Combo of ß-Blocker Plus Digoxin Affirmed In Atrial Fibrillation

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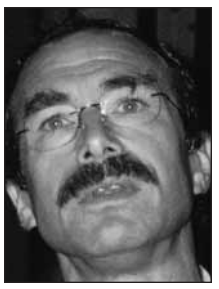
Vancouver — Over time, the most effective approach to pharmacologic rate control in patients with atrial fibrillation is a β-blocker in combination with digoxin, Brian Olshansky, M.D., reported at a meeting sponsored by the International Academy of Cardiology.

He presented a secondary analysis of data from the landmark Atrial Fibrillation Followup Investigation of Rhythm Management (AFFIRM) study, a National Heart, Lung, and Blood Institute–sponsored prospective, randomized trial that was the largest ever to compare rate control with rhythm control as treatment for atrial fibrillation (AF). The retrospective secondary analysis involved the 2,027 AFFIRM participants randomized to ventricular rate control, with an average follow-up of 3.5 years. Selection of the rate-control drugs was left to the discretion of the patient's physician.



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DR. OLSHANSKY

The secondary analysis aimed to answer two key questions: Is pharmacologic rate control achievable over the long haul? And what drugs are most effective—β-blockers, calcium channel blockers, digoxin, or combinations?

The answer to the first question was a clear yes. Adequate rate control, both at rest and during exercise, was achieved in 58% of patients with the first drug or combination of drugs on which they were placed. At 1 year, adequate rate control, as stringently defined by the AFFIRM investigators, was achieved in 64% of patients. And the success rate continued to climb over time. At 2 years, overall rate control, both while resting and exercising, was achieved by more than 70% of patients. By 5 years, the rate approached 80%.

But these success rates required considerable medication changes. Indeed, 37% of patients had a change in rate-control medication over 5 years. Although the initial success rates with β-blocker and calcium channel–blocker monotherapy were similar, over time more patients on a calcium channel blocker or digoxin were changed over to a β-blocker than vice versa. In the first year alone, 23% of patients switched from calcium channel blockers to β-blockers, while 19% switched from β-blockers to calcium channel blockers, noted Dr. Olshansky, chief of electrophysiology at the University of Iowa, Iowa City.

Patients unable to achieve adequate rate control despite multiple attempts (7%) then underwent atrioventricular junctional ablation with insertion of a permanent pacemaker to control ventricular rate.

The definition of rate control used by the AFFIRM investigators was much more rigorous than typical in clinical practice. Adequate rate control in AFFIRM required an average heart rate at rest of 80 bpm or less, plus either a maximum heart rate of no more than 110 bpm during a 6-minute walk or an average heart rate of 100 bpm or less during 24-hour ambulatory Holter monitoring.

One big surprise in the secondary analysis was how well patients did on digoxin as a single rate-control drug. Indeed, rate control with digoxin alone during exercise was similar to that with a β-blocker.

"We've all been taught that digoxin has little effect on atrial fibrillation, but it did appear that rate control occurred in the group taking digoxin," he said.

Audience member Win-Kuang Shen, M.D., a professor of medicine at the Mayo Clinic, Rochester, Minn., said that the repeated office visits and medication adjustments many AF patients require to achieve rate control constitutes a considerable societal burden.

Perhaps earlier resort to an ablate-and-pace strategy makes more sense from the cost-effectiveness and quality of life standpoints, Dr. Shen proposed.

Dr. Olshansky replied that he believes rate control with drugs to be a reasonable strategy, but at some point mutually agreed upon by patient and physician, it's time to say "enough," rather than continue to try various permutations of medications.

"Perhaps after a β-blocker with digoxin at proper doses doesn't work, it might be appropriate to move on to AV junctional ablation and pacing," he said. ■

Pill-in-a-Pocket Dosing Safely Converts Breakthrough Atrial Fib

New Orleans — An extra dose of oral propafenone or flecainide achieves pharmacologic conversion of breakthrough atrial fibrillation in two-thirds of affected patients who are already taking the same class 1C antiarrhythmic agent for daily maintenance therapy, James A. Reiffel, M.D., reported at the annual meeting of the Heart Rhythm Society.

The key to making this strategy work safely is to use as a guide the maximum daily dose as defined in the product label. That would be 900 mg for propafenone immediate release (IR), available generically; 850 mg for the sustained-release formulation (Rythmol SR); and 400 mg for flecainide (Tambocor).

