ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

ABSTRACT

BACKGROUND

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

CONCLUSIONS

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceuticals, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (M.R.Z.). Address reprint requests to Dr. Packer at the Department of Clinical Sciences, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, or at milton.packer@utsouthwestern.edu; or to Dr. McMurray at the BHF Cardiovascular Research Centre, University Pl., University of Glasgow, Glasgow, Scotland G12 8QQ, United Kingdom, or at john.mcmurray@glasgow.ac.uk.

*A complete list of the investigators in the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) is provided in the Supplementary Appendix, available at NEJM.org.

Drs. McMurray and Packer contributed equally to this article.

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Angiotensin-converting–enzyme (ACE) inhibitors have been the cornerstone of the treatment for heart failure and a reduced ejection fraction for nearly 25 years, since enalapril was shown to reduce the risk of death in two trials.[1,2] Long-term treatment with enalapril decreased the relative risk of death by 16% among patients with mild-to-moderate symptoms.[2] The effect of angiotensin-receptor blockers (ARBs) on mortality has been inconsistent,[3,4] and thus, these drugs are recommended primarily for patients who have unacceptable side effects (primarily cough) while receiving ACE inhibitors. Subsequent studies showed that the use of beta-blockers and mineralocorticoid-receptor antagonists, when added to ACE inhibitors, resulted in incremental decreases in the risk of death of 30 to 35% and 22 to 30%, respectively.[5-9]

A video summary is available at NEJM.org

Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin.[10-12] Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.[13,14] Combined inhibition of the renin–angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies,[15,16] but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema.[17,18]

LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, was designed to minimize the risk of serious angioedema.[19,20] In small trials involving patients who had hypertension or heart failure with a preserved ejection fraction, LCZ696 had hemodynamic and neurohormonal effects that were greater than those of an ARB alone.[21,22] We examined whether the long-term effects of LCZ696 on morbidity and mortality were superior to those of ACE inhibition with enalapril in patients with chronic heart failure and a reduced ejection fraction.

Methods

Study Oversight

The executive committee designed and oversaw the conduct of the trial and data analysis in collaboration with the sponsor, Novartis. The trial was reviewed by an independent data and safety monitoring committee. Data were collected, managed, and analyzed by the sponsor according to a predefined statistical analysis plan, and the analyses were replicated by an independent academic statistician. The first draft of the manuscript was prepared by the first two authors, who had unrestricted access to the data, and was reviewed and edited by all the authors. All the authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the analyses.

Study Design

The study design has been reported previously.[23,24] The trial protocol and the statistical analysis plan (included in the Supplementary Appendix) are available with the full text of this article at NEJM.org. The trial was approved by the ethics committee at each study center. All the patients provided written informed consent.

The study consisted of three phases: the screening period; a single-blind run-in period during which all patients received enalapril, which was followed by a single-blind run-in period during which all patients received LCZ696, to ensure an acceptable side-effect profile of the study drugs at target doses; and double-blind treatment in the two study groups.

Study Patients

Eligibility requirements at screening included an age of at least 18 years, New York Heart Association (NYHA) class II, III, or IV symptoms, and an ejection fraction of 40% or less (which was changed to 35% or less by an amendment to the protocol on December 15, 2010). Patients were required to have a plasma B-type natriuretic peptide (BNP) level of at least 150 pg per milliliter (or an N-terminal pro-BNP [NT-proBNP] level ≥600 pg per milliliter) or, if they had been hospitalized for heart failure within the previous 12 months, a BNP of at least 100 pg per milliliter (or an NT-proBNP ≥400 pg per milliliter). Patients taking any dose of an ACE inhibitor or ARB were considered for participation, but for at least 4 weeks before screening, patients were required to take a stable dose of a beta-blocker and an ACE inhibitor (or ARB) equivalent to at least 10 mg of enalapril daily.[23]

Exclusion criteria included symptomatic hypotension, a systolic blood pressure of less than

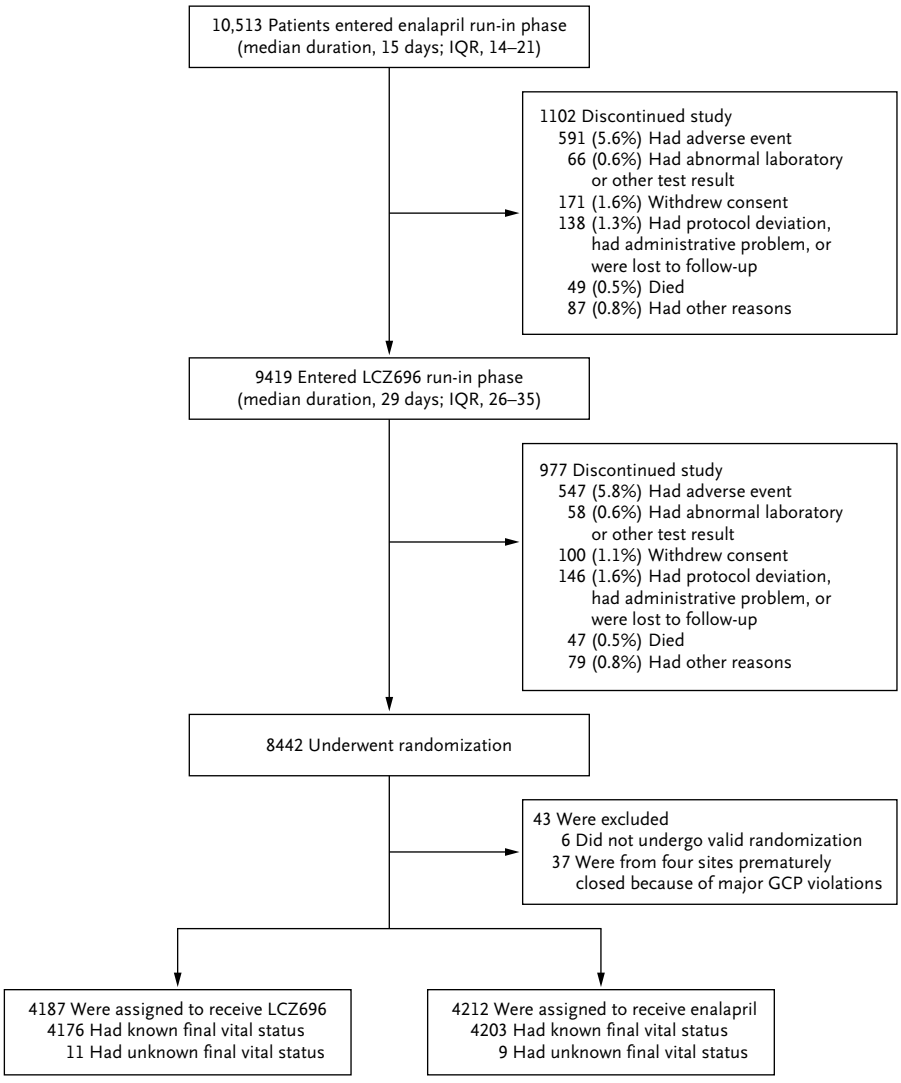

Figure 1. Screening Criteria, Run-in Periods, and Randomization.

The proportion of patients who withdrew from the study because of adverse events was higher during the enalapril run-in period than during the LCZ696 run-in period after adjustment for the longer duration of LCZ696 exposure. The most common reasons for withdrawal from the study during the run-in period were hypotension, cough, hyperkalemia, and renal dysfunction. During the run-in period, 8 patients did not take enalapril and took only LCZ696. IQR denotes interquartile range, and GCP Good Clinical Practice.

100 mm Hg at screening or 95 mm Hg at randomization, an estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m^2 of body-surface area at screening or at randomization or a decrease in the eGFR of more than 25% (which was amended to 35%) between screening and randomization, a serum potassium level of more than 5.2 mmol per liter at screening (or above 5.4 mmol per liter at randomization), or a history of angioedema or unacceptable side effects during receipt of ACE inhibitors or ARBs.

