



Ablation vs. drug use for atrial fibrillation

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The relative merits of rate and rhythm control in the treatment of patients with atrial fibrillation (AF) have been compared in several major clinical trials, none of which demonstrated a significant difference in all-cause mortality. Yet, there is clear evidence that restoration and maintenance of sinus rhythm is associated with beneficial reverse atrial and ventricular remodelling. In addition, patients may feel better if AF is resolved, and data from some *post hoc* analyses suggest a possible mortality benefit. These apparently contradictory findings may reflect the high risk of serious adverse events associated with currently available antiarrhythmic drugs (AAD), counterbalancing their beneficial effect in restoring sinus rhythm. Catheter ablation offers an alternative means of restoring sinus rhythm in patients with AF and several clinical trials have indicated superior outcomes in certain subgroups after ablation with or without AAD vs. antiarrhythmic therapy alone. This study reviews the relative advantages and actual use of catheter ablation and other therapeutic options in the treatment of AF, with or without concomitant heart failure or structural heart disease. Catheter ablation is recognized in the latest ACC/AHA/ESC guidelines as a valid second-line option in patients who have failed or were intolerant of first-line antiarrhythmic therapy. In the absence of new antiarrhythmics with an improved benefit/risk profile, it could become a first-line strategy for certain patient populations. The ongoing CABANA trial should confirm its impact on overall survival relative to that of pharmacological rate or rhythm control.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice, affecting ~4.5 million people in Europe¹ and 2.2 million people in the United States.² It has been shown to be an independent predictor of stroke and death, contributing to an estimated 15–20% of strokes annually in the United States^{3,4} and almost doubling the risk of death relative to that of people with sinus rhythm.^{5,6} The prevalence of AF doubles with each advancing decade of age, from 0.5% at age 50–59 years to almost 9% at age 80–89 years, men having a 1.5-fold greater risk of developing AF than women after adjustment for age and predisposing conditions.⁷

Prompt treatment of AF may be essential to avoid detrimental atrial and ventricular remodelling, favouring persistence of the disorder and increasing vulnerability to relapse, as well as deterioration of left ventricular systolic and diastolic function.⁸ Current treatment strategies are designed either to control the ventricular response (rate control) or to restore sinus rhythm (rhythm control), and the relative merits of these two approaches have been compared in several major clinical trials, including PIAF,⁹ AFFIRM,^{10,11} RACE,¹² STAF,¹³ and HOT CAFE.¹⁴

None of these studies demonstrated a significant advantage of one treatment strategy over the other with regard to all-cause mortality. A meta-analysis of these trials similarly revealed no significant difference between rate and rhythm control with regard to either all-cause mortality (pool of all five trials) or incidence of ischaemic strokes (pool of the three trials reporting

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this parameter: AFFIRM, STAF, and HOT CAFE).¹⁵ An earlier overview of the relative merits of rate and rhythm control in AF based on these trials noted that rhythm control was associated with more hospitalizations and more adverse drug effects.¹⁶ Further analysis of the relationship of survival to cardiac rhythm and treatment in the AFFIRM study revealed that sinus rhythm was associated with a lower risk of death, but the use of antiarrhythmic drugs (AAD) was associated with increased mortality when the effect of sinus rhythm and treatment were analysed separately. One explanation for these results could be that the potential survival benefit of maintaining sinus rhythm is negated by the potential proarrhythmic effects and/or non-cardiac toxicities of the currently available AAD.¹¹

There is clear evidence that restoration and maintenance of sinus rhythm is associated with beneficial reverse atrial and ventricular remodelling^{17,18} and the results of *post hoc* analyses of the DIAMOND and AFFIRM trial data suggest a possible mortality benefit.^{11,19} Furthermore, several studies have demonstrated that restoration of sinus rhythm is associated with significantly improved quality of life.^{20–22}

