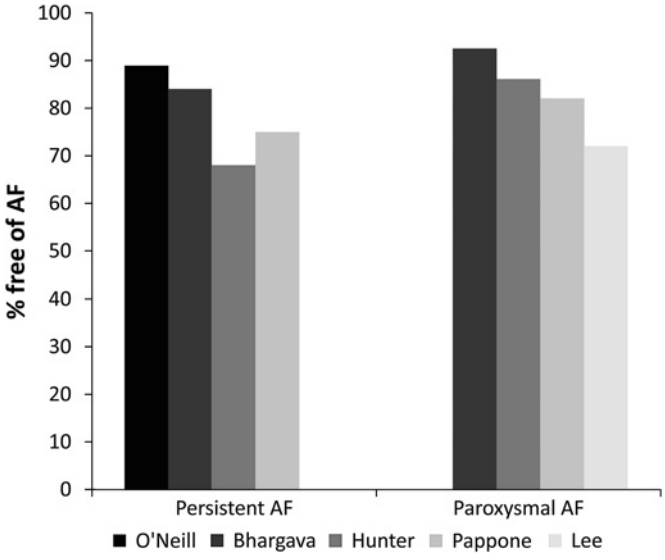

Figure 1 Long-term success following catheter ablation for atrial fibrillation (AF). Long-term freedom from AF or other atrial tachyarrhythmias for paroxysmal AF and persistent AF. The studies shown have the longest follow-up reported to date (2.5–4.7 years). Note the study by Lee *et al* included only patients with paroxysmal AF, and the study by O'Neill *et al* included only patients with persistent AF.

SAFETY OF CATHETER ABLATION FOR AF

Major complications have been reported to be as high as 6%.[18] Published case series from leading single centres typically report lower rates of major complications in the region of 2–3%.[30 32 34 37–41] These consist mostly of stroke/transient ischaemic attack (TIA) or tamponade. PV stenosis was initially reported after around 1% of cases but has become much rarer now most groups target ablation at a distance from the ostia to encircle the PVs in pairs (wide-area circumferential ablation).[18] Although a serious and often fatal complication, atrio-oesophageal fistula is very rare.[18]

Death following CA for AF is rare. As few centres have sufficiently large registries and as reporting of results is voluntary, the true mortality is difficult to determine. Expanding on his work with the worldwide survey on CA for AF, Cappato has produced an analysis of procedural mortality.[42] Of 45 115 procedures, there were 13 intraoperative deaths (0.02%), the 30-day mortality was 25 (0.06%), and including all late deaths potentially related to the procedure this rose to 32 (0.07%). This was reported in the study as a mortality of 0.098% per patient, as some patients underwent more than one procedure. Stroke, tamponade and atrio-oesophageal fistula accounted for more than half of these deaths. Other large registries have reported similar mortalities of approximately 0.07–0.2%.[18 31 34 35 39]

An analysis of consecutive patients undergoing CA for AF at St Bartholomew's, London, UK from 2002 to 2007 included 285 patients undergoing 530 procedures (starting when wide-area circumferential ablation with confirmation of electrical isolation became a consistent part of our lesion set).[31] There were no periprocedural deaths. Stroke or TIA occurred in 0.6%, all resolving without permanent neurological deficit. Pericardial effusion requiring drainage occurred in 1.7% and all were drained without sequelae.

From the end of this analysis until October 2009, a further 643 CA have been performed for AF, bringing the total to 1173 cases. Two periprocedural deaths have occurred in this period: one due to myocardial infarction and one tamponade. This gives a periprocedural mortality of 2 (0.17%) which is similar to the published figures above. The major complications of AF ablation and their frequency in large studies are listed in table 2.

LONG-TERM PROGNOSIS: STROKE AFTER CATHETER ABLATION FOR AF

Oral *et al* examined rates of stroke in 755 consecutive patients undergoing CA of AF during 2.1 years of follow-up, 69% of whom remained in sinus rhythm.[36] They reported periprocedural stroke in 0.9% (up to 2 weeks), with only two strokes subsequently (0.1% stroke rate per year). Of these, one remained in AF and the other was deemed high risk and still with therapeutic anticoagulation. Of the 69% who remained in sinus rhythm, anticoagulation was halted after a minimum of 3 months in 69% (approximately half had one or more risk factor for stroke) without a single stroke during follow-up.

