EDITORIALS

Early Ablation for Paroxysmal Atrial Fibrillation — Safety First

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Catheter ablation of atrial fibrillation by means of pulmonary vein isolation has undergone substantial improvements in efficacy and safety since it was introduced 20 years ago, and it has become an established treatment for patients with symptomatic atrial fibrillation.[1] Although clinical practice guidelines have generally recommended at least one trial course of antiarrhythmic drug therapy before consideration of ablation therapy, the 2014 U.S. guideline introduced a class IIa recommendation that "In patients with recurrent symptomatic paroxysmal AF [atrial fibrillation], catheter ablation is a reasonable initial rhythm-control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy."[2] The early clinical trials of first-line catheter ablation of atrial fibrillation with radiofrequency energy that were cited to support this recommendation, however, had mixed results.[3]

Two articles in this issue of the *Journal* report the results of randomized, multicenter trials that improve our knowledge base. In STOP AF First (involving 203 patients)[4] and EARLY-AF (involving 303 patients),[5] patients with paroxysmal atrial fibrillation were randomly assigned to initial rhythm control with either antiarrhythmic drug therapy (most commonly with flecainide) or catheter ablation with a cryothermy balloon. Both trials showed substantially lower recurrence rates and greater improvement in quality of life in the ablation groups. In EARLY-AF, there was also a significant, although modest, benefit with respect to the total atrial fibrillation burden. In STOP AF First, serious adverse events occurred in 14% of patients in each treatment group. In EARLY-AF, serious adverse events occurred in 3.2% of the patients in the ablation group and in 4.0% of those in the antiarrhythmic drug group.

Strengths of the trials include their randomized design and rigorous follow-up, particularly in EARLY-AF, which used implantable cardiac monitors with daily transmissions in all patients. These independent trials had similar designs, study populations, and results, which mutually reinforce their findings and conclusions. Relative weaknesses include their lack of blinding; however, the significant between-group differences in atrial fibrillation recurrence rates argue for a true and substantial biologic effect. The most effective antiarrhythmic drug, amiodarone, was rarely used, but this mirrors clinical practice and guidelines for treatment of this patient population.[2] The use of background risk reduction (e.g., with weight loss, exercise, alcohol reduction, or treatment of sleep apnea) was not described.[6] Finally, the trials did not attempt to show between-group differences with respect to other important clinical end points, such as mortality or stroke rates.

The results of STOP AF First and EARLY-AF raise several important questions. Does ablation early in the course of paroxysmal atrial fibrillation prevent progression of atrial structural and cellular changes that lead to persistent and permanent atrial fibrillation?[7] Seen in the context of the recently published EAST-AFNET 4 trial,[8] which showed better outcomes with early rhythm control of atrial fibrillation, it is tempting to conclude that it does. However, this conclusion should await the results of further research. Late recurrence of atrial fibrillation (more than 1 year) after

successful ablation has been shown in 3 to 5% of patients per year in other trials, and the 1-year follow-up in the present trials represents less than 5% of the remaining life expectancy in this relatively young and healthy population.

Can the results be extended to other patients with atrial fibrillation? We should consider the select nature of the populations studied, which had a mean age of 58 to 61 years. Most patients had normal left ventricular function, normal left atrial size, and few coexisting conditions. Therefore, the results of the present research cannot be readily extrapolated to patients with persistent atrial fibrillation, significant structural heart disease, or substantial coexisting conditions that might reduce the efficacy and safety of ablation.

Can the results be extended to other forms of ablative therapy? Although previous trials of early ablation with radiofrequency energy had mixed results, there have been significant interval improvements in radiofrequency catheter design and procedural technique. Other trials have shown substantial therapeutic equivalence between cryoballoon and radiofrequency ablation for drug-refractory paroxysmal atrial fibrillation.[9] There is consensus that durable electrical isolation of the pulmonary veins, however achieved, is the primary therapeutic target in this setting. Therefore, it seems reasonable to extend the present results to other established ablative technologies, provided pulmonary vein isolation can be achieved with the same high success and low complication rates.

This last proviso is critical. As with primary prevention of stroke with carotid endarterectomy, the net clinical benefit depends on the safety of the invasive procedure as performed in real-world practice. Even a small increase in major complications might negate the benefits in symptom control and quality of life seen in these two trials. Clinicians recommending catheter ablation as first-line therapy should be confident that their centers can achieve pulmonary vein isolation reliably and with few adverse events. Participation in clinical registries, morbidity and mortality conferences, and continuous quality-improvement programs are important components in achieving this goal.[10]

The STOP AF First and EARLY-AF investigators have made valuable contributions to the treatment of patients with paroxysmal atrial fibrillation by clarifying "the risks and outcomes of drug and ablation therapy."[2] We can now offer pulmonary vein isolation–based ablation with greater confidence as first-line therapy for selected patients with paroxysmal atrial fibrillation, particularly those who are disinclined to take antiarrhythmic drugs. The new data will inform shared decision-making discussions with all patients with paroxysmal atrial fibrillation. Finally, to offer atrial fibrillation ablation early, we must first ensure that it can be performed safely.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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