Factors Associated With Noncompletion During the Run-In Period Before Randomization and Influence on the Estimated Benefit of LCZ696 in the PARADIGM-HF Trial

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Background—The 8442 patients randomized in the Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, in which sacubitril/valsartan (LCZ696) reduced both death and HF hospitalization more than enalapril, were a subset of 10521 patients entering sequential, single-blind run-in periods (enalapril 10 mg twice daily for 2 weeks followed by LCZ696 200 mg twice daily for 4 to 6 weeks) to ensure short-term tolerability of the 2 study medications. We identified the predictors of run-in noncompletion and estimated the implications of noncompletion for the overall study result.

Methods and Results—Patient factors associated with run-in noncompletion were defined in multivariable logistic regression models. The effectiveness of LCZ696 in a broader cohort approximating the full run-in population was estimated by weighting randomized patients according to the inverse probability of run-in completion; 2079 (19.8%) subjects discontinued the study during the run-in period, including 1102 (10.5%) during the enalapril phase and 977 (9.3%) during the LCZ696 phase. In multivariable models, lower systolic blood pressure, lower estimated glomerular filtration rate, higher N-terminal pro–B-type natriuretic peptide, and ischemic cause of heart failure were associated with higher risk for run-in noncompletion. Repeat analysis of the effect of randomized treatment giving greater weight to randomized patients resembling those who did not complete the run-in did not alter the hazard ratio favoring LCZ696 over enalapril for the primary end point of cardiovascular death or heart failure hospitalization, or the additional key end points of cardiovascular death and all-cause mortality.

Conclusions—Patients with lower blood pressure, lower glomerular filtration rate, and more severe heart failure were at higher risk for noncompletion during the run-in period of PARADIGM-HF. Weighted analysis of key study outcomes accounting for the effect of run-in noncompletion did not alter the benefit of LCZ696 over enalapril.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01035255.

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Key Words: angiotensin-converting enzyme inhibitor ■ clinical trial ■ heart failure ■ LCZ696 ■ neprilysin ■ renin–angiotensin system ■ sacubitril

Although randomized controlled trials represent the "gold standard" for assessment of comparative efficacy, there are frequent concerns about the generalizability of the results to the broader population of patients seen in clinical practice.[1] In the Prospective Comparison of ARNI With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, treatment with sacubitril/valsartan (LCZ696) led to statistically significant and clinically important reductions in cardiovascular death, all-cause death, and heart failure (HF) hospitalization, compared with enalapril.[2] However, the randomized patients in PARADIGM-HF represent a subset of a larger cohort eligible for the initial single-blind, sequential run-in period ensuring short-term tolerability of target doses of both enalapril and LCZ696 before randomization. In an effort to better understand the applicability of the PARADIGM-HF results to a less-selected population, we analyzed the patient characteristics associated with run-in noncompletion before randomization

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and the implications of these prerandomization exclusions for the observed study result.

Methods

PARADIGM-HF Trial

The detailed study design, methods, and principal results of the PARADIGM-HF study have been previously reported.[2,3] Briefly, the study was a randomized, double-blind, prospective comparison of the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in subjects with chronic HF and reduced left ventricular ejection fraction. Key eligibility criteria at the time of screening included: age of at least 18 years, New York Heart Association class II–IV symptoms, left ventricular ejection fraction ≤40%, elevated plasma B-type natriuretic peptide (BNP) ≥150 pg/mL (or N-terminal pro-BNP ≥600 pg/mL) at the time of screening or BNP ≥100 pg/mL (or N-terminal pro-BNP ≥400 pg/mL) and a hospitalization for HF in the 12 months before enrollment, treatment with a stable dose of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker equivalent to at least 10 mg enalapril daily for at least 4 weeks, and treatment with a stable dose of β-blocker for at least 4 weeks unless contraindicated or not tolerated. Key exclusion criteria at screening included symptomatic hypotension, systolic blood pressure (BP) <100 mm Hg, estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 of body surface area, serum potassium >5.2 mmol/L, and history of angioedema or other serious side effects during treatment with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker.

