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EDITORIAL

Did PALLAS Deliver the Final Blow to Dronedarone?

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The Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (**PALLAS**) included patients aged over 65 years, who had at least 6-month history of permanent atrial fibrillation (AF) and risk factors for major vascular events.[1,2] The latter comprised coronary artery disease, previous stroke or transient ischemic attack, symptomatic heart failure, which was defined as current New York Heart Association class II or III symptoms and admission to the hospital for heart failure in the previous year (but not in the most recent month), a left ventricular ejection fraction of ≤40%, peripheral arterial disease, or the combination of an age of 75 years or older, hypertension, and diabetes. They were randomized to receive either dronedarone at a dose of 400 mg twice daily or placebo. On July 5, 2011, the data monitoring committee recommended that the study be terminated for safety reasons. A total of 3236 patients had undergone randomization with median follow-up of 3.5 months. The investigators had defined as the first coprimary outcome: stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes; and as a second coprimary outcome: unplanned hospitalization for a cardiovascular cause or death.

The first coprimary outcome occurred in 43 patients receiving dronedarone and 19 receiving placebo (hazard ratio, 2.29; P = 0.002). There were 21 deaths from cardiovascular causes in the dronedarone group and 10 in the placebo group (hazard ratio-HR, 2.11; P = 0.046), including death from arrhythmia in 13 patients and 4 patients, respectively (HR, 3.26; P = 0.03). Stroke occurred in 23 patients in the dronedarone group and 10 in the placebo group (HR, 2.32; P = 0.02). Hospitalization for heart failure occurred in 43 patients in the dronedarone group and 24 in the placebo group (HR, 1.81; P = 0.02). Thus, the authors concluded that dronedarone increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent AF who were at risk for major vascular events and therefore this drug should not be used in such patients.

In an earlier trial, the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (**ANDROMEDA**) study, after inclusion of 627 patients (310 in the dronedarone group and 317 in the placebo group), the trial was prematurely terminated again for safety reasons.[3] During a median follow-up of 2 months, 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (HR in the dronedarone group, 2.13; P = 0.03). The excess mortality was predominantly related to worsening of heart failure — 10 deaths in the dronedarone group and

2 in the placebo group. The primary end point (composite of death from any cause or hospitalization for heart failure) did not differ significantly between the two groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%) (HR, 1.38; P = 0.12). More increases in the creatinine concentration were reported as serious adverse events in the dronedarone group than in the placebo group. The authors concluded that in patients with severe heart failure and left ventricular systolic dysfunction, treatment with dronedarone was associated with increased early mortality related to the worsening of heart failure.

The results of the above two studies diverge from those of earlier studies, like the ATHENA trial,[4] but this does not offer any re-assurance on the use of dronedarone in patients with any risk factors. Dronedarone's use has thus been restricted to maintenance of sinus rhythm in patients with paroxysmal AF and no underlying heart disease. It is contraindicated in patients with permanent AF and patients with current or previous episodes of heart failure or left ventricular systolic dysfunction, as detrimental effects of dronedarone have been documented in these groups of patients. In the ATHENA trial, patients with persistent AF also received the drug without apparent harm, but the definition of persistent and permanent AF is not that clear, and thus, great caution should be exercised in the persistent AF group, as well. Whether there will be a return of dronedarone for a second chance after this recent potentially fatal blow or setback remains doubtful. All these drawbacks taken together with the harmful effects of the drug on the liver with reported cases of liver damage necessitating liver transplantation make everybody heavily pensive and hesitant in ever using this pharmaceutical agent.[5,6]

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