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.

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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.

Editorial see p 11
Clinical Perspective on p 61

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.[12] 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.[12] 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,[12] 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[19]; higher doses have not been more effective or well tolerated during long-term treatment.[20–22] 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 by using the Kansas City Cardiomyopathy Questionnaire [KCCQ]),[23] and, in approximately 27% of randomized patients, biomarkers of neprilysin 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 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 neprilysin 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). 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 duration of follow-up as the offset),[24] 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 functional 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,[25] 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.[26] 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 randomly 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 baseline 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%, respectively, 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 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

	Enalapril (n=4212)	LCZ696 (n=4187)	Hazard/Rate Ratio (95% CI) *P* Value
Patients with worsening heart failure leading to intensification of outpatient therapy, n (%)	604 (14.3)	520 (12.4)	0.84 (0.74–0.94) 0.003
Patients with worsening NYHA functional class (≥1 class)			
In patients surviving at 4 mo, n (%)	218 (5.5)	186 (4.7)	0.113
In patients surviving at 8 mo, n (%)	266 (7.0)	205 (5.4)	0.004
In patients surviving at 12 mo, n (%)	271 (7.4)	225 (6.1)	0.023
Patients with worsening KCCQ total symptoms score (≥5 points)			
In patients surviving at 4 mo, n (%)	1012 (28.3)	899 (25.1)	0.002
In patients surviving at 8 mo, n (%)	1087 (31.8)	974 (28.2)	0.001
In patients surviving at 12 mo, n (%)	1029 (31.5)	964 (29.0)	0.03
Patients with ED visit for heart failure, n (%)	150 (3.6)	102 (2.4)	0.66 (0.52–0.85) 0.001
Patients with 1 ED visit for heart failure, n (%)	111 (2.6)	78 (1.9)	0.003
Patients with 2 ED visits for heart failure, n (%)	27 (0.6)	15 (0.4)	
Patients with ≥3 ED visits for heart failure, n (%)	12 (0.3)	9 (0.2)	
Total number of ED visits for heart failure	208	151	0.70 (0.52–0.94)* 0.017
Patients hospitalized for heart failure, n (%)	658 (15.6)	537 (12.8)	0.79 (0.71–0.89) <0.001
Patients with 1 admission for heart failure, n (%)	418 (9.9)	367 (8.8)	
Patients with 2 admissions for heart failure, n (%)	143 (3.4)	110 (2.6)	<0.001
Patients with 3 admissions for heart failure, n (%)	53 (1.3)	33 (0.8)	
Patients with ≥ 4 admissions for heart failure, n (%)	44 (1.0)	27 (0.6)	
Total number of hospitalizations for heart failure	1079	851	0.77 (0.67–0.89)* <0.001
Number of days in the hospital per admission per patient	9.7±9.5	10.8±17.5	0.86
Number of patients requiring intensive care	623	549	0.87 (0.78–0.98) 0.019
Total number of stays in intensive care	879	768	0.82 (0.72–0.94)* 0.005
Patients receiving IV positive inotropic drugs, n (%)	229 (5.4)	161 (3.9)	0.69 (0.57–0.85) <0.001
Patients requiring cardiac resynchronization, ventricular assist device implantation, or cardiac transplantation, n (%)	119 (2.8)	94 (2.3)	0.78 (0.60–1.02) 0.07
Patients hospitalized for cardiovascular reason, n (%)	1344 (31.9)	1210 (28.9)	0.88 (0.81–0.95) <0.001
Total number of hospitalizations for cardiovascular reason	2537	2216	0.84 (0.76–0.92)* <0.001
Patients hospitalized for any reason, n (%)	1827 (43.4)	1660 (39.7)	0.88 (0.82–0.94) <0.001
Total number of hospitalizations for any reason	4053	3564	0.84 (0.78–0.91)* <0.001

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

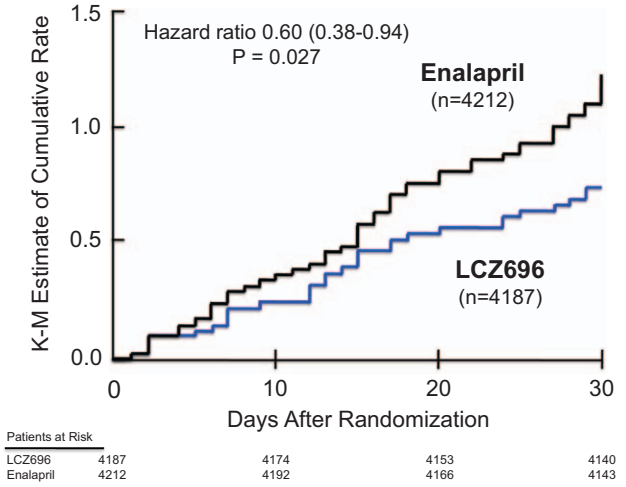

Figure 1. Kaplan–Meier curve for the time to first hospitalization for heart failure during first 30 days after randomization, according to study group. Shown is the Kaplan–Meier estimate of the cumulative probability of a first hospitalization for heart failure during the first 30 days after randomization. The analysis at 30 days was prespecified and also represented the earliest time point, at which the difference between the LCZ696 and enalapril groups was statistically significant. K-M indicates Kaplan–Meier.