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The combined total of an individual's daily maintenance dose plus the supplemental dose should not exceed these ceilings, said Dr. Reiffel, professor of clinical medicine at Columbia University, New York.

For example, a patient who experiences an episode of atrial fibrillation (AF) while on propafenone IR at 600 mg/day for maintenance therapy would take a single 300-mg bolus of the drug at least 3 hours after the prior maintenance dose. A patient on 450 mg/day would take a 300-mg extra dose, then another 150 mg 4 hours later if conversion hasn't occurred.

The pharmacokinetic curve of propafenone IR at 450 mg/day approximates that of propafenone SR at 650 mg/day, whereas 675 mg/day of propafenone IR is similar pharmacokinetically to 850 mg/day of propafenone SR. So a patient who experiences an episode of AF on 325 mg b.i.d. of propafenone SR as maintenance would take a single 300-mg supplemental dose of propafenone IR. An individual on 425 mg b.i.d. of propafenone SR would take no more than 150 mg of propafenone IR, he said.

He reported on 24 patients who had experienced a total of 42 episodes of recurrent AF despite taking daily maintenance doses of propafenone IR or SR or flecainide. The rate of conversion to sinus rhythm in response to the extra dose was 67% in all three patient groups. Adverse effects were limited to mild nausea and vague dizziness.

The appeal of this strategy is that it is safe, effective, and falls within the scope of the approved Food and Drug Administration (FDA) indications for these drugs. The FDA has deemed both propafenone and flecainide to be appropriate drugs for initiation of management of AF in outpatient settings in individuals without structural heart disease. The additional dose appears to be as well tolerated in patients on maintenance doses as in patients not on daily antiarrhythmic therapy.

Dr. Reiffel noted that this treatment approach is based on the "pill-in-a-pocket" strategy recently described by Italian investigators. They showed in 210 patients with recurrent AF who were not on daily antiarrhythmic therapy that out-of-hospital, self-administered oral loading doses of propafenone or flecainide converted 94% of recent-onset episodes of AF to sinus rhythm in a mean of 113 minutes.

This suggests that supplemental doses in patients already on daily antiarrhythmic therapy may not be quite as effective as in patients not yet on daily maintenance therapy.

During the 15-month study of Italian patients, both emergency department visits and hospital admissions were reduced roughly 10-fold in this population, compared with the time period immediately before the institution of the pill-in-a-pocket approach (N. Engl. J. Med. 2004;351:2384-91). ■

Propafenone Deemed First Choice for Rhythm Control in Recurrent Atrial Fib

Orlando — Propafenone bested sotalol for long-term maintenance of sinus rhythm in patients with recurrent atrial fibrillation in a randomized, single-blind, placebo-controlled trial, Nikos E. Igoumenidis, M.D., reported at the annual meeting of the American College of Cardiology.

Based on the results of this unsponsored study, propafenone should be considered the drug of first choice for maintenance of sinus rhythm in patients with atrial fibrillation (AF), according to Dr. Igoumenidis of Heraklion (Greece) University Hospital.

The drug that is cited in the literature as being the most effective antiarrhythmic agent for preventing recurrent AF, amiodarone, is fraught with side effects that tend to limit its usefulness, he added.

Dr. Igoumenidis reported on 254 consecutive patients, 126 of them women, with recurrent symptomatic AF who were cardioverted to sinus rhythm and randomized to 450 mg/day of propafenone, 160-480 mg/day sotalol as tolerated, or placebo.

Of 85 patients in the sotalol group, 69 (81%) experienced relapse and/or side effects requiring drug discontinuation after a mean of 18 months. Of the 83 on placebo, 73 (88%) developed recurrent AF after a mean of 11 months.

In contrast, only 45 of 86 patients (52%) in the propafenone arm had relapse and/or discontinued treatment due to intolerable side effects after a mean of 26 months.

Three of the five patients who discontinued sotalol did so because of symptomatic bradycardia that arose during the loading phase. The other two patients dropped out due to severe dizziness, once again early in the course of treatment.

Seven other patients experienced significant side effects on sotalol that remitted when the dose was lowered, enabling them to continue on the medication.

Five patients quit taking propafenone because of side effects. All were early in therapy and in sinus rhythm at the time.

One developed unpleasant taste sensations, another had dizziness, and another experienced symptomatic bradycardia. The remaining two dropped out upon showing an increase in QRS duration or elevated liver enzymes. ■