# Panel Backs Approval of Atrial Fibrillation Drug

## *Dronedarone reduced cardiac hospitalizations, but not mortality, in a multinational trial.*

BY ELIZABETH MECHCATIE

ADELPHI, MD. — A Food and Drug Administration panel voted 10-3 that dronedarone, an amiodarone analogue, be approved for treating patients with nonpermanent atrial fibrillation, with recommendations that the label include a boxed warning cautioning against use of the drug in patients with heart failure.

At a meeting of the FDA's Cardiovascular and Renal Drugs Advisory Committee, panelists supporting approval agreed that the claim for dronedarone should be narrower than the primary end point in the ATHENA trial, which was defined as time to first event of cardiovascular hospitalization or death from any cause.

Panelists supporting approval agreed that the indication should make clear that cardiac hospitalizations, but not mortality, were reduced in patients treated with dronedarone in the study.

The multinational ATHENA trial compared 400 mg of dronedarone twice a day to placebo in 4,628 patients (approximately 1,400 in the United States) with at least one episode of atrial fibrillation (AF) or atrial flutter (AFL) and at least one normal ECG during the previous 6 months.

After 2 years, dronedarone was associated with a 24% reduction in the combined risk of cardiovascular hospitalization or all-cause death, a highly statistically significant difference. But most of the benefit was due to the difference in cardiac hospitalizations, and nearly all that effect was due to hospitalizations for AF.

Manufacturer Sanofi Aventis has proposed that dronedarone be approved for treating patients with either a recent history of or current nonpermanent atrial fibrillation or flutter with associated risk factors, and also for the claim that treatment has been shown to decrease the combined risk of cardiovascular hospitalization or death.

Dr. Sanjay Kaul, director of the cardiovascular diseases fellowship training program at Cedars-Sinai Heart Institute in Los Angeles, described his vote as a "cautious yes," supporting approval for patients at low to intermediate risk who have a history of nonpermanent AF, excluding patients with New York Heart Association (NYHA) class III heart failure, and left ventricular dysfunction (an ejection fraction under 35%). Dr. Kaul said the manufacturer should conduct a long-term study comparing dronedarone to amiodarone, which remains the treatment of choice for patients with structural heart disease.

Dr. Lewis Nelson, director of the medical toxicology fellowship at New York University, voted against approval. He said more information is needed on the drug's effects in patients with renal failure and cardiac failure, drug interactions, and long-term adverse effects.

Sanofi-Adventis has proposed that dronedarone be approved for patients with "a recent history of or current nonpermanent atrial fibrillation or flutter with associated risk factors," and that it not be used to treat patients with symptoms of heart failure at rest, or with minimal exertion within the immediately preceding month, or patients who have been hospitalized for HF within the immediately preceding month.

The FDA meeting was held almost 4 years after the company first filed for approval of dronedarone in June 2005.

The FDA did not approve dronedarone because it was associated with a greater rate of mortality, hospitalization for heart failure, and hospitalization for cardiovascular causes in the ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) study, which compared 400 mg of dronedarone twice a day to placebo in patients with NYHA Class class II-IV heart failure, and was stopped early when these associations became evident. The company filed another new drug application in July 2008, which included the previous data and the results of the ATHENA study.

The two populations differed: Those in ANDROMEDA had been recently hospitalized or had had a clinic visit for heart failure, requiring at least intravenous diuretics. In ATHENA, patients with NYHA class IV were excluded, which was the major difference between the two studies.

Gastrointestinal side effects—particularly nausea, vomiting and diarrhea—were the most common side effects associated with dronedarone in ATHENA. In studies, the rate of increases in serum creatinine has been higher among those treated with dronedarone, but this plateaus early and is reversible. Thyroid-related adverse events have been low, and pulmonary-related adverse events, which have been associated with amiodarone, have been uncommon and similar to placebo, according to the company.

If approved, Sanofi-Aventis plans to market dronedarone as Multaq.

The FDA usually follows the recommendations of its advisory panels. ■

# Debut of Five-in-One Polypill Triggers Therapeutic Debate

BY MITCHEL L. ZOLER

ORLANDO — The multiplicity of reactions to a new drug-treatment concept has helped put "poly" in the polypill.

