LCZ696, an Angiotensin–neprilysin Inhibitor Versus Enalapril in Heart Failure – Summary of PARADIGM-HF Results

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Abstract

This editorial summarises important findings from the PARADIGM-HF study. PARADIGM-HF indicated that the angiotensin receptor-neprilysin inhibitor, LCZ696, is superior to enalapril in reducing the risks of cardiovascular death and of hospitalisation for heart failure in patients with heart failure and reduced ejection fraction.

Keywords

LCZ696, PARADIGM-HF, heart failure

Since enalapril was shown to reduce the risk of all-cause death in the CONSENSUS1 and SOLVD-T trials,2 angiotensin-converting enzyme inhibitors (ACEIs) have been the mainstay of treatment for patients with heart failure (HF) and a reduced ejection fraction (HFrEF). In the SOLVD-T trial there was a relative risk reduction (RRR) of 16% in all-cause death and of 26% in HF hospitalisation among patients with mild-to-moderate symptoms with long-term enalapril treatment.2 Further studies showing additional reductions on mortality and HF hospitalisation by the subsequent addition of beta-blockers (BB) and mineralocorticoid receptor antagonists (MRA) to ACEIs, established triple neurohormonal blockade as the current paradigm of medical therapy in HFrEF.3,4 However, there is an unmet need to further reduce mortality and morbidity risk; 5-year mortality risk among HF patients is >50%.7

The current therapeutic strategy in HFrEF is based on the antagonism of the regulatory systems (renin-angiotensin-aldosterone system and the sympathetic nervous system among others) that produce vasoconstriction, sodium and water retention, hypertrophy, apoptosis and fibrosis, all of them having a negative impact on ventricular remodelling and prognosis in the long term.4 To improve further ventricular remodelling and clinical outcomes a complimentary strategy would be the stimulation of the counter-regulatory systems (natriuretic peptides [NPs] system and others) which have effects that oppose those of the regulatory systems. LCZ696 (Entresto™, Novartis AG, Basel, Switzerland) is a drug that antagonises the regulatory systems and, in addition, stimulates the counter-regulatory systems.

LCZ696 comprises the neprilysin inhibitor, sacubitril (AHU377) and the angiotensin receptor blocker (ARB), valsartan.9,10 Neprilysin is a neutral endopeptidase that degrades a range of endogenous vasoactive peptides,11,12 among them NPs and angiotensin–II. Inhibition of neprilysin by sacubitril therefore increases the levels of NPs providing beneficial haemodynamic and molecular effects. However, sacubitril, when used alone, also increases the levels of angiotensin-II, counteracting the beneficial effects derived from NPs levels increase. Therefore, to obtain full benefit from sacubitril an ARB must be added to block angiotensin receptor-1 stimulation by the increased levels of angiotensin-II.13,14

The addition of counter-regulatory systems stimulation to the traditional strategy of regulatory systems blockage constitutes a new paradigm in HF treatment that was evaluated in the PARADIGM-HF study. The hypothesis was tested that LCZ696 would be superior to enalapril in reducing cardiovascular mortality and morbidity in patients with HFrEF. When considering the ethical aspects of not using an ACEI in the LCZ696 arm it is relevant to mention that the latter contains a valsartan moiety and that ARBs remain recommended as an alternative to ACEIs in patients with HFrEF.15

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LCZ696, an Angiotensin–neprilysin Inhibitor Versus Enalapril in Heart Failure

PARADIGM-HF
In the randomised, double-blind, multicentre, international trial PARADIGM-HF (ClinicalTrials.gov number NCT01035255), 8,442 patients with HF and a left ventricular ejection fraction ≤40%, in New York Heart Association (NYHA) class II–IV were randomised to either LCZ696 200 mg twice daily or enalapril 10 mg twice daily in addition to recommended therapy, including βB and MRAs.16,17 The boundary for an overwhelming benefit of LCZ696 was crossed which meant that, according to pre-specified rules, after a median follow up of 27 months, the trial was stopped early.18 Primary outcome, which was a composite of death from cardiovascular causes or first hospitalisation for HF, occurred in 914 patients (21.8%) in the LCZ696 group compared with 1117 patients (26.5%) in the enalapril group (95% confidence interval [CI], 0.73 to 0.87; p=0.0000002, number needed to treat [NNT]=21) (Figure 1A and Table 1).17,19

Both components of the primary composite endpoint were reduced by LCZ696 compared with enalapril: time to cardiovascular death (hazard ratio = 0.80 [95% CI: 0.73–0.87]; p=0.00004, NNT=32) (Figure 1B and Table 1) and time to first HF hospitalisation (hazard ratio = 0.79 [95% CI: 0.71–0.89]; p=0.00004, NNT=36) (Figure 1C and Table 1).17,19

LCZ696 was more efficacious than enalapril both in terms of reducing sudden cardiac deaths and reducing deaths from worsening HF; this accounted for the majority of cardiovascular deaths.20 The LCZ696 treatment effect for sudden cardiac death was not influenced by the presence of defibrillator devices.20 The efficacy of LCZ696 was superior to that of enalapril across the spectrum of age of the PARADIGM-HF patients, with a favourable benefit–risk profile apparent in all age groups.21 Although most PARADIGM-HF patients had mild symptoms, many were at high risk for adverse outcomes and obtained a large absolute benefit from LCZ696, compared with enalapril.22 In addition, in surviving patients with HF, LCZ696 prevented clinical progression more effectively than enalapril.23