All patients deemed eligible at the screening visit entered sequential, single-blind run-in periods to assess tolerability of enalapril and LCZ696 at target doses. During the first run-in period, patients received enalapril 10 mg twice daily for 2 weeks. Those tolerating enalapril (defined as maintenance of serum potassium ≤5.4 mmol/L, eGFR ≥30 mL/min per 1.73 m^2 of body surface area with decline of ≤35% from screening value, and systolic BP ≥95 mm Hg without symptomatic hypotension, postural symptoms, or other adverse events precluding continued participation) were permitted to enter the second run-in period, during which they received LCZ696 at an initial dose of 100 mg twice daily for 1 to 2 weeks, titrated to 200 mg twice daily for an additional 2 to 4 weeks. Those tolerating LCZ696 (defined as for the enalapril run-in) were then randomly allocated in 1:1 fashion to double-blind treatment with either enalapril 10 mg twice daily or LCZ696 200 mg twice daily. The study was approved by the institutional review board or ethics committee at each site, and all enrolled subjects provided written informed consent before participation.

Statistical Methods

We tabulated the reasons for study discontinuation during each phase of the run-in period before randomization. Baseline characteristics were defined at screening to compare those who did not complete the run-in period with those who were ultimately randomized, with continuous variables assessed using Student *t* test and categorical variables assessed using standard χ^2 tests. Multivariable predictors of prerandomization dropout for any reason were identified via a logistic regression model using a stepwise forward selection algorithm derived from available patient characteristics including region of enrollment (see Methods section in the Data Supplement for full list of candidate variables). To evaluate the stability of these predictors, sensitivity analyses were performed restricting the models to those in whom the reason for noncompletion was either related to an adverse event or abnormal laboratory value or was unknown. These logistic regression models were used to estimate the probability of being randomized for each run-in patient. To account for the impact of prerandomization noncompletion on the efficacy of LCZ696 relative to enalapril during the double-blind treatment period, we reanalyzed the treatment effect for the primary composite end point (death from cardiovascular causes or first hospitalization for HF) using Cox proportional hazards models, using inverse probability weighting, based on the previously described probability estimates. The effect of these inverse probability weighting models is to add additional weight to randomized patients most closely resembling the profile of patients excluded during the run-in, to minimize the effect of having excluded such patients from the trial. Sensitivity analyses were conducted using alternative weights reflecting dropouts for adverse events, abnormal laboratories, or unknown reasons only (excluding dropouts for death, protocol violations, or administrative reasons) and using overweighting to simulate varied assumptions about the proportion of patients discontinuing study before randomization. As additional analysis, we performed simulations in which 1040 patients were added to each treatment arm to represent the patients who failed to complete the run-in. For these simulated patients, we assumed no impact of LCZ696 and generated primary end point event times and censoring times from exponential and uniform distributions, respectively, intended to mimic those from the actual trial data. We then increased the imputed event rates for these patients to reflect the frailty of the run-in failures. For each setting, we simulated data for 2080 run-in HF patients, calculated the resulting treatment effect hazard ratio (HR) and confidence interval (CI) for each augmented data set, repeated this process 200 times, and then reported the average HR and CI across these 200 replications. *P* values <0.05 were considered statistically significant. All analyses were conducted in STATA version 13.0 (College Station, TX).

Results

Of 10521 initially eligible subjects, 8442 (80.2%) were eventually randomized during the double-blind treatment period. Of the 2079 (19.8%) subjects who discontinued the study before randomization, 1102 (10.5%) failed to complete the enalapril run-in phase and 977 (9.3%) did not complete the LCZ696 phase. The reasons for noncompletion are detailed in Table 1. Roughly two thirds of subjects failed to complete the run-in because of adverse events or abnormal test results. Among adverse events prompting study drug discontinuation, the most common were hypotension, hyperkalemia, and worsening renal function. Angioedema was rare, occurring in 25 subjects (0.2%) entering the run-in. A larger proportion of noncompletion for cough and hyperkalemia occurred during the initial (enalapril) run-in phase, whereas rates of discontinuation for hypotension and worsening renal function were higher during the second (LCZ696) phase of the run-in period.