STUDY PROCEDURES

Eligible patients were switched from the ACE inhibitor or ARB that they had been receiving to single-blind treatment with enalapril (at a dose of 10 mg twice daily) for 2 weeks. If no unacceptable side effects occurred, this regimen was fol-

lowed by single-blind treatment with LCZ696 for an additional 4 to 6 weeks (initially at a dose of 100 mg twice daily, which was increased to 200 mg twice daily). (The ARB component of the 200-mg dose of LCZ696 is equivalent to 160 mg of valsartan.) During this run-in period, to minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, enalapril was withheld a

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Age — yr	63.8±11.5	63.8±11.3
Female sex — no. (%)	879 (21.0)	953 (22.6)
Race or ethnic group — no. (%)†		
White	2763 (66.0)	2781 (66.0)
Black	213 (5.1)	215 (5.1)
Asian	759 (18.1)	750 (17.8)
Other	452 (10.8)	466 (11.1)
Region — no. (%)		
North America	310 (7.4)	292 (6.9)
Latin America	713 (17.0)	720 (17.1)
Western Europe and other‡	1026 (24.5)	1025 (24.3)
Central Europe	1393 (33.3)	1433 (34.0)
Asia–Pacific	745 (17.8)	742 (17.6)
Systolic blood pressure — mm Hg	122±15	121±15
Heart rate — beats/min	72±12	73±12
Body-mass index§	28.1±5.5	28.2±5.5
Serum creatinine — mg/dl	1.13±0.3	1.12±0.3
Clinical features of heart failure		
Ischemic cardiomyopathy — no. (%)	2506 (59.9)	2530 (60.1)
Left ventricular ejection fraction — %	29.6±6.1	29.4±6.3
Median B-type natriuretic peptide (IQR) — pg/ml	255 (155–474)	251 (153–465)
Median N-terminal pro–B-type natriuretic peptide (IQR) — pg/ml	1631 (885–3154)	1594 (886–3305)
NYHA functional class — no. (%)¶		
I	180 (4.3)	209 (5.0)
II	2998 (71.6)	2921 (69.3)
III	969 (23.1)	1049 (24.9)
IV	33 (0.8)	27 (0.6)
Missing data	7 (0.2)	6 (0.1)
Medical history — no. (%)		
Hypertension	2969 (70.9)	2971 (70.5)
Diabetes	1451 (34.7)	1456 (34.6)
Atrial fibrillation	1517 (36.2)	1574 (37.4)
Hospitalization for heart failure	2607 (62.3)	2667 (63.3)
Myocardial infarction	1818 (43.4)	1816 (43.1)
Stroke	355 (8.5)	370 (8.8)
Pretrial use of ACE inhibitor‖	3266 (78.0)	3266 (77.5)
Pretrial use of ARB‖	929 (22.2)	963 (22.9)

Table 1. (Continued.)

Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

* Plus–minus values are means ±SD. There were no significant differences between the two groups except for the use of digitalis (P=0.04) and mineralocorticoid-receptor antagonists (P=0.01), with values not adjusted for multiple testing. Percentages may not total 100 because of rounding. More details about the baseline characteristics are provided in Section 3 in the Supplementary Appendix. To convert the values for creatinine to micromoles per liter, multiply by 88.4. IQR denotes interquartile range.
† Race or ethnic group was reported by the investigators.
‡ This category includes South Africa and Israel.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The data for New York Heart Association (NYHA) class reflect the status of patients at the time of randomization. Patients were required to have at least NYHA class II symptoms at screening.
‖ At the screening visit, 20 patients were not receiving the protocol-required treatment with an angiotensin-converting–enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB), and 45 patients were taking both drugs. Doses of pretrial ACE inhibitors and ARBs are provided in the Supplementary Appendix.

day before the initiation of treatment with LCZ696, and LCZ696 was withheld a day before randomization.

Patients who had no unacceptable side effects of the target doses of the two study medications were randomly assigned in a 1:1 ratio to double-blind treatment with either enalapril (at a dose of 10 mg twice daily) or LCZ696 (at a dose of 200 mg twice daily) with the use of a computerized randomization system involving concealed study-group assignments. Patients were evaluated every 2 to 8 weeks during the first 4 months of double-blind therapy and every 4 months thereafter. The dose of the study drug could be reduced in patients who had unacceptable side effects at target doses.

