Editorials

Management of Atrial Fibrillation — Radical Reform or Modest Modification?

THE concept that the restoration of sinus rhythm in patients with atrial fibrillation is always an important goal has been largely uncontested for many years. Now, in this issue of the *Journal*, two trials comparing heart-rate control with rhythm control have tested this assumption and have found it wanting. Both the Atrial Fibrillation Follow-up Investigation of Rhythm Management, a North American study,[1] and the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study, conducted in Europe,[2] tested the hypothesis that among patients with atrial fibrillation, attempted maintenance of sinus rhythm would be equivalent in outcome to control of the ventricular rate. Although the primary end points of the two trials differed — mortality from any cause in the North American study and a composite of mortality and serious events in the smaller European study — each trial showed that rhythm control was not superior to rate control in a population of older patients, most of whom had persistent, recurrent arrhythmia. Indeed, in both studies, analysis of the primary end point showed a trend in favor of rate control, and in both, there were some unexpected secondary observations. The findings in these trials deserve careful consideration, since they may influence the way in which atrial fibrillation is treated.

The patient populations in both studies were representative of the majority of patients with atrial fibrillation.[3,4] Perhaps because of the stringent enrollment criteria (persistent atrial fibrillation and at least one previous cardioversion), the low rate of maintenance of sinus rhythm in the European trial is at odds with the rates in other studies that used antiarrhythmic drugs to maintain sinus rhythm, including some of the same investigators' earlier data.[5,6] Although this raises the possibility that the outcome might have been different had patients with less chronic arrhythmia been studied, this possibility appears unlikely, since the North American trial had a much higher rate of maintenance of sinus rhythm but a very similar outcome.

One surprising secondary finding was that attempted maintenance of sinus rhythm did not reduce the risk of ischemic stroke. Among the patients with strokes in the North American study, the majority either were not receiving warfarin or had a subtherapeutic international normalized ratio at the time of the stroke. Intriguingly, only 53.8 percent of the patients with ischemic stroke in the rate-control group and 30.5 percent of the patients with ischemic stroke assigned to rhythm control had atrial fibrillation at the time of the event. Although the high prevalence of sinus rhythm might suggest a noncardiogenic source of cerebral infarction, it is perhaps more likely, given the study population, that most of the strokes were related to atrial fibrillation. What might be the mechanism? It is well recognized that asymptomatic paroxysmal episodes of atrial fibrillation may occur in patients who present with symptomatic paroxysmal atrial fibrillation,[7] and recent data suggest that asymptomatic paroxysmal episodes also occur in over 25 percent of patients with previously persistent arrhythmia who have undergone cardioversion.[8] In some cases, the brevity of the episode may account for the absence of symptoms. In other cases, the atrial fibrillation may not cause symptoms because antiarrhythmic drugs have slowed the ventricular rate. This high prevalence of transient, asymptomatic atrial fibrillation raises the possibility that such episodes were responsible for many of the ischemic strokes in the North American and European studies. Although this remains a hypothesis, the data are suggestive enough to warrant future studies, with more frequent monitoring for arrhythmia in patients in whom atrial fibrillation appears to have been abolished.

The statistically significant excess in the number of primary end points among women randomly assigned to rhythm control in the European study should be interpreted with caution. It was not a prespecified analysis, and in the rate-control group, women had fewer end points than did men. If this is not a chance finding, it suggests that the larger number of end points in the rhythm-control group represents an interaction between treatment and sex, instead of being a function of sex alone. The women may have had a different spectrum of underlying heart disorders, predisposing them to drug-related events. In the Framingham Heart Study, among patients with atrial fibrillation who survived for more than 30 days, women had a greater relative risk of death than did men, but therapies were not specified.[9] Women are also more prone to serious side effects of antiarrhythmic drugs, since they are at greater risk for excessive drug-induced prolongation of the QT interval and torsade de pointes.[10,11] Female sex, independent of concomitant risk factors, may also be a risk factor for stroke among older patients with atrial fibrillation.[12] Unfortunately, the European investigators did not present the results of a specific analysis of the causes of the end points in women, and the North American investigators did not address the question of sex-related differences, so the consistency and potential cause of these findings remain unknown.

Hypertension was also a marker of a worse outcome

in the rhythm-control group in the European study, and in the North American study there was a strong trend toward increased mortality among the patients with hypertension in the rhythm-control group. A possible explanation is that hypertension is the most common cause of left ventricular hypertrophy, and hypertrophy is associated with an increased risk of drug-related arrhythmic events.[13] Hypertension, even if treated, is also a risk factor for embolic stroke among patients with atrial fibrillation and inadequate anticoagulation.[12] Whatever the mechanism, these two studies underscore both the importance of hypertension as a risk factor for atrial fibrillation and the need to consider it when choosing a treatment strategy.

What are the practical implications of the North American and European studies for the treatment of a patient with atrial fibrillation? At first glance, it may seem that the results render an attempt at cardioversion obsolete, since the quality of life, the risk of stroke, and mortality were not affected by an attempt to maintain sinus rhythm. However, all the patients in the European study and the majority of those in the North American study had already had an episode of atrial fibrillation, indicating that they had a propensity for recurrent arrhythmia. Whether or not the findings of these studies can be generalized to a first episode of arrhythmia is unclear.

A reasonable approach to a first episode of atrial fibrillation is to undertake a careful assessment of symptoms and the underlying cardiac disease. An attempt to restore sinus rhythm is appropriate, although it can no longer be deemed imperative. Cardioversion might even be performed initially without the use of antiarrhythmic drugs, thereby avoiding potential side effects. This approach may result in the maintenance of sinus rhythm for a year or more in about 25 percent of patients.[14] If arrhythmia recurs and if symptoms persist despite rate control, repeated cardioversion with the addition of antiarrhythmic drugs should be considered. For an asymptomatic recurrence of persistent atrial fibrillation, it is reasonable to simply control the ventricular rate, particularly if the patient has a history of high blood pressure. Whatever the strategy, careful attention to anticoagulation is mandatory. Whether lifelong anticoagulant therapy is necessary in a patient who has undergone cardioversion from recurrent atrial fibrillation to sinus rhythm, on the basis of these new observations, or whether warfarin therapy should simply be continued for a longer period than the recommended 4 to 12 weeks[1,15] remains uncertain.

A word of caution is needed. Although the European and North American trials represent a landmark in the management of atrial fibrillation, there remains a substantial proportion of patients in whom atrial fibrillation causes symptoms despite pharmacologic attempts to control heart rate. Younger patients with structurally normal hearts and paroxysmal arrhythmia may be disproportionately represented in this group. For them, the goal is still the maintenance of sinus rhythm, and the quest for better drugs and techniques to achieve this goal will, and should, continue.

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