Patient characteristics assessed at the screening visit for those who did not complete the run-in period versus those who were randomized are displayed in Table 2 and are further categorized by phase of run-in discontinuation in Table I in the Data Supplement. Subjects who discontinued the study before randomization were more commonly enrolled outside of Central/Eastern Europe and more likely to be older, nonwhite, and female with more severe HF symptoms, an ischemic pathogenesis, lower systolic BP, lower eGFR, higher natriuretic peptide levels, and higher rate of utilization of implantable cardioverter-defibrillator/cardiac resynchronization therapy. After multivariable adjustment, the predictors of dropout during the run-in period included lower systolic BP, higher N-terminal pro-BNP, eGFR <60 mL/min per 1.73 m^2, ischemic cause of HF, and region of enrollment (Table 3). Other than the cause of HF, which was associated with dropout only during the enalapril portion of the run-in, these predictors were largely consistent across the 2 run-in phases (Table II in the Data Supplement). Sensitivity analyses that focused on those who did not complete the run-in period specifically because of adverse events, laboratory abnormalities,

Table 1. Reasons for Dropout During Run-In Period

Reason	Discontinued Study During Enalapril Run-In Period (n=1102)	Discontinued Study During LCZ696 Run-In Period (n=977)
Adverse event*	591 (53.7%)	547 (56.1%)
Cough	49/591 (8.3%)	15/547 (2.7%)
Hyperkalemia	174/591 (29.4%)	123/547 (22.5%)
Hypotension	146/591 (24.7%)	163/547 (29.8%)
Renal dysfunction	181/591 (30.6%)	173/547 (31.6%)
Angioedema	15/591 (2.5%)	10/547 (1.8%)
Other	102/591 (17.3%)	131/547 (23.9%)
Abnormal laboratory test	55 (5.0%)	49 (5.0%)
Other abnormal test result	11 (1.0%)	9 (0.9%)
Withdrew consent	171 (15.5%)	100 (10.3%)
Protocol violation or deviation	79 (7.2%)	91 (9.3%)
Lost to follow-up	39 (3.5%)	26 (2.7%)
Administrative problems	20 (1.8%)	29 (3.0%)
Death	49 (4.5%)	47 (4.8%)
Other specified cause	5 (0.5%)	12 (1.2%)
Unknown	81 (7.4%)	65 (6.7%)

*Patients may have reported >1 adverse event.

or unknown reasons did not substantially alter the key predictors. Those who discontinued either drug for hypotension during the run-in period tended to have lower mean systolic BP at screening than those who failed to complete the run-in for other reasons (117±14 mm Hg versus 126±17 mm Hg, $P<0.001$).

To determine whether the primary results would have been different had we included more patients like those who did not complete the run-in period, we used inverse probability weighting, in which patients in the randomized set with baseline characteristics were most similar to those who did not complete the run-in period were weighted more heavily. This approach did not alter the HR favoring LCZ696 over enalapril with regard to the primary outcome of cardiovascular death or HF hospitalization (HR, 0.80; 95% CI, 0.73–0.87; $P<0.001$) or with regard to the key additional end points of cardiovascular death (HR, 0.80; 95% CI, 0.71–0.89; $P<0.001$) and all-cause mortality (HR, 0.84; 95% CI, 0.76–0.92; $P<0.001$; Figure). Sensitivity analyses using overweighting to simulate extreme scenarios in which 50%, 80%, and 100% of the randomized population were similar to the patients who failed to complete the run-in period did not alter these results (Table III in the Data Supplement), nor did assigning drug-specific weights based on phase-specific noncompletion data from the run-in period. Estimates of treatment benefit in the full-screened population when assuming a neutral effect of randomized treatment for those who failed to complete the run-in period were largely consistent for the primary end point (HR, 0.84; 95% CI, 0.78–0.91; $P<0.001$) and were not materially influenced by variation in the assumed event rate for run-in failures (Table IV in the Data Supplement).

