Angiotensin-Neprilysin Inhibitor Could Become a New Standard for HF

Written by Wayne Kuznar

Clinical outcomes, including mortality, are improved with the use of a dual angiotensin receptor blocker–neprilysin inhibitor (ARNI), LCZ696, compared with the existing gold standard in the treatment of patients with chronic heart failure (CHF). John McMurray, MD, discussed findings and insights from a study that evaluated the efficacy and safety of LCZ696 vs enalapril on the morbidity and mortality of patients with CHF—namely, the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial [PARADIGM-HF; McMurray JJV et al. *N Engl J Med*. 2014].

The finding represents a new way to attack the physiologic basis of CHF, according to Dr McMurray. The current treatment strategy targets inhibition of harmful neurohumoral pathways to slow progression of heart failure (HF) through the use of drugs that inhibit the renin-angiotensin-aldosterone system and the sympathetic nervous system. In addition to harmful neurohumoral systems in CHF, other neurohumoral pathways promote sodium and water excretion and have growth-inhibiting properties. The new paradigm in CHF treatment lies in inhibiting detrimental neurohumoral pathways while augmenting the potentially beneficial neurohumoral pathways. The ARNI LCZ696 does both, inhibiting the renin-angiotensin-aldosterone system while augmenting natriuretic peptides and other vasoactive substances, such as bradykinin and substance P.

In PARADIGM-HF, 8442 patients with class NYHA II to IV symptoms, an elevated level of plasma brain-type natriuretic peptide or N-terminal fragment of the prohormone brain-type natriuretic peptide, and an ejection fraction ≤ 40% were randomized in a 1:1 ratio to either LCZ696 (200 mg, BID) or enalapril (10 mg, BID) in addition to other standard CHF therapy. Enalapril was chosen because it was the angiotensin-converting enzyme inhibitor demonstrated to reduce mortality and hospitalization of patients with CHF with reduced ejection fraction in the SOLVD-T trial [SOLVD Investigators. *N Engl J Med.* 1991].

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The trial was scheduled to conclude around October 2014, but the Data Monitoring Committee recommended stopping it in March 2014 because of an overwhelmingly statistically significant benefit in favor of LCZ696 on (1) the primary composite end point of death from cardiovascular (CV) causes or first hospitalization for HF and (2) the major secondary end point of CV mortality. After a median follow-up of 27 months, the primary composite outcome had occurred in 21.8% of the LCZ696 group and 26.5% of the enalapril group (HR, 0.80; 95% CI, 0.73 to 0.87; $P = .0000004$).

Compared with enalapril, LCZ696 reduced the risk of death from CV causes by 20% ($P < .001$) and the risk of hospitalization for HF by 21% ($P < .001$). The rate of all-cause mortality was reduced from 19.8% with enalapril to 17.0% with LCZ696, a 16% reduction ($P < .001$). The effect of LCZ696 vs enalapril on mortality was larger than the effect that enalapril had when compared with placebo in SOLVD-T.

LCZ696 had a significantly favorable effect over enalapril on other end points, including all hospital admissions, CV-related hospital admissions, the number of emergency room visits, the need for device implantation, and the number of patients developing renal dysfunction. Patients randomized to LCZ696 who were admitted to the hospital were less likely than hospitalized enalapril patients to be admitted to an intensive care unit.

Patients randomized to LCZ696 had more symptomatic hypotension when compared with those randomized to enalapril ($P < .001$), but hypotension rarely required discontinuation of LCZ696. Fewer patients in the LCZ696 group vs the enalapril group stopped their study medication due to an adverse event (10.7% vs 12.3%; $P = .03$). Unlike the combination

of a neprilysin inhibitor and an angiotensin-converting enzyme inhibitor, known to cause serious angioedema, there was no increased risk of serious angioedema with the ARNI when compared with enalapril.

No Increased Coronary or Mortality Risk Associated With Changes in DAPT

Written by Mary Beth Nierengarten

For patients discharged after acute coronary syndrome (ACS), changing from dual-antiplatelet therapy (DAPT) to less potent antiplatelet therapy is not associated with increased coronary or mortality risk despite a short-term excess of cardiovascular (CV) events.

Héctor Bueno, MD, PhD, Hospital General Universitario Gregorio Maranon, Madrid, Spain, presented the results of the Long-term Follow-up of Anti-thrombotic Management Patterns in Acute Coronary Syndrome Patients [EPICOR; NCT01171404], a real-world-practice cohort study conducted to describe current international patterns of DAPT use following ACS and the clinical outcomes associated with changes in DAPT.

Between September 2010 and March 2011, patients (n = 10 568) from 555 hospitals in 20 countries across Latin America and Europe were enrolled in the study. All patients were hospitalized for an ACS within 24 hours of symptom onset, and all survived to hospital discharge. Of these patients, 4943 had STEMI, and 5625 had non–ST segment elevation ACS.

This prospective, observational study was designed to look at short- and long-term antithrombotic management patterns in patients with ACS among the hospitals. It also examined the relationship between antithrombotic management patterns and in-hospital and postdischarge clinical outcomes, quality of life, and economic aspects.

At discharge, the medication status was known for 10 069 patients; 8593 (85.3%) remained on DAPT, while others switched to single-antiplatelet therapy or oral anticoagulation. At 2 years, 43.8% of patients remained on DAPT.

Prof Bueno said that the data show that patients frequently remained on DAPT after ACS much longer than the recommendation guidelines of 12 months. The study found that a maximum of 65.9% of patients in Latin America and a minimum of 55.7% in Southern Europe remained on DAPT at 2 years ($P < .001$).

To look at the association between change in DAPT status and clinical outcomes, Prof Bueno presented the 2-year follow-up results of 8593 patients who were interviewed per study design every 3 months after discharge up to 24 months. Results at 2 years showed an increase in CV events in patients who discontinued DAPT versus those who remained on DAPT. Despite the increase in nonfatal CV events, there was no association with changes in DAPT status and the risk of either coronary or all-cause mortality, although there were few number of events (Tables 1 and 2).

Prof Bueno highlighted several limitations of the study, including its observational nature, potential for recall bias, lack of accurately recording the date of all medication changes, few number of deaths, potential to underestimate CV events, and lack of systematic recording of the cause of death.

Table 1. Relationship Between Change in DAPT Status and Nonfatal Cardiovascular Events and Death

	No. of Eligible Participants	No. of Changes in Medication	No. of Events (%)	Event Rate per 100 Person-Years at Risk
During time on DAPT	8593	—	655 (85)	5.9
After DAPT change (any time)	3551	3976	114 (15)	3.4
< 7 d after stop	3551	3976	7	9.2
7 to 30 d after stop	3520	3936	9	3.7
> 30 d after stop	3406	3796	98	3.2

DAPT, dual-antiplatelet therapy.

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