Although still considered as the first-line treatment to prevent symptomatic and recurrent AF, AAD are frequently ineffective and may be associated with serious adverse effects, raising concerns about the life-long use of these drugs to suppress AF.²³ In this context, catheter ablation for AF, although also not devoid of risk, may offer a viable alternative for restoring sinus rhythm in certain patients. The use of catheter ablation for AF has increased rapidly over the last decade and the techniques are being continuously refined and developed, potentially allowing this method to be applied to a wider range of patients with better long-term outcome and greater safety. Data on the benefits and risks of catheter ablation for the control of AF, relative to those of AAD therapy, are now available from several randomized clinical trials, and several recent surveys have provided a wealth of information on the use and outcomes of this approach in routine clinical practice. Catheter ablation is currently recognized as a therapeutic option for patients with recurrent paroxysmal or persistent symptomatic AF who fail to respond to or are intolerant of AAD in the latest edition of the guidelines for the management of patients with AF issued jointly by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC).²⁴

The objective of this study was to review the current status of catheter ablation in the treatment of AF, as an alternative to pharmacological treatment options.

Clinical trials comparing the use of antiarrhythmic drugs to catheter ablation

The results of five randomized trials comparing these two methods of restoring sinus rhythm have been published recently. Four of these trials investigated the benefit of catheter ablation vs. AAD in patients who had already failed at least one course of AAD therapy: one in

patients with paroxysmal or persistent AF [(Catheter Ablation for the Cure of Atrial Fibrillation (CACAF)), two in patients with paroxysmal AF [Atrial Fibrillation Ablation vs. Antiarrhythmic Drugs (A4) and Ablation for Paroxysmal Atrial Fibrillation (APAF) trials], and one in patients with chronic AF. The fifth trial [Radiofrequency Ablation for Atrial Fibrillation Trial (RAAFT)] compared the respective benefits of ablation vs. AAD as first-line treatment for AF (predominantly paroxysmal in the population included in the completed pilot phase).

The CACAF trial²⁵ was an open, prospective, multicentre, randomized trial investigating the benefit of performing catheter ablation in addition to AAD therapy in 137 patients with paroxysmal or persistent AF (mean age, 62 years) who were either intolerant of AAD or had failed at least two previous AAD regimens. Overall, one-third of the patients had persistent AF and most had heart disease. Patients were randomized to a single catheter ablation plus AAD (ablation group; $n = 68$) or AAD alone (control group; $n = 69$). Twenty-five per cent and 30% of the patients, respectively, had previously undergone catheter ablation. The primary endpoint was the absence of any recurrence of atrial arrhythmia lasting >30 s during the 12 month follow-up period, after a 1 month blanking period, analysed according to intention to treat.

During the 12 month follow-up, 63 of 69 (91.3%) control patients experienced at least one AF recurrence, whereas 30 of 68 (44.1%) of the ablation group had at least one atrial arrhythmia recurrence (AF: 26, atrial flutter: 4) ($P < 0.001$). Thirty-six of 63 control group patients experiencing AF recurrence (57.1%) underwent catheter ablation while continuing AAD therapy and 22 of these (61.1%) experienced no further recurrences of atrial arrhythmia within a median follow-up of 18 months (range, 14–23 months). The overall incidence of major complications related to the ablation procedure was 4.4%. The median per patient number of hospitalizations during the 12 month follow-up period did not differ significantly between the two groups.

The A4 trial²⁶ was a randomized multicentre study comparing catheter ablation [circumferential pulmonary vein isolation (PVI); $n = 53$] with AAD ($n = 59$) in patients with symptomatic paroxysmal AF (at least two episodes per month) who had failed treatment with at least one class I or III AAD. The mean age of the 112 patients was 51 years, 84% were male (51 ± 11 years). The primary endpoint was symptomatic or documented AF for at least 3 min beyond the initial 3 month blanking period, during which patients in the AAD group could receive up to three different AAD, alone or in combination, and those in the ablation group could undergo up to three ablations (mean 1.8 ablations). Crossovers were permitted at 3 months in the event of treatment failure and by the end of the study, 37 patients (63%) in the AAD arm had crossed over to the ablation arm.

