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ORIGINAL INVESTIGATIONS

Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization

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CME Objective for This Article: After reading this article, the reader should be able to: 1) define the burden of readmissions after heart failure hospitalization in a contemporary population with heart failure and reduced ejection fraction; 2) explain the rationale for targeting early readmissions after heart failure hospitalization as a quality metric; and 3) compare the impact of different pharmacologic therapies for heart failure on rates of readmission after heart failure hospitalization.

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Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization

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ABSTRACT

BACKGROUND Patients with heart failure (HF) are at high risk for hospital readmission in the first 30 days following HF hospitalization.

OBJECTIVES This study sought to determine if treatment with sacubitril/valsartan (LCZ696) reduces rates of hospital readmission at 30-days following HF hospitalization compared with enalapril.

METHODS We assessed the risk of 30-day readmission for any cause following investigator-reported hospitalizations for HF in the PARADIGM-HF trial, which randomized 8,399 participants with HF and reduced ejection fraction to treatment with LCZ696 or enalapril.

RESULTS Accounting for multiple hospitalizations per patient, there were 2,383 investigator-reported HF hospitalizations, of which 1,076 (45.2%) occurred in subjects assigned to LCZ696 and 1,307 (54.8%) occurred in subjects assigned to enalapril. Rates of readmission for any cause at 30 days were 17.8% in LCZ696-assigned subjects and 21.0% in enalapril-assigned subjects (odds ratio: 0.74; 95% confidence interval: 0.56 to 0.97; $p = 0.031$). Rates of readmission for HF at 30-days were also lower in subjects assigned to LCZ696 (9.7% vs. 13.4%; odds ratio: 0.62; 95% confidence interval: 0.45 to 0.87; $p = 0.006$). The reduction in both all-cause and HF readmissions with LCZ696 was maintained when the time window from discharge was extended to 60 days and in sensitivity analyses restricted to adjudicated HF hospitalizations.

CONCLUSIONS Compared with enalapril, treatment with LCZ696 reduces 30-day readmissions for any cause following discharge from HF hospitalization. (J Am Coll Cardiol 2016;68:241–8) © 2016 by the American College of Cardiology Foundation.

Despite considerable progress in the development of effective medical therapy, patients with heart failure (HF) remain at high risk for recurrent hospitalization (1). Among those >65 years of age, roughly 1 in 4 patients is readmitted within 30 days of hospitalization and nearly one-half are readmitted within 6 months (2). High costs associated with in-hospital care threaten a doubling of health care expenditure on HF by 2030 (3). This anticipated financial burden, coupled with the concern that many early readmissions may be preventable by improving the quality of in-hospital care and care transitions (4,5) has focused attention on HF readmission rates as a metric of quality of care. In 2009, the Centers for Medicare & Medicaid Services began public reporting of all-cause readmission rates in the United States, and since 2010, U.S. hospitals with higher than expected risk-standardized readmission rates at 30 days are at risk for substantial financial penalties as part of the Hospital Readmissions Reduction Program.

In the PARADIGM-HF (Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on

CardioMEMS. Dr. Swedberg has received a grant from Servier; and has consulted for Astrazeneca, Novartis, Amgen, and Servier. Drs. Shi and Lefkowitz are employees of Novartis Pharmaceuticals Corporation. Dr. Teerlink has received research grants from Amgen, Bayer, Cytokinetics, Mast Therapeutics, Novartis, and Trevenal; and has consulted for Amgen, Bayer, Cytokinetics, Mast Therapeutics, Novartis, Relypsa, Trevena, and ZS Pharma. Dr. McMurray's employer, University of Glasgow, was paid by Novartis for his time spent as cochairman of the PARADIGM-HF trial. Drs. Zile, Rouleau, Starling, and Solomon have consulted for or received research support from Novartis. Dr. Claggett has reported that he has no relationships relevant to the contents of this paper to disclose.

