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].

PE is one of the most preventable causes of death among hospitalized patients [Goldhaber SZ et al. *Lancet* 1999]. Recent improvements in inpatient thromboprophylaxis have reduced in-hospital mortality rates. Although average hospital stays are shortening, patients remain vulnerable to VTE-related complications after discharge [Ridker PM et al. *N Engl J Med* 2003]. The ADOPT trial evaluated whether extended thromboprophylaxis with a novel oral factor Xa anticoagulant, apixaban, compared with standard short-term treatment, would reduce the risk of VTE and VTE-related death in hospitalized medically ill patients.

The ADOPT trial enrolled 6528 patients who were hospitalized with congestive heart failure, acute respiratory failure, or other risk factors for VTE. Patients were randomly assigned to treatment with oral apixaban 2.5 mg twice daily for 30 days (n=3255) or subcutaneous enoxaparin 40 mg daily for 6 to 14 days (n=3273). Patients were evaluated with systemic compression ultrasonography at hospital discharge and on Day 30. The primary efficacy endpoint was the 30-day composite of death that was related to VTE, PE, symptomatic DVT, or asymptomatic proximal leg DVT.

Samuel Z. Goldhaber, MD, Senior Cardiologist, Brigham and Women's Hospital, Professor of Medicine, Harvard Medical School, Boston, Massachusetts, USA, presented findings from the ADOPT trial.

Overall, 2.71% of patients in the apixaban group and 3.06% of those in the enoxaparin group reached the primary endpoint by Day 30 (RR, 0.87; 95% CI, 0.62 to 1.23; p=0.44). This 13% reduction in events favored apixaban but did not achieve statistical significance. Apixaban did increase the risk of major bleeding compared with enoxaparin (0.47% vs 0.19%; RR, 2.53; p=0.04), but there were no deaths from bleeding and no intracranial hemorrhages.

"The ADOPT trial does not provide evidence to justify a policy of extended prophylaxis in a broad population of medically ill patients after hospital discharge," Dr. Goldhaber said. However, findings from ADOPT illustrate the importance of effective thromboprophylaxis beyond hospital discharge. The cumulative risk of VTE and VTE-related death continued to increase during follow-up, particularly after thromboprophylaxis was discontinued.

In a secondary endpoint analysis, investigators examined outcomes during the postparenteral period, when blinded parenteral therapy was discontinued in the enoxaparin group and oral prophylaxis continued in the apixaban group. During this period, patients in the apixaban group had a 56% reduction in the risk of VTE-related death and symptomatic VTE compared with those in the enoxaparin group (95% CI, 0.19 to 1.00).

Several limitations of the study are worthy of consideration when interpreting the results. Because one-third of all protocol-mandated ultrasonography examinations were not obtained or nonevaluable, resulting in a high rate of patient exclusion from the efficacy analysis, the ADOPT trial had substantially less statistical power than initially planned. In addition, the study protocol mandated treatment with enoxaparin for at least 6 days and up to 14 days, even if patients were discharged earlier. This resulted in better efficacy with enoxaparin than would be expected in routine practice, in which VTE prophylaxis is discontinued at the time of hospital discharge. The Day 10 ultrasonography examination also distorted the natural history of DVT because of early identification and treatment of asymptomatic DVT. Despite these measures that went beyond standard practice, the number of primary endpoints in the control group increased steadily throughout the trial after enoxaparin was discontinued. These findings support further VTE prevention studies in high-risk populations.

Results from the TRA•CER Trial

Written by Maria Vinall

The results of the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA•CER trial), reported by Kenneth W. Mahaffey, MD, Duke Clinical Research Institute, Durham, North Carolina, USA, showed that vorapaxar does not significantly improve outcomes in high-risk patients with non-ST-segment elevation (NSTE) acute coronary syndrome (ACS) and significantly increases the risk of major bleeding, including intracranial hemorrhage (ICH).

The TRA•CER trial [NCT00527943] evaluated the efficacy and safety of vorapaxar, a first-in-class, orally active, potent, and selective platelet protease-activated receptor-1 (PAR-1) antagonist, compared with placebo in high-risk patients with NSTE-ACS who were treated with the current standard of care. TRA•CER was a prospective, randomized, double-blind, placebo-controlled trial that enrolled 12,944 ACS patients from 37 countries. Eligible patients had ischemic symptoms within 24 hours of hospital presentation, either elevated troponin or CK-MB or ST-segment changes on ECG, and at least 1 additional high-risk criterion: age ≥55 years, prior myocardial infarction (MI) or revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]), diabetes mellitus (DM), or peripheral arterial disease. Vorapaxar or placebo