Table 2. Baseline Characteristics at Screening (Before Run-In), According to Dropout During Run-In Period

Characteristics at Screening	Discontinued Study During Run-In Period (n=2079)	Randomized (n=8442)	*P* Value
Age, y	64.8±11.8	63.8±11.4	<0.001
Region			
USA/Canada	218 (10.5%)	602 (7.1%)	<0.001
Latin America	381 (18.3%)	1458 (17.3%)	
Western Europe and Other	593 (28.5%)	2057 (24.4%)	
Central/Eastern Europe	512 (24.6%)	2837 (33.6%)	
Asia-Pacific	375 (18.0%)	1488 (17.6%)	
Race or Ethnic Group			
White	1314 (63.2%)	5579 (66.1%)	0.05
Black	131 (6.3%)	428 (5.1%)	
Asian	380 (18.3%)	1510 (17.9%)	
Other	254 (12.2%)	925 (10.9%)	
Female sex	499 (24.0%)	1847 (21.9%)	0.04
Height, cm	167.7±10.1	168.7±9.6	<0.001
Weight, kg	77.9±19.4	80.4±19.3	<0.001
Systolic BP, mm Hg	124.9±17.0	128.4±16.7	<0.001
BMI, kg/m^2	27.5±5.7	28.1±5.66	<0.001
eGFR, mL/min per 1.73 m^2	63.9±22.6	68.1±19.3	<0.001
Serum creatinine, mg/dL	1.20±0.35	1.11±0.28	<0.001
NYHA class			<0.001
I/II	1274 (61.5%)	5481 (65.0%)	<0.001
III/IV	798 (38.5%)	2952 (35.0%)	<0.001
Median NT-proBNP, pg/mL, [IQR]	2071 [1011, 4669]	1612 [887, 3226]	<0.001
Ejection fraction, %	28.5±6.5	29.5±6.2	<0.001
Ischemic pathogenesis	1325 (63.7%)	5058 (59.9%)	0.001
ICD	417 (20.1%)	1246 (14.8%)	<0.001
CRT	199 (9.6%)	575 (6.8%)	<0.001
Diabetes mellitus	753 (36.2%)	2916 (34.5%)	0.15
Hypertension	1371 (65.9%)	5970 (70.7%)	<0.001
Coronary heart disease	1149 (55.3%)	4607 (54.6%)	0.57
Atrial fibrillation	697 (33.5%)	3111 (36.9%)	0.005
Pretrial use of ACE-I	1578 (75.9%)	6560 (77.7%)	0.08
Pretrial use of ARB	499 (24.0%)	1907 (22.6%)	0.17

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BP, blood pressure; CRT, cardiac resynchronization therapy eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator IQR, interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide; and NYHA, New York Heart Association.

Table 3. Multivariable Predictors of Dropout Before Randomization

Parameter	OR for Dropout (95% CI)	*Z* Value
eGFR<60	1.49 (1.35–1.65)	7.72
NT-ProBNP (per log increment)	1.20 (1.14–1.26)	7.18
Randomization in Region 4 (Central/ Eastern Europe) vs. Elsewhere	0.68 (0.60–0.76)	–6.64
Systolic BP (per 10 mm Hg decrease)	1.11 (1.07–1.14)	6.56
Ischemic cause of heart failure	1.25 (1.13–1.39)	4.20

BP indicates blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide; OR, odds ratio.

Discussion

Approximately 20% of patients did not complete the run-in period of PARADIGM-HF and were not randomized, therefore, not included in the primary analyses. Roughly half of the early discontinuations occurred during the 2-week enalapril run-in period, with the balance occurring during the 6-week LCZ696 run-in period. The reasons for run-in noncompletion were predominantly related to drug-related adverse events (most commonly cough, hyperkalemia, hypotension, or renal dysfunction) or withdrawal of consent, with a minority related to death, protocol deviations, or administrative reasons. Noncompletion occurred at similar rates and for similar reasons during the enalapril and LCZ696 phases of the run-in period, though by design, patients intolerant of enalapril did not enter the LCZ696 run-in period. Patients with lower BP, higher natriuretic peptide levels, ischemic heart disease, and eGFR <60 mL/min per 1.73 m^2 were at higher risk for discontinuation of either enalapril or LCZ696 during the run-in period of PARADIGM-HF. Reanalysis of the randomized data assigning increased weight to patients with baseline characteristics most similar to those who failed to complete the run-in period did not influence the apparent benefit of LCZ696 over enalapril seen during the trial.