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Global Mortality and Morbidity in Heart Failure) trial, treatment with the angiotensin receptor neprilysin inhibitor sacubitril/valsartan (LCZ696) was associated with a 20% reduction in the primary composite endpoint of cardiovascular death or HF hospitalization compared with enalapril (6). Moreover, LCZ696 reduced both the time to first hospitalization for HF and the cumulative burden of HF hospitalizations during the course of the trial (7). In this analysis, we sought to further assess the effect of LCZ696 on the rates of all-cause 30-day readmission after HF hospitalization.

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METHODS

PARADIGM-HF TRIAL. As previously reported (8), the PARADIGM-HF study was a randomized, double-blind, prospective comparison of LCZ696 with enalapril in subjects with chronic HF, New York Heart Association functional class II to IV symptoms, and left ventricular ejection fraction of ≤40% (subsequently lowered to ≤35% by an amendment to the protocol) treated with guideline-recommended medical therapy. Before randomization, all subjects underwent a sequential, single-blind run-in phase to ensure tolerability of both study drugs at target doses. Subjects who successfully completed the run-in phase (n = 8,399) were randomly allocated in 1:1 fashion to double-blind treatment with either enalapril, 10 mg twice daily or LCZ696, 200 mg twice-daily (sacubitril/valsartan, 97/103 mg twice-daily). Ethics committee approval was obtained for the study at each site, and written informed consent was obtained from all subjects before participation.

STATISTICAL ANALYSES. Baseline characteristics of patients who were hospitalized and subsequently discharged were analyzed by treatment arm, using Student *t* tests and Pearson chi-squared test for continuous and categorical data, respectively. To incorporate data from multiple HF hospitalizations per patient, the primary unit of subsequent analysis was hospitalizations, rather than patients. We compared rates of 30-day readmission after index HF hospitalization by treatment assignment during the median 27-month period of randomized follow-up in the PARADIGM-HF trial. To replicate the approach used in the Hospital Readmissions Reduction Program, all investigator-reported hospitalizations for HF were considered as potential index HF hospitalizations, not merely those that were adjudicated positively by the Clinical Endpoints Committee (CEC). Those in which patients died before discharge, were admitted and discharged on the same day, or for which discharge dates were unavailable were excluded. Discharges for which readmission status was not able to be determined because of study discontinuation were omitted from the analysis. When conflicting admission and/or discharge dates were encountered, we used the widest hospitalization interval from among the conflicting dates (i.e., the earliest admission date and the latest discharge date). In keeping with the Medicare methodology, a readmission was defined as inpatient admission to an acute care facility for any cause within 30-days from the date of discharge of an index HF hospitalization.

ABBREVIATIONS AND ACRONYMS

CEC = Clinical Endpoints Committee
CI = confidence interval
HF = heart failure
LCZ696 = sacubitril/valsartan
OR = odds ratio

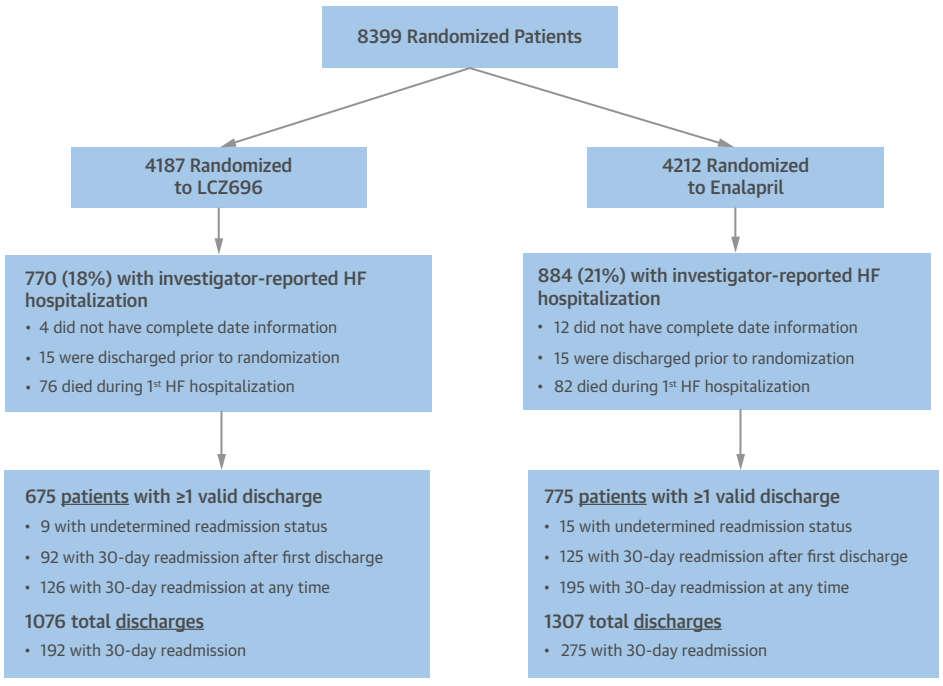
TABLE 1 Baseline Characteristics of Patients With Discharge After Investigator-Reported Heart Failure Hospitalization, by Treatment Assignment

