ATRIAL FIBRILLATION

Dronedarone not suitable for patients with permanent AF

Rather than reducing the incidence of heart failure, stroke, and death in patients who have permanent atrial fibrillation (AF) and are at high risk of major vascular events, dronedarone actually increases the risk of these events. These findings from the PALLAS trial were a surprise, as dronedarone has previously been shown to be beneficial in patients with paroxysmal and persistent forms of this arrhythmia. The PALLAS investigators hypothesize that “for high-risk patients with permanent AF, direct and indirect toxic effects of dronedarone are not offset by the benefit of maintaining sinus rhythm,” which they point out occurs more often in dronedarone-treated patients with paroxysmal or persistent AF, “and

any benefits that might occur from heart-rate slowing, blood-pressure reduction, antiadrenergic action, and suppression of ventricular arrhythmia were either small or nonexistent”.

The investigators originally planned to enrol ~11,000 patients (aged ≥ 65 years) with permanent AF or atrial flutter and additional cardiovascular risk factors in the international, randomized, double-blind, placebo-controlled PALLAS trial. However, in July 2011, after 3,236 patients had been randomly assigned to the treatment groups (median follow-up 3.5 months), the data-monitoring committee recommended study termination because of safety concerns.

Of the enrolled patients, 98% had permanent AF and 2% had atrial flutter. Mean age was 75 years and two-thirds of patients had a history of heart failure. Most patients were taking drugs such as rate-control medication (88%), vitamin K antagonists (84%), diuretics (70%), statins (57%), or ACE inhibitors (51%), and one-third of patients were on digoxin. Overall, the dronedarone ($n = 1,619$) and placebo

($n = 1,617$) groups were well balanced in terms of clinical characteristics.

Stroke, myocardial infarction, systemic embolism, or death from cardiovascular cause—the first coprimary outcome—occurred in 43 dronedarone-treated patients and 19 controls (HR 2.29, 95% CI 1.34–3.94, $P = 0.002$). Death or unplanned hospitalization for a cardiovascular cause—the second coprimary outcome—occurred in 127 and 67 patients in the dronedarone and placebo groups, respectively (HR 1.95, 95% CI 1.45–2.62, $P < 0.001$).

In their report, the PALLAS investigators highlight that dronedarone is known to increase serum digoxin levels and that “it is therefore possible that digoxin toxicity induced by dronedarone played a role in the increased cardiovascular mortality”.

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