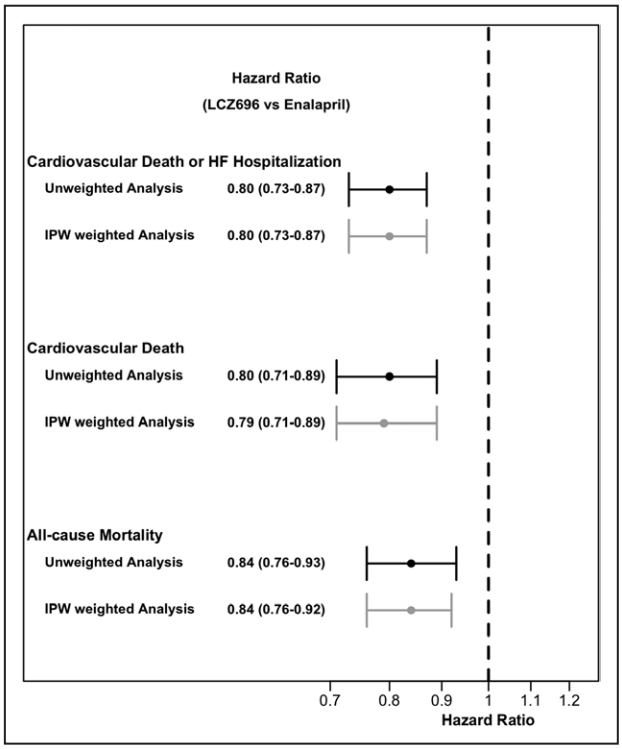

Figure. Impact of LCZ vs placebo on clinical outcomes in Prospective Comparison of ARNI with an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF) with and without inverse probability weighting (IPW) for likelihood of randomization after run-in period.

A run-in period was included in the design of PARADIGM-HF to achieve 2 primary goals. The first was to ensure comparison of LCZ696 to the established standard of care in HF with reduced ejection fraction by selecting patients who could tolerate enalapril at the target dose (10 mg twice daily) that had been demonstrated to reduce mortality in the Studies of Left Ventricular Dysfunction (SOLVD)-Treatment trial. The second, in the absence of any substantial Phase II clinical trial, was to provide open-label, short-term data on the tolerability of LCZ696 at the target dose of 200 mg twice daily.[3]

The inclusion of a run-in period has potential implications for the clinical applicability of the overall study results of a clinical trial because the randomized population reflects a subgroup of initially eligible patients that cannot easily be defined a priori; selecting similar patients in clinical practice requires observation of response to the drug over time. In this article, we address this concern by highlighting the patient characteristics differentiating the run-in eligible population from those ultimately randomized. Because both enalapril and LCZ696 are drugs that inhibit the renin–angiotensin system and cause vasodilation, it is not surprising that subjects with lower systolic BP and worse renal function were at higher risk for noncompletion. Similarly, the association of study discontinuation with higher natriuretic peptide levels and ischemic heart disease may reflect the anticipated intolerance of renin–angiotensin system antagonists in patients with more advanced HF.[4] Importantly, however, none of the patient characteristics examined was a guarantee of run-in noncompletion, and many patients who were at high-risk by these criteria were successfully randomized in PARADIGM-HF. Although the sequential nature of the run-in period makes it challenging to directly compare the tolerability of enalapril and LCZ696, rates of study drug discontinuation for reasons other than death during median 27 months follow-up in the randomized treatment period were similar between the 2 arms (17.8% and 19.8% for patients receiving LCZ696 and enalapril, respectively), suggesting that the overall tolerability of LCZ696 at a dose of 200 mg twice daily is not likely to be meaningfully different than the tolerability of enalapril 10 mg twice daily in clinical practice, even if the specific reasons for intolerance are different.

Some have suggested that the inclusion of a run-in period that allows for the withdrawal of drug-intolerant patients might lead to overestimation of size of the treatment benefit during the randomized phase of the trial.[5] To address the potential impact of patient selection during the run-in for the observed treatment benefit seen in PARADIGM-HF, we reanalyzed the study results by weighting participants according to the inverse probability of being included in the randomized