	Hospitalized for HF		
	LCZ696 (n = 675)	Enalapril (n = 775)	p Value (Enalapril vs. LCZ)
Age, yrs	64.4 ± 11.7	64.3 ± 11.4	0.82
Female	17	19	0.29
White race	69	67	0.50
BMI, kg/m^2	28.5 ± 5.8	28.7 ± 5.8	0.45
SBP, mm Hg	121 ± 16	121 ± 16	0.74
Heart rate, bpm	74 ± 12	74 ± 13	0.91
Creatinine, mg/dl	1.2 ± 0.3	1.2 ± 0.3	0.66
Ischemic CMP	60	60	0.91
Ejection fraction, %	29 ± 6	29 ± 7	0.92
Median NT-proBNP, pg/ml	2,270 (1,178–4,749)	2,000 (1,079–4,587)	0.10
NYHA class			0.16
I	3	4	
II	65	69	
III	30	26	
IV	2	1	
Past medical history			
Hypertension	74	75	0.83
Diabetes	44	43	0.81
Hospitalization for HF	74	74	0.95
MI	48	45	0.29
Stroke	11	11	0.96
Atrial fibrillation	39	45	0.015
Treatment at randomization			
Diuretics	87	87	0.70
Digitalis	31	35	0.08
Beta-blocker	92	93	0.79
MRA	57	56	0.68
ICD	21	20	0.92
CRT	10	9	0.44

Values are mean ± SD, %, or median (interquartile range).

BMI = body mass index; CMP = cardiomyopathy; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LCZ696 = sacubitril/valsartan; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

FIGURE 1 Summary of Patient Flow for the Analysis



The diagram summarizes for each treatment arm the number of patients with an investigator-reported HF hospitalization, the subset with at least 1 valid discharge following an investigator-reported HF hospitalization, the total number of HF discharges considered as index admissions for the readmissions analysis, and the number of 30-day readmissions in each group. HF = heart failure; LCZ696 = sacubitril/valsartan.

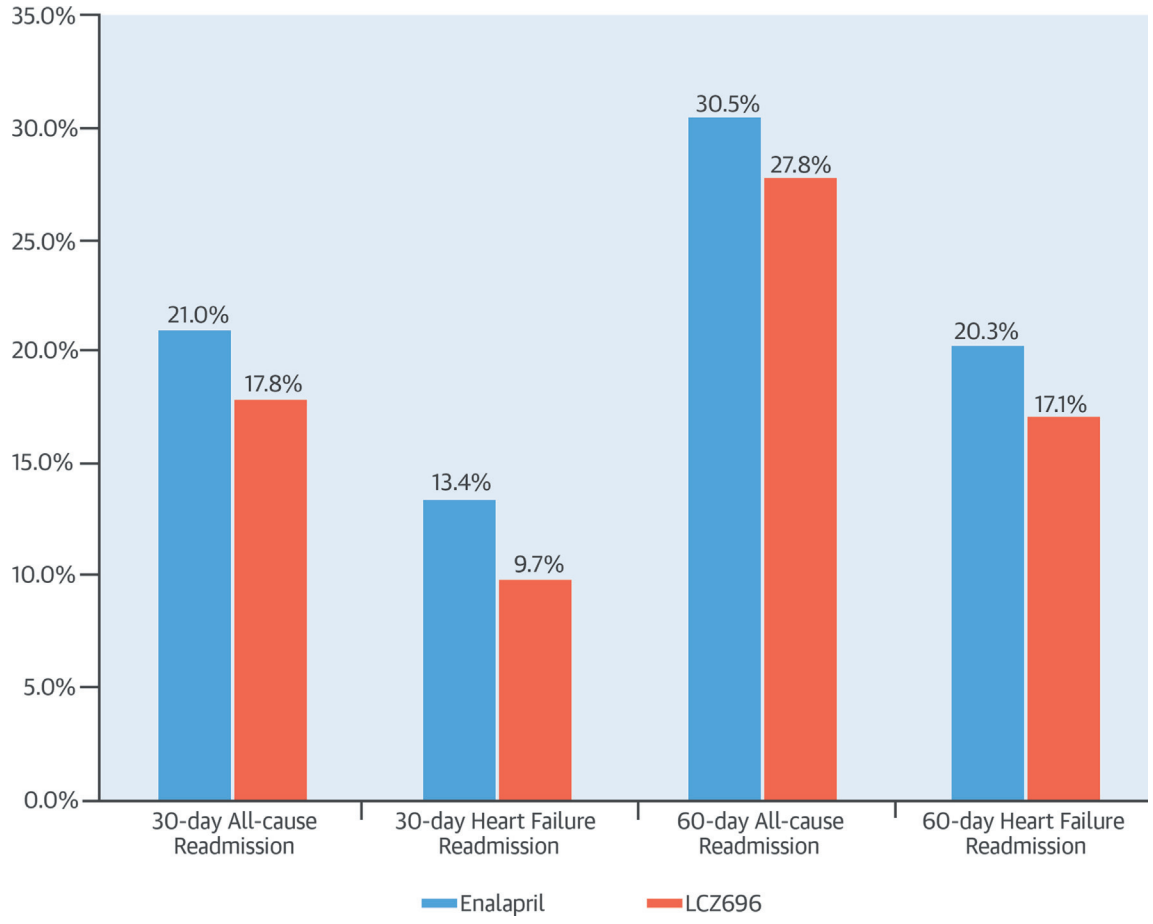
Odds ratios (ORs) for readmission in LCZ696- versus enalapril-treated patients were calculated in random-effects logistic regression models to account for multiple HF discharge windows experienced by the same patient. Sensitivity analyses were conducted examining only patients >65 years of age, examining all-cause readmissions at 60 days, examining only cause-specific readmission for HF, restricting the analysis to patients enrolled in the United States (where financial penalties for 30-day readmissions after HF hospitalization are most applicable), and using only the subset of investigator-reported HF hospitalizations confirmed by the CEC. Sensitivity analyses restricted to the first HF discharge for each patient used standard logistic regression models.

RESULTS

Of 8,399 randomized subjects, 1,654 (19.7%) experienced an investigator-reported HF hospitalization. Excluding those hospitalizations for which complete date information was unavailable, or the patient died while hospitalized, there were 1,450 (17.3%) subjects who survived at least 1 HF hospitalization including 675 (16.1%) assigned to LCZ696 and 775 (18.4%) assigned to enalapril. Among patients hospitalized at least once for HF, patient characteristics were similar at baseline between treatment groups (**Table 1**).

