

► atrial fibrillation, one versus *amiodarone* and the other versus placebo (2). Another trial involved heart-failure patients without arrhythmia. There are no comparative trials versus commonly used antiarrhythmic drugs such as betablockers.

**The trial versus amiodarone.** The Dionysos double-blind trial included 504 patients aged 28 to 90 years (mean: 64 years) who had atrial fibrillation for more than 72 hours (2,3). After randomisation, they were treated for at least 6 months with either *dronedarone* (400 mg twice a day) or *amiodarone* (600 mg/day for 4 weeks, then 200 mg/day). Treatment failure was defined as recurrence of fibrillation, or premature discontinuation due to adverse effects, or a lack of efficacy at 12 months. Failure was significantly more frequent with

*dronedarone* than with *amiodarone* (75.1% versus 58.8%) (3). Reports of this trial released by the company and the European Medicines Agency do not provide details concerning adverse effects.

**The placebo-controlled trial.** The Athena double-blind trial included 4630 patients with paroxysmal or persistent atrial fibrillation, atrial flutter, or sinus rhythm after cardioversion, and at least one of the following risk factors: age of at least 70 years, hypertension, diabetes, previous stroke or embolism, left atrial diameter at least 50 mm on echocardiography, or left ventricular ejection fraction less than or equal to 40% (2-7). The exclusion criteria included permanent atrial fibrillation and class IV heart failure based on the NYHA classification (a). The patients were ran-

domised to receive either *dronedarone* (400 mg twice a day) or placebo for at least a year.

The all-cause mortality rate was about 6% at two years, with no significant difference between the groups (5).

Hospitalisation for cardiovascular disorders was significantly less frequent in the *dronedarone* group after two years of follow-up (29.3% versus 36.9%) (5).

Cardiovascular deaths were also less frequent in the *dronedarone* group (2.8% versus 4%,  $p=0.025$ ) (5), but an FDA statistician questioned the validity of this difference, mainly because there was no difference in overall mortality and the number of cases was small. Therefore, we cannot draw firm conclusion about the preventive effect of *dronedarone* on cardiovascular mortality.

**Heart-failure patients: excess mortality?**

The Andromeda double-blind trial included patients hospitalised for symptomatic heart failure (NYHA class III or IV) who had a marked reduction in the left ventricular ejection fraction (35% maximum) but without arrhythmia (2,8). They were randomised to receive either *dronedarone* (400 mg twice a day) or placebo.

The trial was intended to include 1000 patients, but it was halted when an interim analysis of 627 patients monitored for an average of 7 months showed excess mortality in the *dronedarone* group (25 deaths, versus 12 in the placebo group;  $p=0.03$ ) (8).

Given the different selection criteria used in the two trials in heart failure, (patients in the Athena trial were less severely ill), it is impossible to draw firm conclusions from these conflicting results.

**Fewer short-term adverse effects**

The company's report of adverse effects is based on data for 3282 patients treated with *dronedarone* and 2875 patients given placebo (3).

**Comparison with amiodarone.** In the trial comparing *dronedarone* and *amiodarone*, the overall incidence of adverse effects was similar with the two drugs. However, various disorders were less frequent with *dronedarone* than with *amiodarone*, including thyroid disorders, mainly hypothyroidism (3 cases

**The dronedarone odyssey**

Sanofi Aventis based the names of its clinical pharmacology studies and clinical trials of *dronedarone* on Greek mythology. Quite appropriately as it turned out: the marketing authorisation procedures in the United States and Europe took the form of a veritable odyssey.

In June 2005, the company applied for marketing authorisation from the US Food and Drug Administration (FDA) and, a few months later, from the European Medicines Agency (EMA) (1,2). These applications were mainly supported by three placebo-controlled clinical pharmacology studies: "Erato" in patients with permanent fibrillation, and the "Euridis" and "Adonis" studies of relapse prevention in patients with atrial fibrillation (3,4).

As these studies failed to provide convincing evidence of a clinical benefit, the company then conducted a placebo-controlled trial, "Andromeda", in patients with heart failure. But this trial was halted prematurely when an interim analysis showed excess mortality in the *dronedarone* arm.

Serious doubts concerning the adverse effects of *dronedarone* led both agencies to issue unfavourable opinions and refuse marketing authorisation.

The company then conducted another placebo-controlled trial, "Athena", in

patients without heart failure or with less severe heart failure than in the previous trial. Furthermore, at the request of the European agency, the company finally decided to conduct a long-overdue head-to-head comparison with *amiodarone*, the "Dionysos" trial.

Although these trials failed to answer all outstanding questions, marketing authorisation was finally, but grudgingly, granted. However, the FDA advisory committee voted 10 to 3 to recommend restricting the indications to the suppression of atrial fibrillation (not mortality prevention).

The regulatory history of *dronedarone* is an excellent illustration of how some companies end up obtaining marketing authorisation by wearing down regulatory agencies that are not vigorously defending patients' interests.

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