Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure - PARADIGM-HF

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Contribution To Literature:

The PARADIGM-HF trial showed that LCZ696 was superior to enalapril in patients with heart failure due to reduced EF.

Description:

The goal of the trial was to evaluate treatment with the combined angiotensin-receptor blocker (valsartan)/neprilysin inhibitor (sacubitril) LCZ696 compared with enalapril among participants with heart failure due to reduced ejection fraction (EF).

Inhibition of neprilysin increases levels of natriuretic peptides, bradykinin, and adrenomedullin, thus resulting in natriuresis and vasodilatation.

Study Design

- Randomized
- Blinded
- Parallel

Patient Populations:

- Participants at least 18 years of age with heart failure due to reduced LVEF and B-type natriuretic peptide (BNP) ≥150 pg/ml or NT-proBNP ≥600 pg/ml

Number of screened applicants: 10,513
Number of enrollees: 8,442
Duration of follow-up: median 27 months
Mean patient age: 64 years
Percentage female: 21%
EF: 30%

Exclusions:

- Symptomatic hypotension
- Estimated glomerular filtration rate <30 ml/min/1.73 m2
- Serum potassium >5.2 mmol/L
- Angioedema

Primary Endpoints:
- Cardiovascular death or hospitalization for heart failure

Drug/Procedures Used:

Participants with heart failure (New York Heart Association class II-IV) due to reduced EF (≤40%) were randomized to LCZ696 200 mg twice daily (n = 4,187) versus enalapril 10 mg twice daily (n = 4,212) in addition to standard therapy.

Concomitant Medications:
- Digitalis: 29%
- Beta-blocker: 93%
- Mineralocorticoid antagonist: 54%

Principal Findings:

Overall, 8,442 participants were randomized. The mean age was 64 years, 21% were women, mean body mass index was 28 kg/m2, 60% had ischemic etiology for heart failure, 43% had prior myocardial infarction, and 35% had diabetes. The mean left ventricular (LV) EF was 30%. Systolic blood pressure at 8 months was 3.2 mm Hg lower with LCZ696 compared with enalapril.

The trial was stopped early due to prespecified stopping rules for benefit. At a median of 27 months, the primary outcome of cardiovascular death or hospitalization for heart failure occurred in 21.8% of the LCZ696 group vs. 26.5% of the enalapril group ($p < 0.001$). Benefit was consistent among all subgroups. The association for the primary outcome did not vary according to time from heart failure hospitalization to screening.

- Cardiovascular death: 13.3% vs. 16.5% ($p < 0.001$), respectively
- All-cause death: 17.0% vs. 19.8% ($p = 0.0009$), respectively
- Hospitalization for heart failure: 12.8% vs. 15.6% ($p < 0.001$), respectively
- Symptomatic hypotension: 14.0% vs. 9.2% ($p < 0.001$), respectively
- Elevated serum creatinine (≥2.5 mg/dl): 3.3% vs. 4.5% ($p = 0.007$), respectively
- Elevated serum potassium (≥5.5 mmol/L): 16.1% vs. 17.3% ($p = 0.15$), respectively
- Cough: 11.3% vs. 14.3% ($p < 0.001$), respectively

There were no episodes of angioedema causing airway compromise in either group.

- Improved NYHA class: 16.7% vs. 14.9% ($p = 0.0015$), respectively
- Treatment failure: (hazard ratio [HR] = 0.84, $p = 0.0029$), respectively for LCZ696 vs. enalapril
- Number of emergency room visits: (HR = 0.70, $p = 0.017$), respectively for LCZ696 vs. enalapril
- Number of HF admissions: (HR = 0.77, $p = 0.0004$), respectively for LCZ696 vs. enalapril

Interpretation:

Among patients with heart failure due to reduced EF, the use of LCZ696 was beneficial compared with enalapril. LCZ696 was associated with a reduction in cardiovascular death or hospitalization for heart failure. LCZ696 also slowed progression of heart failure. This study medication was compared against a comparable dose of enalapril that had previously been shown to reduce mortality in heart failure patients. LCZ696 was well tolerated, with a higher frequency of symptomatic hypotension, but a lower frequency of elevated serum creatinine, hyperkalemia, and cough.

In an earlier study, omapatrilat, which inhibits angiotensin-converting enzyme, neprilysin, and aminopeptidase P, failed to demonstrate improvement over enalapril in the treatment of chronic heart failure. Combined angiotensin-receptor blocker/neprilysin inhibition represents an important change in the treatment of heart failure patients.

References:

Solomon SD, Claggett B, Packer M, et al. Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation: The PARADIGM-HF Trial. JACC Heart Fail 2016;4:816-22.

Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 2015;131:54-61.

Presented by Dr. John McMurray at the American Heart Association Scientific Sessions, Chicago, IL, November 17, 2014.

McMurray JJ, Packer M, Desai AS, et al., on behalf of the PARADIGM-HF Investigators and Committees. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med 2014;371:993-1004.

Editorial: Jessup M. Neprilysin Inhibition — A Novel Therapy for Heart Failure. N Engl J Med 2014;371:1062-4.

Presented by Dr. Milton Packer at the European Society of Cardiology Congress, Barcelona, Spain, August 30, 2014.

Clinical Topics: Heart Failure and Cardiomyopathies, Acute Heart Failure, Heart Failure and Cardiac Biomarkers

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- See more at: http://www.acc.org/latest-in-cardiology/clinical-trials/2014/08/30/12/22/paradigm-hf#sthash.2pgKWsHe.dpuf