Original Article

Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial

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Background—The angiotensin receptor neprilysin inhibitor sacubitril/valsartan (LCZ696) reduced cardiovascular morbidity and mortality compared with enalapril in patients with heart failure (HF) and reduced ejection fraction (EF) in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. We evaluated the influence of EF on clinical outcomes and on the effectiveness of sacubitril/valsartan compared with enalapril.

Methods and Results—Eight thousand three hundred ninety-nine patients with New York Heart Association class II to IV HF with reduced EF [left ventricular EF (LVEF) ≤40%] were randomized to sacubitril/valsartan 97/103 mg twice daily versus enalapril 10 mg twice daily and followed for a median of 27 months. The primary study end point was cardiovascular death or HF hospitalization. LVEF was assessed at the sites and recorded on case report forms. We related LVEF to study outcomes and assessed the effectiveness of sacubitril/valsartan across the LVEF spectrum. The mean LVEF in PARADIGM-HF, reported by sites, was 29.5 (interquartile range, 25–34). The risk of all outcomes increased with decreasing LVEF. Each 5-point reduction in LVEF was associated with a 9% increased risk of cardiovascular death or HF hospitalization (hazard ratio, 1.09; 95% confidence interval, 1.05–1.13; *P*<0.001), a 9% increased risk for CV death (hazard ratio, 1.09; 95% confidence interval, 1.04–1.14), a 9% increased risk in HF hospitalization (hazard ratio, 1.09; 95% confidence interval, 1.04–1.14) and a 7% increased risk in all-cause mortality (hazard ratio, 1.07; 95% confidence interval, 1.03–1.12) in adjusted analyses. Sacubitril/valsartan was effective across the LVEF spectrum, with no evidence of heterogeneity, when modeled either in tertiles (*P* interaction=0.87) or continuously (*P* interaction=0.95).

Conclusions—In patients with HF and reduced EF enrolled in PARADIGM-HF, LVEF was a significant and independent predictor of all outcomes. Sacubitril/valsartan was effective at reducing cardiovascular death and HF hospitalization throughout the LVEF spectrum.

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

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Key Words: heart ■ heart failure ■ humans ■ mineralocorticoid receptor antagonists ■ neprilysin

Left ventricular ejection fraction (LVEF) remains the most commonly utilized metric of cardiac function[1] and has been related to outcomes in patients across the spectrum of heart failure (HF).[2] In patients with HF and reduced ejection fraction (EF), LVEF had been shown to be predictive of cardiovascular death, HF hospitalization, and all-cause mortality in a relatively linear fashion, with those patients at the lowest end of the EF spectrum at the greatest risk.[3,4]

See Clinical Perspective

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial randomized patients with New York Heart Association class II to IV HF and reduced EF (LVEF 40% or less) to the angiotensin receptor neprilysin inhibitor sacubitril/valsartan (LCZ696) 200 mg twice daily or enalapril 10 mg twice daily, and showed that sacubitril/valsartan significantly reduced cardiovascular death, HF hospitalization, and all-cause mortality.[5] The initial LVEF entry criteria were lowered from <40% to ≤35% after ≈1 year of study start to ensure that the event rate remained high after the release of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) results and anticipated increased use of mineralocorticoid receptor antagonists.[6,7] We assessed the relationship between LVEF and outcomes and the effectiveness of sacubitril/valsartan across the spectrum of EF in PARADIGM-HF.

Methods

Patients and Study Design

Inclusion and exclusion criteria and the design of the PARADIGM-HF trial have been previously described.[5,6] Briefly, enrolled patients
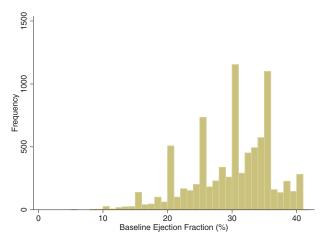

Figure 1. Distribution of left ventricular ejection fraction in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.

had New York Heart Association class II to IV HF with reduced EF (LVEF ≤40%, which was reduced to 35% via amendment) and were clinically stable and on optimal medical therapy including an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor

Table 1. Baseline Characteristics by Ejection Fraction

	<17.5% (n=339)	≥17.5% to <22.5% (n=930)	≥22.5% to <27.5% (n=1500)	≥ 27.5% to < 32.5% (n=2486)	≥ 32.5% (n=3143)	P
Mean LVEF	14±2	20±1	25±1	30±1	36±2	<0.001
Age	61±13	61±12	62±12	64±11	66±11	<0.001
Female sex	67 (19.8%)	180 (19.4%)	307 (20.5%)	523 (21.0%)	755 (24.0%)	0.004
Body mass index	27.3±5.6	27.2±5.6	27.6±5.4	28.1±5.3	28.9±5.6	<0.001
New York Heart Association class						<0.001
1	26 (7.7%)	66 (7.1%)	91 (6.1%)	105 (4.2%)	101 (3.2%)	
2	234 (69.0%)	680 (73.2%)	1075 (71.7%)	1761 (71.0%)	2168 (69.1%)	
3	76 (22.4%)	178 (19.2%)	328 (21.9%)	595 (24.0%)	841 (26.8%)	
4	3 (0.9%)	5 (0.5%)	5 (0.3%)	18 (0.7%)	29 (0.9%)	
Prior HF hospitalization	215 (63.4%)	602 (64.7%)	967 (64.5%)	1553 (62.5%)	1936 (61.6%)	0.25
History of hypertension	197 (58.1%)	578 (62.2%)	906 (60.4%)	1789 (72.0%)	2469 (78.6%)	<0.001
White race	174 (51.3%)	529 (56.9%)	837 (55.8%)	1616 (65.0%)	2388 (76.0%)	<0.001
Systolic blood pressure	116±14	117±15	119±15	122±15	124±15	<0.001
Diabetes mellitus	115 (33.9%)	315 (33.9%)	505 (33.7%)	863 (34.7%)	1109 (35.3%)	0.82
Heart rate	74±13	73±12	73±11	72±12	72±12	0.20
Ischemic cardiomyopathy	172 (50.7%)	498 (53.5%)	865 (57.7%)	1481 (59.6%)	2019 (64.2%)	<0.001
Prior MI	123 (36.3%)	368 (39.6%)	625 (41.7%)	1112 (44.7%)	1406 (44.7%)	<0.001
History of AF	84 (24.8%)	273 (29.4%)	451 (30.1%)	873 (35.1%)	1410 (44.9%)	<0.001
History of stroke	30 (8.8%)	75 (8.1%)	129 (8.6%)	219 (8.8%)	272 (8.7%)	0.97
Creatinine	1.17±0.30	1.13±0.30	1.12±0.30	1.12±0.30	1.11±0.29	0.012
ICD or CRT-D	86 (25.4%)	212 (22.8%)	285 (19.0%)	367 (14.8%)	293 (9.3%)	<0.001
CRT	33 (9.7%)	95 (10.2%)	140 (9.3%)	168 (6.8%)	138 (4.4%)	<0.001
Medications						
Diuretics	293 (86.4%)	765 (82.3%)	1254 (83.6%)	1969 (79.2%)	2456 (78.1%)	<0.0001
β-Blockers	318 (93.8%)	856 (92.0%)	1398 (93.2%)	2330 (93.7%)	2908 (92.5%)	0.30
Digoxin	137 (40.4%)	321 (34.5%)	534 (35.6%)	727 (29.2%)	820 (26.1%)	<0.001
MRA	202 (59.6%)	589 (63.3%)	910 (60.7%)	1413 (56.8%)	1557 (49.5%)	<0.001

AF indicates atrial fibrillation; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and MRA, mineralocorticoid receptor antagonist.

