

## EDITORIAL



## Rhythm Control in Atrial Fibrillation — One Setback after Another

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Atrial fibrillation, the most common sustained arrhythmia observed in hospitalized patients, is associated with substantial morbidity, and its occurrence approximately doubles the rate of death as compared with that of patients in whom sinus rhythm is maintained. The global effect of atrial fibrillation on public health is so great that international professional organizations have integrated the results of seminal studies to progressively formulate data-driven management guidelines.<sup>1</sup>

Patients with heart failure are at increased risk for atrial fibrillation and constitute an important subgroup of all patients with this arrhythmia. Data from trials involving patients with atrial fibrillation have shown that a “rhythm-control strategy,” in which antiarrhythmic drugs are used along with serial electrical cardioversion when necessary, is not superior to a “rate-control strategy,” in which no specific efforts are made to maintain sinus rhythm and heart-rate control is the main objective.<sup>2,3</sup> However, the same outcome may not hold true for the large subgroup of patients with heart failure. In this issue of the *Journal*, two groups of international investigators — Roy et al.<sup>4</sup> and Køber et al.<sup>5</sup> — describe the results of clinical trials that will contribute to the evolution of guidelines for the treatment of patients with heart failure and atrial fibrillation.

The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial (ClinicalTrials.gov number, NCT00597077)<sup>4</sup> was a prospective, randomized, multicenter comparison of a rhythm-control strategy and a rate-control strategy. All 1376 patients in the study by Roy et al. had a left ventricular ejection fraction of 35% or less, heart-failure symptoms, and a history of atrial fibrillation. The primary outcome was the time to death from car-

diovascular causes. Patients were followed for a mean of 37 months. Not only was there no significant difference in the rate of death from cardiovascular causes (27% in the rhythm-control group and 25% in the rate-control group,  $P=0.59$ ), but there was no significant difference in any of the secondary outcomes, including death from any cause and worsening heart failure.

Nature has equipped the human heart with a complex electrical system for the purpose of coordinated propulsion of blood under a variety of physiologic conditions. Considerable effort is expended by the heart to maintain sinus rhythm. Cardiac electrophysiologists view atrial fibrillation as a system failure. They are likewise frustrated by the conundrum that atrial fibrillation is associated with increased morbidity and mortality, yet attempts to prove that a strategy to maintain nature’s rhythm has a favorable effect on patients have been met with one setback after another.<sup>2-4</sup> Fortunately, the story does not end here. There are at least four concepts that help reconcile this paradox.

First, the rhythm-control strategies used in the AF-CHF trial and the other cited studies do not guarantee the maintenance of sinus rhythm, and not all patients in the rate-control group had persistent atrial fibrillation. Similar to the findings in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial (ClinicalTrials.gov number, NCT00000556),<sup>2</sup> the absolute difference in actual heart rhythm during follow-up in the AF-CHF trial was approximately 40%, since sinus rhythm was not maintained in 100% of the patients in the rhythm-control group and was maintained in some of the patients in the rate-control group. Some 58% of patients in the

rhythm-control group had at least one recurrence of arrhythmia during follow-up. Moreover, some patients in the rhythm-control group were needlessly exposed to the adverse effects of antiarrhythmic drugs, since they were unlikely to have a recurrence of atrial fibrillation anyway.

Second, the toxicity of antiarrhythmic drugs probably contributed to the lack of benefit observed in the rhythm-control group. Only amiodarone and dofetilide have been shown to have a neutral effect on survival in patients with heart failure.<sup>6-8</sup> In the AF-CHF study, amiodarone, sotalol, and dofetilide were all permitted, but the majority of patients in the rhythm-control group received amiodarone. Given the neutral effect of amiodarone on survival, it is possible that amiodarone was not sufficiently effective to show superiority of the rhythm-control approach. In this regard, the proportion of patients who were receiving amiodarone after 36 months of follow-up declined by nearly 10 percentage points from baseline, indicating intolerance to or inefficacy of therapy. Moreover, 21% of patients crossed over to rate control because sinus rhythm could not be maintained despite antiarrhythmic drug therapy and serial cardioversions.

Substantial resources are being invested in the development of new drugs that promise to be more efficacious and safer for use in patients with atrial fibrillation. The challenges that are associated with this goal are illustrated in the Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA; ClinicalTrials.gov number, NCT00543699).<sup>5</sup> Dronedarone has multichannel blocking properties similar to those of amiodarone but without the iodine moiety, which is responsible for some of amiodarone's toxicity. In ANDROMEDA, Køber et al. tested whether dronedarone could reduce the composite end point of death from any cause or hospitalization for heart failure, as compared with placebo, in patients with heart failure. However, the inclusion criteria did not include a history of atrial fibrillation. The trial was stopped prematurely because of an excess rate of death in the active treatment group, which was primarily attributed to worsening heart failure. Although conventional antiarrhythmic drugs often prove to be only modestly effective in preventing atrial fibrillation, there is increasing evidence that angiotensin-converting-enzyme inhibitors, statins, and other non-

antiarrhythmic drugs can favorably modulate the natural course of atrial fibrillation and appear to be protective in many settings, even in patients with heart failure.<sup>9,10</sup>

Third, as was described by investigators in the AF-CHF study, atrial fibrillation may be a marker of poor prognosis, in which the primary problem is poor ventricular function, neurohormonal activation, or inflammation, with no independent effect of atrial fibrillation on outcome.

Finally, the results of the AF-CHF study are concordant with those from other studies that also did not show superiority of a rhythm-control strategy dependent on the administration of antiarrhythmic drugs for patients with atrial fibrillation, even among those with concomitant heart failure. Sufficient data are available to lay the blame for these setbacks on the drug-based rhythm-control strategy itself, rather than on the conclusion that sinus rhythm is no better for patients than atrial fibrillation.

Driven by these circumstances, investigators should next focus on a rhythm-control strategy that eliminates the confounding contributions of low efficacy and high toxicity associated with antiarrhythmic drug therapy to better determine the desirability of maintaining sinus rhythm in patients with atrial fibrillation. Ablation therapy serves this purpose. There are clinical trials in progress and being planned to test catheter ablation of atrial fibrillation, as compared with conventional antiarrhythmic drug therapy. Although the initial goal will be to show better maintenance of sinus rhythm and amelioration of symptoms with the use of ablation, a second goal needs to be the assessment of survival and cardiovascular morbidity in the two approaches. Ultimately, studies must also test the superiority of ablation therapy, as compared with rate control, since ample data show that rate control is an acceptable strategy and one that is almost certainly more cost-effective than any other approach.

Until such questions are answered, it is difficult to support a primary approach of rhythm control that relies on antiarrhythmic drugs in any patient with atrial fibrillation, including those with heart failure. Even for symptomatic patients, it seems prudent first to attempt to eliminate symptoms with drugs that control the ventricular rate and then to consider therapy with antiarrhythmic drugs only if symptoms persist. Anticoagulation should be prescribed to all appropriate patients on

the basis of the CHADS<sub>2</sub> score.<sup>1</sup> Champions of sinus rhythm must await the results of comparative ablation trials to learn whether the field suffers another setback or moves forward.

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