Dronedarone Reduces Atrial Fib Hospitalizations

BY BRUCE JANCIN
Denver Bureau

DALLAS — The novel investigational antiarrhythmic agent dronedarone reduced by 27% the 1-year combined incidence of hospitalization or death compared with placebo in a large group of patients with paroxysmal or persistent atrial fibrillation, Dr. Stefan H. Hohnloser reported at the annual scientific sessions of the American Heart Association.

He presented a post hoc analysis of two pivotal phase III, double-blind, randomized trials totalling 1,237 patients with atrial fibrillation: EURIDIS (the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (the American-Australian-African Trial With Dronedarone in Atrial Fibrillation or Atrial Flutter Patients for the Maintenance of Sinus Rhythm).

In EURIDIS/ADONIS, the combined 1-year rate of all-cause hospitalization or mortality was 30.9% with placebo, compared with 22.8% in patients who received dronedarone at 400 mg b.i.d. The rate of death or hospitalization for a cardiovascular cause was 19.2% with placebo and 16.1% with dronedarone, added Dr. Hohnloser, professor of medicine and director of clinical electrophysiology at Johann Wolfgang Goethe University in Frankfurt am Main, Germany.

This potential clinical benefit—and Dr. Hohnloser stressed that "potential" needs to be emphasized because this was a post hoc analysis—distinguishes dronedarone from the various antiarrhythmic agents currently marketed for maintenance of sinus rhythm, all of which have been shadowed by safety concerns. In the previously reported primary efficacy outcomes in EURIDIS/ADONIS, the recurrent atrial fibrillation rate was cut by 22% and 28%, respectively, with dronedarone.

Dronedarone is an amiodarone derivative designed to provide the parent drug's efficacy without its toxicities. Sanofi-Aventis has applied to the Food and Drug Administration and to European authorities for marketing approval for dronedarone for maintenance of sinus rhythm and ventricular rate control in those patients with atrial fibrillation or flutter.

The potential reduction in morbidity and mortality noted with dronedarone in EURIDIS/ADONIS, coupled with new evidence presented at the AHA meeting that the drug is effective for rhythm control for rate control, and suggests the drug may provide an important new treatment approach in atrial fibrillation, he said.

Dr. Jean-Marc Davy reported that in the double-blind efficacy and safety of dronedarone for the control of ventricular rate (ERATO) trial, dronedarone provided additional rate control in patients not adequately controlled with standard agents including β-blockers, calcium channel blockers, and/or digitalis.

ERATO involved 174 patients with permanent atrial fibrillation and a baseline heart rate in excess of 80 beats per minute despite standard rate-control agents. They were randomized to dronedarone at 400 mg b.i.d. or placebo while continuing on their previous medications.

The primary study end point—heart rate as assessed by 24-hour Holter monitoring on day 14—was decreased by a mean of 11.7 beats per minute with dronedarone, compared with baseline, but it was unchanged in the placebo arm. Maximal exercise ventricular rate was reduced by 24.5 beats per minute in the dronedarone arm, added Dr. Davy, who is with Arnaud de Villeneuve Hospital in Montpellier, France.

Dr. Hohnloser and Dr. Davy are consultants to Sanofi-Aventis. ■

AFib Outcomes From Catheter Ablation Surpass Drug Management

BY MITCHEL L. ZOLER
Philadelphia Bureau

BOSTON — Catheter ablation plus amiodarone therapy was substantially better than amiodarone treatment alone for preventing recurrent atrial fibrillation during 1 year of follow-up in a randomized, controlled study with 146 patients.

"This is the first illustration in a randomized study that patients with chronic atrial fibrillation can kept be in sinus rhythm," Dr. Carlo Pappone said at an international symposium on atrial fibrillation sponsored by Massachusetts General Hospital.

The investigation enrolled participants with more than a 6-month history of chronic atrial fibrillation.

Their average age was 56, and about 23% of patients had structural heart disease, most commonly nonischemic cardiomyopathy.

Their average left ventricular ejection fraction was 55%, and the average duration of atrial fibrillation was more than 4 years.

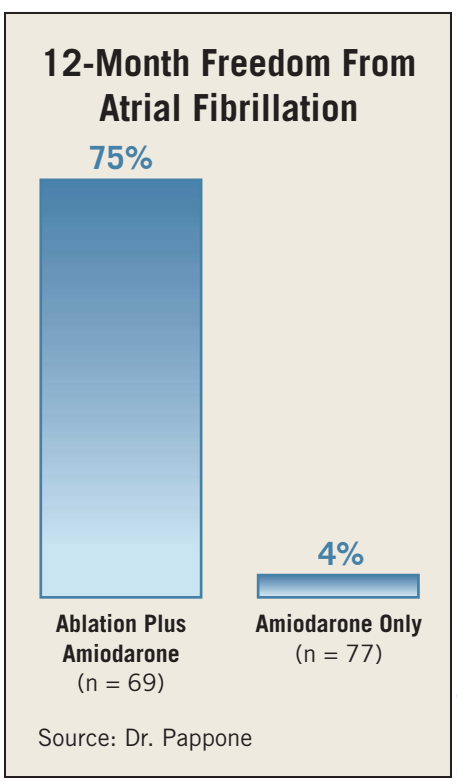
All participants in the study had failed prior treatment with an average of two antiarrhythmic medications.

