Among the major advances in invasive electrophysiology over the last 15 years are cardiac resynchronization therapy for heart failure and ablation for atrial fibrillation (AF). Before the widespread adoption of cardiac resynchronization therapy as an approved therapy for our patients, several carefully designed trials had documented improvement in quality of life when compared with optimal medical management.1–3 Ablative therapy for AF, however, evolved as an option for patients who remained symptomatic from AF despite medical therapy. Although ablation for AF has a class IIa indication in HRS/EHRA/ECAS guidelines4 for AF management and is frequently used, pressing questions as to whether we affect patient outcomes with ablation remain. In the absence of large randomized, multicenter trials comparing ablation with drug therapy for AF, we have had to rely on relatively small, sometimes single-center, and a few recent meta-analyses of the published smaller trials on which to base our recommendations.5–7

The meta-analysis by Piccini et al6 includes 6 trials (2 single-center) and 693 patients. The trials involve comparison of ablation with antiarrhythmic therapy and postablation follow-up for 1 year. The authors concluded that pulmonary vein isolation dramatically increased freedom from AF at 1 year when compared with nonablation treatment strategies.

Before we can accept their conclusions, we must examine the difficulties inherent in performing the meta-analysis, the original trials, and, more generally, in assessing the clinical role for AF ablation.

Has the AF Ablation Procedure Worked? Defining Success

A major source of difficulty with designing a prospective trial or interpreting results from published trial data for AF ablation efficacy involves the complexity of defining success with the procedure. With most arrhythmias for which ablation is an established therapy (atrioventricular node reentrant tachycardia, Wolff-Parkinson-White syndrome), success is very simply the elimination of the arrhythmia after ablation. With AF ablation, however, multiple methods are used for defining success in published trials and individual practice.13–19

Monitoring for Recurrence

Because AF occurrence may be paroxysmal or asymptomatic and confused with other symptoms that other patients may have, documentation of freedom from AF is difficult. The present meta-analysis included trials that used electrocardiography, periodic 24-hour Holter monitors,20,21 and event monitors (30 seconds to 3 minutes per day),15,22–24 as well as symptoms to document rhythm. Given the difficulty of defining symptoms, nocturnal episodes, and the limited monitoring used, underestimation of AF recurrence in these studies may have occurred. Although similar difficulties exist for monitoring for AF with drug therapy and ablation, amiodarone and other agents may result in relative organization of the arrhythmia, and potential side effects may have resulted in more frequent transmissions being sent in the drug-treated group.

However, because the goal is to relieve symptoms, do we need to detect and record asymptomatic episodes? The answer to this question depends on future data that will explain the relationship between asymptomatic AF episodes and stroke risk, as well as possible late development of symptoms in patients as they age or develop comorbidities.

The “Blanking” Period

AF recurrence soon after ablation is of uncertain significance in terms of long-term freedom from symptomatic AF. Piccini et al6 included trials in which the “blanking” period—during which recurrent AF is not considered failure of therapy—ranged from 1 to 3 months. These recurrences, however, may have received treatment either with drug therapy, aggressive management of sleep apnea, or invasive therapy and affected the 1-year outcome for the patients receiving ablation. Symptomatic recurrence in the “blanking period” also may have resulted in more aggressive atrioventricular nodal blockade,

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thus reducing symptoms during subsequent recurrences during longer follow-up.

**Macoreentrant Atrial Tachycardia**

After ablation for AF, perhaps when linear ablation has been performed, atrial flutters may result. Stable atrial flutters may result in symptoms identical to those that the patient was having before ablation. There is presently no consensus on whether these arrhythmias represent a “more organized recurrent AF,” and thus a failure of the index procedure exists.

**Concomitant Antiarrhythmic Therapy**

Only 2 of the referenced studies included data detailing freedom from antiarrhythmic therapy and freedom from documented AF at 1 year. Thus, patients for whom ablation was considered successful may have been treated with medication. Further, nontraditional antiarrhythmic therapy, including statins, and measures to improve diastolic dysfunction, ACE inhibitors, and so forth, could have been instituted after ablation possibly for early recurrence and resulted in “freedom” from AF. Thus, in these intention-to-treat studies, changes in these therapies that may be more likely in the ablation treatment arm could result in more favorable outcomes and less detection of symptomatic AF than in the drug therapy arm.