At 1 year follow-up, significantly more patients in the ablation arm were free of AF recurrence (75 vs. 6%; $P < 0.0001$). Furthermore, 60% of patients in the ablation group were able to discontinue oral anticoagulation, compared with 34% of AAD patients. Kaplan–Meier plots

for time to AF recurrence also showed significant superiority of ablation over AAD therapy ($P < 0.0001$). Most quality-of-life measures were significantly better in the ablation group (intention-to-treat [ITT] analysis). At day 365, the exercise duration and performance in the ablation group were higher than those observed in the AAD group (ITT analysis), 12.4 ± 5.3 min and 9.5 ± 2.3 metabolic equivalents (METs) vs. 10.3 ± 4.6 min and 8.1 ± 2.6 METs, $P = 0.08$ and 0.003 , respectively. Complications in the ablation group included two cases of tamponade (one in a crossover patient), two groin haematomas, and one pulmonary vein stenosis, complications in the AAD group comprising one case of hyperthyroidism and one death because of cancer, probably not related to AAD. No strokes or transient ischaemic attacks were seen in either group during the 12 month follow-up.

The APAF trial²³ was a controlled, randomized, single-centre study including 198 patients with paroxysmal AF (mean AF episodes/month, 3.4; mean age, 56 ± 10 years) who had failed at least one AAD (mean, 2 ± 1). Patients were randomized to circumferential pulmonary vein ablation (CPVA; $n = 99$) or AAD therapy other than that administered unsuccessfully ($n = 99$). All patients were anticoagulated with warfarin. Crossover from AAD to ablation was permitted at 3 months after failure of two different AAD regimens. The primary endpoint was the absence of atrial tachyarrhythmia recurrence lasting >3 s during the 12 month follow-up (following an initial 6 week blanking period).

Using Kaplan–Meier analysis, 86% of the patients in the ablation group were free of AF at 12 month follow-up after a single ablation procedure compared with 22% of those in the AAD group responding to the first AAD ($P < 0.001$). Overall, taking into account patients undergoing a repeat ablation procedure and those in the AAD group who were switched to a second, combination AAD regimen, freedom from atrial arrhythmias at 1 year was achieved by 93 vs. 25% of patients in the ablation and AAD groups, respectively. Forty-two patients (42%) in the AAD group crossed over to ablation after failure of the second AAD regimen, of whom 36 (86%) had no recurrent AF in the absence of AAD therapy at a mean of 6.2 months after crossover. The rate of hospitalization for cardiovascular events was significantly lower in the ablation group ($P < 0.001$): 24 hospital admissions vs. 167 (excluding hospitalizations for crossover to ablation). Maintenance of sinus rhythm after ablation was associated with reverse left atrial remodelling (significant decrease in left atrial size), whereas no such remodelling was observed in the patients randomized to AAD therapy. No serious complications were observed in any patient undergoing ablation, whereas significant adverse events leading to permanent drug withdrawal occurred in 23 patients (23%) in the AAD group.

Oral *et al.*²⁷ investigated the benefit of CPVA in addition to amiodarone treatment in a randomized, controlled study in two centres in 146 patients with chronic AF (mean age \pm SD: 57 ± 9 years; 88% male; 8% with clinically significant structural heart disease). Overall, the study population had failed a mean of two prior AAD regimens. Patients were randomized to receive

amiodarone and undergo two cardioversions during the first 3 months either alone (control group; $n = 69$) or with CPVA. Patients in the control group who developed recurrent AF >3 months after the first cardioversion could either resume amiodarone therapy or undergo CPVA. The primary endpoint was the absence of AF or atrial flutter without AAD therapy 1 year after ablation in the CPVA group or 1 year after cardioversion in the control group.

Intention-to-treat analysis showed a significantly higher percentage of patients in sinus rhythm at 12 months in the CPVA group (74 vs. 58%, $P < 0.05$). Moreover, 77% of the patients in the control group underwent CPVA for recurrent AF, a mean of 128 ± 57 days after cardioversion, and this population accounted for 93% of the patients in the control group with sinus rhythm at 12 months. Only 4% of the patients in the control group were free of recurrent AF at 12 months in the absence of AAD therapy or CPVA. In the CPVA group, restoration of sinus rhythm was associated with a slight but significant decrease in left atrial diameter ($12 \pm 11\%$; 40 ± 6 vs. 45 ± 6 mm; $P < 0.001$) and symptom severity score ($59 \pm 21\%$; 6 ± 2 vs. 17 ± 4 points; $P < 0.001$) and with a significant increase in left ventricular ejection fraction (LVEF) (0.62 ± 0.08 vs. 0.55 ± 0.06 , $P < 0.001$) at 12 month follow-up relative to baseline. Complications were limited to atypical atrial flutters in the ablation group (6%).

