EDITORIALS

Revisiting Rate versus Rhythm Control in Atrial Fibrillation — Timing Matters

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Treatment approaches for atrial fibrillation are characterized broadly into two categories: "rhythm control," attempting to maintain sinus rhythm, and "rate control," to slow ventricular rate. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), in which rhythm control was compared with rate control in 4060 patients with atrial fibrillation, there were no significant differences between rhythm control and rate control at 5 years with respect to mortality (23.8% and 21.3%, respectively; P=0.08) or the percentage of patients with ischemic stroke (7.1% and 5.5%, P=0.79).[1] A meta-analysis of five randomized trials of rhythm control as compared with rate control likewise showed no significant differences with respect to all-cause mortality and stroke, although the results appeared to favor rate control.[2] Therefore, rate-control strategies are used preferentially, and rhythm-control strategies are recommended primarily to improve atrial fibrillation–related symptoms.[3]

In AFFIRM, rhythm-based treatment in two thirds of the patients consisted of amiodarone or sotalol, and, at 5 years of follow-up, the prevalence of sinus rhythm was 63% (35% in the rate-control group), with 38% having crossed over to rate control, primarily because of side effects or poor efficacy of the drugs.[1] However, in a post hoc analysis, the presence of sinus rhythm was significantly associated with a lower risk of death (hazard ratio, 0.53; 99% confidence interval [CI], 0.39 to 0.72).[4] In hindsight, this trial did not clearly answer the question of whether maintaining sinus rhythm is beneficial, owing to the limited efficacy and risks associated with the antiarrhythmic drugs that were used, including proarrhythmic effects.[5]

Advances in atrial fibrillation rhythm control have led to greater safety and effectiveness and, with augmented experience, improvements in patient selection. Dronedarone, a newer antiarrhythmic drug (not available in previous trials), was found to be associated with lower risks of stroke and of the composite outcome of stroke, acute coronary syndrome, or death from cardiovascular causes than placebo.[6] Catheter ablation has become broadly available and, when successful, minimizes exposure to antiarrhythmic drugs and favorably affects clinical outcomes.[7] In the Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial,[8] ablation was associated with a lower risk of recurrent atrial fibrillation (hazard ratio, 0.52; 95% CI, 0.45 to 0.60) and of the composite of mortality or hospitalization for cardiovascular causes (hazard ratio, 0.83; 95% CI, 0.74 to 0.93) than antiarrhythmic drugs. Because atrial fibrillation represents a progressive disease driven by systemic vascular disease and worsening atrial cardiomyopathy, studies have shown improved efficacy of rhythm therapy when it is started earlier.[9] However, it has not been clear whether earlier rhythm control improves clinical outcomes.

Enter the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4), an international, randomized, open, blinded-outcome-assessment trial comparing early rhythm control with usual care among patients with atrial fibrillation and additional cardiovascular risk factors, the results of which are now published in the *Journal*.[10] A defining aspect of the trial is that these patients had atrial fibrillation that had recently been diagnosed (<1 year earlier), with one third of the patients having their first episode of atrial fibrillation. Patients who were randomly assigned to early rhythm control had a lower risk of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome (hazard ratio, 0.79; 96% CI, 0.66 to 0.94; P=0.005), as well as

a lower risk of the individual components of death from cardiovascular causes (hazard ratio, 0.72; 95% CI, 0.52 to 0.98) and stroke (hazard ratio, 0.65; 95% CI, 0.44 to 0.97). The number of nights spent in the hospital did not differ significantly between the treatment groups. Rhythm-control–related adverse events were infrequent, occurring in 4.9% of patients in the group assigned to early rhythm control, with drug-related bradycardia the most common event.

The rhythm-control approach at 2 years in the group assigned to early rhythm control was broad and somewhat evenly distributed among catheter ablation (19%), class 1c antiarrhythmic drugs, dronedarone, amiodarone, and "other" drugs. Long-term adherence to rhythm control remained a challenge, as in previous trials, with 65% still receiving active rhythm control at 24 months. Sinus rhythm was present at 24 months in 82% of the patients assigned to early rhythm control and 60% of the patients assigned to usual care; only 15% of those assigned to usual care ultimately received rhythm control.

The strongest predictor of survival in AFFIRM was not the presence of sinus rhythm but the use of warfarin, which was continued in 70% of patients; ischemic strokes in either treatment group largely occurred in patients in whom anticoagulation was withheld.[4] In EAST-AFNET 4, the use of anticoagulation was common and continued over time (approximately 90% of patients in both groups at 2 years), and the incidence of stroke was correspondingly low (0.6% of patients assigned to early rhythm control and 0.9% of patients assigned to usual care).

A limitation of EAST-AFNET 4, with its low event rates, was that 9.0% and 6.6% of follow-up years in the early-rhythm-control group and usual-care group, respectively, were lost because patients withdrew from the trial or were lost to follow-up (characteristics of the patients not presented). The burden of atrial fibrillation was not reported, and its role as a contributor to outcomes remains unknown. The reported percentages of patients with sinus rhythm were probably overestimated, since they were assessed by electrocardiography rather than continuous monitoring.

The results of this trial support the use of rhythm control to reduce atrial fibrillation–related adverse clinical outcomes when applied early in the treatment of patients with atrial fibrillation. The use of other cardiovascular therapies (including anticoagulants, renin–angiotensin–aldosterone system inhibitors, beta-blockers, and statins) in the trial probably contributed to the low rates of stroke, heart failure, acute coronary syndrome, and death and highlight the need to treat atrial fibrillation with comprehensive management.[11]

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

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