STUDY OUTCOMES

The primary outcome was a composite of death from cardiovascular causes or a first hospitalization for heart failure. The secondary outcomes were the time to death from any cause, the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ)[25] (on a scale from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure), the time to a new onset of atrial fibrillation, and the time to the first occurrence of a decline in renal function (which was defined as end-stage renal disease or as a decrease in the eGFR of at least 50% or a decrease of more than 30 ml per minute per 1.73 m^2 from randomization to less than 60 ml per minute per 1.73 m^2). Adjudication of these outcomes was carried out in a blinded fashion by a clinical-end-points committee according to prespecified criteria.

STATISTICAL ANALYSIS

We estimated that the annual rate of the primary end point would be 14.5% and the rate of death from cardiovascular causes would be 7.0% in the enalapril group. Calculation of the sample size was based on mortality from cardiovascular causes. We estimated that we would need to follow approximately 8000 patients for 34 months, with 1229 deaths from cardiovascular causes, to provide the study with a power of 80% to detect a relative reduction of 15% in the risk of death from cardiovascular causes in the LCZ696 group, at an overall two-sided alpha level of 0.05. On the basis of these calculations, we estimated that the primary end point would occur in 2410 patients, which would provide a power of 97% to detect a 15% reduction in the risk of this outcome.

The data and safety monitoring committee

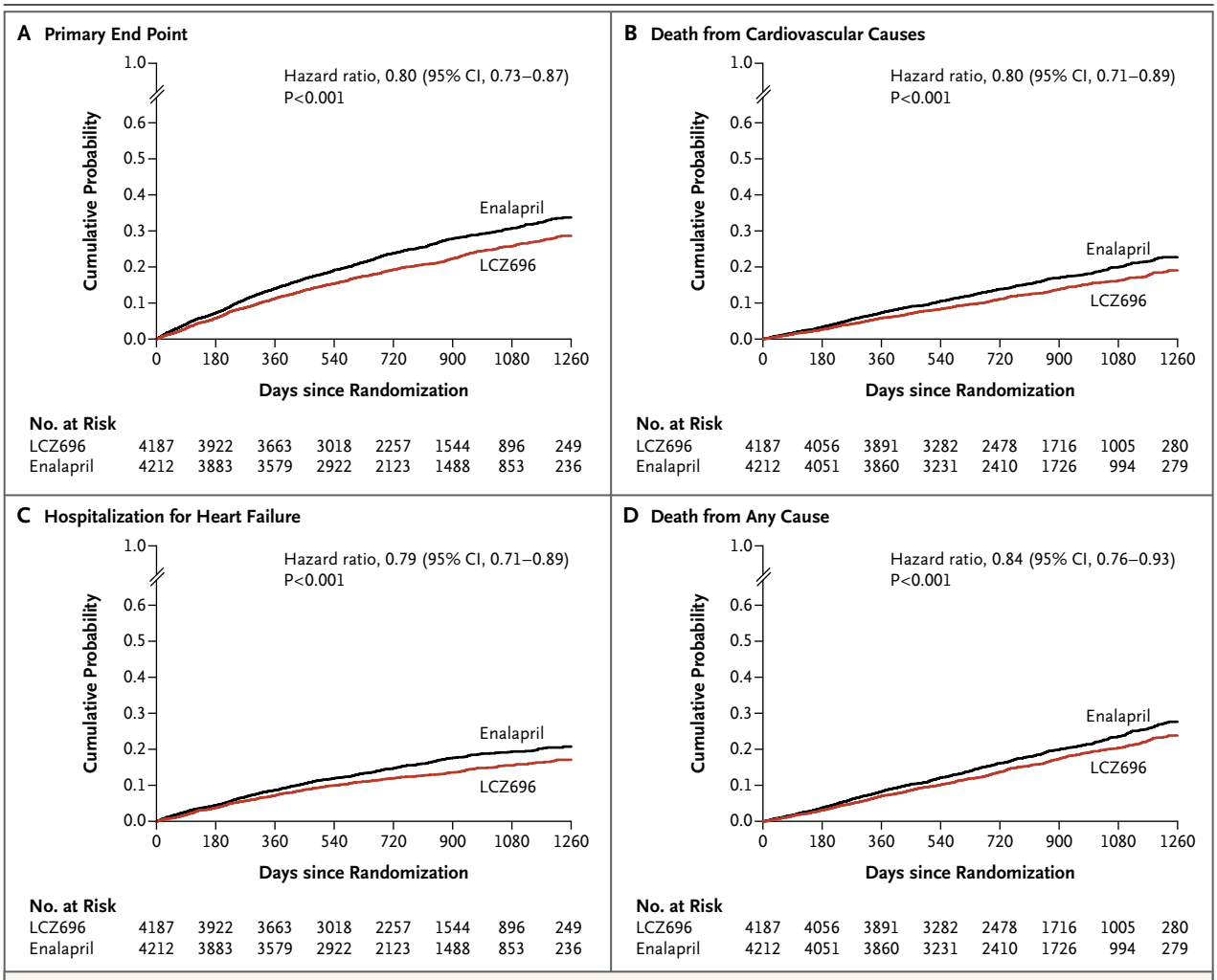

Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

specified that three interim efficacy analyses should be conducted after the accrual of one third, one half, and two thirds of the events, and the statistical stopping guideline for a compelling benefit required a one-sided nominal P value of less than 0.0001 at the first analysis and less than 0.001 at the second and third analyses in favor of LCZ696 for both death from cardiovascular causes and the primary end point. On March 28, 2014, at the third interim analysis (after enrollment had been completed), the committee informed the two coprincipal investigators that the prespecified stopping boundary for an overwhelming benefit had been crossed. The executive committee voted to stop the trial and selected March 31, 2014, as the cutoff date for all efficacy analyses; the sponsor accepted this decision.

We included data from all patients who had undergone a valid randomization in the analyses of the primary and secondary outcomes, according to the intention-to-treat principle. A sequentially rejective procedure was used for analysis of the secondary efficacy end points, with the first two secondary end points at the highest level of the testing sequence. (For details, see the statistical analysis plan in the Supplementary Appendix.) Time-to-event data were evaluated with the use

Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	−2.99±0.36	−4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

* 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 to 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 2638 patients in the enalapril group who did not have atrial fibrillation at the randomization 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 randomization or a decrease in the eGFR of more than 30 ml per minute per 1.73 m^2, to less than 60 ml per minute per 1.73 m^2.

of Kaplan–Meier estimates and Cox proportional-hazards models, with treatment and region as fixed-effect factors; hazard ratios, 95% confidence intervals, and two-sided P values were calculated with the use of the Cox models. We assessed the consistency of the treatment effect among 18 prespecified subgroups and used a repeated-measures covariance model to evaluate the KCCQ score, with baseline values, study group, region, study visit, and the interaction between study visit and study group as covariates; a score of zero was used for patients who had died. We used Fisher's exact test to compare rates of adverse events. Data on symptomatic hypotension, worsening renal function, hyperkalemia, cough, and angioedema were collected prospectively as events of interest.

RESULTS

STUDY PATIENTS

From December 8, 2009, through November 23, 2012, a total of 10,521 patients at 1043 centers in 47 countries entered the run-in period. Of these patients, 2079 did not fulfill the criteria for randomization, and 43 patients underwent randomization erroneously or were enrolled at sites that were closed owing to serious Good Clinical Practice violations; these patients were prospectively omitted from all analyses before the end of the trial. Accordingly, 4187 patients were randomly assigned to receive LCZ696 and 4212 to receive enalapril for the intention-to-treat analysis (Fig. 1). The groups were balanced with respect to baseline characteristics. Most patients were receiving recommended pharmacologic therapy for chronic heart failure (Table 1).

STUDY-DRUG ADMINISTRATION AND FOLLOW-UP

Except for discontinuations owing to death, the study drug was discontinued in 746 patients (17.8%) receiving LCZ696 and 833 patients (19.8%) receiving enalapril (P=0.02). At the last assessment, among patients taking the study medication, the mean (±SD) doses in the LCZ696 and enalapril groups were 375±71 mg and 18.9±3.4 mg, respectively. Eleven patients in the LCZ696 group and 9 patients in the enalapril group were lost to follow-up, and their data were censored at the last contact. The median duration of follow-up was 27 months, with no significant between-group difference.

