Influence of Study Discontinuation during the Run-in Period on the Estimated Efficacy of Sacubitril/valsartan in the PARAGON-HF Trial

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Abstract

Aims: The 4822 patients randomized in the PARAGON-HF trial were a subset of 5746 initially eligible patients who entered sequential run-in periods. We identified patient factors associated with study discontinuation during the run-in period and estimated the implications of these discontinuations for the overall study result.

Methods and Results: We utilized multivariable logistic regression models to identify patient factors associated with study discontinuation during the run-in. The efficacy of sacubitril/valsartan 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. A total of 924 (16.1%) subjects failed to complete the run-in period. In multivariable models, noncompletion was associated with region other than Central Europe, lower systolic blood pressure, lower serum sodium, lower hemoglobin, lower estimated glomerular filtration rate, higher NT-proBNP, higher NYHA functional class, prior HF hospitalization, and lack of prior use of renin-angiotensin system inhibitors or beta-blocker. In repeat analysis of the effect of randomized treatment in PARAGON-HF giving greater weight to participants resembling those who failed to complete the run-in period, the incidence of HF hospitalizations and cardiovascular death was higher, and sacubitril/valsartan treatment reduced the composite of total HF hospitalizations and cardiovascular death compared with valsartan (rate ratio, 0.86; 95% confidence interval, 0.74-1.00).

Conclusion: Patients with more advanced heart failure were at higher risk for noncompletion of the run-in period in PARAGON-HF. Reanalysis of study outcomes accounting for the effect of run-in noncompletion did not alter the estimated treatment effects of sacubitril/valsartan vs

valsartan.

Key words: run-in; HFpEF; neprilysin

Background

In the Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blockers Global Outcomes in Heart Failure (HF) with Preserved Ejection Fraction (HFpEF) (PARAGON-HF) trial, sacubitril/valsartan lowered rates of total HF hospitalizations and death from cardiovascular cause compared with valsartan, but this apparent treatment benefit narrowly missed the pre-specified margin for statistical significance.[1] The randomized population in PARAGON-HF was selected from of a larger group of initially-eligible patients who entered sequential, single-blind run-in periods designed to ensure tolerability of both study drugs. Although run-in periods are commonly employed in randomized trials to enhance the ability to discern treatment differences, it has been argued that this approach may lead to overestimation of treatment benefits and underestimation of risks.[2] Accordingly, we explored the factors associated with study discontinuation during the run-in period in PARAGON-HF and utilized this data to model the impact of run-in noncompletion on the treatment effects of sacubitril/valsartan relative to valsartan.

Methods

PARAGON-HF was a prospective, randomized, multicenter, double-blind active controlled trial comparing sacubitril/valsartan 97/103 mg twice daily with valsartan 160 mg twice daily in 4822 patients with chronic HF requiring diuretic therapy, New York Heart Association (NYHA) functional classification II-IV symptoms, left ventricular ejection fraction (LVEF) of 45% or greater, elevated natriuretic peptide levels, and evidence of structural heart disease.[1] Prior to randomization, all eligible patients had to successfully complete single blind run-in treatment with valsartan 80 mg twice daily for 1-2 weeks followed by sacubitril/valsartan 49/51 mg twice daily for 2-4 weeks to ensure tolerability of both study drugs at half-target doses. The primary study efficacy endpoint was the composite of total HF hospitalizations and death from cardiovascular causes analyzed using the semiparametric method of Lin, Wei, Yang, and Ying stratified by geographical region.[3] Additional prespecified efficacy outcomes included the individual components of the composite, all-cause mortality, and a renal composite outcome defined as time to first occurrence of either: ≥50% reduction in estimated glomerular filtration rate (eGFR), end-stage renal disease, or death from renal causes. The rate of drug discontinuation due to either adverse events other than death or any causes were key safety outcomes. The study protocol was approved by the institutional review board or ethics committee at each site and written informed consent was obtained from all patients before enrollment.