population. This approach has been applied in observational studies and in clinical trials in settings where not all patients are able to be observed over time,[6,7] and attempts to reduce the effect of selection bias by assuming that run-in noncompletion is nonrandom, and more likely in particular types of patients; accordingly, patients most similar to those who dropped out during the run-in period are weighted more heavily in the final analysis. The method rests on the assumption that the key factors associated with noncompletion can be identified and that there are no significant unmeasured confounders. Although the weighted analysis cannot account for patient factors that are not in some measure represented in the randomized population (eg, factors that would have excluded patients from randomization), there was considerable overlap in the clinical phenotype of those who failed to complete the run-in and in those who were successfully randomized. In PARADIGM-HF, this inverse probability–weighted analysis produced nearly identical results to those seen in the primary analysis for all key outcome variables. Sensitivity analyses using overweighting to simulate extreme scenarios in which 50%, 80%, and 100% of the randomized population were similar to the patients who failed to complete the run-in period also did not alter the point estimates favoring LCZ696 over enalapril for all-cause mortality or the primary composite outcome. Consistent results in an alternative analysis imputing neutral effect of randomized treatment to the run-in failure suggest that this result is not peculiar to the statistical methodology we used. Such model-based approaches to estimating the effects of therapy in alternative populations are inherently limited by the available baseline data and the extent to which run-in failure can be attributed to those characteristics used in the modeling process. However, in aggregate, these data suggest that the size of the treatment effect of LCZ696 over enalapril during the randomized phase of the trial was not meaningfully influenced by the pattern of discontinuations during the run-in period.

Run-in periods have historically been a part of the design of many pivotal HF trials. The SOLVD-Treatment trial included a sequential run-in phase during which all screen-eligible patients were treated with enalapril 2.5 mg twice daily for 2 to 7 days followed by matching placebo for 14 to 17 days before randomization. Noncompletion of ≈4.2% of patients (roughly half for adverse events and half for nonadherence) in each phase resulted in prerandomization exclusion of 605 of 7402 (8.2%) initially eligible subjects.[8] The Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) included a 2-week, single-blind placebo run-in period designed primarily to assess patient adherence.[9] As well, the US Carvedilol Heart Failure Study Group excluded 103 (8.6%) of 1197 otherwise eligible patients during a 2-week run-in period during which patients received carvedilol at a dose of 6.25 mg twice daily.[10] Importantly, in nearly all of these cases, subsequent analyses have affirmed the validity of the primary study results, suggesting that the study design did not introduce important data distortions or confounding. Moreover, in practice, clinicians frequently use a run-in period during introduction of any new therapy, with initial challenge at low dose and subsequent titration, or discontinuation based on tolerability or patient preference.

We conclude that the effects of including a run-in period before randomization in PARADIGM-HF to ensure that patients tolerated both study drugs in the short term did not affect the magnitude of the treatment benefit of LCZ696 over enalapril for any of the key outcomes of interest in PARADIGM-HF. Patients with low BP, eGFR <60 mL/min per 1.73 m^2, and more advanced HF may have difficulty in tolerating target doses of both enalapril and LCZ696, and thus, should undergo closer monitoring during the uptitration of these drugs or the conversion of patients from enalapril to LCZ696 in clinical practice. The fact that many patients with these characteristics were successfully randomized in PARADIGM-HF despite the run-in period, however, highlights the difficulty in predicting study drug intolerance based on clinical criteria and underscores the importance of a therapeutic trial in selecting patients for treatment with LCZ696.

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Disclosures

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CLINICAL PERSPECTIVE

Although run-in periods have been a part of the design of many pivotal heart failure clinical trials, some have questioned the implications of including a run-in period for the generalizability of study results as well as the anticipated magnitude of treatment benefits for less-selected populations in clinical practice. The 8442 patients randomized in the Prospective Comparison of ARNI With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, in which sacubitril/valsartan (LCZ696) reduced both death and heart failure hospitalization more than enalapril, were a subset of 10 521 patients entering sequential, single-blind, run-in periods to ensure short-term tolerability of the 2 study medications. In this analysis, we provide new data on the predictors of noncompletion during the run-in phase of PARADIGM-HF and estimate the implications of noncompletion for the overall study result. Among the 20% of patients who did not complete the run-in period, roughly half discontinued the study drug during the 2-week enalapril run-in period and the balance during the 6-week LCZ696 run-in period. The majority of discontinuations was related to drug-related adverse events, and patients with lower blood pressure, higher natriuretic peptide levels, ischemic heart disease, and estimated glomerular filtration rate <60 mL/min per 1.73 m^2 were higher risk for run-in noncompletion during either phase. Reanalysis of the randomized data assigning increased weight to patients with baseline characteristics most similar to those who failed to complete the run-in period did not influence the apparent benefit of LCZ696 over enalapril seen during the trial. Collectively, these data suggest that the inclusion of a run-in period did not meaningfully influence the observed study result for any of the key outcomes of interest in PARADIGM-HF.

