

## EDITORIAL COMMENT

# Ablation of Atrial Fibrillation: Awaiting the New Paradigm\*

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In this issue of the *Journal*, Pappone et al. (1) and his colleagues from Milan present the results of a non-randomized prospective trial comparing ablation therapy to medical therapy for management of atrial fibrillation (AF). In this provocative study, these investigators analyze the impact of a “curative ablative” approach to AF compared with drug therapy for sinus rhythm (SR) maintenance. The end points were mortality after a median follow-up of 900 days, quality of life measured with the 36-item short-form general health survey (SF-36), morbidity (heart failure [HF] and embolic events), and recurrent AF. Their results are striking. A total of 1,171 patients were studied between January 1998 and March 2001. The patients who had ablation of AF had a lower mortality due exclusively to a

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lower rate of cardiovascular deaths, primarily HF, stroke, and sudden death. In patients with a history of coronary artery disease, ejection fraction <45%, and age >65 years, survival was improved by 54%. Overall, survival for patients who underwent ablation was identical to that for age- and gender-matched persons in the Italian population.

With respect to the study's other end points, there were fewer episodes of HF and stroke in patients receiving ablation therapy than in those receiving medical therapy. Recurrence of AF was lower among patients receiving ablation therapy (20% vs. 58%). Quality of life returned to normal within six months in patients who underwent ablation. Finally, for the first time, outcomes can be assessed in a general population of patients with AF having a low incidence both of recurrences of AF and of antiarrhythmic drug use.

**Historical perspective.** Cox et al. (2) deserve credit for pioneering an effective surgical approach for the treatment of persistent AF. The maze procedure achieves a high success rate for restoration of SR (>90%) and presumably works by modifying atrial substrate with suture lines placed in both atria. In retrospect, it is likely that the placement of many of the suture lines in or near the pulmonary veins and in the posterior left atrium (LA) results in significant

reduction of the posterior LA available to sustain AF and possibly also prevents conduction from triggering foci within the pulmonary veins to the LA. The surgical lesions created during the maze procedure formed electrical barriers that prevented the maintenance of AF. The most widely practiced catheter-based “curative” approach to the treatment of AF was pioneered by Haissaguerre and his colleagues from Bordeaux in the late 1990s (3). This group highlighted the importance of the pulmonary veins as triggers for the initiation of paroxysmal AF (3,4). These investigators showed that in patients with frequent atrial ectopy and short bursts of AF, the site of initiation of AF could be mapped to a location in or near the pulmonary veins in over 90% of patients. Later, they were able to show that empiric isolation of the pulmonary veins or the electrical connections between the pulmonary veins and LA cured many patients with paroxysmal AF, regardless of whether they had frequent atrial ectopy.

Pappone et al. (1) have developed an approach to the treatment of AF that combines aspects of both the maze and pulmonary vein isolation approaches (i.e., ablation targeted at both triggers and substrate modification). This technique was initially described as “circumferential pulmonary vein ablation” and has been applied successfully to patients with both paroxysmal and chronic AF. In contrast, isolation of the pulmonary veins near the os has shown disappointing results for the treatment of chronic AF. The Pappone et al. (1) approach is an anatomic-based strategy and often results in pulmonary vein isolation or at least delay of PV activation, but it also significantly reduces posterior LA substrate and probably extrapulmonary vein triggers too. To date, follow-up studies of patients undergoing ablation with the “Pappone approach” show that no patient has developed pulmonary vein stenosis, one of the most feared complications of ablative approaches to AF.

**What does this study mean in the post-AFFIRM era?** The recently published data from AFFIRM and RACE suggest that patients enrolled in these trials did equally well with respect to mortality and quality of life whether they were maintained in SR with antiarrhythmic drug therapy or left in AF with adequate heart rate (HR) control (5,6). The failure of rhythm control to enhance survival in these studies may be due to a true neutral effect of the antiarrhythmic agents used, drug discontinuation, or offsetting enhanced survival by maintaining SR with the proarrhythmic effect of drugs. The conservative approach to therapy of AF by these studies is in direct contrast to the more aggressive interventional approach proposed by Pappone et al. (1).

The study in this issue of the *Journal* raises a crucially important question. If we can *nonpharmacologically* maintain SR in a high percentage of patients with AF safely, survival may be better than with either HR control or antiarrhythmic drugs. This pivotal question must be answered in light of the results of AFFIRM and RACE: Do we now have the

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ability to provide a better treatment for AF than antiarrhythmic drug therapy, potentially one that can also alleviate the risk of long-term anticoagulation and stroke? In the present trial, patients were not randomized to ablation or medical therapy, and we do not know how the patients or physicians made the decision to enroll individuals for drug or ablation therapy. It is only through large-scale prospective randomized clinical trials that compare ablation therapy for AF to antiarrhythmic drug therapy and to HR control that we will get the answers clinicians need to best manage these patients.

**The current ablation therapy scenario.** Most clinical centers performing radiofrequency ablation for the treatment of AF perform pulmonary vein isolation using either lasso catheters or baskets placed in the pulmonary veins (7). Overall reported success rates for empiric pulmonary vein isolation have been summarized to range between 47% and 83%, with 20% to 40% of patients taking antiarrhythmic drugs and 10% to 30% of patients requiring a second procedure (7–13). From a survey of centers with more than 1,000 patients who have undergone this procedure, tamponade has been reported to occur in 1%, stroke in 1%, and pulmonary vein stenosis in 1% to 3% (A. Natale, personal communication, 2003). Unfortunately, results comparing survival after pulmonary vein isolation with survival after other therapies are not yet available. The approach advocated by the Milan group has the advantage of avoiding pulmonary vein stenosis by performing the ablation further outside the pulmonary vein os. The low rate of tamponade (0.7%) and stroke (0%) reported here is remarkable but may, at least in part, be related to the need for only a single transseptal puncture and less manipulation inside and near the pulmonary vein os. The average procedure time was only 3 h, which is quite acceptable to most clinicians. Additionally, the evolution of the procedure developed by Pappone as it is now practiced relies on the use of 8-mm electrode catheters and higher radiofrequency energy to create larger and potentially continuous LA lesions (14,15).

**Future perspective.** Pappone et al. (1) have now challenged us to re-evaluate the way we treat patients with AF. Questions remain about how these findings apply to the large population of patients with AF. The mean age of patients in their study was 65 years, compared with mean ages of 70 years in AFFIRM and 69 years in RACE. Pappone routinely screened patients for asymptomatic recurrences only at 1, 3, 6, 9, and 12 months. Symptomatic arrhythmias were aggressively evaluated, but we know that 80% to 90% of AF episodes may be asymptomatic (16). Future trials should make a concerted effort to evaluate patients for asymptomatic AF. The majority of patients with adverse events in this study (72%) had AF at the time of the event. All four cases of peripheral embolism, 89% of the transient ischemic attacks, and 79% of the ischemic strokes occurred in patients with AF. These findings argue

strongly for the realization that AF is not a benign disease in many patients.

In the present study, anticoagulation with warfarin was stopped after SR had been maintained for three months. As a result, about 50% of the patients who had thromboembolic complications were receiving inadequate or no anticoagulant therapy. In light of AFFIRM, the number of embolic events in patients receiving antiarrhythmic agents would have been likely to decrease if anticoagulation had been maintained throughout the study period. The issue of when and if all patients with ablation can safely discontinue warfarin is not answered by this study. The overall average risk of major or potentially fatal bleeding events while being treated with warfarin is 0.7% per year (17). Finally, the rationale for the choice of individual antiarrhythmic drugs was not discussed in the manuscript, and the patients in this trial were taking a large number of different agents. The dosing and monitoring of these patients receiving antiarrhythmic agents is not well detailed.

Pappone et al. (1) are to be congratulated on the logistics of this careful long-term follow-up of patient outcomes after circumferential pulmonary vein ablation. The number of patients studied, the low risk of complications, and the high incidence of SR are impressive. Importantly, many of these patients had significant structural heart disease, and the patient population studied was fairly diverse. Because of these findings, interventional electrophysiologists will need to closely study the methods and results of AF described in the *Journal*. Reproducibility of these findings by other interventional electrophysiologists will also be an important early goal (18). Future randomized trials of therapy for AF must now seriously consider inclusion of an ablation arm. Both the work of Pappone et al. (1) and the work of Haissaguerre et al. (3,4) have begun a new chapter in the therapy for AF. It will be the work of clinical trialists to help us decide how these ablation therapies will find a place among our therapies for patients with AF.

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