EDITORIALS

Rate Control in Atrial Fibrillation

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Untreated atrial fibrillation is usually associated with a rapid, irregular ventricular response and is often accompanied by symptoms including palpitations, fatigue, dyspnea, and dizziness. It is widely accepted that slowing the ventricular response, both at rest and during activity, with the use of drugs that prolong the refractory period of the atrioventricular (AV) node (so-called rate-control agents) will result in an improvement in symptoms and most likely reduce the future risk of adverse cardiovascular events. The strategy of rate control is preferred by most physicians to the strategy of rhythm control as initial therapy for patients with atrial fibrillation,[1] given the failure to show that rhythm-control strategies result in lower rates of death, stroke, or hospitalizations or better quality of life in large, well-conducted, randomized clinical trials.[2]

When choosing to administer a rate-control agent to a patient, it seems reasonable to attempt to achieve ventricular rates similar to those present during sinus rhythm in patients with a similar degree of heart disease. These targets are based on the belief that lower heart rates will result in fewer symptoms, are likely to be associated with better cardiovascular function because of longer diastolic filling times and more satisfactory hemodynamics, and are associated with a lower risk of tachycardia-related cardiomyopathy. Extrapolation from epidemiologic studies showing that faster heart rates in sinus rhythm are associated with increasing mortality from cardiovascular causes, and the documented clinical and quality-of-life benefits of the "pace and ablate" approach to ventricular rate control,[3] also imply that the more closely ventricular rates during atrial fibrillation approximate those during normal sinus rhythm, the better the outcome.

These considerations have led to widely adopted guidelines for the ventricular rate targets in patients with atrial fibrillation,[4] which recommend resting heart-rate targets of less than 80 beats per minute and targets during moderate physical activity of less than 110 beats per minute. These admittedly arbitrary targets, measured with the use of electrocardiography, are based on the expectation that the benefits of more intensive rate control outweigh its disadvantages and risks.

A number of previous lines of evidence, however, suggest possible flaws in the concept of targeting heart rates to near-normal levels. First, the relation between the achieved heart rate and the quality of life or symptoms is inconsistent, and the degree of symptoms during atrial fibrillation is more strongly related to severity of the underlying cardiac disease, age, and sex than it is to heart rate itself.[5,6] In retrospective substudies of AFFIRM (the Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial[7] and the RACE (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation) trial,[2] in which patients were randomly assigned to undergo a rate-control strategy or a rhythm-control strategy, there was no evidence of a reduction in morbidity or mortality or improved quality of life in patients with "tight" versus "less tight" rate control.[6,8] In patients with heart failure, in whom the potential deleterious effects of a high ventricular rate might be particularly prominent, there is no evidence that bisoprolol, as compared with placebo, reduced the rates of death or hospitalization in a subgroup of patients who had atrial fibrillation at baseline.[9]

In this issue of the *Journal*, Van Gelder and colleagues report on the RACE II (Rate Control Ef-

ficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) trial (ClinicalTrials.gov number, NCT00392613).[10] They have made an important contribution to our understanding of the potential benefits and risks of the current guideline-recommended approach to ventricular rate control in patients with persistent atrial fibrillation.

By means of a variety of AV nodal blocking agents, which included beta-blocker therapy in 79% and calcium-blocker therapy in 37% of patients, a resting heart rate of less than 80 beats per minute at rest was achieved in 67% of patients who were randomly assigned to this strict rate-control target. In this group, the average (±SD) heart rate measured with the use of 24-hour Holter monitoring was 78±11 beats per minute, and 88% of patients had resting heart rates of 90 beats per minute or less after the dose-adjustment phase. Conversely, in the lenient-control group, in which the resting heart-rate target was less than 110 beats per minute, 98% of patients achieved this target; resting heart rates were faster than 80 beats per minute in 98% and faster than 100 beats per minute in 23%. This less stringent rate-control target was achieved with the use of lower doses of beta-blockers, and beta-blockers were required in only 65% of patients; a combination of AV nodal blockers was necessary in 30% of patients, in contrast to 69% in the strict-control group.