**What Is the Goal of Therapy?**

Some patients choose to undergo AF ablation, believing that stroke and/or mortality may be reduced beyond symptom amelioration. The 1-year follow-up for the limited number of patients in these studies cannot provide answers for these important patient-care questions.

Patients also may have had periods in their illness with minimal recurrence in a 6- to 12-month time frame and wish to be counseled on whether relatively longer-term recurrences would occur and what treatment options are available. Given that even in limited follow-up (1 year) approximately 1 in 6 patients (17%) needed reablation,25 longer-term recurrence rates may be high. The present analysis does not help us in counseling patients with these questions or expectations.

**Has Pulmonary Vein Isolation Worked?**

**Defining Success**

All the studies included in the present meta-analysis6 involved circumferential ablation around the pulmonary vein ostia as part of the ablation approach. Knowing whether pulmonary veins have been effectively electrically isolated from the left atria is not straightforward.26,27 In 2 of the studies included, loss of pulmonary vein potentials (entrance block) and/or exit block from the vein were used as an end point. In the others, criteria that presently would not be considered appropriate were used, including diminution (80% reduction in 1 study) in pulmonary vein potential amplitude. Because present approaches do not involve ablating within the pulmonary vein, fragmentation or a decrease in pulmonary vein potential amplitude (which can only occur if the pulmonary vein myocardium is being ablated) would not be relevant. Defining the efficacy of pulmonary vein isolation, however, may be important as we define the prevalence of late recurrence of AF and whether repeat ablation targeting venous isolation should be recommended. On the other hand, it could be that venous isolation is not required for the success of AF ablation, although this question cannot be answered from the present analysis or the existing literature assessing ablation efficacy.13-19

**How Do We Assess and Compare Moving Targets?**

AF ablation is not a single procedure. Even in the trials included in this study,26 some operators used purely anatomic perivenous ablation and others looked for physiological end points (venous isolation) with or without linear ablation. Other variables in ablation approach include superior vena cava ablation, vein of Marshall ablation, targeting the retroatrial ganglionated plexi, number and type of ablation lines, and targeting fractionated atrial electrograms. The end points for the ablation procedure itself are variable and may include noninducibility of AF, high-dose isoproterenol testing, targeted ablation of all induced macroreentrant tachycardias, or no stimulation/electrophysiology testing with only anatomic ablation being performed.28 These highly individualized approaches not only make comparing the approaches complex but also make comparison with antiarrhythmic therapy very difficult.

Pharmacotherapy for AF is heterogeneous. The side effect profiles, efficacy, and ease of use of presently approved agents are significantly dissimilar and affect patient outcomes and satisfaction. Dronaderone, a recently approved agent for use with AF, was not included in any of the studies analyzed in the present report.6–12

The aim in treating AF may involve stroke reduction or improvement in ventricular function. Newer approaches to reduce thromboembolic stroke include left atrial appendage occlusion29,30 and improving ventricular function.1–3

Thus, a definitive, comparative study assuming the variations in ablation paradigms, approaches to stroke prevention, and newer antiarrhythmic agents is unlikely to be available in the near future for clinicians when counseling patients with AF.

**Complications Associated With AF Treatment**

The authors conclude from their meta-analysis that the complications associated with invasive ablative therapy are similar to other diagnostic and therapeutic cardiac procedures. However, the studies that were included have considerably lower rates of procedural complication reported when compared with a large international registry or other smaller studies.13 Although the authors suggest that the experience of the operators who reported the primary trials is the reason for these extraordinarily low complication rates (no gastroesophageal fistula, 1 symptomatic pulmonary vein stenosis in nearly 700 patients), a clear explanation is not available for this discrepancy. This underscores a major problem in extrapolating the literature to our understanding of whether our patients really benefit when we ablate AF, which is underreporting complications and the lack of uniform tests and follow-up requirements monitored by an independent site or board. This may particularly be true given the short follow-up in these studies and the nonspecific symptoms associated with
many AF-related complications (pulmonary vein stenosis, esophageal thermal injury, and vagal nerve injury, etc).31,32

Because of the multiple initial trials with drug therapy before approval for use, the potential risks and side effects are well documented, and patients can be clearly instructed in terms of follow-up as to whether untoward effects are occurring. Knowledge of complications with AF ablation is largely an evolving field with “recognized” complications becoming obvious only over time. Thus, the earlier trials included in the present meta-analysis were conducted before some presently recognized complications had been reported.

Ablation or Drugs for AF? The CABANA Trial

The difficult issues surrounding any attempt to answer the question of whether ablation or drug therapy is superior for managing AF may only begin to be answered with large randomized trials.

The CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial probably will provide critically important, long-term follow-up data that include objective end points after catheter ablation (NCT00911508). This multicenter trial, with planned recruitment of 3000 patients in North America, Europe, Australia, and Asia, has all-cause mortality as a primary end point. The trial will include patients with paroxysmal, persistent, and chronic AF more than 65 years of age (or less than 65 years with hypertension, low ejection fraction, prior stroke, or transient ischemic attacks). Patients will be randomly assigned to catheter ablation or rate or rhythm control pharmacological therapy as first-line treatment. All patients will be anticoagulated accordingly, and cross-over is not permitted. The planned follow-up is a minimum of 2 years, with a median of 3.5 years. The pilot phase for this trial has recently been completed.

Several important questions will potentially be answered by this trial, including whether AF ablation reduces mortality rates. The present data on AF ablation and survival are limited to substudies or post hoc analysis of larger trials. A substudy of the Diamond trial, a randomized, multicenter trial in patients with AF or atrial flutter and left ventricular dysfunction at baseline, did show lower mortality rates when patients were converted to sinus rhythm (spontaneously or with pharmacological treatment) (relative risk, 0.44; 95% CI, 0.30 to 0.64; \( P<0.0001 \)).33 Of the 2796 patients with AF treated with rate or rhythm control in the AFFIRM trial,24 post hoc analysis showed that when sinus rhythm was achieved, there was a significantly lower risk of death (hazard ratio, 0.54; 95% CI, 0.42 to 0.72; \( P<0.0001 \)).

The relationship between maintenance of sinus rhythm and mortality represents a conundrum. It is possible that maintaining sinus rhythm occurs successfully only in patients who have less abnormal substrate and less overall comorbidity (ventricular dysfunction, diastolic dysfunction, and so forth). There is a need for a randomized, prospective trial to determine whether otherwise similar patients do achieve a mortality benefit simply as a result of maintaining sinus rhythm. CABANA will also establish the long-term impact of ablative versus pharmacological therapy on quality of life, health care costs, complications, and related hospitalizations. The results of such a trial would significantly affect how we treat our patients. At the present time, ablation as well as any other rhythm measure is meant for patients who have symptomatic AF despite attempts at rate control.

Putting It All Together: How Do We Counsel Our Patients?

Piccini et al9 have performed a careful meta-analysis of the major published trials comparing ablation and drug therapy, but can we extrapolate their conclusions to the patients who seek our care? The average patient in the studies that they analyzed had paroxysmal AF (70%), was 55 years old, and had an average ejection fraction of 60±4%. AF is a disease of the elderly, and patients who seek attention may be particularly symptomatic as a result of coexisting heart failure or ventricular dysfunction and have longstanding, persistent, or chronic AF.21 Perhaps what we learn from the present study, as we await completion and results from the CABANA trial, is that AF ablation can be recommended for symptomatic patients with paroxysmal AF who are young and do not have coexisting heart disease.5 These patients should be made aware that being free from AF may involve adjunctive drug therapy and possible repeat ablation procedures and that the likelihood of long-term recurrence requiring further therapy is not known.

Trials assessing both AF efficacy and comparing AF ablation methods, newer antiarrhythmic agents, and comparison with atrioventricular nodal ablation and device implantation when available may then allow us to counsel our patients on the best approach for managing their AF.

Disclosures

None.

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