A more recent multicentre study also examined the incidence of stroke after CA of AF, and in particular the impact of anticoagulation.[43] Of 3355 patients studied for a mean of 2.3 years, 2692 went on to stop warfarin. The annual incidence of stroke was 0.03% in the cohort stopping warfarin (CHADS2 score ≥2 in 13%), with major haemorrhage in 0.02% per year. This compared with an annual incidence of stroke of 0.2% in those continuing warfarin (CHADS2 score ≥2 in 37%) with major haemorrhage in 1% per year. Although retrospective, these data suggest a very low incidence of stroke following CA for AF. Although current guidelines advocate continuing anticoagulation guided by CHADS2 score,[27] prospective studies are underway examining the role of anticoagulation in populations at moderate risk of stroke after CA for AF.

LONG-TERM PROGNOSIS: SURVIVAL AFTER CATHETER ABLATION FOR AF

As yet the data examining the prognostic benefit for CA of AF are slight and consist of only registries and a single meta-analysis (summarised in table 3). Pappone's group compared outcomes for a registry of consecutive patients referred to their group for AF, 589 of whom underwent CA and 582 received medical treatment.[38] After a median follow-up of 2.5 years they found mortality was reduced by over 50% in those who underwent CA, which was found to be no different from age-matched controls without a history of AF. This was driven mostly by a reduction in strokes and heart failure.

A similar study published only in abstract form followed up 731 patients after CA of AF for 18 months and compared mortality with a cohort living in the same area with AF.[44] They showed a significantly lower mortality in the group who underwent CA. However, their control group had a very high mortality and was significantly older than the patients undergoing ablation. The authors claim the results remained significant after adjusting for age, but as this was only published in abstract form the data are difficult to scrutinise.

Nademanee examined outcomes for 'high-risk' patients undergoing CA for AF from his registry.[30] These patients effectively had a CHADS2 score of ≥1 and hence were at high risk of stroke. They followed up 635 patients at 2.3 years since their last ablation. Sinus rhythm was maintained in 81% and their outcomes were compared with those with recurrent AF. They

Table 2 Procedural complications from catheter ablation of atrial fibrillation (AF) expressed as a percentage per procedure

	Worldwide survey I[18]	Worldwide survey II[35]	Bhargava[34]	Dagres[39]
Procedures (n)	11762	20825	1691	1000
TIA or stroke (%)	0.6	0.7	0.3	0.4
Tamponade (%)	0.9	1.0	0.3	1.3
Symptomatic PV stenosis (%)	0.4	0.23	1.1	0.1
Atrio-oesophageal fistula (%)	0	0.03	0	0.2
Periprocedural death (%)	0.05	0.12	0.06	0.2
Total major complications* (%)	4.5	3.6	2.7	3.9

*Major complications are those that are deemed serious, those that have lasting sequelae, or that delay discharge.
PV, pulmonary vein; TIA, transient ischaemic attack.

Table 3 Impact of catheter ablation on survival*

	Follow-up (years)	Ablation group n/N (%pa)	Comparator group n/N (%pa)
Pappone, 2003[38]	2.5	38/589 (2.4)†	83/582 (5.6)
Compared with a registry of patients treated medically			
Bunch, 2006[44]	1.5	10/731 (0.9)†	668/4609 (7.3)
Compared with a matched local population treated medically			
Nademanee, 2008[30]	2.3	15/517 (1.3)†	14/118 (5.2)
Comparison of those in sinus rhythm after ablation with those with recurrent AF			
Sonne, 2009[33]	5.8	3/146 (0.4)†	60/306 (3.4)
Compared with a matched registry treated medically/AV node ablation and pacing			
Dagres, 2009[46]	1	3/486 (0.6)	4/444 (0.9)
Meta-analysis of eight trials comparing ablation with medication			

