

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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Background

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

Methods

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

Results

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; $P < 0.001$). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; $P < 0.001$); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; $P < 0.001$). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% ($P < 0.001$) and decreased the symptoms and physical limitations of heart failure ($P = 0.001$). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

Conclusions

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

Angiotensin-converting–enzyme (ACE) inhibitors have been the corner- stone of the treatment for heart failure and a reduced ejection fraction for nearly 25 years, since enalapril was shown to reduce the risk of death in two trials. Long-term treatment with enalapril decreased the relative risk of death by 16% among patients with mild-to-moderate symptoms. The effect of angiotensin- receptor blockers (ARBs) on mortality has been inconsistent, and thus, these drugs are recommended primarily for patients who have unacceptable side effects (primarily cough) while receiving ACE inhibitors. Subsequent studies showed that the use of beta-blockers and miner- alocorticoid-receptor antagonists, when added to ACE inhibitors, resulted in incremental decreases in the risk of death of 30 to 35% and 22 to 30%, respectively.

Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and mal- adaptive remodeling. Combined inhibition of the renin–angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies, but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema.

LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, was designed to minimize the risk of serious angioedema. In small trials involving patients who had hypertension or heart failure with a preserved ejection fraction, LCZ696 had hemodynamic and neurohormonal effects that were greater than those of an ARB alone. We examined whether the long-term effects of LCZ696 on morbidity and mortality were superior to those of ACE inhibition with enalapril in patients with chronic heart failure and a reduced ejection fraction.

Study Oversight

The executive committee designed and oversaw the conduct of the trial and data analysis in collaboration with the sponsor, Novartis. The trial was reviewed by an independent data and safety monitoring committee. Data were collected, man- aged, and analyzed by the sponsor according to a predefined statistical analysis plan, and the analyses were replicated by an independent academic statistician. The first draft of the manuscript was prepared by the first two authors, who had unrestricted access to the data, and was reviewed and edited by all the authors. All the authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the analyses.

Study Design

The study design has been reported previously. The trial protocol and the statistical analysis plan (included in the Supplementary Appen- dix) are available with the full text of this article at