PARAMOUNT Trial Results

Written by Maria Vinall

In about half of all patients with heart failure (HF), the ejection fraction (EF) is normal or nearly normal, despite high morbidity and mortality in these patients. Now, the findings of a Phase 2 trial suggest that a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), LCZ696, may be beneficial for patients who have HF with preserved EF.

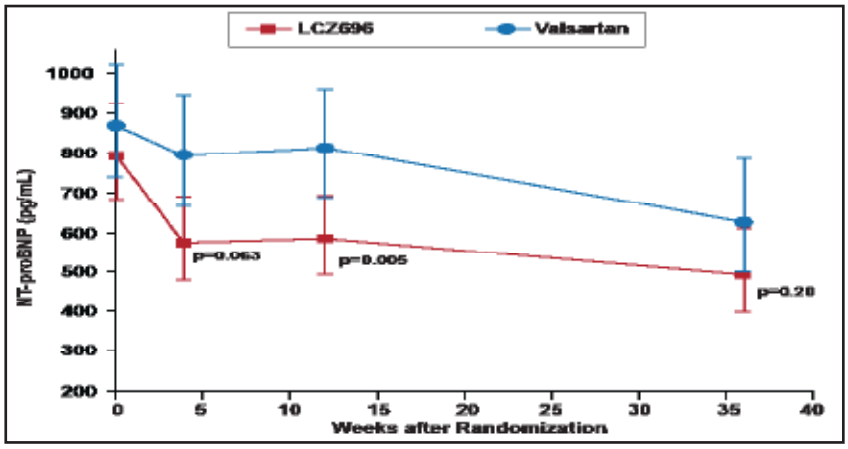
LCZ696 is the first agent to be associated with 2 powerful predictors of outcome in HF: reduction in the concentration of N-terminal prohormone brain natriuretic peptide (NT-proBNP) and decrease in the size of the left atrium, said Scott D. Solomon, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, who reported the findings. The study was published to coincide with its presentation at the ESC 2012 Congress [Solomon SD et al. *Lancet* 2012].

Dr. Solomon explained that LCZ696 simultaneously blocks the renin angiotensin system while augmenting the body's intrinsic natriuretic peptide system through neprilysin inhibition. These dual effects may be important in the treatment of HF with preserved EF.

The Prospective Comparison of ARNI with ARB (angiotensin receptor blocker) on Management of Heart Failure with Preserved Ejection Fraction [PARAMOUNT; NCT00887588] trial enrolled 308 patients who were randomly assigned to LCZ696 (200 mg BID after 1 week each of 50 and 100 mg BID) or the ARB valsartan (160 mg BID after 1 week each of 40 and 80 mg BID). The primary endpoint, NT-proBNP, was evaluated as the ratio of the concentration at 12 weeks to that at baseline. Secondary objectives included echocardiographic measures of left atrial size, left ventricular size and function, and diastolic function, and safety and tolerability.

Over 12 weeks, both LCZ696 and valsartan led to a decrease in the NT-proBNP concentration, with a greater reduction in the LCZ696 group (from 783 to 605 pg/mL) than in the valsartan group (from 862 to 835 pg/mL; HR, 0.77; 95% CI, 0.64 to 0.92; p=0.005). The decrease was evident at 4 weeks and was sustained over the 12-week period (Figure 1). The NT-proBNP concentration continued to decrease in both groups over 36 weeks; the difference no longer significant at that time (p=0.20).

Figure 1. Comparison of the Primary Endpoint—Concentration of NT-proBNP at 12 Weeks.



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A similar treatment effect was found in all predefined subgroups, including those defined by age (≥65 vs <65 years), gender, systolic blood pressure (>140 vs ≤140 mm Hg), presence or absence of diabetes, EF (≥50% vs <50%), presence or absence of atrial fibrillation, previous hospitalization for HF, NYHA class (III vs II), and median NT-proBNP concentration (>median vs ≤median).

