Rhythm versus rate control for atrial fibrillation management: what recent randomized clinical trials allow us to affirm

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and generates significant health care costs.[1] About 10% of people aged 65 years or more will develop AF during their remaining lifetime. There are 2 general approaches to managing AF: the first is to attempt to restore and maintain sinus rhythm (the so-called "rhythm-control" approach); the second is to leave patients in AF while minimizing their symptoms and preventing deterioration of ventricular function by controlling the ventricular response rate (the "rate-control" approach). Although the former approach is theoretically preferable because it normalizes cardiac electrical function, sinus rhythm can be maintained in only about 25% of patients without long-term antiarrhythmic drug therapy. Antiarrhythmic drugs have a variety of potentially significant adverse effects and are only moderately effective in maintaining sinus rhythm; therefore, it has been argued by some that rate control should be the primary approach to managing AF.

In 2 recently completed studies, patients were randomly assigned to rate control or rhythm control for AF management. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators studied 4060 patients with a history of AF and risk factors for stroke or death. Two-thirds of patients had experienced more than 1 previous episode of AF, about one-half had hypertension, one-quarter had coronary artery disease or heart failure, or both, and one-sixth had had a previous antiarrhythmic drug failure.[2] Van Gelder and colleagues studied 522 patients with AF with risk factors for stroke. The composition of this group was generally similar to that of the AFFIRM trial,[3] although, in the Van Gelder trial, significantly more patients treated with rhythm control had hypertension than did those treated with rate control (55% v. 43%).[3]

Neither trial found a beneficial effect of rhythm control on mortality rate or other principal outcome variables. On the contrary, a variety of adverse outcomes were noted in the rhythm-control groups. In the AFFIRM trial, adverse events more common in the rhythm-control group included torsades de pointes (0.8% rhythm control, 0.2% rate control), severe bradyarrhythmias (0.6% v. < 0.1%), readmission to hospital (80% v. 73%), pulmonary events (7.3% v. 1.7%) and gastrointestinal events (8.0% v. 2.1%). Five-year mortality was marginally higher in the rhythm-control group (23.8% v. 21.3%, $p = 0.08$). In the smaller Van Gelder study, mortality from cardiovascular causes was 7.0% in the rate-control group and 6.8% with rhythm control. The composite primary endpoint was nonsignificantly more prevalent in the rhythm-control group (22.6%) than in the rate-control group (17.2%), largely because of higher rates of heart failure (4.5% v. 3.5%), thromboembolic complications (7.9% v. 5.5%), adverse effects of antiarrhythmic drugs (4.5% v. 0.8%) and pacemaker implantations (3.0% v. 1.2%). Of note, adverse outcomes in the rhythm-control group were particularly frequent in female and hypertensive patients. This observation is consistent with the known predilection of women and patients with organic heart disease to proarrhythmic drug reactions;[4] however, more information is needed about the specific composition of adverse events by group.

What do these results mean? Clearly, they cannot be interpreted as favouring rhythm control as the primary approach to AF management. Rhythm control did not produce favourable outcomes and, indeed, was associated with a variety of unfavourable ones. Most of the adverse outcomes were predictable consequences of the presently available antiarrhythmic drug therapy required to maintain sinus rhythm: electrical events (torsades de pointes or bradyarrhythmias) and pulmonary or gastrointestinal adverse effects. Sinus rhythm was maintained in only 62.6% of patients at 5 years in the AFFIRM trial and in only 39% at end of study or withdrawal in the Van Gelder trial. Thromboembolic complications were often noted during sinus rhythm and were associated with a lack of therapeutic anticoagulation. Thus, sinus rhythm maintenance may not prevent thromboemboli; however, it remains to be determined whether thromboembolic events during sinus rhythm reflect asymptomatic AF episodes resulting in thromboemboli on conversion to sinus rhythm or events unrelated to AF per se in a population at risk for thromboembolic events. Overall, the results reflect the limited efficacy and the nontrivial adverse effects of presently available antiarrhythmic drug therapy.

How should these findings affect our clinical practice? They certainly indicate that we should not aim for "sinus rhythm at all costs." Sinus rhythm maintenance may be difficult in many patients with AF, and when antiarrhythmic drug therapy is necessary, the limited efficacy and nontrivial risk of adverse effects of currently available agents must

be considered. For patients presenting with asymptomatic or minimally symptomatic AF, rate control is now a viable option for first-line therapy. On the other hand, it would be wrong to go to the other extreme and conclude that rate control should be the primary approach for all patients with AF. First, it must be remembered that the study populations in the AFFIRM and Van Gelder trials were selected because they were at high risk of stroke or death, and that most patients had already had more than one AF episode (making sinus rhythm maintenance less likely than in a population with a primary episode). We must be cautious in extrapolating from these results to the broader population with AF, particularly patients presenting with a first episode of AF. Second, rate control is not always easy to achieve, particularly in patients with paroxysmal atrial fibrillation. In such individuals, rhythm control may be an effective alternative. Third, some patients do not feel well when they are in AF and are clearly symptomatically better with a rhythm-control approach. Although an important previous randomized study found no difference in overall quality of life in patients with AF managed with rhythm control as opposed to rate control, performance on a 6-minute walk test was significantly better in patients treated with rhythm control.[5]

The most important consequence of these studies should be to encourage us to take a more thoughtful approach to AF management. AF is not a "disease" that must be eradicated. It is a cardiac rhythm disorder with some adverse effects and some risks, which need to be weighed against the adverse effects and risks of therapies that may be used to control it. Moreover, the population of patients with AF is not a homogeneous entity for which a single therapeutic approach can be recommended. The adverse effects and risks of AF, as well as those of its treatment, vary from patient to patient.[4,6] Patient-specific factors need to be considered in choosing the best treatment for each person.

Finally, what are the implications of these trials for the future development of AF therapy? Some may argue in a simplistic way that these well-performed studies indicate that sinus rhythm maintenance is not a desirable goal, and that research energies should be invested in achieving better rate-control modalities rather than in developing new approaches for rhythm control. The results certainly reflect the limitations of current sinus rhythm maintenance therapy. As such, they are an argument for the development of improved approaches to maintaining sinus rhythm. Areas under active investigation include new devices for AF prevention, novel ablation approaches to curing AF, new forms of antiarrhythmic drug therapy that may be more atrium selective and novel approaches to preventing the development of the AF substrate.[7] Hopefully, these efforts will bear fruit and make sinus rhythm maintenance a more achievable and favourable goal in the future.

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