Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 58, No. 16, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.05.058

YEAR IN CARDIOLOGY SERIES

The Year in Clinical Cardiac Electrophysiology

Gregory M. Marcus, MD, MAS,* Melvin M. Scheinman, MD,* Edmund Keung, MD†
San Francisco, California

Atrial Fibrillation

Several important studies related to the treatment of atrial fibrillation (AF) were published in the past year. In addition, building on recent data, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the Heart Rhythm Society (HRS) provided updates to the AF guidelines.

Van Gelder et al. (1) published the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) trial, the first formal assessment of alternative rate control goals in AF. Six hundred and fourteen patients in the Netherlands were enrolled in this prospective, multicenter, randomized, open-label, noninferiority trial and randomly assigned to a "lenient rate-control" strategy (target resting heart rate <110 beats/min) versus a "strict rate-control" strategy (target resting heart rate <80 beats/min and a target heart rate <110 beats/min during moderate exercise). Rate control was achieved during a dose-adjustment phase by the use of 1 or more negative dromotropic drugs, including beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin, at various doses. The primary endpoint was a composite of death from cardiovascular causes, hospitalization for heart failure (HF), stroke, systemic embolism, major bleeding, arrhythmic events including syncope, sustained ventricular tachycardia (VT), cardiac arrest, life-threatening adverse effects of rate control drugs, and insertion of a pacemaker and implantable cardioverter-defibrillator (ICD). To test the hypothesis that a lenient rate-control strategy would be noninferior to strict rate control, the power of the study was based on the ability to exclude an absolute increase in 10 percentage points in the rate of the primary outcome at 2.5 years in the lenient-control group. At enrollment, participants had to have permanent AF for up to 12 months, with a mean resting heart rate >80 beats/min, and receiving anticoagulant therapy dictated by thromboembolic risk factors. Important exclusion criteria included New York Heart Association (NYHA) functional class IV HF, HF necessitating hospital admission, or cardiac surgery within the previous 3 months (2).

The baseline characteristics of the patients were generally well balanced, with the exception of more coronary artery disease, statin use, and higher diastolic blood pressure in the lenient-control group. The mean resting heart rate was 93 ± 9 beats/min in the lenient-control group compared to 76 ± 12 beats/min in the strict-control group ($p < 0.001$). A total of 81 patients (38 in the lenient-control group and 43 in the strict-control group) reached the primary outcome. The 3-year estimated cumulative incidence of the primary outcome was 12.9% in the lenient-control group and 14.9% in the strict-control group, resulting in an absolute difference between lenient control and strict control of −2 percentage points (90% confidence interval [CI]: −7.6 to 3.5 percentage points). The criteria for noninferiority in the lenient-control group was achieved with a p value <0.001. These results did not meaningfully change after adjustment for covariates that were not well balanced between the groups. In addition, no differences in the reports of various AF-related symptoms were observed. Finally, fewer visits were required to achieve the target heart rate in the lenient-control group (median of 0 compared to median of 2 for the strict-control group).

This study suggests that a lenient rate-control approach targeting resting heart rates <110 beats/min may be reasonable and more easily achieved in AF patients compared to the conventionally recommended target of <80 beats/min. Several caveats should be considered before applying this broadly to clinical practice. First, as patients with a recent HF hospitalization were excluded, these results may not apply to such patients. Second, the adverse effects of prolonged faster ventricular rates may require several years, and follow-up was terminated in this study after a maximum of 3 years. In fact, as the primary outcome was specifically time to first occurrence of the composite outcome (meaning participants were censored after that first outcome), the cumulative effects of these strategies for patients who experienced 1 of the many adverse events that comprised that composite outcome is not known. Third, whereas 98% of patients in the lenient-group achieved the target heart rate, only 67% in the strict-control group achieved their target heart rate—this may have reduced the power to detect an advantage (or disadvantage) of the "on treatment" out-

From the *Department of Cardiac Electrophysiology, University of California San Francisco, San Francisco, California; and the †Veterans Affairs Medical Center, San Francisco, California. Dr. Marcus has received speaker's fees from Medtronic and St. Jude Medical; is a consultant for InCarda; and has received research support from St. Jude Medical, Sanofi-Aventis, and Astellas. Dr. Scheinman has received speaker's fees from Biotronik, St. Jude Medical, Boston Scientific, and Medtronic. Dr. Keung has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received April 27, 2011; accepted May 5, 2011.

comes. Perhaps most importantly, it must be remembered that "lenient" still required a heart rate <110 beats/min.