Accounting for multiple hospitalizations per patient, there were 2,383 investigator-reported HF hospitalizations, of which 1,076 (45.2%) occurred in subjects assigned to LCZ696 and 1,307 (54.8%) occurred in subjects assigned to enalapril (**Figure 1**). Length of stay during index HF hospitalization did not differ by treatment arm (7.5 days vs. 7.0 days, sacubitril/valsartan vs. enalapril; p = 0.10). The number of readmissions per patient is summarized in Online Figure 1 and Online Table 1. Rates of readmission for any cause at 30 days were 17.8% in LCZ696-assigned subjects and 21.0% in enalapril-assigned subjects (OR: 0.74; 95% confidence interval [CI]: 0.56 to 0.97; p = 0.031). Rates of readmission for HF at 30 days were also reduced in subjects assigned to LCZ696 (9.7% vs. 13.4%; OR: 0.62; 95% CI: 0.45 to 0.87; p = 0.006). The reduction in both all-cause and HF readmissions with LCZ696 was maintained when the time window from discharge was extended to 60 days (all-cause readmissions: 27.8% vs. 30.5%; OR:

CENTRAL ILLUSTRATION **Influence of LCZ696 on Readmission: Rates After Investigator-Reported HF Hospitalization According to Treatment Assignment**



Desai, A.S. et al. J Am Coll Cardiol. 2016;68(3):241–8.

Shown are the proportion of investigator-reported HF hospitalizations associated with readmissions for any cause or for heart failure at 30 days and 60 days following discharge. LCZ696 = sacubitril/valsartan.

0.77; 95% CI: 0.60 to 0.99; p = 0.045) (HF readmissions: 17.1% vs. 20.3%; OR: 0.68; 95% CI: 0.50 to 0.92; p = 0.01) (Central Illustration, Figure 2).

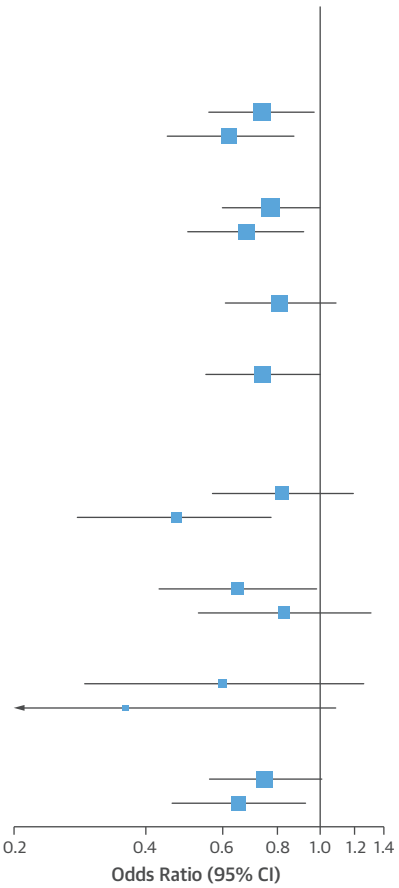
The results of sensitivity analyses are reported in Figure 2. Among analyses restricted to CEC-adjudicated HF hospitalizations, 30-day all-cause readmission rates were similarly lower in subjects assigned to LCZ696 (17.7% vs. 20.7%; OR: 0.74; 95% CI: 0.55 to 0.99; p = 0.043). Numerically fewer all-cause and HF-related readmissions at 30 days were also noted for LCZ696-assigned subjects 65 years and older (Medicare-eligible, 17.8% vs. 20.7%; OR: 0.82; 95% CI: 0.57 to 1.19; p = 0.30) and those enrolled in the United States (17.3% vs. 26.0%; OR: 0.60; 95% CI: 0.29 to 1.26; p = 0.18), with more pronounced effect on HF readmissions in each of these subgroups. The effect of LCZ696 on all-cause and HF readmissions did not differ significantly across regions pre-specified in the primary analysis (p = 0.81 for all-cause and p = 0.09 for HF readmissions) (Online Figure 2).

DISCUSSION

Among patients with HF and reduced ejection fraction enrolled in the PARADIGM-HF trial, treatment with LCZ696 reduced the cumulative incidence of HF hospitalizations relative to treatment with enalapril. Nearly 1 in 5 HF hospitalizations during the trial was followed by a repeat hospitalization within 30 days, of which more than half were related to recurrent HF.

FIGURE 2 Sensitivity Analyses of Impact of LCZ696 Relative to Enalapril on Readmission Rates After HF Hospitalization

Analysis	LCZ696	Enalapril	Odds Ratio	P-Value
30-day (after any investigator-reported HF Hosp)				
All-cause readmission	192/1076 (17.8%)	275/1307 (21.0%)	0.74 (0.56-0.97)	0.031
HF readmission	104/1074 (9.7%)	175/1302 (13.4%)	0.62 (0.45-0.87)	0.006
60-day (after any investigator-reported HF Hosp)				
All-cause readmission	294/1059 (27.8%)	391/1283 (30.5%)	0.77 (0.60-0.99)	0.045
HF readmission	180/1055 (17.1%)	259/1275 (20.3%)	0.68 (0.50-0.92)	0.013
30-day (after first investigator-reported HF Hosp)				
All-cause readmission	92/666 (13.8%)	125/760 (16.4%)	0.81 (0.61-1.09)	0.17
30-day (after any CEC-confirmed HF Hosp)				
All-cause readmission	171/967 (17.7%)	243/1172 (20.7%)	0.74 (0.55-0.99)	0.043
30-day (after any investigator-reported HF Hosp):				
Subgroup: Patients at least 65 years				
All-cause readmission	101/567 (17.8%)	133/644 (20.7%)	0.82 (0.57-1.19)	0.30
HF readmission	47/565 (8.3%)	94/643 (14.6%)	0.47 (0.28-0.77)	0.003
Subgroup: Patients less than 65 years				
All-cause readmission	91/509 (17.9%)	142/663 (21.4%)	0.65 (0.43-0.98)	0.041
HF readmission	57/509 (11.2%)	81/659 (12.3%)	0.83 (0.53-1.31)	0.42
Subgroup: US Patients				
All-cause readmission	18/104 (17.3%)	34/131 (26.0%)	0.60 (0.29-1.26)	0.18
HF readmission	6/104 (5.8%)	21/131 (16.0%)	0.36 (0.12-1.09)	0.07
Subgroup: non-US Patients				
All-cause readmission	174/972 (17.9%)	241/1176 (20.5%)	0.75 (0.56-1.01)	0.06
HF readmission	98/970 (10.1%)	154/1171 (13.2%)	0.65 (0.46-0.93)	0.018



Shown are the proportion of readmissions for any cause or for HF, by treatment arm, along with odds ratios for readmission (LCZ696 vs. enalapril) and 95% CIs, for varying definitions of index HF events (investigator-reported vs. CEC-confirmed), varying time horizons (30 vs. 60 days), and key subgroups of interest. CEC = Clinical Endpoints Committee; CI = confidence interval; Hosp = hospitalization; other abbreviations as in Figure 1.

In this analysis, we noted a 26% lower rate of 30-day readmission for any cause among patients allocated to LCZ696 and a 38% lower rate of 30-day readmission for HF. These differences persisted at 60 days following hospital discharge and were robust in analyses restricted to CEC-adjudicated HF hospitalizations, patients enrolled in the United States, and the subset of Medicare-eligible subjects >65 years of age. These data suggest that LCZ696 is likely to be more effective than enalapril in reducing the risk of early readmission after HF hospitalization.

Recurrent hospitalizations are a primary driver of the burgeoning costs associated with HF care (3) and are a potent marker of risk for subsequent mortality (9,10). Although patients discharged with HF are at risk for readmission well beyond 30 days, the early post-discharge interval is known to be a particularly vulnerable period (11,12). In the United States, financial penalties imposed as part of the Hospital Readmission Reduction Program have focused considerable attention on improving the quality of pre-discharge education, care transitions, and early post-discharge follow-up to reduce the burden of preventable admissions (13). However, few evidence-based strategies for readmission prevention are available. Guidelines encourage prescription of neurohormonal antagonists before hospital discharge to improve adherence and long-term clinical outcomes in patients with HF and reduced ejection fraction (14), but there are limited data assessing the impact of existing guideline-directed medical therapies on the risk of readmissions in the 30- or 60-day window following discharge. A recent observational study of digoxin prescription before discharge suggested a significant reduction on 30-day readmissions among patients with HF and ejection fraction <45%

(15), but studies examining pre-discharge prescription of angiotensin-converting enzyme inhibitors (16), beta-blockers, (17) and fixed-dose isosorbide dinitrate/hydralazine (18) have not shown similar benefits, despite important effects on mortality.