In contrast to the four trials described above, the ongoing multicentre, prospective, randomized RAAFT is investigating the feasibility of radiofrequency catheter ablation (PVI) as first-line therapy for patients with symptomatic AF. The primary endpoint is any recurrence of symptomatic AF or asymptomatic AF lasting >15 s in the 1 year follow-up period. The pilot phase of the trial, now completed in Europe, randomized 70 patients with monthly AF episodes for at least 3 months (mean, 5 months) who had not received AAD therapy prior to ablation ($n = 33$; mean age, 53 ± 8 years) or AAD ($n = 37$; mean age, 54 ± 8 years).²⁸ All patients were anticoagulated with warfarin. The majority of patients presented paroxysmal AF (97% in the PVI group and 95% in the AAD group) and 25 and 28%, respectively, had structural heart disease and hypertension.

At 12 month follow-up, the rate of symptomatic AF recurrence was significantly lower in the PVI group than in the AAD group (13 vs. 63%; $P < 0.001$), as was the hospitalization rate (9 vs. 54%; $P < 0.001$). Quality of life, assessed at 6 months relative to baseline, was significantly better in the PVI group with respect to five subclasses of the Short-Form 36 health survey, including general health ($P < 0.001$) and physical functioning ($P = 0.001$). Asymptomatic AF was documented in 16% of patients in the AAD group and in 2% of those in the PVI group. No repeat ablation procedures were performed in the PVI group during the 1 year follow-up period. Subsequently, four patients in this group who experienced recurrent AF underwent repeat ablation, three of these patients were free of AF and not on AAD therapy at the time of publication, and one was in sinus rhythm with AAD treatment. Complications in the PVI

group were limited to asymptomatic moderate stenosis of one pulmonary vein in one patient (3%).

Use of catheter ablation for atrial fibrillation in routine clinical practice

The methods, safety, and efficacy of catheter ablation to cure AF were investigated in a worldwide survey conducted in 2002, in which a total of 777 electrophysiology centres were contacted.²⁹ Among the 181 centres responding to the survey questionnaire, 100 had started a programme of catheter ablation for AF between 1995 and 2002. Data were obtained on 9370 patients undergoing 11 762 ablation procedures (median per centre, 37.5; range, 1–600). For 93% of the centres, drug refractoriness was a criterion for ablation. Patients presenting paroxysmal AF were eligible for ablation in all centres, 53% of the centres also performing ablation on patients with persistent AF and 20% on those with permanent AF. Exclusion criteria included an upper limit of left atrial size (between 55 and 60 mm) in 46% of centres, a lower limit of LVEF (between 30 and 35%) in 65%, and prior heart surgery in 64%.

The total number of patients undergoing catheter ablation for AF practically doubled each successive year from 1995 to 2002, the preferred technique shifting from right atrial compartmentalization in 1995–1997 to catheter ablation of the triggering focus in 1998 and 1999 and finally to PVI from 2000 onwards, this technique accounting for 80% of the procedures reported in 2002. Only 26% of the centres adhered to the same procedure throughout the period surveyed. Among the patients undergoing PVI, isolation of all four PV was the aim in 58% of cases and isolation of three PV in 30% of cases in the 79 centres reporting this procedure. Complete data regarding the source of energy used was available for 4918 patients, of whom 84% received radiofrequency current ablation. Pre-ablation, subcutaneous, low-molecular weight or intravenous heparin was used by all centres in practice, irrespective of whether the patients were taking long-term oral anticoagulants. After ablation, 83% of the centres reported the use of oral anticoagulants, aspirin being administered in the remaining 17% of centres over a follow-up ranging from 1 to 6 months.

Complete data for the assessment of efficacy over 11.6 ± 7.7 months (median, 12 months; range, 1–98 months) were available for 8745 patients aged from 16 to 86 years (64% male) treated in 90 centres. Of these, 52% (range between centres, 15–77%) became asymptomatic in the absence of any AAD therapy, whereas a further 24% (range, 9–50%) became asymptomatic with continued use of formerly ineffective AAD. Overall, 76% of the patients undergoing catheter ablation for AF obtained symptom resolution with or without AAD (range, 22–91%), 24% requiring two ablation procedures, and 3% requiring three procedures to achieve this aim. The rate of successful symptom resolution in the absence of AAD treatment ($P < 0.001$) and the overall success rate ($P < 0.05$) significantly increased with the number of procedures performed per centre. Success

rate did not seem to depend on the type of AF treated, being 53% in the 65 centres including patients with paroxysmal AF only, 49% in the 17 centres including patients with paroxysmal or permanent AF, and 57% in the eight centres including patients with all forms of AF. One of the explanations for this finding could be that ablation of more complex forms of AF was attempted only by the more experienced centres.