We included all patients entering the valsartan run-in period (n=5746) in the present study. One patient who directly entered the sacubitril/valsartan run-in period was excluded. Multivariable logistic regression models were derived to identify baseline factors associated with dropout for any reason during the entire or each phase of run-in period, with covariates selected

by forward stepwise selection with a cut-off P-value of 0.05. These logistic regression models were used to estimate a probability of successful run-in completion for all randomized patients. Study efficacy and safety outcomes were re-analyzed in inverse probability-weighted (IPW) models designed to give greater relative weight to randomized patients most closely resembling the profile of patients excluded during the run-in period.[4] The IPW models were used to minimize the effect of having excluded run-in failures from the trial by reducing the effect of selection bias by assuming that study discontinuation during the run-in was non-random and more likely to happen in particular types of patients. All analyses were performed using Stata version 15.1 (Stata Corporation, College Station, TX), with 2-sided $p<0.05$ considered significant.

Results

Of 5746 patients entering the sequential run-in periods, 541 patients (9.4%) discontinued the study during the valsartan run-in period and 383 (6.7%) patients discontinued the study during the sacubitril/valsartan run-in period, leaving 4822 patients (83.9%) to be randomized. Study discontinuation during either portion of the run-in period was most commonly attributed to adverse events (n=602, 65.2% of patients who discontinued the study during the run-in), including hypotension (n=196), renal impairment (n=153) and hyperkalemia (n=126) (**Table 1**). A comparison of baseline characteristics between run-in completers and non-completers has been published[5], and is further broken down by run-in phase in **Supplemental Table I**, which showed that NYHA functional class and NT-proBNP were comparable between patients who discontinued the study during the valsartan run-in period and those who discontinued the study during the sacubitril/valsartan run-in period. In multivariable models, non-Central European region, prior HF hospitalization, lack of pretrial use of a renin-angiotensin system inhibitor, lack of use of a beta-blocker at the beginning of the run-in period, lower systolic blood pressure, lower serum sodium, lower hemoglobin, higher NYHA functional class, and higher NT-proBNP (but not sex or LVEF) were associated with a higher risk for study discontinuation during the entire run-in period, and most of those factors were also related to study discontinuation during each run-in phase (**Table 2, Supplemental Table II**). Factors associated with study drug discontinuation due to specific adverse events of hyperkalemia, hypotension, and worsening renal function are summarized in **Supplemental Table III**. The distribution of propensity scores for run-in completion was similar between treatment groups (**Supplemental Figure I**).

Despite higher predicted incidence rates for key CV outcomes among run-in failures compared with run-in completers (estimated incidence of the primary endpoint, 18.8 vs 13.7 per 100 person-year (PY); total HF hospitalizations, 14.9 vs 10.7 per 100 PY) (**Figure 1**), sacubitril/valsartan-assigned patients were at lower risk for the primary composite endpoint (rate ratio (RR) 0.86; 95% confidence interval (CI), 0.74-1.00), total HF hospitalizations (RR, 0.84; 95% CI, 0.71-0.99), and the renal composite outcome (hazard ratio (HR), 0.47; 95% CI, 0.30-0.72) than valsartan-assigned patients in models weighting patients according to the inverse probability of run-in completion (**Figure 1**). Previous treatment by subgroup interactions for sex and LVEF above/below the median reported in the primary PARAGON-HF analysis were similarly apparent in IPW-weighted analyses (**Supplemental Table IV**). For patients successfully completing the run-in period, the risk of study drug discontinuation for adverse events other than death or for any reason was also lower (HR, 0.90; 95% CI, 0.78-1.04: HR, 0.90; 95% CI,0.81-1.01) among sacubitril/valsartan-assigned patients in IPW models (**Figure 1**). Causes of study drug discontinuation after randomization are shown in **Supplemental Table V.**

Conclusion

In summary, roughly 16% of patients initially eligible for participation in the PARAGON-HF trial discontinued the study prior to randomization during one of the 2 sequential run-in periods. Most discontinuations were related to adverse events typical of renin-angiotensin inhibitors including hypotension, renal impairment and hyperkalemia. Consistent with prior findings from a similar analysis of PARADIGM-HF[4], patients failing to complete the run-in period typically had features of more severe heart failure including worse NYHA class, lower systolic blood pressure, lower eGFR, higher NT-proBNP levels, and other features of more advanced heart failure, but many patients with these characteristics were successfully randomized in the PARAGON-HF trial.