Table 2.   Incidence Rates (Per 100 Patient-Years) of Outcomes by Ejection Fraction Group

	<17.5%	≥17.5% to <22.5%	≥ 22.5% to <27.5%	≥27.5% to <32.5%	≥32.5%
CV death or HF Hospitalization	18.7 (15.6, 24.5)	15.2 (13.5, 17.1)	13.2 (12.0, 14.6)	11.9 (10.9, 12.9)	9.7 (9.0, 10.4)
CV death	10.9 (8.6, 13.6)	9.1 (7.8, 10.5)	7.3 (6.4, 8.3)	6.8 (6.1, 7.5)	5.5 (5.0, 6.1)
HF hospitalization	11.9 (9.4, 14.9)	8.7 (7.5, 10.2)	7.6 (6.7, 8.7)	7.3 (6.6, 8.1)	5.5 (5.0, 6.1)
All-cause death	12.5 (10.1, 15.4)	11.1 (9.7, 12.6)	8.6 (7.6, 9.7)	8.3 (7.6, 9.1)	7.2 (6.6, 7.8)

CV indicates cardiovascular; and HF, heart failure.

blocker (ARB), β-blockers if tolerated, and mineralocorticoid receptor antagonist if appropriate. Patients were required to have elevated natriuretic peptides, the level of which depended on whether or not they had been hospitalized for HF within the previous 12 months. Patients were excluded if they had symptomatic hypotension, estimated glomerular filtration rate <30 mL/min/1.73 m,^{2} potassium concentration >5.2 mmol/L at screening, or history of angioedema.

After enrollment, participants entered back-to-back single blind run-in phases with enalapril titrated to a dose of 10 mg twice daily for 2 weeks, followed by sacubitril/valsartan, titrated to 97/103 mg twice daily for 4 to 6 weeks. Eight thousand three hundred ninety-nine participants were then randomized to receive enalapril 10 mg twice daily or sacubitril/valsartan 97/103 mg twice daily and were followed for a median duration of 27 months. The protocol was approved at each participating site by an ethics committee or institutional review board. All participants provided written informed consent in accordance with established guidelines for the protection of human subjects.

LVEF was measured at the sites and recorded on case report forms. In addition to EF, the type of imaging and date of imaging were recorded. There were 963 (11.4%) patients randomized with a baseline LVEF recorded as >35% and ≤40%, and an additional 1093 (13%) patients with LVEF recorded as exactly 35%.

Statistical Methods

EF was divided into the following categories: <17.5%, ≥17.5% to <22.5%, ≥22.5% to <27.5%, ≥27.5% to <32.5%, ≥32.5% to avoid digit preference for multiples of 5. Baseline characteristics were assessed across EF categories and summarized using means and standard deviations or percentages for continuous and binary data, respectively. Tests

for equality across EF categories were conducted using ANOVA and Pearson's χ^2 test. Incidence rates were calculated for each EF category and for the primary outcome (cardiovascular death or HF hospitalization), cardiovascular death, HF hospitalization, and all-cause mortality and expressed as a rate per 100 patient-years. The risk of these outcomes by EF was assessed in a multivariable model, adjusting for age; sex; race; body mass index; New York Heart Association class; prior HF hospitalization; prior history of hypertension, myocardial infarction, stroke, diabetes mellitus, and atrial fibrillation; and baseline use of ACE inhibitors or ARB, digoxin, diuretics, β-blockers, mineralocorticoid receptor antagonists, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT), NT-proBNP, and serum creatinine. We investigated potential nonlinear relationships between EF and outcomes through the use of restricted cubic spline terms in unadjusted and adjusted Cox models, using 3 knots. We tested for interaction between LVEF and treatment in both tertiles and using LVEF as a continuous variable. We further tested for interaction between the elapsed time between the EF measurement and randomization and the EF measurement to assess whether more recent measurements were differentially prognostic for the outcomes of interest.

Results

LVEF ranged from 5% to 42% (mean, 29.5±6.2%; median, 30; interquartile range, 25–34), and 46% of measurements were reported as a multiple of 5 (Figure 1). Echocardiography was the predominant imaging mode used to assess EF (96%), and the median time between assessment of EF and screening was 27 days (interquartile range, 2–73 days). Baseline characteristics
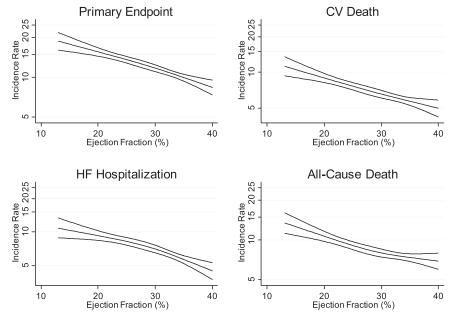

Figure 2. Relationship between left ventricular ejection fraction and incident outcomes adjusted for baseline covariates (upper left, primary end point; upper right, CV death; lower left, HF hospitalization; lower right, all-cause death). CV indicates cardiovascular; and HF, heart failure.