Given promising, but conflicting, data regarding the efficacy of omega-3 fatty acid supplementation for the prevention of AF recurrence, Kowey et al. (3) randomly allocated 663 AF patients stratified by a baseline diagnosis of paroxysmal AF or persistent AF in a ratio of 5:1 to 4 g a day of prescription omega-3 or placebo in a double-blind, multicenter trial. Patients with persistent AF had to have been successfully pharmacologically or electrically cardioverted, and the presence of sinus rhythm at study entry was required for all participants. Each 1 g of the prescription omega-3 included approximately 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid. Patients receiving antiarrhythmic drugs, patients taking omega-3 fatty acids within 30 days of enrollment, and patients with specific structural heart disease were excluded. Five hundred and eighty-four participants (88% of those enrolled) completed the 6-month study. The baseline characteristics and proportions with paroxysmal and persistent AF were generally well balanced between the treatment groups. No statistical difference was noted in the primary endpoint of first symptomatic recurrence of AF or atrial flutter: in patients with paroxysmal AF, there were 129 events (48%) in the placebo group and 135 (52%) in the prescription group (hazard ratio [HR]: 1.15, 95% CI: 0.90 to 1.46, $p = 0.26$). In patients with persistent AF, 33% of the placebo group and 50% of the prescription drug group achieved this primary endpoint (HR: 1.64, 95% CI: 0.92 to 2.92). Of note, these outcomes were examined in multiple ways (including with and without a pre-specified intention to treat analysis and including analyses within multiple subgroups), without any detection of benefit in the prescription arm.

Interestingly, patients receiving the prescription omega-3 fatty acid exhibited a statistically significantly lower average heart rate during the first occurrence of symptomatic AF or atrial flutter compared to patients on placebo, with a mean difference of −6.99 beats/min (95% CI: −13.12 to −0.64 beats/min, $p = 0.03$).

Although this study suggests there is no benefit of omega-3 fatty acid prescription to prevent recurrent AF, there are several limitations that should be considered. First, follow-up was limited to 6 months. This likely provides ample evidence that an acute and efficacious electrophysiologic effect is not present, but chronic anti-inflammatory or antifibrotic effects that might reduce the risk of AF over longer follow-up may still be present. In addition, the primary endpoint involved only symptomatic episodes, and potential differences in the true underlying AF burden (and long-term sequelae of AF such as stroke) between groups remain unknown. However, that ventricular rates during atrial arrhythmia episodes were slower in the prescription group may suggest that the chances of asymptomatic episodes would be higher in that group. Although the study was powered based on event rate estimates that were higher than those actually observed (potentially resulting in a type II error or false negative results), the point estimates generally favored placebo, making such a type II error in favor of the prescription unlikely. Finally, as acknowledged by the authors, this study does not exclude the possibility of benefit in other more specific AF populations, such as patients with severe heart disease or patients in the post-operative setting.

Several important studies involving new ways to think about and prevent stroke in AF were published in the last year. First, a large trial of a factor Xa inhibitor in AF was published. Connolly et al. (4) published the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial, in which 5,599 AF patients with at least 1 additional risk factor for stroke not receiving vitamin K antagonist therapy (either because it had already been demonstrated to be unsuitable or because it was expected to be unsuitable) were randomly assigned to the direct factor Xa inhibitor, apixaban, 5 mg twice daily, or aspirin at a dose of 81 to 324 mg daily. A reduced dose of apixaban of 2.5 mg twice daily was used for participants who were older than 80 years of age, had a body weight of 60 kg or less, or a serum creatinine of 1.5 mg/dl or higher. The primary efficacy outcome was the occurrence of stroke or systemic embolism, and the primary safety outcome was the occurrence of major bleeding.

The baseline characteristics were well balanced between treatment groups. Two thousand sixteen (40%) participants had previously received and discontinued a vitamin K antagonist. In 43% of cases, the physician had determined that international normalized ratio (INR) measurements could not be or were unlikely to be maintained, and vitamin K antagonist therapy was considered unsuitable in 21% because the risk of stroke was only moderate (a $CHADS_2$ score of 1). In 15%, the only reason vitamin K antagonists were unsuitable was because the patient did not want to take them. The study was terminated early with a mean follow-up duration of 1.1 years for an interim analysis that met the pre-specified stopping rule for efficacy in favor of apixaban. There were 51 primary outcome events (1.6% per year) in the apixaban group and 113 (3.7% per year) in the aspirin group (HR with apixaban: 0.45, 95% CI: 0.32 to 0.62, $p < 0.001$). There were 44 major bleeding events (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (HR with apixaban: 1.13, 95% CI: 0.74 to 1.75, $p = 0.57$). While no significant differences in hemorrhagic stroke were observed, more minor bleeding with apixaban occurred with borderline statistical significance (HR: 1.24, 95% CI: 1.00 to 1.53, $p = 0.05$). The risk of permanent discontinuation was 12% lower in the apixaban group (HR: 0.88, 95% CI: 0.78 to 0.99). Serial liver function tests revealed no differences between the groups. In multiple subgroup analyses, the superior efficacy of apixaban with similar adverse events was generally consistent.

It appears that, in AF patients with at least 1 additional risk factor for stroke that are deemed unsuitable for vitamin K antagonist therapy, treatment with apixaban compared to