Overall, fewer patients stopped their study medication because of an adverse event in the LCZ696 group than in the enalapril group (10.7% versus 12.3%; p=0.03).17 No major safety signals emerged for LCZ696 therapy.24 The LCZ696 group had lower proportions of patients with renal impairment, hyperkalaemia and cough than the enalapril group, though the proportion of patients with hypotension was higher in the LCZ696 group (Table 2). Angioedema occurred very rarely and although it was more frequent in the LCZ696 than in the enalapril group, the study was not powered to show differences in such rare events (Table 2).
Editorial  Heart Failure

Table 1: Primary and secondary outcomes from the PARDIGM-HF trial

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>LCZ696 (n=4,187)</th>
<th>Enalapril (n=4,212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome – number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalisation for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1,117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalisation for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes – number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</td>
<td>–2.99±0.36</td>
<td>–4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function §</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons; †Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0–100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference; ‡A total of 2670 patients in the LCZ696 group and 2,638 patients in the enalapril group who did not have atrial fibrillation at the randomisation visit were evaluated for new-onset atrial fibrillation during the study; §A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate (eGFR) from the value at randomisation; or a decrease in the eGFR of more than 30 ml per minute per 1.73 m². Reproduced with permission from McMurray et al.18

Table 2: Adverse events during randomised treatment

<table>
<thead>
<tr>
<th>Event*</th>
<th>LCZ696 (n=4,187)</th>
<th>Enalapril (n=4,212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>588 (14.0)</td>
<td>388 (9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic with systolic blood pressure &lt;90 mm Hg</td>
<td>112 (2.7)</td>
<td>59 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.5 mg/dl</td>
<td>139 (3.3)</td>
<td>188 (4.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥3.0 mg/dl</td>
<td>63 (1.5)</td>
<td>83 (2.0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5.5 mmol/L</td>
<td>567 (16.1)</td>
<td>772 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>≥6.0 mmol/L</td>
<td>181 (4.3)</td>
<td>236 (5.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>474 (11.3)</td>
<td>601 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment or use of antihistamines only</td>
<td>30 (0.2)</td>
<td>5 (0.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Use of catecholamines or glucocorticoids without hospitalisation</td>
<td>6 (0.1)</td>
<td>4 (0.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalisation without airway compromise</td>
<td>3 (0.1)</td>
<td>1 (0.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Airway compromise</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

*Shown are results of the analyses of prespecified safety events at any time after randomisation. The number of patients who permanently discontinued a study drug were as follows: for hypotension, 36 (0.9%) in the LCZ696 group and 29 (0.7%) in the enalapril group (p=0.38); for renal impairment, 29 (0.7%) and 59 (1.4%), respectively (p=0.003); and for hyperkalemia, 11 (0.3%) and 15 (0.4%), respectively (p=0.56); †Angioedema was adjudicated in a blinded fashion by an expert committee. Reproduced with permission from McMurray et al.18

When comparing the results of the SOLVD-T and the CHARM-alternative trials with those of the PARADIGM-HF study it may be inferred that LCZ696 doubles the effect on cardiovascular mortality of renin angiotensin aldosterone system inhibitors.21,23 Furthermore, an indirect comparison of LCZ696 with a putative placebo from SOLVD-T study20 showed that LCZ696 may induce a RR of 34% (95% CI: 21–44%, p<0.0001) in cardiovascular death, of 28% (95% CI: 16–39%, p<0.0001) in all-cause mortality and of 49% (95% CI: 39–58%, p<0.0001) in HF hospitalisation compared to placebo. These benefits were obtained even though LCZ696 was added to comprehensive background beta-blocker and MRA therapy.

LCZ696 was added to comprehensive background BB and MRA therapy. Patients in PARADIGM-HF had similar rates of implantable cardioverter-defibrillator (ICD) device use as in other contemporary trials such as EMPHASIS-HF and RED-HF26 and more than in SHIFT trial.27

More patients with HFrEF will soon be able to benefit from this new treatment. LCZ696 [sacubitril/valsartan tablets] was approved by the US Food and Drug Administration (FDA) for the treatment of HFrEF in July 2015.29 Further, the agent is approved in the EU as well as in Switzerland. In addition, the 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update recommended that in patients with mild to moderate HFrEF, an EF<40%, and treated with appropriate doses of guideline-directed medical therapy should be treated with LCZ696 in place of an ACEI or an ARB.30 It will be of interest to discover what approach will be adopted in future European and US guidelines.

Summary

PARADIGM-HF findings underscore the benefits of LCZ696 treatment versus enalapril for patients with HFrEF; with strong evidence based on: a rigorous trial design, large sample size, clinically meaningful endpoint, and a powerful beneficial effect with a very small p-value indicating high statistical significance. Further, a consistent effect was observed across a wide range of studied subgroups and benefits were achieved even though...


15. McMurray JJ, Adamopoulos S, Anker SD, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC, Eur Heart J, 2012;33:1787–847.