Overweighting the experience of randomized patients similar to those who failed to complete the run-in period in IPW models (in an effort to minimize the effect of having excluded such patients from the trial) increased the estimated event rates for key cardiovascular and renal outcomes but did not alter the estimated treatment effects of sacubitril/valsartan compared with valsartan with regard to the primary study composite, renal composite, or total HF hospitalizations for the population as a whole or key subgroups. Although overall rates of drug discontinuation during the randomized period were likely lowered by exclusion of patients intolerant of one or both study drugs during the run-period, relative estimates of the tolerability of sacubitril/valsartan versus valsartan were also unaltered in IPW models.

Run-in periods have been included in many pivotal heart failure trials to select out nonadherent or drug-intolerant patients prior to randomization and thereby enhance statistical

power to discern a treatment effect.[6-8] However, it is alleged that the inclusion of a run-in period may result in overestimation of treatment benefit in clinical practice by representing the 'best case' of treatment in a selected population known to tolerate and take drugs as prescribed. Despite these concerns about generalizability, run-in periods do not guarantee study drug adherence, and there is limited evidence that previous HF trials employing this design feature have generated less valid or reliable results. Moreover, run-in periods replicate the therapeutic trial that most clinicians use to select patients for pharmacologic treatment, and may therefore more faithfully represent the results clinicians can expect to derive amongst patients who are successfully treated in clinical practice.

Our re-analysis of PARAGON-HF relies on a statistical method for estimating treatment effects in a hypothetical population enriched for patients with clinical characteristics similar to those who failed to complete the run-in period. While this method has been used in other contexts to address potential selection bias [4, 9, 10], we must acknowledge important limitations including *post hoc* design, low event rates for some outcomes, and, importantly, residual confounding by unmeasured factors influencing run-in period discontinuation that leaves residual uncertainty regarding the precise treatment benefits in nonrandomized patients. As well, it should be emphasized that the observed rates of study drug discontinuation post-randomization likely overestimate drug tolerability in clinical practice due to exclusion of drug-intolerant patients during the run-in period. Nonetheless, these data suggest that the inclusion of a run-in period may not have meaningfully biased study efficacy and safety results and that the estimates of treatment efficacy observed in the randomized population are similar to those that might have been observed had the study been conducted without a run-in period. Since many patients predicted to be at high-risk for study drug discontinuation during the run-in were nonetheless successfully

randomized in PARAGON-HF, these data also support the value of a therapeutic trial in consideration of patients with HFpEF for treatment with angiotensin-receptor neprilysin inhibitors.

Disclosures

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Figure Legends

Figure 1. Estimated effects of sacubitril/valsartan compared with valsartan on safety and efficacy outcomes in PARAGON-HF in models weighted according to the inverse probability of run-in completion

Multivariable logistic regression models were developed to estimate the probability of run-in completion. Event rates and estimates of treatment effects on various study outcomes derived from inverse probability-weighted semiparametric proportional rates models with greater weight assigned to randomized patients similar to those who failed to complete the run-in period. 'All patients' refers to the full population of patients who entered the run-in period (run-in completers + run-in failures). The primary PARAGON-HF endpoint was a composite of total HF hospitalizations and death from cardiovascular cause. The renal composite outcome was time to first occurrence of either: ≥50% reduction in estimated glomerular filtration rate, end-stage renal disease, or death from renal causes. Drug discontinuation due to AEs did not include death and was censored after randomization. AE, adverse event; HF, heart failure; HR, hazard ratio; PY, patient-year; RR, rate ratio.