Table 3.   Crude and Adjusted Risk of Outcomes Per 5 Points of Ejection Fraction

Outcome	Crude (HR, 95% CI)	Adjusted* (HR, 95% CI)
CV death or HF Hospitalization	1.15 (1.12, 1.19)	1.09 (1.05, 1.13)
CV Death	1.17 (1.12, 1.22)	1.09 (1.04, 1.14)
HF Hospitalization	1.17 (1.12, 1.22)	1.09 (1.04, 1.14)
All-cause Death	1.14 (1.09, 1.18)	1.07 (1.03, 1.12)

CV indicates cardiovascular; CI, confidence interval, HF, heart failure; and HR, hazard ratio.

*Adjusted for randomization arm; age; sex; race; region; body mass index; New York Heart Association class; systolic blood pressure; heart rate; serum creatinine; ischemic status; log(NTproBNP); medical history of hypertension, diabetes mellitus, and atrial fibrillation; hospitalization for heart failure, MI, and stroke; use of ACEi; use of ARB; concomitant treatments at randomization: implantable cardioverter-defibrillator, cardiac resynchronization therapy, diuretic, β-blocker, digitalis, and aldosterone antagonist.

by EF range are shown in Table 1. Patients with lower EF were younger and more likely to be male; were less likely to have a history of hypertension, prior myocardial infarction, or atrial fibrillation; and more likely to be in New York heart Association functional class III/IV (than I/II) than patients with a higher LVEF. Lower EF patients were more likely to have lower systolic blood pressure and higher serum creatinine, more likely to have received an ICD or CRT, and were more likely to be taking diuretics, digoxin, and a mineralocorticoid receptor antagonist.

The incidence of all outcomes was greatest at the lower end of the EF spectrum (Table 2; Figure 2). Each 5-point reduction in EF was associated with a 9% increased risk of cardiovascular death or HF hospitalization (hazard ratio, 1.09; 95% confidence interval, 1.05–1.13; $P<0.001$), a 9% increased risk for CV death (hazard ratio, 1.09; 95% confidence interval, 1.04–1.14), a 9% increased risk in HF hospitalization (hazard ratio, 1.09; 95% confidence interval, 1.04–1.14), and a 7%

increased risk in all-cause mortality (hazard ratio, 1.07; 95% confidence interval, 1.03–1.12) in adjusted analyses (Table 3). There was no evidence of nonlinearity in the relationship between LVEF and any of the clinical outcomes in either unadjusted or adjusted models.

Sacubitril/valsartan was effective across the spectrum of EF for the primary outcome (Figure 3, upper left, P interaction=0.87), for cardiovascular death (Figure 3, upper right, P interaction=0.55), for HF hospitalization (Figure 3, lower left, P interaction=0.78), and for all-cause mortality (Figure 3, lower right, P interaction = 0.93). We observed similar findings when the treatment-LVEF interaction was assessed continuously. There was no evidence that the hazard ratio associated with EF was modified by the timing of the EF measurement relative to randomization.

Discussion

In this post hoc analysis from the PARADIGM-HF trial, we found that in patients with HF and reduced EF, LVEF was a powerful independent predictor of cardiovascular outcomes and all-cause mortality. The angiotensin receptor neprilysin inhibitor sacubitril/valsartan was effective across the LVEF spectrum, with no evidence of effect modification for any end point.