Patients were randomized, with 69 treated by circumferential pulmonary vein ablation (PVA) using radiofrequency followed by daily treatment with amiodarone for 3 months. The 77 control patients were treated with amiodarone only.

Patients were then followed in a blinded manner by daily, transtelephonic monitoring. During 12 months of follow-up, 75% of the patients treated with pulmonary vein ablation remained free of new episodes of atrial fibrillation, compared with 4% who were free of atrial arrhythmias in the control group, said Dr. Pappone, director of the division of arrhythmology at San Raffaele Hospital in Milan.

Dr. Pappone also reported his group's total, updated safety experience using catheter ablation to treat atrial fibrillation. From the 1990s through June 2005, his group at San Raffaele had used catheter ablation to treat more than 9,000 patients. The rate of major complications in treated patients was about 0.4%, a rate that included no deaths. However, Dr. Pappone acknowledged that the outcome of catheter ablation varied from center to center.

"There is no doubt that safety and efficacy are strongly operator dependent," Dr. Pappone said at the conference, which was also sponsored by the Academy of Health Care Education. ■



ELSEVIER GLOBAL MEDICAL NEWS

70 Million Americans Affected

Prehypertension *from page 1*

than what is now the norm. That's because nearly two-thirds of those on placebo converted to stage 1 hypertension in 4 years.

"Since there was a very high rate of transition, we are rather confident in recommending that once you have diagnosed prehypertension, these patients should be followed more frequently than they are followed now in order to then detect the development of stage 1 hypertension—and we think that follow-up at 3-month intervals is reasonable," said Dr. Julius, professor emeritus of medicine and physiology at the University of Michigan, Ann Arbor.

TROPHY participants had to have baseline prehypertension as defined by repeated automated blood pressure readings of either 130-139 mm Hg systolic and 89 mm Hg or lower diastolic, or a systolic pressure of 139 mm Hg or lower plus a diastolic value of 85-89 mm Hg. Their mean age was 48 years. While that's far younger than the patients in other hypertension trials, Dr. Julius expressed regret they weren't even younger, since that might have enabled TROPHY to show whether a brief drug intervention, given early enough, could permanently arrest the hypertensive process.

TROPHY participants were randomized to 2 years of double-blind candesartan (Atacand) at 16 mg once daily or placebo, followed by 2 years in which all participants received placebo.

The primary end point was development of clinical hypertension. At the 2-year mark, it had developed in 14% of the candesartan group and 40% of the patients on placebo, for a 66% relative risk reduction. Blood pressure began to climb soon after drug therapy stopped, and at 4 years, stage 1 hypertension was present in 53% of the candesartan arm and 63% of the placebo arm, for a still significant 16% relative reduction. Drug side effects were mild and similar to those of placebo.

It has been estimated that up to 70 million Americans have prehypertension as defined by blood pressures of 120-139 mm Hg systolic or 80-89 mm Hg diastolic. So why consider redefining this vast group as having a condition warranting drug therapy?

Because prehypertension—previously called transient hypertension, borderline hypertension, and high-normal blood pressure—is an established precursor of clinical hypertension and is associated with increased cardiovascular morbidity and mortality. Furthermore, hypertension is a self-accelerating condition, and animal studies have suggested that a relatively brief period of drug therapy during the prehypertensive phase might favorably alter the natural history and prevent clinical hypertension.

"It is important to acknowledge that although nonpharmacologic therapy has been recommended first as a population strategy, it hasn't worked," Dr. Julius said. He noted that the best-ever performance of lifestyle modification, seen in the Trials of Hypertension Prevention, showed an absolute 8% reduction in new-onset hypertension over 2 years (Arch. Intern. Med. 1997;157:657-67), versus 27% with candesartan in TROPHY.

Dr. William J. Elliott, professor of preventive medicine, internal medicine, and pharmacology at Rush Medical College, Chicago, expressed concern that the slope of the curve of new-onset hypertension in the candesartan arm during years 2-4 appeared to be the same as in years 0-2 in the placebo arm. This suggests, disappointingly, that drug therapy didn't halt the hypertensive express train and prehypertensive individuals might need to take drugs for their entire lives to benefit.

He added that lowering the traditional threshold for drug therapy from 140/90 mm Hg to encompass some portion of the 70 million Americans with prehypertension could be a health care budget buster.

TROPHY was funded by AstraZeneca, from which Dr. Julius receives grant support. ■