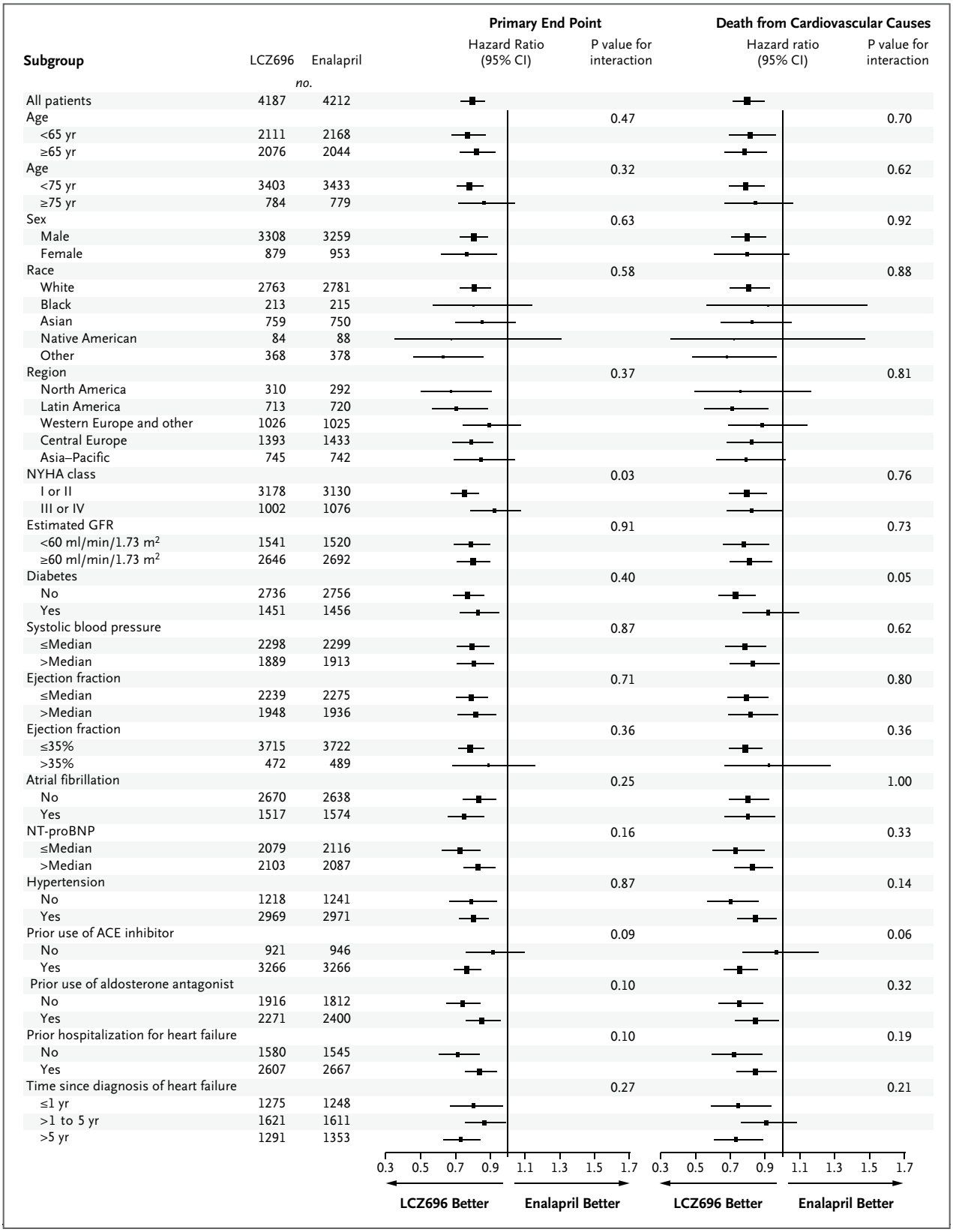

Figure 3 (facing page). Prespecified Subgroup Analyses.
Shown are hazard ratios for the primary end point (death from cardiovascular causes or first hospitalization for heart failure) and for death from cardiovascular causes among patients in prespecified subgroups. The size of the square corresponds to the number of patients in each subgroup. Patients who were not taking a pretrial angiotensin-converting–enzyme (ACE) inhibitor were taking an angiotensin-receptor blocker (except for 20 patients who received neither drug before the trial). GFR denotes glomerular filtration rate, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.

