

Lenient Rate Control in Atrial Fibrillation Not Worse Than Strict Rate Control

Van Gelder IC, Groeneweld HF, Crijns HJG, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;362:1363–73.

Study Overview

Objective. To determine whether aggressive control of heart rate during treatment of atrial fibrillation leads to improved outcomes.

Design. Prospective, open-label, noninferiority randomized controlled trial comparing a goal resting heart rate of < 80 beats per minute and < 110 beats per minute during moderate exercise (strict control) to a goal resting heart rate of < 110 beats per minute (lenient control).

Setting and participants. The study was conducted in 33 centers in the Netherlands. Subjects were 614 patients with permanent atrial fibrillation for less than 12 months. The sample included only adults \leq 80 years old who had a mean resting heart rate of > 80 beats per minute at baseline and were currently receiving oral anticoagulant treatment (or aspirin if they had no risk factors for thromboembolic disease). Exclusions included a diagnosis of paroxysmal atrial fibrillation, contraindications to either strict or lenient control, unstable heart failure, cardiac surgery within 3 months, history of stroke, use of any implanted rate or rhythm control device such as a pacemaker or defibrillator, AV conduction disturbances, untreated hyperthyroidism or < 3 months of euthyroid, and an inability to walk or bike [1]. Medications utilized for rate control included dromotropic medications, such as beta blockers, calcium channel blockers (nondihydropyridine), and digoxin.

Main outcome measures. The primary endpoint was a composite of death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. Secondary outcomes included adverse events and symptoms. Subjects were followed for at least 2 years and up to 3 years.

Main results. The average age of subjects was 68 years, and two-thirds were male. The median duration of any atrial fibrillation was 18 months, with 3 months of permanent atrial

fibrillation. Most had undergone a prior electrical cardioversion; 45% were using a beta blocker alone for rate control at baseline with another 21% using a beta blocker in combination with other rate control medications. 97.7% of subjects in the lenient control arm met the goal heart rate compared to only 67% for the strict control group. No difference was noted in the primary outcome between the strict rate control protocol versus lenient control at 3 years (estimated cumulative incidence, 14.9% vs. 12.9%; 90% confidence interval for difference between the arms, -7.6%–3.5%; $P < 0.001$ for noninferiority margin). Symptoms and adverse events were similar in the groups.

Conclusion. Lenient rate control (goal heart rate < 110 beats per minute) was equivalent to strict rate control (< 80 beats per minute) for the treatment of atrial fibrillation.

Commentary

The treatment of atrial fibrillation has been the subject of intensive investigation. Since the release of the landmark AFFIRM trial in 2002 and other trials, which have found no difference in outcomes between patients who were rate-controlled versus rhythm-controlled, rate control has been a mainstay of therapy unless symptoms preclude such an approach [2,3]. Rate control actually may be the preferred treatment strategy because of fewer hospitalizations and fewer adverse drug events associated when compared with rhythm control. Strict rate control, rather than lenient control, may decrease symptoms and reduce the incidence of heart failure associated with atrial fibrillation through increased diastolic filling time and the prevention of tachycardia-induced cardiomyopathy [4,5]. However, despite guidelines recommending rate control between 60 and 80 beats per minute, limited evidence is available to support this goal [4]. Van Gelder et al examined the goal of rate control in this noninferiority randomized controlled trial. The study was reasonably large and attained good follow-up of patients.

Noninferiority trials, which was the design in this study, allow for active comparison between an accepted treatment

(in this case, strict control) and an experimental treatment (lenient control) and are commonly used when use of a placebo arm would be considered unethical [6]. The goal of such a trial is to demonstrate that the experimental treatment is no worse than the accepted treatment. This trial found that lenient control was noninferior to strict control with respect to the primary outcome and in all subgroup analyses. Side effects also were similar between arms. Frequent office visits were required to achieve rate control targets in the strict-control arm (median of 2 visits) compared to a median of 0 office visits to achieve targets in the lenient-control arm.

Several limitations were evident with this study. First, randomization was not perfect as subjects in the lenient control arm had more coronary artery disease, higher use of statin medications, and higher diastolic blood pressure than in the strict control arm. Second, the trial achieved the goal heart rate in only 67% of subjects in the strict control arm, limiting the ability to discriminate between the 2 arms. However, outcomes were similar across heart rate categories, shown as subgroup analyses in a supplemental table accompanying the online version of the paper. Strict rate control is also difficult, and 25% of those who failed to reach the goal heart rate in the strict-rate arm did so because of adverse drug events. Third, the sample enrolled was a healthy population with low cardiovascular event rates and low CHADS2 scores (61% in the lowest CHADS2 score category); the CHADS2 index predicts the risk for an embolic complication from atrial fibrillation. These results may not be applicable to a sample of patients who have atrial fibrillation and are at high risk for cardiovascular events.

This study is only a first look at an important component of treatment for atrial fibrillation. This approach may lead to fewer office visits, with no change in symptoms or outcomes. Future studies must confirm these results, especially

in patient populations at risk for poor outcomes and through use of a longer follow-up time to capture potential negative consequences of longer-term lenient rate control.

Applications for Clinical Practice

Clinicians should consider a less aggressive rate control goal for the treatment of atrial fibrillation in healthy patients.

—Review by Jason P. Block, MD, MPH

References

1. Van Gelder IC, Van Veldhuisen DJ, Crijns HJ, et al. Rate Control Efficacy in permanent atrial fibrillation: a comparison between lenient versus strict rate control in patients with and without heart failure: background, aims, and design of RACE II. *Am Heart J* 2006;152:420–6.
2. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825–33.
3. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834–40.
4. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e257–354.
5. Dorian P. Rate control in atrial fibrillation. *N Engl J Med* 2010;362:1439–41.
6. D’Agostino R, Massaro J, Sullivan J. Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics. *Stat Med* 2003;22:169–86.