

Atrial Fibrillation in Heart Failure Should Catheter Ablation Play a Larger Role?

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Heart failure (HF) promotes atrial fibrillation (AF) by contributing to electric and structural changes. The development of AF in patients with preexisting congestive HF is associated with increased adverse events, including HF progression and mortality.^{1,2} However, large, randomized trials have failed to demonstrate that maintenance of sinus rhythm with antiarrhythmic drug therapy improves mortality.³ Some would argue that the development of AF is a marker of deterioration and that therapy will have little benefit. However, many would agree that sinus rhythm is a good thing. AF patients who have sinus rhythm restored have better functional capacity than those who remain in sinus rhythm.⁴ However, the electrophysiological changes that accompany HF are likely to reduce the chances of long-term maintenance of sinus rhythm. There is also concern that adverse effects of antiarrhythmic drugs, often amiodarone, in this population offset the benefit of sinus rhythm. Achieving sinus rhythm with catheter ablation offers the potential to maintain sinus rhythm without offsetting adverse drug effects.

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Catheter ablation has evolved from a therapy for selected patients with paroxysmal AF and no or minimal structural disease, in whom ablation is more effective than antiarrhythmic drug therapy, to include patients with heart disease and persistent AF.⁵ Despite procedural risks and a healing period of several weeks during which arrhythmia recurrence is not uncommon, current clinical guidelines support catheter ablation for selected patients with symptomatic paroxysmal AF and persistent AF.⁶ In paroxysmal AF, catheter ablation (pulmonary vein isolation) is associated with freedom from recurrent arrhythmias for 1 to 2 years in ≈70% of patients.⁵ In contrast, in patients with persistent AF, ablation with pulmonary vein isolation alone often fails, and additional ablation strategies seeking to deal with presumptive arrhythmia substrates or triggers that extend outside the pulmonary venous antra are commonly used but vary among centers. A recent trial found that fewer than half of patients were free of recurrent atrial arrhythmias after a single procedure.⁷ Efficacy improves with multiple procedures.

HF can be anticipated to adversely affect the response to ablation and the risk of complications. However, initial small studies suggest the potential for significant benefit. Khan⁸ and coworkers compared pulmonary vein isolation with atrioventricular junction ablation/biventricular pacing in 81 patients with AF (paroxysmal in approximately half) and observed a greater improvement in left ventricular ejection fraction (LVEF), 6-minute walk, and quality of life for the pulmonary vein isolation group. Another small, randomized trial demonstrated improvement in functional status with ablation compared with a conservative strategy of rate control in a cohort of subjects with reduced EF and AF.⁹ The feasibility of catheter ablation for patients with HF is further supported by a recent meta-analysis that identified 1838 patients with HF (mean LVEF, 40%) from 26 studies treated with catheter ablation for AF (paroxysmal in 45%).¹⁰ Over follow-ups ranging from 18 to 40 months, single-procedure efficacy was 36% to 44%, and efficacy after multiple procedures was 54% to 67%. Major complications occurred in 4.2% of the patients. However, the role of ablation versus antiarrhythmic drugs in the subset of patients with HF remains ill-defined.

In this issue of *Circulation*, Di Biase et al¹¹ provide results from a randomized, clinical trial of catheter ablation versus amiodarone therapy in a population of 202 patients with AF, New York Heart Association class II or III congestive HF with reduced LVEF (mean LVEF, 29% and 30%), and an implanted defibrillator. Freedom from recurrence of AF or atrial tachycardia (the primary end point) was substantially higher in those receiving catheter ablation compared with those treated with amiodarone (70% versus 34%) over a 2-year follow-up. The ablation group also had lower mortality (8% versus 18%). Enrollment of patients with implantable defibrillators that incorporate an atrial lead for the detection of recurrent atrial arrhythmias was a strength of the study. These findings are rather impressive in favor of catheter ablation, but there are a number of important considerations.

A major issue concerns how widely applicable these findings are to the population of HF patients with depressed systolic function. Unavoidable biases are encountered in the recruitment of HF patients for a trial involving an interventional procedure. A bias toward recruiting “healthier” patients felt likely to tolerate the procedure would be expected, not only for this trial but for other reports of catheter ablation in HF patients. Eligibility for the trial included EF ≤40%, New York Heart Association class II to III HF, and the presence of a defibrillator. A total of 866 patients were screened to enroll 203. These patients were relatively young (mean age, 62 and 60 years) for an HF or AF population. However, their LVEF (29% and 30%), 6-minute walk distance (348 and 350 m), and HF questionnaire scores indicate significant

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impairment. Although they had persistent AF, it is important to recognize that they did not have long-standing chronic AF; the median length of time in AF before enrollment was 8.5 months. It would not be appropriate to extrapolate these results to patients with significantly longer durations of AF because the success rate of ablation is worse when the duration is longer.¹² Amiodarone up to 200 mg/d and redo ablation procedures (average, 1.4 procedures) were permitted within the 3-month postablation blanking period. Pre-enrollment amiodarone therapy was present in slightly more than 10% of the cohort, who presumably already failed this antiarrhythmic drug, which would tend to bias the results in favor of ablation.

