Dronedarone Slashes Hospital Days in Atrial Fib

BY BRUCE JANCIN
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NEW ORLEANS — Patients with atrial fibrillation who were treated with the investigational antiarrhythmic agent dronedarone spent 35% fewer total days in the hospital for cardiovascular reasons than did patients in the placebo arm of the landmark phase III ATHENA trial.

Moreover, the dronedarone group spent 47% fewer days in intensive care or coronary care units and 45% fewer days in midlevel care units. Those differences will add up to serious cost savings favoring dronedarone when an ongoing ATHENA cost-effectiveness analysis is completed, Dr. Christian Torp-Pedersen said at the annual scientific sessions of the American Heart Association.

For a patient who can't tolerate amiodarone, 'you'd go a bit further with dronedarone. And if a patient readily tolerates amiodarone, you might be tempted to switch to it when heart failure worsens.'

Dronedarone also reduced by 28% the total number of days of hospitalization for all causes—cardiovascular as well as noncardiovascular—reaffirming the drug's relatively benign safety profile as seen in earlier studies. If dronedarone were associated with significant pulmonary, dermatologic, thyroid, or other toxicities—as is true of its structural relative amiodarone—the dronedarone group would have had more hospital time for noncardiovascular reasons than the placebo group, observed Dr. Torp-Pedersen of Gentofte University Hospital, Copenhagen.

ATHENA was a double-blind randomized trial that involved 4,628 patients with paroxysmal or persistent atrial fibrillation or atrial flutter in 37 countries. The patients received 400 mg b.i.d. of dronedarone (Multaq) or placebo and were followed for a mean of 21 months. The participants had to be either at least 75 years old or aged 70 or older with comorbid diabetes, hypertension, low left ventricular ejection fraction, enlarged left atrial size, or prior stroke.

The primary results of ATHENA were presented at the 2008 annual meeting of the Heart Rhythm Society. The risk of the combined primary end point of all-cause mortality or cardiovascular hospitalization was reduced by 24% in the dronedarone arm.

Dr. Torp-Pedersen presented a secondary post hoc analysis of the ATHENA data that focused on dronedarone's impact upon the total hospitalization burden. During the 21 months of follow-up, the dronedarone group collectively spent nearly 4,000 fewer days in the hospital. (See box.)

What's particularly intriguing, he observed, is that the dronedarone group showed a consistent trend for fewer cardiovascular hospitalizations for reasons other than atrial fibrillation as well as for atrial fibrillation. The dronedarone-treated patients were not only 37% less likely to be admitted for atrial fibrillation, they were also 14% less likely to be hospitalized for cardiovascular reasons unrelated to atrial fibrillation. They were also 30% less likely than the control group to be admitted for acute coronary syndrome. All of these differences were statistically significant.

The dronedarone group's 14% relative risk reduction in heart failure admissions did not achieve significance because of the limited number of patients in the analysis, since only 20% of ATHENA participants had heart failure at baseline. Still, this trend for fewer heart failure hospitalizations is welcome news, Dr. Torp-Pedersen said, because an earlier, smaller clinical trial was halted early because of an apparent increase in deaths among dronedarone-treated patients with New York Heart Association class IV heart failure. Patients with class IV heart failure were excluded from ATHENA.

A likely explanation for dronedarone's ability to reduce cardiovascular admissions not related to atrial fibrillation involves the drug's dual effects: It is both a rhythm- and a rate-control drug. Dronedarone reduced the mean heart rate during atrial fibrillation episodes to 78 beats per minute, as compared with 87 bpm with placebo, Dr. Torp-Pedersen noted.

Although dronedarone was similarly safe and effective in ATHENA participants with class II and class III heart failure, Dr. Torp-Pedersen said that in clinical practice, he'd be cautious in using it in patients with class III heart failure. Dr. Torp-Pedersen is on the ATHENA steering committee and has received research grants and consulting fees from Sanofi-Aventis, which is developing dronedarone.

The only adverse effect that was more common with dronedarone than with placebo in the trial was an elevated serum creatinine level, which occurred in 4.7% of the dronedarone group and 1% on placebo.