STUDY OUTCOMES

Death from cardiovascular causes or hospitalization for heart failure (the primary end point) occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001 [exact $P=2.0\times10^{-7}$]) (Fig. 2A and Table 2). The difference in favor of LCZ696 was seen early in the trial and at each interim analysis.

A total of 558 deaths (13.3%) in the LCZ696 group and 693 (16.5%) in the enalapril group were due to cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001) (Fig. 2B and Table 2). Of the patients receiving LCZ696, 537 (12.8%) were hospitalized for heart failure, as compared with 658 patients (15.6%) receiving enalapril (hazard ratio, 0.79; 95% CI, 0.71 to 0.89; P<0.001) (Fig. 2C and Table 2). Over the duration of the trial, the numbers of patients who would need to have been treated to prevent one primary event and one death from cardiovascular causes were 21 and 32, respectively.

A total of 711 patients (17.0%) in the LCZ696 group and 835 patients (19.8%) in the enalapril group died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001) (Fig. 2D and Table 2). The effect of LCZ696 was consistent across all prespecified subgroups. A nominally significant interaction between NYHA class at randomization and the effect of treatment on the primary end point (P=0.03, without adjustment for multiple comparisons) was not seen for the interaction between NYHA class and the effect on death from cardiovascular causes (P=0.76) (Fig. 3).

The mean change from baseline to month 8 in the KCCQ clinical summary score was a reduction of 2.99 points in the LCZ696 group and a reduction of 4.63 points in the enalapril group (between-group difference, 1.64 points; 95% CI, 0.63 to 2.65; P=0.001). When zero values were not imputed for patients who died, the score improved in the LCZ696 group and declined in the enalapril group, and the between-group difference (0.95 points; 95% CI 0.31 to 1.59) remained significant (P=0.004).

New-onset atrial fibrillation developed in 84 patients in the LCZ696 group and 83 patients in the enalapril group (P=0.84) (Table 2). A total of 94 patients in the LCZ696 group and 108 patients in the enalapril group had a protocol-defined decline in renal function (P=0.28) (Table 2); 8 patients in the LCZ696 group and 16 in the enalapril group had progression to end-stage renal disease (P=0.11).

SAFETY

Four patients (two in each group) did not start the study medication and were excluded from the safety analyses. During the run-in period, 12.0% of the patients withdrew because of an adverse event (most frequently cough, hyperkalemia, renal dysfunction, or hypotension), with a higher rate of withdrawal after adjustment for the shorter duration of treatment in the enalapril group than in the LCZ696 group. After randomization, patients in the LCZ696 group were more likely than those in the enalapril group to have symptomatic hypotension, but these events rarely required the discontinuation of treatment (Table 3). In contrast, cough, a serum creatinine level of 2.5 mg per deciliter (221 μmol per liter) or more, and a serum potassium level of more than 6.0 mmol per liter were reported less frequently in the LCZ696 group than in the enalapril group (P<0.05 for all comparisons) (Table 3). Overall, fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an adverse event (10.7% vs. 12.3%, P=0.03) or because of renal impairment (0.7% vs. 1.4%, P=0.002). The most frequent serious adverse events and adverse events leading to discontinuation of the study drug are summarized in Sections 6 and 7 in the Supplementary Appendix.

As compared with the value at randomization, the mean systolic blood pressure at 8 months was 3.2±0.4 mm Hg lower in the LCZ696 group than in the enalapril group (P<0.001) (Section 8 in the Supplementary Appendix). However, when the between-group difference in blood pressure

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

* Shown are results of the analyses of prespecified safety events at any time after randomization. The numbers 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=0.002); 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.

was modeled as a time-dependent covariate, it was not a determinant of the incremental benefit of LCZ696. At 8 months, there were no significant changes from baseline in heart rate or serum creatinine level between the two groups. Angioedema was confirmed by blinded adjudication in 19 patients in the LCZ696 group and in 10 patients in the enalapril group (P=0.13). No patient had airway compromise or required mechanical airway protection.