LVEF is used as the primary determinant of eligibility for many therapies, including most pharmacological therapies for HF, CRT, and ICD. In PARADIGM-HF, for which LVEF >40% was an exclusion criterion, the relationship between LVEF and outcome appeared relatively linear between 15% and 40%, with each 5% drop in EF associated with approximately a 10% increased risk in cardiovascular death or HF hospitalization after adjusting for baseline covariates. These findings are consistent with those from the Candesartan in Heart Failure Reduction in Mortality (CHARM) program, in which LVEF was a powerful predictor of all outcomes in the range up to ≈45%.[2]
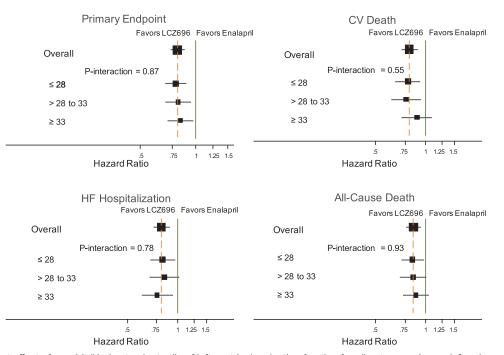

Figure 3. Treatment effect of sacubitril/valsartan by tertile of left ventricular ejection fraction for all outcomes (upper left, primary end point; upper right, cardiovascular death; lower left, HF hospitalization; lower right, all-cause death). CV indicates cardiovascular; and HF, heart failure.

We found no evidence of effect modification for the effectiveness of sacubitril/valsartan by LVEF, assessed either in tertiles or continuously. These findings are also similar to those observed in the low LVEF CHARM trials, but are in contrast to findings in several other HF trials, including Val-HeFT, where the benefit of valsartan appeared greatest in the lowest EF groups, in a meta-analysis of ACE inhibitor trials,[8] and in MERIT-HF, where the benefit of metoprolol was greatest in patients with the lowest EF.[9] Nevertheless, these findings should assuage concerns that patients at either end of the LVEF spectrum benefited from therapy with sacubitril/valsartan to a greater extent than any others and are consistent with other analyses from PARADIGM-HF showing that there was no heterogeneity based on other measures of HF severity using a validated comprehensive risk score.[10]

At the time the LVEF criteria in PARADIGM-HF were changed, a substantial number of patients had already been enrolled in the LVEF range between 35% and 40%, representing nearly 25% of the enrolled cohort. Despite this change in inclusion criteria, the benefit of sacubitril/valsartan was preserved in the upper LVEF range, and the lowering of the LVEF inclusion criterion should not be used as a justification to restrict the use of sacubitril/valsartan in patients with LVEF between 35% and 40%. Whether sacubitril/valsartan would benefit patients with HF and preserved EF is currently being tested in the ongoing PARAGON-HF trial (clinicaltrials.gov NCT01920711).

Some limitations of this analysis should be noted. LVEF measurements were made at each site, not centrally, and recorded on case report forms. Thus, although echocardiography was the predominant mode used to assess LVEF, the exact method by which the measurement was made is unknown. Moreover, a large percentage of LVEF measurements in PARADIGM-HF were multiples of 5, suggesting that these LVEF estimates were made semiquantitatively at best. Nevertheless, these limitations are mitigated by the large number of patients in PARADIGM-HF and the fact that the relationship between LVEF and outcomes was similar to other studies in which core laboratory measurements were made.

In summary, we found that LVEF was a potent predictor of outcome in patients with HF and reduced EF enrolled in PARADIGM-HF, and this relationship was approximately linear between LVEF of 15% and 40%. Despite the change in inclusion criteria lowering the LVEF upper limit to 35% or less, approximately a quarter of patients in PARADIGM-HF fell within this range. Sacubitril/valsartan was effective at reducing cardiovascular death and HF hospitalization throughout the spectrum of LVEF studied.

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CLINICAL PERSPECTIVE

Sacubitril/valsartan had previously been shown to reduce morbidity and mortality in patients with heart failure and reduced ejection fraction compared with enalapril in the PARADIGM-HF trial. We investigated the relationship between ejection fraction and outcome, as well as the relationship between ejection fraction and the efficacy of sacubitril/valsartan, in PARADIGM. We found that all outcomes increased with worsening ejection fraction. However, we found no evidence of effect modification by ejection fraction for the benefit of sacubitril/valsartan. Patients at the lower end and higher end of the ejection fraction spectrum benefited equally. These findings suggest that sacubitril/valsartan is effective irrespective of ejection fraction in patients with heart failure and reduced ejection fraction.

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