Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure

Milton Packer, MD*; John J.V. McMurray, MD*; Akshay S. Desai, MD, MPH; Jianjian Gong, PhD; Martin P. Lefkowitz, MD; Adel R. Rizkala, PharmD; Jean L. Rouleau, MD; Victor C. Shi, MD; Scott D. Solomon, MD; Karl Swedberg, MD, PhD; Michael Zile, MD; Karl Andersen, MD, PhD; Juan Luis Arango, MD; J. Malcolm Arnold, MD; Jan Bělohlávek, MD, PhD; Michael Böhm, MD; Sergey Boytsov, MD; Lesley J. Burgess, MBBSCh, PhD; Walter Cabrera, MD; Carlos Calvo, MD; Chen-Huan Chen, MD; Andrej Dukat, MD; Yan Carlos Duarte, MD; Andrejs Erglis, MD, PhD; Michael Fu, MD; Efraim Gomez, MD; Angel González-Medina, MD; Albert A. Hagège, MD, PhD; Jun Huang, MD; Tzvetana Katova, PhD; Songsak Kiatchoosakun, MD; Kee-Sik Kim, MD, PhD; Ömer Kozan, Prof Dr; Edmond Bayram Llamas, MD; Felipe Martinez, MD; Bela Merkely, MD; Iván Mendoza, MD; Arent Mosterd, MD, PhD; Marta Negruz-Kawecka, MD, PhD; Keijo Peuhkurinen, MD; Felix J.A. Ramires, MD, PhD; Jens Refsgaard, MD, PhD; Arvo Rosenthal, MD, PhD; Michele Senni, MD; Antonio S. Sibulo Jr, MD; José Silva-Cardoso, MD, PhD; Iain B. Squire, MD; Randall C. Starling, MD, MPH; John R. Teerlink, MD; Johan Vanhaecke, MD, PhD; Dragos Vinereanu, MD, PhD; Raymond Ching-Chiew Wong, MBBS; on behalf of the PARADIGM-HF Investigators and Coordinators†

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From the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX (M.P.); BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, UK (J.J.V.M.); Brigham and Women’s Hospital, Cardiovascular Medicine, MA (A.S.D., S.D.S.); Novartis Pharmaceutical Corporation East Hanover, NJ (G.L., M.P.L., A.R.R., V.C.S.); Université de Montréal, Institut de Cardiologie, Montréal, Canada (J.L.R.); Department of Molecular and Clinical Medicine, Gothenburg, Sweden (K.S.); The Medical University of South Carolina and RHI Department of Veterans Administration Medical Center, Charleston, SC (M.Z.); School of Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland (K.A.); Unidad de Cirugía Cardiovascular de Guatemala, Guatemala City, Guatemala (J.L.A.); Western University, Department of Medicine and Physiology, Ontario, Canada (J.M.A.); 2nd Department of Medicine, Cardiovascular Medicine, University Hospital and 1st Medical School, Charles University in Prague, Prague, Czech Republic (J.B.); Department of Cardiology, University of the Saarland, Homburg/Saar, Germany (M.B.); National Research Center for Preventive Medicine, Moscow, Russia (S.B.); TREAD Research, Cardiology Unit, Department of Internal Medicine, Stellenbosch University and Tygerberg Hospital, Parow, South Africa (L.B.); Clínica Vasalio, Lima, Peru (W.C.); Unidad de Hipertensión Arterial y Riesgo Vascular, Hospital Clínico Universitario, Santiago de Compostela, A Coruña, Spain (C.C.); Department of Medicine, National Yang-Ming University, Taiwan, Republic of China (C.H.C.); Second Department of Internal Medicine, Comenius University in Bratislava, Bratislava, Slovakia (A.D.); Luis Vernaza Hospital, Guayaquil, Ecuador (Y.C.D.); Faculty of Medicine, Institute of Cardiology, University of Latvia, Riga, Latvia (A.E.); Department of Medicine, Sahlgrenska University Hospital/Ostra Hospital, Göteborg, Sweden (M.F.C.); Clinic Shaio, Bogota, Colombia (E.G.); Hospiten Santo Domingo, Universidad Autonoma de Santo Domingo, Santo Domingo, Dominican Republic (A.G.-M.); Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Département de Cardiologie; Paris Descartes University, Sorbonne Paris Cité; INSERM U3970, Paris Cardiovascular Research Center; Paris, France (A.A.H.); First Affiliated Hospital with Nanjing Medical University, China (J.H.); National Hospital of Cardiology, Sofia, Bulgaria (T.K.); Cardiology, Medicine, Khon Kaen University, Thailand (S.K.); Daegu Catholic University Hospital, Daegu, Korea (K.-S.K.); Dokuz Eylul University Medicine Faculty, İzmir, Turkey (O.K.); Fundación Cardiovascular de Aguascalientes A.C., Hidalgo, Mexico (E.B.L.); Titular de Medicina Interna, Universidad Nacional de Córdoba, Instituto DAMIC/Fundacion Ruscudella, Cordoba, Argentina (F.M.); Heart and Vascular Center Semmelweis University, Budapest, Hungary (B.M.); Universidad CentroTropical de Medicina Universidad Central Venezuela, Caracas, Venezuela (L.M.); Department of Cardiology, Meander Medical Centre, Amersfoort and WCN Dutch Network for Cardiovascular Research, Utrecht, The Netherlands (A.M.); Department and Clinic of Cardiology, Wroclaw Medical University, Poland (M.N.-K.); Department of Medicine, Kuopio University Hospital, Kuopio, Finland (K.P.); Heart Institute (InCor) – University of São Paulo, Medical School, Brazil (F.J.A.R.); Department of Cardiology, Viborg Hospital, Viborg, Denmark (J.R.); Dr. Arno Rosenthal LLC, Estonia (A.R.); Azienda Ospedaliera Papa Giovanni XXIII, Cardiologia 1 – Scompenso e Trapianti di Cuore, Bergamo, Italy (M.S.); St. Luke’s Heart Institute, Qezen City, Philippines (A.S.S.); Center for Health Technology and Services Research (CINTESIS), Porto Medical School, University of Porto, Portugal (J.S.-C.); Department of Cardiovascular Sciences, University of Leicester, and NIHR Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, UK (B.M.); Heart & Vascular Institute, Cleveland Clinic, Cleveland, OH (R.C.S.); San Francisco Veterans Affairs Medical Center and University of California San Francisco, San Francisco, CA (J.R.T.); Department of Cardiovascular Diseases, University Hospitals KU Leuven, Leuven, Belgium (J.V.); University of Medicine and Pharmacy Carol Davila – University and Emergency Hospital, Bucharest, Romania (D.V.); and Department of Cardiology, National University Heart Centre, Singapore (R.C.-C.W.).

*Drs Packer and McMurray contributed equally.

†A complete list of the investigators and committees in the PARADIGM-HF trial is provided in the online-only Data Supplement Appendix.

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Correspondence to Milton Packer, MD, Department of Cardiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390. E-mail milton.packer@utsouthwestern.edu; or John J.V. McMurray, MD, BHF Cardiovascular Research Centre, University PI, University of Glasgow, Glasgow, Scotland G12 9QQ, United Kingdom. E-mail john.mc_murray@glasgow.ac.uk

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**Background**—Clinical trials in heart failure have focused on the improvement in symptoms or decreases in the risk of death and other cardiovascular events. Little is known about the effect of drugs on the risk of clinical deterioration in surviving patients.

**Methods and Results**—We compared the angiotensin-neprilysin inhibitor LCZ696 (400 mg daily) with the angiotensin-converting enzyme inhibitor enalapril (20 mg daily) in 8399 patients with heart failure and reduced ejection fraction in a double-blind trial. The analyses focused on prespecified measures of nonfatal clinical deterioration. In comparison with the enalapril group, fewer LCZ696-treated patients required intensification of medical treatment for heart failure (520 versus 604; hazard ratio, 0.84; 95% confidence interval, 0.74–0.94; \( P=0.003 \)) or an emergency department visit for worsening heart failure (hazard ratio, 0.66; 95% confidence interval, 0.52–0.85; \( P=0.001 \)). The patients in the LCZ696 group had 23% fewer hospitalizations for worsening heart failure (851 versus 1079; \( P<0.001 \)) and were less likely to require intensive care (768 versus 879; 18% rate reduction, \( P=0.005 \)), to receive intravenous positive inotropic agents (31% risk reduction, \( P<0.001 \)), and to have implantation of a heart failure device or cardiac transplantation (22% risk reduction, \( P=0.07 \)). The reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization. Worsening of symptom scores in surviving patients was consistently more common in the enalapril group.

**Conclusions**—Angiotensin-neprilysin inhibition prevents the clinical progression of surviving patients with heart failure more effectively than angiotensin-converting enzyme inhibition.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01035255. ([Circulation. 2015;131:54–61. DOI: 10.1161/CIRCULATIONAHA.114.013748.])

**Key Words:** heart failure ■ neprilysin ■ receptors, angiotensin

Although heart failure increases the risk of death, nonfatal worsening of symptoms is the most common problem encountered by patients, who experience progressive impairment of functional capacity and quality of life. Nonfatal worsening may require intensification of oral medications or it can necessitate emergent treatment, including hospitalization, intensive care, or expensive medical or surgical interventions. Therefore, in addition to prolonging survival, a major goal in the management of chronic heart failure is maintenance of the clinical stability of patients, specifically by preventing nonfatal worsening of heart failure with its attendant consequences.

**Editorial see p 11**

**Clinical Perspective on p 61**

The activation of detrimental neurohormonal pathways contributes to the clinical progression of heart failure. However, despite the use of angiotensin-converting enzyme (ACE) inhibitors, \( \beta \)-blockers, and mineralocorticoid receptor antagonists patients remain at high risk of worsening heart failure. Such progression may be related to inadequate activation of or a diminished response to the compensatory actions of endogenous adaptive neurohormonal systems. Several peptides (ie, natriuretic peptides, bradykinin, and adrenomedullin) can attenuate vasoconstriction and sodium retention, and retard cardiac and vascular hypertrophy and remodeling, and thus act to ameliorate many of the pathophysiological abnormalities of heart failure. Neprilysin is the key enzyme responsible for the breakdown of these peptides, and its activity may be increased in heart failure. Inhibition of neprilysin enhances the effects of these beneficial vasoactive substances and exerts favorable effects in patients with heart failure, when combined with existing agents that act on detrimental neurohormonal systems. Concurrent inhibition of angiotensin synthesis or action is particularly important, because neprilysin inhibition alone is accompanied by the activation of the renin-angiotensin system, possibly because angiotensin itself may be a substrate for neprilysin. Although the actions of angiotensin may be attenuated by inhibition of the ACE, simultaneous blockade of ACE and neprilysin can lead to serious angioedema. Therefore, the preferred approach to parallel modulation of these neurohormonal systems is the combined use of a neprilysin inhibitor with an angiotensin receptor blocker.

The PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial compared the long-term effects of LCZ696—a complex of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan—with enalapril in patients with heart failure with mild-to-moderate symptoms. The trial demonstrated the superiority of LCZ696 over enalapril on both death from any cause, and on death from cardiovascular causes. Here, we describe the incremental effects of LCZ696 over enalapril on the nonfatal progression of heart failure in surviving patients.

**Methods**

The design and primary results of the PARADIGM-HF trial have been previously described. The institutional review board of each of the 1043 participating institutions (in 47 countries) approved the protocol, and all patients gave written, informed consent.

**Study Patients**

Patients had New York Heart Association (NYHA) class II to IV symptoms, an ejection fraction of ≤40% (changed to ≤35% by amendment), and a plasma B-type natriuretic peptide (BNP) ≥150 pg/mL (or N-terminal pro-BNP [NTproBNP] ≥600 pg/mL). Patients with lower levels of natriuretic peptides were eligible if they had been hospitalized for heart failure within 12 months. Patients taking any dose of ACE inhibitors or angiotensin receptor blockers were...
considered for enrollment, but were required to tolerate the equivalent of enalapril 10 mg daily for at least 4 weeks before screening along with stable doses of a β-blocker (unless contraindicated or not tolerated) and a mineralocorticoid antagonist (if indicated). Among the exclusion criteria, patients were not eligible for the trial if they had a history of intolerance of ACE inhibitors or angiotensin receptor blockers.

Study Procedures

On trial entry, ongoing therapy with an ACE inhibitor or angiotensin receptor blocker was stopped, but other treatments for heart failure were continued. Patients first received enalapril 10 mg twice daily for 2 weeks (single-blind) and then LCZ696 (single-blind) for an additional 4 to 6 weeks, initially at 100 mg twice daily and then 200 mg twice daily. To minimize the potential for angioedema, enalapril was withheld a day before starting LCZ696, and LCZ696 was withheld a day before starting randomized therapy. Patients tolerating both drugs at target doses were randomly assigned in a 1:1 ratio to double-blind treatment with either enalapril 10 mg twice daily or LCZ696 200 mg twice daily. The dose of enalapril was selected based on its effect to reduce the risk of death in the Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial; higher doses have not been more effective or well tolerated during long-term treatment. Following randomization, patients were maintained on the highest tolerated doses of the study medication. Surviving patients underwent periodic evaluation of NYHA functional class, symptoms of heart failure (measured using the Kansas City Cardiomyopathy Questionnaire [KCCQ]), and, in approximately 27% of randomized patients, biomarkers of natriuretic and heart failure progression. Worsening heart failure was treated by adjusting the doses of any concomitant drug and using any interventions that were clinically indicated.

Statistical Analysis

The trial was designed to recruit ≈8000 patients and continue until the occurrence of 1229 cardiovascular deaths and 2410 cardiovascular deaths or first hospitalizations for heart failure. However, an independent Data and Safety Monitoring Board recommended early termination of the study (approximately 50 months after the first patient was randomized) when the boundary for overwhelming benefit for cardiovascular mortality had been crossed.

The principal analyses for this article focused on (1) worsening NYHA functional class, as assessed by the physician; (2) worsening KCCQ total symptom score, as assessed by the patient; (3) worsening heart failure requiring an increase in the dose of diuretic for >1 month, the addition of a new drug for heart failure, or the use of intravenous therapy (prospectively defined in the protocol as a treatment failure); (4) worsening heart failure leading to an emergency department visit (without subsequent hospitalization); (5) worsening heart failure requiring hospitalization, with a prespecified analysis at 30 days after randomization; (6) the use of interventions for advancing heart failure; and (7) changes in biomarkers reflecting cardiac injury, wall stress, and the effects of natriuretic inhibition. All deaths and all hospitalizations possibly related to heart failure were adjudicated blindly according to prespecified criteria by a clinical-events committee, which had no knowledge of the patient’s drug assignment. Of the 4 biomarkers of interest, plasma NTproBNP and troponin T were measured by using the Roche Elecsys proBNP and high-sensitivity Troponin T assays (Roche Diagnostics GmbH, Germany); plasma BNP was measured by using the Advia Centaur assay (Siemens, USA); and cGMP was measured in first-morning-void urine samples by using an enzyme-linked immunosorbent assay (R & D Systems, USA).

Effect on Death or Hospitalization for Any Reason

There were 835 patients in the enalapril group and 711 in the LCZ696 group who died for any reason, corresponding to annualized rates of 7.5% and 6.0%, respectively. These differences reflected a 16% incremental reduction in the risk of death (hazard ratio, 0.84; 95% confidence interval [CI], 0.76–0.93, P=0.0009). There were 2093 patients who died or who were hospitalized for any reason in the enalapril group and 1892 such patients in the LCZ696 group, corresponding to annualized rates of 30.3% and 26.3%, respectively. These differences reflected a 12.6% lower risk as a result of treatment with LCZ696 instead of enalapril (hazard ratio, 0.87; 95% CI, 0.82–0.93; P<0.0001).

Effect on Occurrence of Clinical Worsening

In comparison with enalapril-treated patients, there were fewer LCZ696-treated patients who had worsening heart failure requiring the addition of a new drug, intravenous therapy, or an increase in the daily dose of diuretic for >1 month (520 versus 604; hazard ratio, 0.84; 95% CI, 0.74–0.94; P=0.003). Fewer patients in the LCZ696 group than in the enalapril group were evaluated and treated for worsening heart failure in the emergency department but discharged without hospital admission (102 versus 150; hazard ratio, 0.66; 95% CI, 0.52–0.85; P=0.001; Table). When all (including repeat) emergency department evaluations for heart failure were considered, the LCZ696 group had 30% lower rate of such visits than the enalapril group (P=0.017).
Table. Measures of Nonfatal Worsening Heart Failure in the Enalapril and LCZ696 Groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Enalapril (n=4212)</th>
<th>LCZ696 (n=4187)</th>
<th>Hazard/Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with worsening heart failure leading to intensification of outpatient therapy, n (%)</td>
<td>604 (14.3)</td>
<td>520 (12.4)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>Patients with worsening NYHA functional class (≥1 class)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients surviving at 4 mo, n (%)</td>
<td>218 (5.5)</td>
<td>186 (4.7)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.113</td>
</tr>
<tr>
<td>In patients surviving at 8 mo, n (%)</td>
<td>266 (7.0)</td>
<td>205 (5.4)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.004</td>
</tr>
<tr>
<td>In patients surviving at 12 mo, n (%)</td>
<td>271 (7.4)</td>
<td>225 (6.1)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.023</td>
</tr>
<tr>
<td>Patients with worsening KCCQ total symptoms score (≥5 points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients surviving at 4 mo, n (%)</td>
<td>1012 (28.3)</td>
<td>899 (25.1)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>In patients surviving at 8 mo, n (%)</td>
<td>1087 (31.8)</td>
<td>974 (28.2)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>In patients surviving at 12 mo, n (%)</td>
<td>1029 (31.5)</td>
<td>964 (29.0)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Patients with ED visit for heart failure, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients surviving at 4 mo, n (%)</td>
<td>150 (3.6)</td>
<td>102 (2.4)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>In patients surviving at 8 mo, n (%)</td>
<td>111 (2.6)</td>
<td>78 (1.9)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>In patients surviving at 8 mo, n (%)</td>
<td>27 (0.6)</td>
<td>15 (0.4)</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In patients surviving at 12 mo, n (%)</td>
<td>12 (0.3)</td>
<td>9 (0.2)</td>
<td>0.84 (0.74–0.94)</td>
<td></td>
</tr>
<tr>
<td>Total number of ED visits for heart failure</td>
<td>208</td>
<td>151</td>
<td>0.84 (0.74–0.94)</td>
<td>0.017</td>
</tr>
<tr>
<td>Patients hospitalized for heart failure, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients surviving at 4 mo, n (%)</td>
<td>658 (15.6)</td>
<td>537 (12.8)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>In patients surviving at 8 mo, n (%)</td>
<td>418 (9.9)</td>
<td>367 (8.8)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>In patients surviving at 12 mo, n (%)</td>
<td>143 (3.4)</td>
<td>110 (2.6)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>In patients surviving at 12 mo, n (%)</td>
<td>53 (1.3)</td>
<td>33 (0.8)</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In patients surviving at 12 mo, n (%)</td>
<td>44 (1.0)</td>
<td>27 (0.6)</td>
<td>0.84 (0.74–0.94)</td>
<td></td>
</tr>
<tr>
<td>Total number of hospitalizations for heart failure</td>
<td>1079</td>
<td>851</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of days in the hospital per admission per patient</td>
<td>9.7±9.5</td>
<td>10.8±17.5</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of patients requiring intensive care</td>
<td>623</td>
<td>549</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total number of stays in intensive care</td>
<td>879</td>
<td>768</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients receiving IV positive inotropic drugs, n (%)</td>
<td>229 (5.4)</td>
<td>161 (3.9)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients requiring cardion resynchronization, ventricular assist device implantation, or cardiac transplantation, n (%)</td>
<td>119 (2.8)</td>
<td>94 (2.3)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients hospitalized for cardiovascular reason, n (%)</td>
<td>1344 (31.9)</td>
<td>1210 (28.9)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total number of hospitalizations for cardiovascular reason</td>
<td>2537</td>
<td>2216</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients hospitalized for any reason, n (%)</td>
<td>1827 (43.4)</td>
<td>1660 (39.7)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total number of hospitalizations for any reason</td>
<td>4053</td>
<td>3564</td>
<td>0.84 (0.74–0.94)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ED, emergency department; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; and NYHA, New York Heart Association. *Asterisk denotes rate ratio estimated from a negative binomial model; ratios without an asterisk are hazard ratios derived by using the Cox proportional hazards model.

Fewer patients in the LCZ696 group than in the enalapril group were hospitalized for heart failure (hazard ratio, 0.79; 95% CI, 0.71–0.89; P<0.001), for a cardiovascular reason (hazard ratio, 0.88; 95% CI, 0.81–0.95; P<0.001) or for any reason (hazard ratio, 0.88; 95% CI, 0.82–0.94; P<0.001; Table). The between-group difference in the risk of hospitalization for heart failure was statistically significant as early as 30 days following randomization (hazard ratio at 30 days, 0.60; 95% CI, 0.38–0.94; P=0.027; Figure 1).

In comparison with enalapril, patients treated with LCZ696 were not only less likely to be hospitalized for heart failure at least once, but were also less likely to be hospitalized multiple times; 240 patients in the enalapril group but only 170 patients in the LCZ696 group were hospitalized...
for heart failure more than once (a 29% reduction in the LCZ696 group, \( P = 0.001 \)). When all (including repeat) hospitalizations were considered, the LCZ696 group had 15.6% fewer hospitalizations than the enalapril group for any reason \( (P<0.001) \), 16.0% fewer hospitalizations for a cardiovascular reason \( (P<0.001) \), and 23.0% fewer admissions for heart failure \( (P<0.001) \) than patients in the enalapril group (Table). The cumulative number of hospitalizations for heart failure per 100 patients is shown in Figure 2. The 2 groups were similar with respect to the average duration of each admission for heart failure, but, in comparison with the enalapril group, the patients in the LCZ696 group had 18% fewer stays in intensive care \( (P=0.005) \) and were 31% less likely to receive intravenous positive inotropic agents \( (P<0.001) \) and 22% less likely to have cardiac transplantation or implantation of a cardiac device for heart failure \( (P=0.07) \). The number of patients who received a left ventricular assist device or underwent cardiac transplantation was 23 in the enalapril group and 13 in the LCZ696 group.

Despite greater intensification of treatment and greater loss of more severely ill patients because of death in the enalapril group, a larger proportion of surviving patients in that group were considered by their physicians to be worse (by at least 1 NYHA class) than in the LCZ696 group; the difference between the 2 groups was significant at both 8 and 12 months of follow-up \( (P=0.004 \text{ and } P=0.023, \text{ respectively; Table}) \). Moreover, fewer surviving patients considered themselves worse (by at least 5 points in the KCCQ total symptom score) in the LCZ696 group than in the enalapril group; the difference between the groups was significant at 4, 8, and 12 months \( (P=0.002, P=0.001, \text{ and } P=0.03, \text{ respectively; Table}) \).

**Effect on Biomarkers of Heart Failure Progression**

Levels of urinary cyclic GMP and plasma BNP were higher during treatment with LCZ696 than with enalapril

(Figure 3A), but circulating levels of NTproBNP and troponin were lower during treatment with LCZ696 than with enalapril (Figure 3B). The differences between groups were apparent within 4 weeks and were sustained at 8 months, \( P<0.0001 \) for the difference between groups at both time points.

**Discussion**

In patients with a reduced ejection fraction and mild-to-moderate symptoms, combined inhibition of the angiotensin receptor and neprilysin with LCZ696 reduced the risk of developing worsening heart failure more than ACE inhibition with enalapril. Fewer patients in the LCZ696 group were considered to be worse by themselves or by their physicians, and fewer patients in the LCZ696 group had worsening symptoms requiring intensification of outpatient therapy or the use of medical or device treatments for advancing heart failure.

Not only was LCZ696 superior to enalapril in reducing the risk of a first emergency department visit or hospitalization for heart failure, but the drug was also more effective than ACE inhibition alone in decreasing the need for repeated emergency visits and hospitalizations for heart failure. These advantages were apparent even though (1) the enalapril group had a meaningfully higher mortality rate throughout the trial, leading to the preferential exclusion of high-risk enalapril-treated patients with progressing symptoms from our analyses; and (2) the enalapril group had greater intensification of background therapy, which would have been expected to ameliorate deleterious changes in clinical status. Therefore, the observed effect sizes reported in our analyses may underestimate the true magnitude of the treatment difference. Despite the biases against the drug, LCZ696 was superior to enalapril in reducing the risk of symptom progression and exerting a favorable effect on the clinical course of surviving patients with mild-to-moderate heart failure.

Few trials have focused on the ability of new drugs to prevent worsening of clinical status in patients with mild-to-moderate heart failure.\(^{27}\) Previous studies in such patients...
have primarily reported improvements in exercise tolerance or functional class or decreases in the risk of hospitalization for heart failure. \(28-30\) In the few trials that have reported worsening of symptoms, quality of life, or functional class, active treatments produced a meaningful reduction in the risk of clinical worsening only when missing data were imputed or when patients who died were included in the analysis and assigned the worst possible score. \(29,31-33\) In contrast, the PARADIGM-HF study is among the first trials to demonstrate a reduction of clinical worsening of surviving patients, which is not only of paramount importance to those afflicted with the disease and their families, but also to the physicians who care for them and the insurers who pay for the intensification of treatments. The advantage of LCZ696 over enalapril in preventing clinical deterioration was apparent early in the trial and persisted for the duration of double-blind therapy.

Our clinical findings are supported by the effects on biomarkers measured in surviving patients in the trial. As expected from neprilysin inhibition, \(34\) levels of both urinary cyclic GMP and plasma BNP were higher during treatment with LCZ696 than with enalapril; the increases in cyclic GMP reflect the fact that the peptides whose levels are enhanced by neprilysin inhibition act through enhancement of cyclic GMP. \(35-37\) In contrast, in comparison with enalapril, patients receiving LCZ696 had consistently lower levels of NTproBNP (reflecting reduced cardiac wall stress) and troponin (reflecting reduced cardiac injury) throughout the trial. The contrasting effects of LCZ696 on the 2 types of natriuretic peptides represents an important finding, because the levels of the 2 peptides characteristically parallel each other during the course of heart failure. \(38\) However, because BNP (but not NTproBNP) is a substrate for neprilysin, \(39\) levels of BNP will reflect the action of the drug, whereas levels of NTproBNP will reflect the effects of the drug on the heart. Furthermore, although differences in the levels of troponin between the 2 treatment groups were small, even very low levels of troponin release are believed to reflect ongoing myocardial injury (possibly related to increased wall stress). \(40\) and even small increases in the levels of troponin reflect a higher risk of disease progression in heart failure. \(41,42\)

In conclusion, in comparison with guideline-recommended doses of an ACE inhibitor, combined inhibition of both the angiotensin receptor and neprilysin was more effective not only in reducing all-cause and cardiovascular mortality, \(43\) but also in reducing the risks and rates of multiple manifestations of clinical deterioration of surviving patients with heart failure. The effect of LCZ696 to stabilize the course of heart failure is likely to have important ramifications for both quality of life and resource utilization in this disorder.

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**Disclosures**

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References


**CLINICAL PERSPECTIVE**

The PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial compared the angiotensin receptor-neprilysin inhibitor LCZ696 (400 mg daily) with the angiotensin-converting enzyme inhibitor enalapril (20 mg daily) in 8399 patients with heart failure and reduced ejection fraction in a double-blind trial. In a previous report, patients in the LCZ696 group had a 20% lower risk of cardiovascular death and a 16% lower risk of death for any reason (both *P*<0.0001). This article reports on the effect of treatment on the clinical progression of heart failure in surviving patients. When compared with enalapril, fewer LCZ696-treated patients required intensification of medical treatment for heart failure (*P*=0.003) or an emergency department visit for worsening heart failure (*P*=0.001). The patients in the LCZ696 group also had 23% fewer hospitalizations for worsening heart failure (*P*<0.001) and were 18% less likely to require intensive care (*P*=0.005), 31% less likely to receive intravenous positive inotropic agents (*P*<0.001), and 22% less likely to have implantation of a heart failure device or cardiac transplantation (*P*=0.07). The reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization. Worsening symptoms of heart failure were consistently more common in the enalapril group. LCZ696 led to an early and sustained reduction in biomarkers of myocardial wall stress and injury (N-terminal pro–B-type natriuretic peptide and troponin) versus enalapril. These findings demonstrate that LCZ696 prevents the clinical progression of surviving patients more effectively than enalapril and provides further support for the use of this new approach to replace the current use of inhibitors of the renin-angiotensin system in chronic heart failure.

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Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure


on behalf of the PARADIGM-HF Investigators and Coordinators

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Correction

In the article by Packer et al, “Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients with Heart Failure,” which published ahead of print on November 17, 2014 (doi:10.1161/CIRCULATIONAHA.114.013748), incorrect labels were displayed on the y-axis of Figure 2. The correct labeled increments indicated on the y-axis should be 0, 20, 40, and 60. The correct figure is below:
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J McMurray, co-chair; M Packer, co-chair; J Rouleau, S Solomon, K Swedberg, M Zile

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S Solomon, co-chair; A Desai, co-chair; A Kaplan, N Brown, B Zuraw

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**Investigators by Country (National Leaders Listed First)**

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