The Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor (ARNI) With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial

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BACKGROUND:

LCZ696 blocks the action of angiotensin II and inhibits neprilysin, the enzyme degrading natriuretic and other vasoactive peptides. PARADIGM-HF tested the hypothesis that LCZ696 200 mg bid would be superior to enalapril 10 mg bid in improving clinical outcomes in patients with HF -REF.

METHODS: A randomized, double-blind, parallel-group, active-controlled, event driven, superiority trial. Single-blind active run-in period to ensure that patients tolerated both study drugs, followed by a double-blind phase in which patients randomized 1:1 to LCZ696 or enalapril. The main run-in inclusion criteria were: NYHA class II-IV, LVEF =40% (changed December 2010 to =35%); BNP =150 pg/mL (or NT-proBNP =600 pg/mL) or a BNP =100 pg/mL (or NT-proBNP =400 pg/mL) if HF hospitalization within the last 12 months. At randomization: eGFR =30 mL/min/1.73 m2 (and no decrease >35% during the run-in), SBP =95 mmHg, and K+ =5.4 mmol/L. Primary endpoint: composite of CV mortality or hospitalization for HF, but trial also specifically designed to evaluate CV mortality which determined both sample size and interim monitoring boundaries.

RESULTS: 8442 patients randomized at 985 sites in 47 countries. Mean age 64 (SD 11) yrs; 78% male; 70% NYHA class II/24% class III; LVEF 29 (SD 6)%; beta-blocker 93%; mineralocorticoid receptor antagonist (MRA) 56%. The primary endpoint was reduced by 20 (95% CI 13-27)% in the LCZ696 group compared with the enalapril group (p=0.0000004); CV death was reduced by 20 (11-29)% (p=0.00008) and HF hospitalization by 21 (11-29)% (p=0.00008).

All -cause death was reduced by 16 (7-24)% (p=0.0009). Both sudden death (relative risk reduction 20%, p=0.008) and death from worsening HF (21%, p=0.04) were reduced by LCZ696. Repeat as well as first admissions for HF were reduced by 23% (p=0.0004). CV admissions as well as admissions for any cause were also reduced significantly by LCZ696. Patient reported outcomes and NYHA Class improved
significantly in the LCZ696 compared with the enalapril group.

CONCLUSION: Combined inhibition of both the angiotensin receptor and neprilysin is more effective than RAS blockade alone in improving outcomes in HF -REF.

DISCLOSURE:
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