Efficacy of angiotensin–neprilysin inhibition versus enalapril in patient with heart failure with a reduced ejection fraction

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Background

Angiotensin-converting enzyme (ACE) inhibitors are the cornerstone of the treatment for heart failure and a reduced ejection fraction (EF) [1].

The effect of angiotensin-receptor blockers (ARBs) on mortality has been inconsistent and these drugs are recommended primarily for patients who have unacceptable side effects while receiving ACE inhibitors [2].

Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin [3] and its inhibitors have been studied as a new therapy for heart failure.

Combined inhibition of the renin–angiotensin system and neprilysin was 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 [4].

LCZ696 consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan and it was expected to minimize the risk of serious angioedema. In a small trial involving patients who had heart failure with a preserved EF, LCZ696 had hemodynamic and neurohormonal effects that were greater than those of an ARB alone [5].

Summary

The PARADIGM-HF was a double-blind randomized controlled trial (RCT) conducted to compare the

angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced EF.

To be eligible, patients needed to have an age of at least 18 years, New York Heart Association (NYHA) class II, III, or IV symptoms, and an EF of 40 % or less (which was changed to 35 % or less by an amendment to the protocol). Patients were required to have a plasma B-type natriuretic peptide (BNP) level of at least 150 pg/ml (or at least 100 pg/ml if they had been hospitalized for heart failure within the previous 12 months) an N-terminal pro-BNP (NT-proBNP) level ≥ 600 pg/ml and to take a stable dose of a beta-blocker and an ACE inhibitor (or ARB) equivalent to at least 10 mg of enalapril daily. Exclusion criteria included symptomatic hypotension, a systolic blood pressure of less than 100 mmHg, an estimated glomerular filtration rate (eGFR) below 30 ml/min, a serum potassium level of more than 5.2 mmol/l at screening or a history of angioedema or unacceptable side effects during receipt of ACE inhibitors or ARBs.

The study consisted of three phases: the screening period; a single-blind run-in period during which all patients received enalapril that was followed by a single-blind run-in period during which all patients received LCZ696, to ensure an acceptable side-effect profile of the study drugs at target doses; and finally the double-blind treatment period in the two study groups. Three interim efficacy analyses were conducted after the accrual of one-third, one half and two-third of the prevented events to stop the trial for a compelling benefit.

The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure. The secondary outcomes were the time to death from any cause, the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy

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Questionnaire (KCCQ), the time to a new onset of atrial fibrillation, and the time to the first occurrence of a decline in renal function.

4,187 patients were randomly assigned to receive LCZ696 and 4,212 to receive enalapril with a median duration of follow-up of 27 months.

The primary outcome (death from cardiovascular causes or hospitalization for heart failure) occurred in 914 patients (21.8 %) in the LCZ696 group and 1,117 patients (26.5 %) in the enalapril group, the difference was statistically significant.

The difference in favor of LCZ696 was seen early in the trial and at each interim analysis and so the trial was stopped because the pre-specified stopping boundary for an overwhelming benefit had been crossed.

A statistically significant difference was observed for death from any cause (17 % of patients in the LCZ696 group and 19.8 % in the enalapril one) and the mean change from baseline to month 8 in the KCCQ clinical summary score (with a reduction of 2.99 points in the LCZ696 group and a reduction of 4.63 points in the enalapril ones). No significant differences were observed for the other secondary outcomes (new onset of atrial fibrillation and decline in renal function).

With regard to the adverse events, patients in the LCZ696 group were more likely than those in the enalapril group to have symptomatic hypotension but cough, an altered serum creatinine and hyperkalemia were reported less frequently in the LCZ696 group than in the enalapril group.

Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an adverse event or because of renal impairment.

Strengths of the study

- A clinically important primary end point was considered.
- It is a well-designed randomized controlled trial (although drug run-in periods are a controversial study-design choice).
- The superiority of LCZ696 was tested to enalapril (the standard of care) in addition to “recommended therapy” (patients in therapy on-top with beta-blockers and mineralocorticoid antagonists).

Question marks

- An amendment to the study protocol on December 2010 modified the inclusion criteria and EF was changed from 40 % or less to 35 % or less. Since the subgroup of patients with an EF less than 35 % showed a

better response to the new treatment, we wonder if the change of the protocol could have influenced the results.

- The study population is mainly composed of middle-aged men; as happens in many RCTs, the generalizability of these findings in the everyday clinical practice could be questioned.
- Enalapril was dosed up to 10 mg BID, whereas LCZ696 was dosed up to 200 mg BID (which includes the maximum heart failure dose of valsartan). We wonder if some of the efficacy of the new treatment could be due to the significant reduction in blood pressure in the LCZ696 group.

Sponsorship

- The trial is sponsored by industry which is involved in design, conduction and analysis of the study; the executive committee designed and oversaw the conduct of the trial and data analysis in collaboration with the sponsor. Although the trial was reviewed by an independent committee, data were collected, managed and analyzed by the sponsor (according to a predefined statistical plan, and replicated by an independent academic statistician).

Clinical bottom line

- In patients with chronic heart failure LCZ696 reduced death from cardiovascular causes and hospitalization for heart failure as compared to enalapril. This therapy can be considered as an option in heart failure patients with reduced EF. More data from other RCTs and observational studies are needed to confirm these findings and to clarify the role of the new therapy in the management of heart failure.

Conflict of interest None.

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