Catheter ablation for AF was associated with a major complication in 524 patients (6%), including four intraoperative or perioperative deaths (two from massive cerebral thromboembolism), 20 strokes, 47 transient ischaemic attacks, and 107 episodes of tamponade. Furthermore, 117 PV sustained significant stenosis ($>50\%$), approximately half of these requiring interventional treatment. New-onset (iatrogenic) atypical atrial flutter was reported in 340 patients (4%) and was significantly more frequent in centres exclusively using 3D-guided compartmentalization strategies than in centres exclusively performing ablation of the triggering substrate or PVI (8.4 vs. 0.8%; $P < 0.001$).

A recently published Spanish registry of catheter ablations,³⁰ centralizing data from 47 centres concerning 6162 ablation procedures (mean, 131 ± 88 per centre), reported AF to be the fourth most common condition treated ($n = 480$, 8%), following atrioventricular nodal reentrant tachycardia (29%), accessory pathways (26%), and atrial flutter (22%). Twenty-four of the 47 centres contributing data performed catheter ablations for this indication in 2005, a two-fold increase relative to 2004. The number of catheter ablations of AF as a percentage of total ablations showed an almost three-fold increase in 2005 relative to 2001–2004, constituting up to 25% of the ablations performed in individual centres. The predominant technique used for the ablation of AF was CPVA, followed by ostial PVI. An irrigated catheter was used in 243 of the 452 ablations of AF for which this information was provided and an 8 mm catheter in 164 ablations. A total of 31 centres had at least one intracardiac mapping system in 2005, compared with only 11 centres in 2001, the first year of the registry.

Compared with the other indications, catheter ablation for AF concerned a particularly low proportion of women (10%) and a low proportion of patients with underlying cardiomyopathy (16%). The incidence of major complications in catheter ablations of AF was 6.8% in 2005, substantially higher than that observed in the context of catheter ablations for other indications (0.4–1.6%), and also higher than that observed in the two previous years (2.6 and 3.4%, respectively, in 2003 and 2004), possibly reflecting the introduction of this procedure in many new centres in 2005. The main complications reported in catheter ablation for AF were pericardial effusion, tamponade, and vascular complications. Only one case of PV stenosis was reported. No data on the success rate of catheter ablation for AF were cited in the publication concerning this registry.

The relative use of catheter ablation and other therapeutic strategies to control AF was illustrated by the Euro Heart Survey conducted in 2003 and 2004 in 182 hospitals

in 35 ESC member countries.³¹ Almost half the participating centres (46%) were university hospitals and 56% possessed an electrophysiology department. A total of 5333 patients were enrolled in the survey. First detected AF was reported in 978 patients (18%), paroxysmal AF in 1517 patients (29%), persistent AF in 1167 patients (22%), permanent AF in 1541 patients (29%), and unknown AF in 130 patients (2%). Altogether, 90% of the patients presented at least one associated medical condition and 86% had at least one risk factor for stroke, according to the ACC/AHA/ESC guidelines. Catheter ablation was used in 5% of patients with paroxysmal AF, 4% of those with persistent AF and 1% of those with permanent AF, whereas 33, 18, and 3% of these patient populations, respectively, underwent pharmacological conversion and 14, 36, and 5% underwent electrical conversion. Altogether, 84% of the patients receiving rhythm control treatment also received rate control therapy. Rate control alone was used in 27% of patients with current AF symptoms and in 18% of patients with paroxysmal or persistent AF.

Discussion

Despite the increasing use of ablation for the treatment of AF and the generally good results obtained, several key issues remain unresolved.

Is atrial fibrillation ablation ready for first-line therapy?