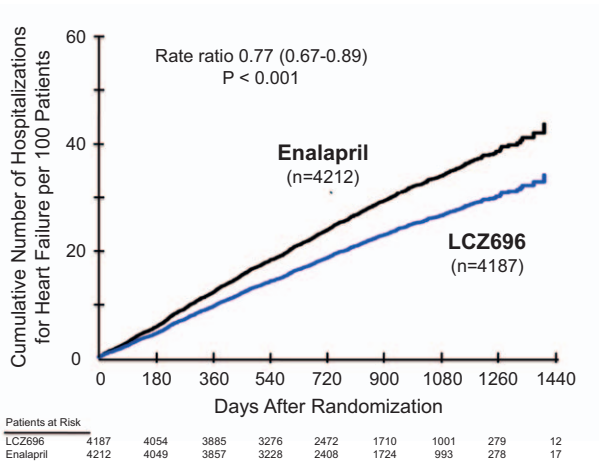

Figure 2. Cumulative number of hospitalizations for heart failure in the enalapril and LCZ696 groups per 100 patients. Shown is the cumulative number of hospitalizations for heart failure in the 2 study groups per 100 patients, ignoring death as an informative dropout, with the rate ratio calculated by using the negative binomial regression model.

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 and P=0.023, 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, and P=0.03, 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

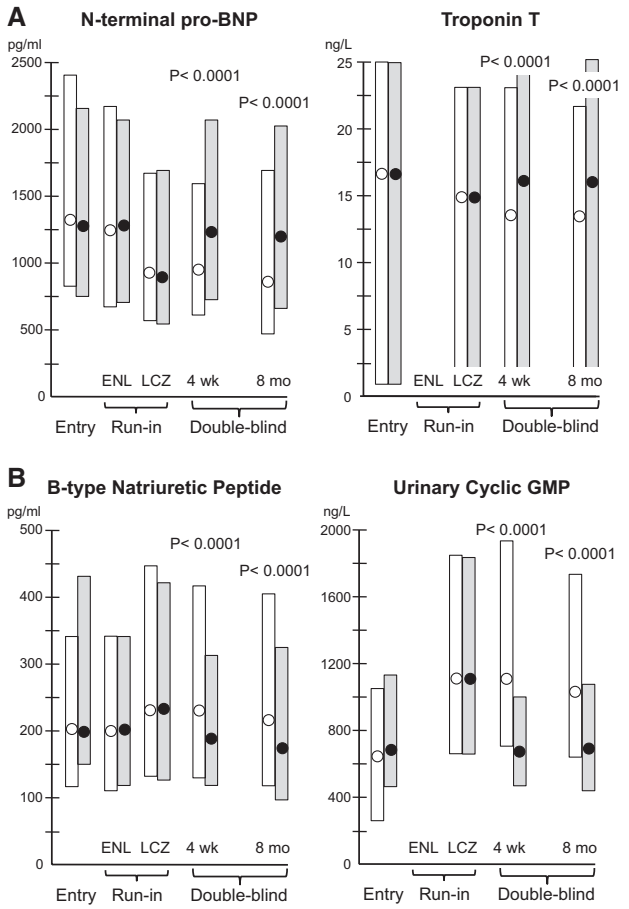

Figure 3. A, Median values for N-terminal pro-BNP and troponin T at entry and during single-blind run-in and double-blind periods. Medians are shown in circles, and 25%/75% interquartile ranges are shown in bars, where patients in the LCZ696 group are shown in white circles and white bars and patients in the enalapril group are shown in black circles and gray bars. *P* values designate the significance of difference between the 2 treatment groups. Troponin T was not measured at the end of the enalapril phase of the run-in period. **B,** Median values for B-type natriuretic peptide and urinary cyclic GMP at entry and during single-blind run-in and double-blind periods. Medians are shown in circles, and 25%/75% interquartile ranges are shown in bars, where patients in the LCZ696 group are shown in white circles and white bars and patients in the enalapril group are shown in black circles and gray bars. *P* values designate the significance of the difference between the 2 treatment groups. Urinary cyclic GMP was not measured at the end of the enalapril phase of the run-in period. BNP indicates B-type natriuretic peptide; ENL, end of the enalapril phase of the run-in period; and LCZ, end of the LCZ696 phase of the run-in period.

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,[12] 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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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

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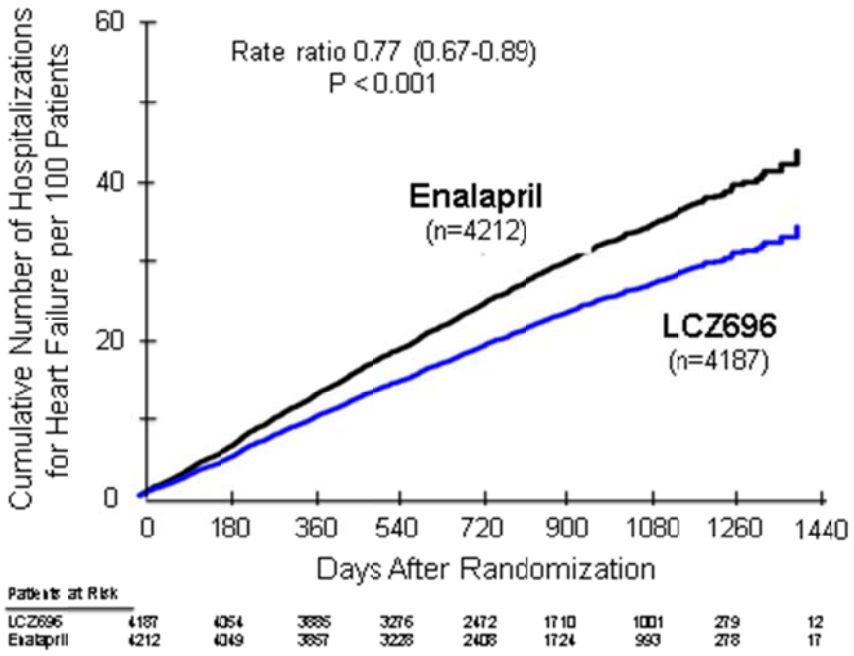
Correction

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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