Although the confidence intervals around the hazard ratios for the composite primary outcome and the components of the primary outcome are wide, there is no indication that there was any clinical benefit to strict rate control with respect to the risk of death, serious adverse outcomes (including heart failure), or symptoms. It is instructive to speculate that symptomatic adverse effects of rate-control drugs could offset the potential symptomatic benefits of strict rate control, given the minority of patients in both groups (24%) who had palpitation as a recorded symptom. In the strict-control group, the reason the target was not achieved was because of drug-related adverse events in 25% of patients. These results suggest that the potential clinical benefits of a "conventional" approach to ventricular rate control, even if present, may be offset by the potential adverse effects of drugs used for this purpose.

A number of limitations of the RACE II study need to be borne in mind. First, it is possible that rapid ventricular rates may take many years to result in cardiac deterioration and illness or death, and thus there may be a benefit of more "strict" ventricular rate control over a period of decades or more. Patients with atrial fibrillation who also have very rapid ventricular responses, present with heart failure, and appear to have tachycardia-related cardiomyopathy may have particular benefit from strict rate control; this subgroup may have been underrepresented or not enrolled in the RACE II trial. The data on symptoms and quality of life collected in the study were somewhat limited, such that subtle benefits in this regard from stricter rate control may not have been easily ascertained. As in all randomized, clinical trials, selection bias most likely limited the enrollment of patients to those who were relatively clinically well, were somewhat younger than the average age for patients with atrial fibrillation, and had some degree of rate control at study entry (mean heart rate in both groups at baseline, 96 beats per minute). Two thirds of the patients were men; women are known to have more severe symptoms than men during atrial fibrillation, possibly in association with more rapid ventricular rates on average.[11]

What clinical inferences can be drawn from the RACE II study, given the previous state of knowledge regarding rate control? First, a heart-rate target of less than 110 beats per minute at rest, although it may make physicians feel uncomfortable, is probably as useful as the current guideline-recommended target heart rates at rest and during exercise, at least in the medium term. Many patients will continue to be symptomatic under the rate-control approach, whether a strict or more lenient target heart rate is used. The RACE II study does not suggest that ventricular rate control is not needed, only that the conventional therapeutic target needs to be reassessed. At a minimum, the study indicates that reflexive, "recipe-based" adherence to a rate-control target does not seem sensible and that an approach emphasizing the adjustment of therapy on the basis of symptoms and general well-being can be safely recommended.

As in many other clinical situations, in patients with atrial fibrillation, treating a laboratory test is not a good substitute for targeting overt clinical outcomes. This important study serves as a reminder that it is better to treat the patient and not the electrocardiogram.

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Optimal Duration of Clopidogrel Use after Implantation of Drug-Eluting Stents — Still in Doubt

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As compared with bare-metal stents, drug-eluting stents reduce restenosis in every clinical situation and every type of lesion studied. Why, then, do some cardiologists use drug-eluting stents in 90% of patients and other cardiologists in 10%? The explanation relates primarily to two questions. First, are drug-eluting stents associated with a greater risk of "very late" (>1 year after implantation) stent thrombosis than bare-metal stents? And second, what is the required duration of dual antiplatelet therapy after implantation of drug-eluting stents? Incredibly, the answers to these questions are still unknown.

Definitions of stent thrombosis are either insufficiently sensitive or insufficiently specific. Since nearly all stent thromboses causes a large myocardial infarction or death, assessing the frequency of death and infarction rather than stent thrombosis ought to be sufficient. However, doing so might result in small infarctions due to restenosis and repeat procedures, the risks of which are reduced by drug-eluting stents, "counterbal-

ancing" large infarctions due to stent thrombosis, the rates of which might be increased by drug-eluting stents. Whether such counterbalancing has in fact clouded the interpretation of analyses is unknown. A meta-analysis of 22 randomized trials comparing drug-eluting stents and bare-metal stents showed no evidence of an increase in the risk of death, myocardial infarction, or stent thrombosis with drug-eluting stents.[1] But the median duration of follow-up in this analysis was only 2.9 years.[1] Concern arises from observational studies indicating absolute rates of very late stent thrombosis of 0.5% per year and higher that persists for years in association with drug-eluting stents but not bare-metal stents.[2,3]

The second question relates to the requisite duration of dual antiplatelet therapy after implantation of drug-eluting stents. This question is addressed in this issue of the *Journal* by Park and colleagues in their report[4] on two trials, called REAL-LATE (Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated