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

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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. 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.

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:•••–•••.)

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.1 Nonfatal worsening may require intensification of oral medications or it can necessitate emergent treatment, including hospitalization, intensive care, or expensive medical or surgical interventions.1,2 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.

Clinical Perspective on p XXX

The activation of detrimental neurohormonal pathways contributes to the clinical progression of heart failure.3 However, despite the use of angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and mineralocorticoid receptor antagonists patients remain at high risk of worsening heart failure.4 Such progression may be related to inadequate activation of or a diminished response to the compensatory actions of endogenous adaptive neurohormonal systems.5–7 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.8–10 Neprilysin is the key enzyme responsible for the breakdown of these peptides, and its activity may be increased in heart failure.11 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.12 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.13,14 Although the actions of angiotensin may be attenuated by inhibition of the ACE, simultaneous blockade of ACE and neprilysin can lead to serious angioedema.15,16 Therefore, the preferred approach to parallel modulation of these neurohormonal systems is the combined use of a neprilysin inhibitor with an angiotensin receptor blocker.17

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.18 The trial demonstrated the superiority of LCZ696 over enalapril on both death from any cause, and on death from cardiovascular causes.12 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.18 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.13 Patients taking any dose of ACE inhibitors or angiotensin receptor blockers were
considered for enrollment, but were required to tolerate the equiva-
lent 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 addi-
tional 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 Trial19; higher doses have not been more effec-
tive or well tolerated during long-term treatment.20–22 Following ran-
domization, patients were maintained on the highest tolerated doses
of the study medication. Surviving patients underwent periodic eval-
uation of NYHA functional class, symptoms of heart failure (measured
by using the Kansas City Cardiomyopathy Questionnaire [KCCQ]);23
and, in approximately 27% of randomized patients, biomarkers of
everlipinyl inhibition 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 inde-
pendent Data and Safety Monitoring Board recommended early ter-
mination 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) worsen-
ing 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 intra-
venous therapy (prospectively defined in the protocol as a treatment
failure); (4) worsening heart failure leading to an emergency depart-
ment 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 neprilysin inhibition. All deaths and
all hospitalizations possibly related to heart failure were adjudicated
blindly according to prespecified criteria by a clinical-events com-
mittee, 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). Data on all outcome measures were collected prospectively,
and their analyses were prespecified as end points of interest.

Cox proportional hazards regression models (with treatment and
region as fixed-effect factors) were used to evaluate between-group
differences in time-to-event end points and to estimate hazard ratios,
95% confidence intervals, and P values. Negative binomial models
(with treatment and region as fixed factors and logarithm of the dura-
tion of follow-up as the offset),26 Wilcoxon rank-sum test, and Fisher
exact test were used to assess the significance of differences in the
number, rate and duration of hospital admissions and emergency
department visits; of the use of medical and device interventions for
advancing heart failure; and of clinical worsening by ≥1 NYHA func-
tional class and ≥5 points in the KCCQ total symptom score (based
on the magnitude of change considered to be clinically relevant).21
The rate of total hospitalizations for heart failure was calculated by
the Nelson-Aalen estimate,21 ignoring death as a potential informative
dropout. Ignoring death as a potential informative dropout may lead
to underestimation of the magnitude of the treatment effects in our
analysis, because heart failure morbidity and mortality are strongly
associated, and thus, the censoring of patients at the time of death
can be expected to minimize estimates of the rate of worsening heart
failure events in the group with a poorer survival.28 Nevertheless, all
analyses were performed on data available at each time point; no
imputation was applied to patients who died or had missing data.

Results
Study Patients and Study Drug Administration
A total of 10521 patients at 1043 centers in 47 countries entered the run-in period, of whom 8399 patients were ran-
donally assigned and prospectively included in the intention-
to-treat analysis (4187 to LCZ696 and 4212 or enalapril). As previously reported,12 the 2 groups comprised primarily
patients with mild-to-moderate symptoms who were well
treated with diuretics, β-blockers, and mineralocorticoid
receptor antagonists and were balanced with respect to base-
line characteristics. Excluding patients who died, 87% of both
the LCZ696 and enalapril groups were receiving the target
dose of the study drug at 8 months; and 76% and 75%, respec-
tively, were maintained at the target dose at the end of the
study.

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 differ-
ces 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 dif-
ferences 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 fail-
ure 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 enala-
pril 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>PValue</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>150 (3.6)</td>
<td>102 (2.4)</td>
<td>0.84 (0.74–0.94)</td>
<td>0.017</td>
</tr>
<tr>
<td>Patients with 1 ED visit for heart failure, n (%)</td>
<td>111 (2.6)</td>
<td>78 (1.9)</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with 2 ED visits for heart failure, 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>Patients with ≥3 ED visits for heart failure, n (%)</td>
<td>12 (0.3)</td>
<td>9 (0.2)</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;0.001</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>&lt;0.001</td>
</tr>
<tr>
<td>Patients hospitalized for heart failure, n (%)</td>
<td>658 (15.6)</td>
<td>537 (12.8)</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with 1 admission for heart failure, n (%)</td>
<td>418 (9.9)</td>
<td>367 (8.8)</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with 2 admissions for heart failure, n (%)</td>
<td>143 (3.4)</td>
<td>110 (2.6)</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with 3 admissions for heart failure, 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>Patients with ≥4 admissions for heart failure, n (%)</td>
<td>44 (1.0)</td>
<td>27 (0.6)</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;0.001</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>&lt;0.001</td>
</tr>
<tr>
<td>Number of days in the hospital per admission per patient</td>
<td>9.7±9.5</td>
<td>10.9±7.5</td>
<td>0.84 (0.74–0.94)</td>
<td>&lt;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>&lt;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>&lt;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>&lt;0.001</td>
</tr>
<tr>
<td>Patients requiring cardiac resynchronization, ventricular assist device implantation, or cardiac transplantation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></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>&lt;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>&lt;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>&lt;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>&lt;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
higher during treatment with LCZ696 than with enalapril. Levels of urinary cyclic GMP and plasma BNP were likely to have cardiac transplantation or implantation of a cardiac device for heart failure, but, in comparison with the enalapril group, similar with respect to the average duration of each admission for heart failure more than once (a 29% reduction in the LCZ696 group, $P<0.001$), and 23.0% fewer admissions for heart failure per 100 patients is shown in Figure 2. The cumulative number of hospitalizations for heart failure in the enalapril and LCZ696 groups per 100 patients. Shown is the cumulative number of hospitalizations for heart failure in the 2 study groups per 100 patients, ignoring death as an informative dropout, with the rate ratio calculated by using the negative binomial regression model.

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.\textsuperscript{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. 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 for heart failure. 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 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 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 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 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 hospitalization for heart failure.28–30

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, 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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Angiotensin Nephrilysin Inhibition in Heart Failure

References


CLINICAL PERSPECTIVES

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


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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:
SUPPLEMENTAL MATERIAL

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