The idea of broadly administering a single, daily capsule containing five drugs proven to cut cardiovascular risk finally had its first field test on more than 2,000 people at 50 centers throughout India. The results proved the principle that three different antihypertensive drugs, a statin, and aspirin could safely and effectively coexist in a single pill, although the treatment effects were modest.

The study also triggered an outpouring of opinions on exactly what principles are involved. What is the potential role for a polypill, and who are the people who should take it?

According to the study's leader, Dr. Salim Yusuf, the underlying premise is that average risk-factor levels are abnormal in all individuals in most urban settings around the world, and so a polypill that reduces cardiovascular disease (CVD) risk could potentially be targeted to most or even all people older than 50 in countries spanning the globe.

The Indian Polycap Study (TIPS) enrolled people aged 45-80 years with a single CVD risk factor: type 2 diabetes, moderately elevated blood pressure (more than 140/90 mm Hg but less than 160/100 mm Hg), smoking within the prior 5 years, serum LDL cholesterol of more than 3.1 mmol/L (121 mg/dL), an HDL cholesterol of less than 1.04 mmol/L (40 mg/dL), or an elevated waist/hip ratio.

"The big question is whether you treat the whole world at large at a certain age. That's been proposed, and it's a possibility. I really don't know the answer right now," Dr. Yusuf said during a press briefing before he reported his findings at the annual meeting of the American College of Cardiology. Accumulating evidence suggests that the threshold for diagnosing a level of blood pressure or serum LDL that poses a CVD risk should move lower than it is today, said Dr. Yusuf, professor of medicine and director of the Population Health Research Institute at McMaster University, Hamilton, Ont.

Others saw the polypill as a way to simplify treatment and boost compliance in the more conventional drug-treatment setting of secondary prevention.

"I would use it to treat people with some elevations of both blood pressure and lipids," said Dr. Steven E. Nissen, chairman of the department of cardiovascular medicine at the Cleveland Clinic. "I wouldn't use a one-size-fits-all pill for many people who are not at a whole lot of risk. I would use it for people with [a few] risk factors and make it easy for them by giving a single pill once a day."

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DR. YUSUF

Others saw as too global and facile the development of a single pill aimed at quickly and easily damping down blood pressure and serum lipids.

"It takes effort to educate the public about hypertension and obesity. If something like [the polypill] becomes prevalent, it takes away from that focus," said Dr. Clyde Yancy, medical director of the Baylor Heart Institute in Dallas. "There is nothing more effective than modifying lifestyle, but people may tend to dismiss that concept if they believe a pill is lowering their risk of heart disease."

Dr. Yusuf himself stressed that no matter where the polypill may lead, "lifestyle modification is the crux of CVD prevention."

The 2,053 people participating in TIPS were recruited during March 2007–August 2008. Their average age was 54, their average blood pressure was 134/85 mm Hg, their average LDL level was 117 mg/dL, and 13% were recent smokers. Of them, 412 were randomized to receive the once-daily polypill, a capsule cocktail with three half-doses of blood pressure–lowering medications (5 mg ramipril, 50 mg atenolol, and 12.5 mg hydrochlorothiazide), 100 mg aspirin, and 20 mg simvastatin. Eight additional groups of about 200 people each were randomized into various treatment arms that received one, two, three, or four of these drugs in different combinations. Treatment was delivered for 12 weeks.

The study was sponsored by Cadila Pharmaceuticals, an Indian company that makes the polypill (Polycap). Dr. Yusuf reported receiving lecture fees and research grants from Cadila.

The polypill lowered blood pressure by an average of 7.4/5.6 mm Hg; LDL levels fell by an average of about 23%. These reductions tracked what was seen in the comparator groups. About 18% of participants discontinued the polypill arm of the study, and similar proportions dropped out of each of the other arms.

Concurrent with Dr. Yusuf's report at the meeting, the results were released in a paper published online (Lancet 2009 March 30 [doi:10.1016/S0140-6736(09)60611-5]).

Based on the risk factor reductions seen, polypill treatment was estimated to cut the average risk for coronary heart disease by 62%, and for stroke by 48%, Dr. Yusuf said.

Further testing is underway in India, and the manufacturer is arranging collaborations with North American drug companies to launch U.S. tests, Dr. Yusuf said in an interview. Asked if the target population for the polypill is the western world or third world, Dr. Yusuf said his target is "the sensible world." ■