Audience concerns focused on using dronedarone in patients with heart failure, a common comorbidity in patients with atrial fibrillation.

"How is this going to play out in clinical practice?" asked session moderator Dr. Sana Al Khatib of Duke University, Durham, N.C. "NYHA class is variable. A patient with class II heart failure can go into class III in a few months. Are you suggesting that we can give this drug to patients with mild heart failure and as soon as they go into class III, we have to stop the drug until we control their symptoms?"

"That's going to be a dilemma for a group of patients: When is the heart failure severe enough to cause an exclusion? There's no simple answer," Dr. Torp-Pedersen replied. "There may be particular reasons why an individual absolutely can't tolerate amiodarone, and in that patient you'd go a bit further with dronedarone. And if a patient readily tolerates amiodarone, you might be tempted to switch to it when heart failure worsens. I think that will be the scenario in real life."

The Food and Drug Administration in August 2006 turned down a request for approval that had relied on two previous trials using a combined end point of all-cause hospitalizations or deaths. In August 2008, the company resubmitted its application for marketing approval based on the ATHENA results and has been granted a priority review; a decision from the FDA is expected in early 2009. Dronedarone is also under regulatory review by the European Medicines Agency. ■

Hospitalization Burden for 21-Month Follow-Up

	Dronedarone	Placebo
All-cause hospitalization	9,995 days	13,986 days
Cardiovascular hospitalization	5,875 days	9,073 days
Medium-care unit stays	833 days	1,525 days
ICU/CCU stays	599 days	1,138 days
Patients with multiple hospitalizations	35%	44%

Note: Based on a study of 4,628 patients with atrial fibrillation.
Source: Dr. Torp-Pedersen

Brief Amiodarone Rx Cuts Atrial Fib After Heart Surgery

BY MITCHEL L. ZOLER
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NEW ORLEANS — Two weeks of treatment with amiodarone starting immediately after cardiac surgery was safe and cut the postsurgical incidence of atrial fibrillation by an absolute rate of 10% in a study with more than 600 patients.

Atrial fibrillation has historically been the most common arrhythmia complication following cardiac surgery, Dr. James R. Cook and his associates said in a poster at the annual scientific sessions of the American Heart Association.

Results from previous studies had shown that perioperatively administered amiodarone was effective for reducing the incidence of atrial fibrillation, but in some cases the treatment was difficult to maintain and the adverse effects presented a problem. This led to the idea of limiting amiodarone treatment to a brief period immediately following surgery, the investigators said.

The study included 311 patients who underwent coronary artery bypass surgery, valve surgery, or combined bypass and valve surgery (either aortic or mitral valve) at Baystate Medical Center in Springfield, Mass., during July-December 2007. All of these patients received a 150-mg bolus of amiodarone immediately after their surgery was complete, followed by a 400-mg oral dose b.i.d. for the first 7 days after surgery. Patients were then switched to 200 mg orally once daily for the next 7 days.

The control group included 307 patients who underwent coronary bypass, valve surgery, or both at Baystate during January-June 2007.

The average age of all 618 patients was 67 years, 67% were men, 80% had hypertension, and 42% had diabetes. Two-thirds of all patients received a β-blocker during surgery, and 90% were on a β-blocker following surgery, Dr. James R. Cook and his associates reported.

During follow-up, the incidence of new-onset atrial fibrillation that required treatment was 24% in the patients treated with amiodarone and 34% in the control patients, a statistically significant difference, reported Dr. Cook, director of cardiac electrophysiology at Baystate, and his associates. Patients in the amiodarone group did not have an increased number of pulmonary complications, nor an increased need for pacemaker treatment.

The two groups were matched for all other peri- and postoperative outcomes studied, including their median ventilation time, the percentage with prolonged ventilation time, and the incidence of pneumonia. The median hospital length of stay was 9 days in the amiodarone group and 10 days for the controls. The mortality rate at 30 days after surgery was 5% in the amiodarone group and 4% in the control group. ■