Early cardiovascular readmissions are frequently caused by recurrent HF decompensation, probably as a consequence of either incomplete decongestion during the index hospital admission or rapid recurrence of congestion in the early post-discharge interval (19). Accordingly, therapeutic approaches that facilitate better management of congestion seem to be effective in reducing readmission rates (20). Our analysis indicates that compared with those treated with enalapril, patients with chronic HF treated with LCZ696 are both less likely to be initially hospitalized for HF decompensation, and less likely to require hospital readmission for any reason within 30 days of hospital discharge. Because angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have comparable clinical benefits in HF with reduced ejection fraction, it seems likely that the improvement in early post-discharge clinical outcomes is related to the incremental benefit of neprilysin inhibition over renin-angiotensin system antagonism alone, particularly with regard to HF readmissions, which were also lower in LCZ696-treated subjects. This impact on readmissions after HF hospitalization should be viewed in context of the already established 21% reduction in risk of first HF hospitalization compared with enalapril, and provides more granular insight into the 23% reduction in cumulative burden of HF hospitalization that has previously been reported (7). Although the mechanisms by which neprilysin inhibition may help to facilitate readmission reduction early after HF hospitalization remain unclear, these data further support the potential benefits of this approach on slowing the clinical progression of patients surviving with HF.

STUDY LIMITATIONS. This analysis must be viewed in the context of its limitations. First, this was not a pre-specified analysis of the PARADIGM-HF study, and patients were not randomized to treatment with LCZ696 or enalapril at the time of index hospitalization. Accordingly, the apparent differences in readmission rates noted in this analysis could be attributed to differences in the patients who were hospitalized for HF in the 2 treatment groups. However, we noted no significant treatment-related differences in baseline characteristics and indices of HF severity among patients discharged following HF hospitalization (**Table 1**). To more closely mimic the approach used in the United States to apply financial penalties for early readmissions, our primary analysis focused on readmissions following investigator-reported HF hospitalizations, which are vulnerable to misclassification; nonetheless, the readmission reductions seen with LCZ696 were consistent in sensitivity analyses limited to HF hospitalizations confirmed by a blinded CEC. Because the risk for readmission persists well beyond 30 days, the focus on early readmissions here may seem shortsighted; however, payers in the United States and Australia have emphasized the rate of 30-day readmissions after HF hospitalization as a key quality metric and U.S. hospitals are increasingly focused on this time point because of the financial penalties for excessive readmissions imposed by Centers for Medicare & Medicaid Services. Consistency in the results for readmission at 60 days and in analyses restricted to Medicare-eligible patients suggests that the benefits of LCZ696 over enalapril are clinically relevant and not simply related to the play of chance.

CONCLUSIONS

Reducing early readmissions after HF hospitalization represents an opportunity to simultaneously improve patient outcomes and reduce the fiscal burden of HF management for hospitals and payers. These data highlighting fewer all-cause and heart-failure readmissions at 30 days during treatment with LCZ696 relative to enalapril provide additional rationale for use of sacubitril/valsartan in preference to enalapril in patients with chronic, symptomatic HF and reduced ejection fraction.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Thirty-day readmission is common among patients hospitalized with heart failure and rates are lower in those treated with sacubitril/valsartan than in patients treated with enalapril.

TRANSLATIONAL OUTLOOK: Future studies should seek to clarify the mechanism by which composite angiotensin receptor-neprilysin inhibition exerts benefit beyond the acute hospital phase of treatment compared with angiotensin-converting enzyme inhibition alone in patients with progressive heart failure and reduced ejection fraction.

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KEY WORDS hospitalization, neprilysin, readmission, sacubitril/valsartan

APPENDIX For supplemental figures and a table, please see the online version of this article.

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