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Factors Associated With Noncompletion During the Run-In Period Before Randomization and Influence on the Estimated Benefit of LCZ696 in the PARADIGM-HF Trial

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SUPPLEMENTAL MATERIAL

Factors Associated with Noncompletion During the Run-in Period Prior to Randomization and the Efficacy of LCZ696 in the PARADIGM-HF Trial

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Supplementary Methods

Candidate Variables (measured at screening) included in stepwise multivariable modelling of run-in noncompletion

Age at screening (yrs)
Region of Randomization (USA/Canada, Latin America, Western Europe and Other, Central/Eastern Europe, Asia-Pacific)
Race or ethnic group (Caucasian, Black, Asian, Other)
Sex (Male/Female)
NYHA class at screening
Diabetes (Y/N)
B-type natriuretic peptide level (pg/mL)
- Continuous, log transformed
- Categorical (above or ≤ median value)

N-terminal-pro-B-type natriuretic peptide level (pg/mL)
- Continuous, log transformed
- Categorical (above or ≤ median value)

Height (cm)
Weight (kg)
Body mass Index (kg/m2)
Left Ventricular Ejection Fraction (%)
- Continuous
- Categorical (above or <=median value)

Prior use of ACE-inhibitor (Y/N)
Prior use of Angiotensin Receptor Blocker (Y/N)
Prior heart failure hospitalization (Y/N)
Time since diagnosis of heart failure
Prior history of hypertension (Y/N)
Estimated Glomerular Filtration Rate (eGFR) mL/min/1.73m^2
- Continuous
- Categorical (above or ≤ 60 mL/min/1.73 m^2)

Systolic blood pressure (mm Hg)
- Continuous
- Categorical (above or ≤ median value)

Diastolic blood pressure (mm Hg), continuous
Ischemic etiology for heart failure (Y/N)
Prior history of unstable angina pectoris (Y/N)
Prior history of myocardial infarction (Y/N)
Prior history of percutaneous coronary intervention (Y/N)
Prior history of coronary artery bypass grafting (Y/N)
Prior history of atrial fibrillation (Y/N)
Prior history of stroke (Y/N)
Prior history of Implanted Cardioverter –Defibrillator (Y/N)
Prior history of Cardiac Resynchronization Therapy (Y/N)
Prior History of Coronary Heart Disease (Y/N)
Prior history of Permanent Pacemaker Implantation (Y/N)
Prior history of any angina pectoris (Y/N)

Supplemental Table 1. Baseline Characteristics at Screening, According to Phase of Run-In Noncompletion

Characteristics at Screening	Discontinued Study During Enalapril Run-In Phase (N=1102)	Discontinued Study During LCZ696 Run-In Phase (N=977)	p
Age (yrs)	65.12 ± 11.41	64.33 ± 12.16	0.13
Region			0.36
USA/Canada	123 (11.2%)	95 (9.7%)	
Latin America	205 (18.6%)	176 (18.0%)	
Western Europe and Other	294 (26.7%)	299 (30.6%)	
Central/Eastern Europe	276 (25.0%)	236 (24.2%)	
Asia-Pacific	204 (18.5%)	171 (17.5%)	
Race or Ethnic Group			0.81
Caucasian	689 (62.5%)	625 (64.0%)	
Black	66 (6.0%)	65 (6.7%)	
Asian	206 (18.7%)	174 (17.8%)	
Other	141 (12.8%)	113 (11.6%)	
Female Sex	274 (24.9%)	225 (23.0%)	0.33
Height (cm)	167.33 ± 10.18	168.07 ± 9.97	0.09
Weight (kg)	77.19 ± 18.75	78.60 ± 20.00	0.1
Systolic BP (mm Hg)	125.30 ± 17.31	124.53 ± 16.72	0.3
BMI (kg/m2)	27.39 ± 5.54	27.62 ± 5.83	0.35
eGFR (mL/min/1.73m2)	63.2 ± 22.9	64.8 ± 22.2	0.09
Serum creatinine (mg/dL)	1.22 ± 0.37	1.18 ± 0.33	0.04
NYHA Class			0.27
I/II	663 (60.2%)	611 (62.5%)	
III/IV	435 (39.6%)	363 (37.3%)	
Median NT-proBNP (pg/mL) [IQR]	2057 [985, 4838]	2078 [1033, 4510]	0.87
Ejection Fraction (%)	28.4 ± 6.5	28.6 ± 6.6	0.43
Ischemic Etiology	721 (65.4%)	604 (61.8%)	0.09
ICD	213 (19.3%)	204 (20.9%)	0.38
CRT	105 (9.5%)	94 (9.6%)	0.94
Diabetes	403 (36.6%)	350 (35.8%)	0.72
Hypertension	748 (67.9%)	623 (63.8%)	0.048
Coronary Heart Disease	612 (55.5%)	537 (55.0%)	0.79
Atrial Fibrillation	373 (33.8%)	324 (33.2%)	0.74
Pretrial Use of ACE-I	811 (73.7%)	767 (78.5%)	0.01
Pretrial Use of ARB	286 (26.0%)	213 (21.8%)	0.026