*As studies were not structured uniformly, the text under each study describes the group against which the ablation group was compared (the comparator group). The number in brackets shows mortality per year of follow-up (or % per annum).
†Denotes statistical significance between groups.

found mortality was 12% in those with recurrent AF and 3% in those who maintained sinus rhythm, again driven mostly by a reduction in strokes and heart failure. They also observed that patients with left ventricular systolic dysfunction had a significant improvement in ejection fraction (mean increase of 10%). Several other studies including two randomised controlled trials (one is continuing at our centre) have investigated the effect of restoring sinus rhythm with CA in the setting of heart failure, demonstrating improved left ventricular function and exercise capacity.[14 45] Consequently AF in the context of heart failure is already considered an indication for CA by some groups.

Registry data from Natale examined outcomes at 7 years for 452 matched patients undergoing either PVI to restore sinus rhythm, AV nodal ablation and pacemaker insertion, or medical treatment.[33] They found a mortality rate of 2%, 26% and 17%, respectively. This was found to be significantly lower in the PVI group, with the excess of deaths in the other groups attributed mostly to heart failure.

Our registry at St Bartholomew's of 285 patients followed up for a mean of 3.3 years has also shown a low rate of long-term adverse sequelae.[31] There were seven deaths in the cohort, two of which were cardiac (one due to pre-existing heart failure and one myocardial infarction, with none related to AF or their ablation procedure), and three had a stroke or TIA. There were no cases of new-onset heart failure. This equates to a mortality of 0.7% per year and a stroke rate of 0.3% per year. With a mean CHADS2 score of 0.8 for the cohort, this equates to an expected stroke rate of around 3% for patients with a history of AF (1% if anticoagulated). According to UK national statistics, an age- and sex-matched population should have an expected mortality of 0.8%. Hence our data confirm that stroke rate after CA for AF is lower than for a population with continuing AF, and survival is similar to that for the general population.

Although these studies suggest a potential survival benefit for rhythm control using an ablation strategy in AF, registry and other non-randomised data are inherently flawed, being prone to bias and confounding. No randomised controlled trials to date have examined this problem. A recent meta-analysis of small randomised controlled trials comparing symptoms in patients having CA to restore sinus rhythm versus medical treatment showed no difference in mortality.[46] However, only 930 patients in total were followed up for 1 year with a mortality of only 0.7%. With such a low event rate many more patient years of follow-up would be needed to show a difference in mortality, and this is perhaps why a prognostic benefit is difficult to demonstrate. The rate of stroke and death in patients with AF is very low in the predominantly low-risk cohorts that have been selected for CA until recently, and data from patients at higher risk (ie, with a high CHADS2 score) are needed if an impact on these hard end points is to be assessed. CABANA has already begun recruitment for its pilot phase. It aims to recruit 3000 high-risk patients (essentially with CHADS2 score of ≥ 1) with AF and randomise them to medical treatment or CA as first-line treatment and will examine these hard end points, including stroke and death.

CONCLUSION

CA is now safe and effective in restoring and maintaining sinus rhythm long term for both paroxysmal and persistent AF, and improves the quality of life for symptomatic patients. However, the only proven indication for CA of AF remains symptoms refractory to drug treatment. The fundamental question as to whether AF is a risk factor for stroke and death that can be eliminated, or simply a risk marker that must be ameliorated, remains unanswered. The need for randomised controlled trials to clarify any benefit for hard end points such as stroke, cardiovascular events, or death cannot be overstated. If such studies confirm a prognostic advantage for restoration of sinus rhythm with CA, this will have massive implications for patients with AF as well as cardiology as a specialty.

Funding RJH is supported by a grant from the British Heart Foundation (PG/08/130).

Competing interests RJS is a member of the scientific advisory board for Biosense Webster. He is listed on the Speakers Bureau for Endocardial Solutions and has received payment for lectures sponsored by them. RJH and RJS have also received support for travel to international meetings from Guidant, Medtronic, St Jude Medical, Endocardial Solutions and Biosense Webster.

Provenance and peer review Not commissioned; externally peer reviewed.

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Heart 2010 96: 1259-1263
doi: 10.1136/hrt.2010.194613

Notes