The most recent ACC/AHA/ESC guidelines for the management of patients with AF²⁴ list catheter ablation as a possible second-line therapeutic option for patients with recurrent paroxysmal or persistent AF after failure or intolerance of first-line AAD therapy, as an alternative to AAD such as amiodarone that are associated with a greater risk of adverse reactions. However, the results of several recently published clinical trials demonstrating superior outcomes with catheter ablation for AF relative to AAD^{23,25-27} suggest that AF ablation may warrant consideration as first-line therapy in selected patients.²³ The results of the pilot phase of the RAAFT study, showing improved clinical outcomes at 1 year with PVI compared with AAD therapy as first-line treatment for patients with symptomatic paroxysmal AF, indicate the feasibility of this approach, although the authors emphasize the necessity of confirming its relative merits in a larger scale trial with a longer follow-up.²⁸

The benefits of catheter ablation for AF are generally most evident in patients with recurrent paroxysmal disease, and younger, highly symptomatic patients with paroxysmal AF not accompanied by structural heart disease probably constitute the ideal candidates. In a study investigating the predictors of success after selective PVI for the treatment of AF, younger age (odds ratio 1.05 per year) and absence of persistent AF were found to be significant independent predictors of the absence of AF after a single ablation procedure.³² However, patients with persistent/permanent AF may also benefit from catheter ablation of AF, as indicated

by the significantly higher 5-year survival (85 vs. 50%) observed in this subgroup in a study comparing patients undergoing catheter ablation for AF relative to a disease-matched control group of residents of Olmsted county, MN, who did not undergo ablation. A significant survival benefit of catheter ablation was also evident in the study population as a whole (94 vs. 52%) and in the subgroup presenting paroxysmal AF (98 vs. 53%).³³ In another study, the percentage of patients free of AF after catheter ablation at a mean follow-up of 18.1 ± 13.5 months did not differ significantly between patients aged under 50 years, between 50 and 65 years, and over 65 years, respectively. At 3 months, total quality-of-life (SF-36) scores and increase in these scores relative to pre-ablation baseline were similar in the three groups.³⁴

Similarly, patients with enlarged atria should not necessarily be excluded, even though ablation is more difficult in this context, as such patients often have a poor quality of life. The standard approach (i.e. CPVA) can achieve a success rate of up to 65% in these patients and does not affect contractility, and in the event of recurrence, the posterior wall may be targeted.

Although the techniques used in catheter ablation for AF are still evolving, there appear to be more common points than differences with regard to procedures for AF ablation in the various centres practising this procedure, at least in patients with relatively simple paroxysmal AF. The importance of introducing continuous lesions encircling the PV proximally, within the atrial tissue, is now generally acknowledged, although the necessity of isolating all four PV may be debated, as modern mapping techniques facilitate the detection of the trigger points for AF. An alternative approach to the pre-determined PVI strategy is to target areas of complex-fractionated electrograms (CFAE) recorded during AF, using mapping techniques to associate CFAE with the anatomy of both atria. To some extent, these two approaches overlap, since both target the triggering foci as well as the substrate, and the PV are the key locations of CFAE, after the intra-atrial septum.³⁵

One of the key questions in assessing the benefits of catheter ablation is how to define success, as there is currently no consensus on this point. Simply the presence or absence of AF is not enough as the longer the follow-up, the more runs of AF tend to be seen. The possibility of an adverse evolution of the atrial substrate over time was suggested by the results of a worldwide survey on the use of catheter ablation, indicating a lower overall success rate of catheter ablation for AF in centres reporting data based on >18 months of follow-up than in those with shorter follow-up durations.²⁹ The Heart Rhythm Society has proposed AF episodes lasting ≤ 1 min as the criterion for success, but this is an arbitrary threshold. It is important to take into account the occurrence of asymptomatic AF when evaluating success rate as asymptomatic episodes of AF may occur even in highly symptomatic patients and may significantly increase in frequency after catheter ablation.³⁶

Success could also be defined clinically, e.g. if a patient who presented permanent AF prior to ablation

experiences only short runs of AF after the procedure and shows a better EF. Reverse atrial remodelling and improved EF may also be considered to be criteria for successful control of AF. Reverse morphological remodelling of the left atria and improvement of left ventricular diastolic and systolic functions after restoration of sinus rhythm by ablation have been demonstrated in a study in patients with isolated AF¹⁷ and other studies have reported similar findings.^{23,37-40}

Although it is difficult to base assessment of long-term outcome on retrospective data, as techniques have changed since catheter ablation for AF was first introduced, available data are encouraging. In Bordeaux University Hospital, for example, the overall success rate of catheter ablation for AF remained quite stable at 62–63% between 1 year and 6 years of follow-up, ~5% of patients moving from failure to success or *vice versa* (P. Jaïs, unpublished results). However, more than one ablation procedure is often necessary to successfully control AF and frequently the same area has to be re-ablated.