Supplemental Table 2. Predictors of noncompletion during the run-in period by phase

	Noncompletion during Enalapril Run-in		Noncompletion during LCZ696 Run-in*	
Parameter	**OR for Dropout (95% CI)**	**Z**	**OR for Dropout (95% CI)**	**Z**
eGFR < 60	**1.54 (1.36-1.76)**	**6.54**	**1.35 (1.18, 1.55)**	**4.24**
NT-ProBNP (per log increment)	**1.17 (1.09-1.24)**	**4.70**	**1.23 (1.15-1.32)**	**5.86**
Randomization in Region 4 (Central/Eastern Europe) vs. Elsewhere	**0.71 (0.61-0.82)**	**-4.55**	**0.69 (0.59-0.81)**	**-4.63**
Systolic Blood Pressure (per 10 mm Hg decrease)	**1.08 (1.04-1.12)**	**3.86**		
Diastolic Blood Pressure (per 10 mm Hg decrease)			**1.19 (1.11-1.27)**	**5.16**
Ischemic Etiology	**1.30 (1.14-1.49)**	**3.81**		

Only patients successfully completing enalapril run-in were eligible for LCZ696 run-in

Supplemental Table 3. Sensitivity analyses estimating the effect of LCZ696 relative to enalapril on mortality and the primary composite in PARADIGM-HF in inverse probability weighted models reflecting hypothetical populations with different proportions of noncompletion during the run-in period.

						Treatment HR (LCZ696 vs. Enalapril)	
Patient Mix	**Population**	**Mean eGFR**	**Mean SBP**	**Median NT-proBNP**	**Mortality Rate (per 100 pt-yrs)**	**Death**	**Primary Composite**
Unadjusted 100% randomized	8399 randomized	68	128	1615	8.3	0.84 (0.76-0.93)	0.80 (0.73-0.87)
Screened Population: 20% run-in failures 80% randomized	2079 run-in failures 8442 randomized	67	128	1693	8.7	0.84 (0.76-0.92)	0.80 (0.73-0.87)
50% run-in failures 50% randomized	5260 run-in failures 5260 randomized	66	127	1806	9.2	0.83 (0.75-0.92)	0.80 (0.73-0.88)
80% run-in failures 20% randomized	8442 run-in failures 2079 randomized	65	126	1934	9.6	0.82 (0.74-0.92)	0.80 (0.73-0.88)
100% run-in failures	10521 run-in failures	64	125	2007	9.9	0.82 (0.73-0.92)	0.80 (0.73-0.89)

Supplemental Table 4. Sensitivity Analysis of Effects of LCZ696 vs. Enalapril on PARADIGM-HF Primary Composite Endpoint Imputing Neutral Effect of Randomized Treatment for Run-in Failures Across a Range of Assumed Event Rates

Assumed Event Rate for Run-in Failures (per 100 py)	Event Rate Relative to Observed	Average HR (LCZ696 vs. Enalapril)	Average CI
11.8	Observed	0.84	(0.78, 0.91)
23.6	100% increase	0.86	(0.80, 0.92)
35.4	200% increase	0.86	(0.81, 0.93)