It should be recognized that the procedures were performed by well-established experts, which has important bearing on efficacy and risks. Procedural complications are a major consideration in the selection of ablation therapy. The risks of AF ablation have improved as technology and understanding have evolved, but major complications can be anticipated to be greater in HF patients.¹⁰ Notably, the substantial saline load that accompanies irrigated radiofrequency ablation has to be well managed and can result in pulmonary edema even in patients without HF. It is notable therefore that in this study the complication rate of 1.96% for femoral hematoma and only 0.98% pericardial effusion is low and unlikely to be achieved in broader use.^{3,14} This trial incorporated a 3-month treatment period for amiodarone loading and for repeat ablation procedures when arrhythmias recurred after the initial procedure. Recurrent arrhythmias are common after ablation, likely related to healing of initial ablation lesions, and ≈40% of ablation-treated patients received multiple procedures, which increases the exposure to procedural risk. As noted above, the optimal ablation strategy for persistent AF remains controversial. The ablation procedure was not uniform in this study, introducing another potential source of bias, with greater success noted in patients who received pulmonary vein isolation and extensive additional ablation of the posterior left atrial wall. This observation, however, supports the concept that non-pulmonary vein triggers or substrate is likely to be important in the HF population. More extensive ablation may also confer a greater procedural risk, including the risk of esophageal injury, and this may factor into weighing the risk/benefit ratio when ablation is considered.

In the present study, ablation was also significantly better than amiodarone therapy with respect to secondary end points, including unplanned hospitalizations (31% versus 57%). This observation must be interpreted with caution because the decision to hospitalize can be subjective. In addition, hospitalizations for repeat procedures, required for ≈40% of the ablation group, were not counted; their inclusion would likely have resulted in a substantially greater number of hospitalizations in the ablation-treated patients. Even though unplanned hospitalizations were fewer during follow-up, overall use of inpatient resources would be expected to be greater with ablation.

Improvements in LVEF, 6-minute walk distance, and quality of life were observed in both groups. This is anticipated because these follow-up measures can be obtained only in the survivors, and the 13% who died before 2 years

of follow-up would likely have been sicker. Modest improvements in LVEF and functional capacity have been observed with pharmacological rate control or rhythm control strategies in other HF trials.^{3,15} In the present trial, the improvement was seen in patients who remained free of arrhythmia recurrence, which was more likely in the ablation-treated group. Thus, it is encouraging that successful therapy is associated with improvement.

This study compares ablation with a specific drug, amiodarone. The drug discontinuation rate as a result of side effects was 10.4%, and whether the discontinuation rate as a result of side effects would have been as high with another agent such as dofetilide is not known. Furthermore, the study mentions that cardioversion was performed in 51% of the patients in the amiodarone arm during the blanking period. Does this mean that the other 49% did not need to be cardioverted because of reversion to sinus rhythm, or were there patients in whom the treating physician chose not to attempt cardioversion?

Another point to be made is that this is a study of ablation versus an antiarrhythmic drug with significant toxicities, not a study in which ablation is compared with conservative management. Whereas a previous study found amiodarone to be no better than placebo in HF patient with AF,¹⁶ it remains unclear whether catheter ablation is better than conservative management in this population, an important question that this study does not address. Mortality was lower in the ablation group (8% versus 18%), but it should be appreciated that this was a secondary end point with a small number of events. It is notable that amiodarone has been associated with worsened mortality compared with placebo in patients with New York Heart Association class III HF.¹⁷ Its toxicities, drug interactions, and bradycardic effect, which could increase ventricular pacing from the implanted defibrillator, leading to adverse hemodynamic effects, are potential mechanisms by which it could exert an adverse effect in this population.

In summary, the findings of Di Biase et al¹¹ support consideration of ablation for selected HF patients with systolic dysfunction who have AF that has become persistent relatively recently, who are deemed good candidates to tolerate the ablation procedure, and for whom a strategy of maintaining sinus rhythm is desired by the patient and physician. Selection of this therapy is also contingent on availability of the expertise to achieve excellent results safely. Although definitive mortality data are not available, we believe that the prevention or elimination of AF in symptomatic HF patients is desirable as long as the treatment strategy does not come at undue risk to the patient. The risks of catheter ablation are largely up front compared with the continually increasing toxicity risks of maintenance therapy with amiodarone. The present study suggests that catheter ablation may be reasonably considered as an alternative to amiodarone in these selected patients. Further clinical trials will help piece together the appropriate strategies for the management of AF in the HF population.

Disclosures

Dr Stevenson is coholder of a patent for needle ablation that is assigned to Brigham and Women's Hospital. Dr Koplan has received consulting fees from St. Jude Medical, Inc.

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