With regard to safety, the ~6% rate of major complications associated with ablation cannot be regarded as trivial. The most serious risks are cardiac tamponade, occurring in 1–4% of ablation procedures, PV stenosis (<2% with current techniques), and stroke (0.5–1%). Oesophageal fistula is relatively rare in patients undergoing AF ablation (~1 in 500), but preliminary studies indicate that oesophageal changes may be detected upon endoscopy in a higher percentage of patients. It is still not feasible to assess the energy delivered to the atrial tissue precisely and control of tissue temperature is impossible.

Overall, despite the good results shown in clinical trials, catheter ablation cannot yet be regarded as a first-line therapy in the absence of more long-term data on its benefits and risks. More studies in patients who are apparently less favourable candidates are also needed to identify the best indications for this technique.

When atrial fibrillation is associated with heart failure and an ejection fraction <35%, what strategy should be considered?

Although a significant percentage of patients with AF have impaired EF, the vast majority of ablation procedures, in particular PVI, have been performed in patients with preserved LV systolic function, the combination of AF and structural heart disease being perceived to represent a different substrate involving a potentially higher risk of procedural complications. Patients with AF associated with heart failure have different symptoms from those presenting AF alone, suffering more from fatigue, dyspnoea, and low energy levels than from palpitations. Restoration of sinus rhythm by catheter ablation may present particular advantages for these patients by achieving not only symptom improvement, but also an enhanced EF and beneficial cardiac remodelling.

In a study comparing the benefits and risks of PVI in patients with normal and impaired LV function, the

percentage of patients free of AF in the absence of AAD following PVI (including a second ablation procedure if necessary) was not significantly different between the two groups. Although the rate of AF recurrence at ~1 year was significantly higher in patients with impaired systolic function (27 vs. 13%), the 73% success rate after the initial PVI is within the range reported in the literature for patients with normal LV systolic function. Sixty per cent of the patients with impaired LV function showed an improvement in LVEF following PVI (mean increase in LVEF, $7.2 \pm 3\%$). Both groups reported significant improvements in several quality-of-life parameters after PVI, including general health, energy, physical functioning, and emotional well-being. Complication rates were low and similar in patients with normal and impaired LV function.⁴¹

Another study comparing ablation outcomes in patients with congestive heart failure (CHF) vs. a matched control group without CHF similarly showed no significant difference between the percentages of patients remaining in sinus rhythm without AAD at a mean follow-up of 12 ± 7 months (69 vs. 71%). The patients with CHF showed significant ($P < 0.001$) improvement in LVEF ($21 \pm 13\%$) and fractional shortening ($11 \pm 7\%$), LV dimensions, exercise capacity, and quality of life. LVEF increased significantly not only in patients without concurrent structural heart disease and those with inadequate rate control before ablation, but also in those with co-existing heart disease and adequate pre-ablation rate control.²⁰

AF ablation tends to be more consistently effective in heart failure patients without structural heart disease, and more extensive and complex ablation is generally required in patients with impaired LV function. However, most studies have been performed in patients with an LVEF of 30–45% and data on patients with more severe heart failure are lacking. Overall, catheter ablation in this patient population remains a challenge.

Asymptomatic atrial fibrillation: what are the therapeutic options?

The current ACC/AHA/ESC guidelines recommend that patients with recurrent paroxysmal AF presenting minimal or no symptoms be managed by anticoagulation and rate control as needed, avoiding the use of AAD.²⁴ The recent Euro Heart Survey on Atrial Fibrillation nevertheless indicated that 44% of patients with AF who had never experienced symptoms and 46% of those who had previously experienced symptoms but were currently asymptomatic were treated using a rhythm control strategy.³¹ Although AF ablation may be beneficial for patients with asymptomatic AF, in terms of atrial and ventricular remodelling, these patients might be reluctant to accept the potential risk of complications. Overall, this procedure is probably unjustifiable in patients with asymptomatic AF. The principal reasons for performing AF ablation, i.e. symptomatic improvement and improvement of quality of life, do not apply to this population and no data on likely survival benefit are currently available.