DISCUSSION

In our study involving patients with chronic heart failure and a reduced ejection fraction, the inhibition of both the angiotensin II receptor and neprilysin with LCZ696 was more effective in reducing the risk of death from cardiovascular causes or hospitalization for heart failure than was ACE inhibition with enalapril. LCZ696 was also superior to enalapril in reducing the risk of death from any cause and reducing symptoms and physical limitations of heart failure. The magnitude of these advantages of LCZ696 over ACE inhibition was highly significant and clinically important, particularly since the drug was compared with a dose of enalapril that has been shown to reduce mortality, as compared with placebo.[1,2] The benefit of LCZ696, which was apparent early in the trial, was seen in patients who were already receiving all other drugs known to improve survival among patients with heart failure (i.e., beta-blockers and mineralocorticoid-receptor antagonists). The benefit with respect to cardiovascular mortality was consistent in all relevant subgroups.

Our study was designed to provide evidence to support the replacement of ACE inhibitors or ARBs with LCZ696 in the management of chronic heart failure. The trial was devised to show an advantage with respect to cardiovascular mortality alone, which was the primary determinant of the sample size and for which a statistically compelling effect was required to stop the trial early because of a benefit. Although in clinical practice, many patients with heart failure receive low (and potentially subtherapeutic) doses of ACE inhibitors and ARBs,[26] we included a run-in pe-

riod to ensure that LCZ696 would be compared with doses of enalapril that have been shown to reduce mortality. The mean dose of enalapril that was used in our study (18.9 mg daily) was higher than or similar to the doses used in the two trials that showed a survival benefit with enalapril in patients with mild-to-moderate or severe symptoms (16.6 mg and 18.4 mg, respectively).[1,2]

The favorable results of our study contrast with the disappointing findings in an earlier large-scale trial involving patients with heart failure,[18] which showed no significant difference in clinical outcomes between enalapril and omapatrilat (a drug that inhibits ACE, neprilysin, and aminopeptidase P). However, in that trial, omapatrilat was given once daily (to reflect its use in patients with hypertension), even though its pharmacologic advantages over enalapril in patients with heart failure were not maintained throughout the 24-hour dosing interval.[18] This experience led us to prescribe LCZ696 twice daily in our study population, despite its once-daily efficacy in patients with hypertension.[21]

The superiority of LCZ696 over enalapril was not accompanied by important safety concerns; fewer patients stopped their study medication overall or because of an adverse event in the LCZ696 group than in the enalapril group. Because of its greater vasodilator effects, treatment with LCZ696 was associated with a higher rate of symptomatic hypotension, but there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects. Although the greater hypotensive effect of LCZ696 might impair renal perfusion, clinically important increases in the serum creatinine level and discontinuation of the study drug because of renal impairment were less frequent in the LCZ696 group than in the enalapril group. These effects of LCZ696 on renal function are consistent with the effects observed in experimental studies[15] and with the findings in earlier trials of omapatrilat.[18,22] The main safety concern with omapatrilat — life-threatening angioedema — was related to its inhibition of three enzymes responsible for the degradation of bradykinin.[27] LCZ696, which does not inhibit ACE or aminopeptidase P,[19,20] was not associated with an increased risk of serious angioedema in our study.

Although we recruited patients with at least mildly increased levels of natriuretic peptides in order to achieve our projected event rate, the characteristics of our patients with heart failure were similar to those of study populations in other relevant trials and patients in the community.[24,26,28] During enrollment, we evaluated patients who were already taking various doses of ACE inhibitors or ARBs and required that they be able to take the equivalent of a relatively low dose of enalapril (10 mg daily) without unacceptable side effects. Doses of the study drugs were increased to target levels during the run-in phase, primarily to ensure that patients in the enalapril group received doses that have been shown to reduce mortality.[2] Only 12% of patients did not complete the run-in period because of adverse events, and the rates of adverse events were higher for patients receiving enalapril than for those receiving LCZ696. Hence, our results are applicable to a broad spectrum of patients with heart failure, including those who are currently taking an ACE inhibitor or ARB or who are likely to be able to take such an agent without having unacceptable side effects.

In conclusion, angiotensin receptor–neprilysin inhibition with LCZ696 was superior to ACE inhibition alone in reducing the risks of death and of hospitalization for heart failure. The magnitude of the beneficial effect of LCZ696, as compared with enalapril, on cardiovascular mortality was at least as large as that of long-term treatment with enalapril, as compared with placebo.[2] This robust finding provides strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the renin–angiotensin system alone in patients with chronic heart failure.

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