Results from the PALLAS Study: Using Dronedarone on Top of Standard Therapy

Written by Maria Vinall

Stuart J. Connolly, MD, Hamilton General Hospital, Hamilton, Ontario, Canada, presented results from the Permanent Atrial FibriLLAtion Outcome Study using Dronedarone on Top of Standard Therapy (PALLAS) study [NCT01151137], which showed that dronedarone increased rates of heart failure, stroke, and death from cardiovascular (CV) causes in patients with permanent atrial fibrillation (AF) who were also at risk for major vascular events.

The PALLAS study was a randomized, double-blind, placebo-controlled, parallel group trial in patients aged at least 65 years with a ≥6-month history of permanent AF and at least one of the following risk factors for major vascular events: history of coronary or peripheral artery disease, stroke, or transient ischemic attack (TIA); hospitalization for heart failure during the past 12 months or left ventricular ejection fraction ≤40%; and age ≥75 years with both hypertension and diabetes mellitus. Participants were randomly assigned 1:1 to receive 400 mg twice-daily dronedarone or matching placebo. The first coprimary outcome was a composite of stroke, myocardial infarction (MI), systemic embolism, or death from CV causes. The second coprimary outcome was unplanned hospitalization for a CV cause or death. Planned study enrollment was 10,800 patients. The study was terminated due to safety concerns. A total of 3236 patients from 489 sites in 37 countries were randomized and followed for a median of 3.5 months.

The majority of patients was elderly (mean age 75 years), carried a high burden of vascular disease, and had permanent AF for more than 2 years. Heart failure was present in 70% of patients. There was substantial use of concomitant β-blockers (74%) and vitamin K antagonists (84%). The mean $CHADS_2$ score was 2.8, and 27% had a prior stroke or TIA.

Dronedarone restored sinus rhythm at 4 months in significantly more patients than placebo (3.5% vs 1.4%; p=0.001). At 1 month, there was a significant decrease in heart rate (-7.6 beats per minute vs +0.1 beats per minute with placebo; p<0.001) and systolic blood pressure (-3.5 mm Hg vs -1.7 mm Hg; p=0.003) in patients who were randomized to dronedarone. Significantly more patients in the dronedarone group discontinued their study medication prematurely (21% vs 11% of placebo patients; p<0.001).

The first coprimary outcome (composite stroke, embolism, MI, or CV death) occurred in more than twice as many patients who were randomized to dronedarone (43, 2.7%) compared with placebo (19, 1.2%; HR, 2.29; 95% CI, 1.34 to 3.94; p=0.002). There was also almost a 2-fold increase in the occurrence of the secondary outcome (unplanned CV hospital or death) with dronedarone (7.8%) compared with placebo (4.1%; HR, 1.95; 95% CI, 1.45 to 2.62; p<0.001). The increase in death was driven mostly by an increase in CV death that was arrhythmic death. The increase in unplanned CV hospitalization was driven by heart failure hospitalizations. The hazard of dronedarone was consistent across the prespecified subgroups.

Adverse events (AEs), serious AEs, and discontinuations due to AEs were more common with dronedarone (49.0% vs 37.3%; p<0.001). AEs that were more common with dronedarone treatment included gastrointestinal problems, breathing difficulties, edema, and bradycardia.

Dronedarone was associated with significantly worse outcomes in this group of high-risk patients with permanent AF and increased mortality than in a prior trial (ANDROMEDA) of patients with severe left ventricular systolic dysfunction who were admitted with symptomatic heart failure [Køber L et al. *N Engl J Med* 2008]. The results of the PALLAS trial stand in contrast to the more favorable results with dronedarone that were seen in the ATHENA trial, the study that led to the approval of dronedarone for management of patients with nonpermanent AF [Hohnloser SH et al. *N Engl J Med* 2009]. The mechanism by which dronedarone increases CV events in some populations but not others is unclear. Overall, the PALLAS investigators concluded that dronedarone should not be used in patients with permanent AF and major risk factors for vascular events.

Further reading: Connolly SJ et al. *N Engl J Med* 2011.

Extended Apixaban Failed to Reduce VTE Risk in Medically Ill Patients

Written by Anne Jacobson

An extended course of thromboprophylaxis with apixaban did not reduce the risk of venous thromboembolism (VTE, which consists of pulmonary embolism (PE) and deep venous thrombosis [DVT]) and VTE-related death in medically ill patients compared with a shorter course of enoxaparin, according to findings from the Apixaban Dosing to Optimize Protection from Thrombosis trial [ADOPT; NCT00457002].