When should anticoagulation be stopped after ablation?

Continued anticoagulation may be necessary in high-risk patients, even if AF ablation is successful, due to the state of the atria. In low-risk patients, anticoagulation may possibly be stopped. For moderate risk patients, the appropriate strategy is not clear and until further evidence is available, the prudent option is to continue anticoagulation. However, it is not known whether the established risk categories are still relevant once AF has been controlled.

Oral *et al.*⁴² studied the risk of thrombo-embolic events after percutaneous left atrial radiofrequency ablation of AF in 755 patients with paroxysmal ($n = 490$) or chronic ($n = 265$) AF. All patients were anticoagulated with warfarin for at least 3 months after ablation. Among 522 patients who remained in sinus rhythm after ablation, anticoagulation was stopped in 79% of 256 patients with no risk factors at a median of 4 months after ablation, and in 68% of 256 patients with at least one risk factor at a median of 5 months after ablation ($P = 0.003$ compared with patients without any risk factors). None of these patients experienced a thrombo-embolic event during 25 ± 8 months of follow-up. Patients older than 65 years or with a history of stroke were more likely to remain anticoagulated despite a successful outcome of ablation. In the Mayo Clinic, anticoagulation is currently stopped in 52% of patients who have undergone successful AF ablation, although this percentage is decreasing as more patients with persistent AF are operated (D. Packer, unpublished results).

Is there a mortality benefit to atrial fibrillation ablation?

There are currently insufficient data to judge whether or not AF ablation has an effect on overall survival. However, several studies have indicated a beneficial effect of sinus rhythm on survival. A substudy of the double-blind, randomized, multicentre DIAMOND trials in patients with AF or atrial flutter, focusing on the 506 patients presenting LV dysfunction at baseline, showed a significantly lower mortality rate in patients who converted to sinus rhythm compared with those who failed to do so (RR, 0.44; 95% CI, 0.30–0.64; $P < 0.0001$). No difference in mortality reduction was seen according to whether conversion to sinus rhythm was achieved by pharmacological treatment, by electrical conversion or occurred spontaneously.¹⁹ Similarly, the *post hoc* analysis of the AFFIRM trial, conducted on 2796 patients with AF treated with rate or rhythm control strategies, showed that achievement of sinus rhythm was associated with a significant decrease in the risk of death (HR, 0.54; 99% CI, 0.42–0.70; $P < 0.0001$).¹¹

The multicentre CABANA trial, with a planned recruitment of 3000 patients in Europe and the United States and a primary endpoint of all-cause mortality, is designed to investigate specifically the impact of AF ablation on survival. This trial will include patients with paroxysmal, persistent, or chronic AF either over 65 years old (with no

exclusions) or under 65 years with hypertension, low LVEF, prior stroke, or prior transient ischaemic attack. Patients will be randomized to catheter ablation or pharmacological therapy (rate or rhythm control) as first-line treatment. All patients will be anticoagulated and crossovers will be strictly prohibited. The planned follow-up is 3.5 years, but this may be extended further. The total trial duration is 6 years. The pilot phase of this trial is currently underway.

Conclusion

Catheter ablation is a viable therapeutic option for managing patients with AF, several clinical trials having demonstrated statistically significantly superior outcomes with this procedure than with currently available AAD. The efficacy and safety of this approach have steadily improved over the last decade with the availability of better cardiac mapping systems and refinement of ablation procedures and is now close to being considered as a first-line treatment in certain patients. However, AF ablation is not devoid of risk and further large-scale studies with longer follow-up periods are still needed to better define the profile of patients likely to obtain the most benefit from this procedure. Pharmacological therapy based on rate control may be more appropriate for certain types of AF, avoiding the risks associated with current AAD, but there is increasing evidence that restoration and maintenance of sinus rhythm confers long-term benefits in terms of reverse atrial and ventricular remodelling. Several studies have shown substantial benefits when sinus rhythm is restored. Pending the availability of new AAD with a better efficacy/safety ratio, catheter ablation represents a promising strategy for achieving this aim.

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