LCZ696 was also associated with a significant decrease in the volume of the left atrium at 36 weeks (p=0.003), and the left atrial dimension (p=0.034). In addition, the NYHA class improved in more patients in the LCZ696 group than in the valsartan group at both 12 and 36 weeks; the difference was significant at the latter time period (p=0.05). The frequency of serious adverse events was similar between therapies: 15% with LCZ696 and 20% with valsartan. The number of patients with hypotension, renal dysfunction, or hyperkalemia did not differ between groups.

Prospective studies are needed to determine whether the effects found in PARAMOUNT translate into improved clinical outcomes.

TRILOGY ACS Outcomes

Written by Lori Alexander

In the largest trial to date of patients with medically managed acute coronary syndrome (ACS) without revascularization, prasugrel did not improve outcomes, compared with clopidogrel during 2.5 years of follow-up among patients <75 years. The findings are from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes [TRILOGY ACS] study, which was published to coincide with its presentation at the European Society of Cardiology Congress [Roe MT et al. *N Engl J Med* 2012].

The TRILOGY ACS trial is important because 40% to 60% of patients with ACS are managed without revascularization, said Matthew T. Roe, MD, MHS, Duke University Medical Center, Durham, North Carolina, USA. These patients are at high risk for subsequent complications, with rates of ischemic events 2-fold greater than those treated with revascularization. The investigators had hypothesized that prasugrel would be a better option than clopidogrel in patients with medically managed ACS, based on the superiority of prasugrel over clopidogrel in patients with ACS who underwent percutaneous revascularization in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction [TRITON-TIMI 38] trial [Wiviott SD et al. *N Engl J Med* 2007].

TRILOGY was an international trial that enrolled 9326 patients who were treated medically for unstable angina or non-ST-segment elevated myocardial infarction (NSTEMI). Patients were randomly assigned to treatment with prasugrel (10 mg QD) or clopidogrel (75 mg QD); the dose of prasugrel was reduced to 5 mg QD for patients weighing <60 kg. All patients also received aspirin as part of medical management. The primary analysis involved 7243 of the patients who were <75 years. A secondary, exploratory analysis was performed in 2083 patients who were ≥75 years, who were randomly assigned to prasugrel 5 mg QD or clopidogrel 75 mg QD. The primary endpoint was a composite of cardiovascular death, MI, or stroke. Patients were followed for as long as 30 months.

Dr. Roe reported the findings for the patients <75 years and for the overall population. At a median follow-up of 17 months for the younger patients, the rates of the primary composite endpoint were 13.9% in the group randomized to prasugrel and 16.0% in the clopidogrel group (HR, 0.91; 95% CI, 0.79 to 1.05; p=0.21). The results were similar for the overall patient population (18.7% vs 20.3%; HR, 0.96; 95% CI, 0.86 to 1.07; p=0.45).

Among patients <75 years, rates of bleeding were assessed according to the Global Use of Strategies to Open Occluded coronary arteries (GUSTO) and Thrombolysis in Myocardial Infarction (TIMI) criteria. Bleeding was low in both treatment groups, with no significant differences except for TIMI major or minor bleeding (1.8% in the prasugrel group vs 1.3% in the clopidogrel group; p=0.02). For the overall population, the rates of TIMI major bleeding were similar with prasugrel compared with clopidogrel (2.5% vs 1.8%; HR, 1.23; 95% CI, 0.84 to 1.81; p=0.29).

Dr. Roe noted that despite the absence of a significant benefit in the primary endpoint, the findings of a prespecified analysis suggested that prasugrel was associated with a lower risk of multiple recurrent ischemic events (not just the first event among all components of the primary endpoint [HR, 0.85; 95% CI, 0.72 to 1.00; p=0.04]) as well as a trend towards a lower risk of ischemic events after 12 months (HR for >12 months, 0.64; 95% CI, 0.48 to 0.86; p=0.02).

Though TRILOGY ACS failed to meet its primary endpoint, it contributes to the knowledge base about ACS patients who are medically managed. Additional analyses and studies will be needed to try to evaluate the role of prasugrel in the management of NSTEMI.