Table 1. Causes of dropouts during the run-in periods

	Study discontinuation		
	Valsartan Run-in Period (n=541)	Sac/Val Run-in Period (n=383)	Entire Run-in Period (n=924)
Adverse Events	340 (62.9%)	262 (68.4%)	602 (65.2%)
Angioedema	6	5	12
Hepatotoxicity	2	1	3
Hyperkalemia	64	55	126
Hypotension	119	71	196
Renal impairment	86	56	153
Death	6 (1.1%)	7 (1.8%)	13 (1.4%)
Lost to Follow up	5 (0.9%)	0 (0%)	5 (0.5%)
Non-compliance with study treatments	24 (4.4%)	25 (6.5%)	49 (5.3%)
Physician Decision	4 (0.7%)	4 (1.0%)	8 (0.9%)
Protocol Deviation	62 (11.5%)	48 (12.5%)	110 (11.9%)
Subject/Guardian Decision	98 (18.1%)	37 (9.7%)	135 (14.6%)
Technical Problem	2 (0.4%)	0 (0%)	2 (0.2%)

Some patients had multiple adverse events for study discontinuation.

Sac/Val, sacubitril/valsartan

Table 2. Baseline patient characteristics associated with study discontinuation during run-in period

	Dropouts during Valsartan Run-in Period (n=541)		Dropouts during Sac/Val Run-in Period (n=383)		Dropouts during Entire Run-in Period (n=924)	
Parameters	**Adjusted OR**	**Z-value**	**Adjusted OR**	**Z-value**	**Adjusted OR**	**Z-value**
ARB (pretrial use)	0.31 (0.25-0.40)	-9.47	0.63 (0.47-0.84)	-3.17	0.41 (0.34-0.50)	-9.02
ACEI (pretrial use)	0.40 (0.32-0.51)	-7.56	0.56 (0.42-0.76)	-3.74	0.44 (0.36-0.54)	-8.13
Sodium per 1 mmol/L increase	0.95 (0.92-0.98)	-3.54	0.95 (0.92-0.99)	-2.65	0.95 (0.93-0.97)	-4.30
Region						
Central Europe	1.00 (Reference)	---	1.00 (Reference)	---	1.00 (Reference)	---
Asia/Pacific	1.57 (1.17-2.12)	2.98	1.11 (0.78-1.57)	0.56	1.36 (1.08-1.73)	2.56
Latin America	1.35 (0.89-2.05)	1.40	1.22 (0.77-1.92)	0.84	1.29 (0.94-1.79)	1.56
North America	1.71 (1.26-2.33)	3.41	1.60 (1.12-2.28)	2.59	1.70 (1.33-2.17)	4.21
Western Europe	1.45 (1.11-1.88)	2.73	1.36 (1.02-1.82)	2.11	1.43 (1.16-1.75)	3.43
NT-proBNP per 1 log-unit increase	1.16 (1.04-1.29)	2.63	1.16 (1.03-1.32)	2.40	1.16 (1.07-1.27)	3.45
Systolic BP per 10 mmHg increases	0.89 (0.83-0.95)	-3.41	0.95 (0.89-1.03)	-1.23	0.92 (0.87-0.97)	-3.26
NYHA (III and IV vs II)	1.38 (1.14-1.68)	3.26	1.16 (0.92-1.46)	1.24	1.30 (1.11-1.52)	3.24
eGFR per 10 ml/min/1.73m^2 increases	0.94 (0.89-0.99)	-2.42	0.94 (0.89-1.00)	-1.97	0.94 (0.90-0.98)	-3.12
Hemoglobin per 1 g/dL increase	0.94 (0.88-1.00)	-1.91	0.91 (0.84-0.98)	-2.55	0.93 (0.88-0.97)	-3.02
Prior HF Hospitalization	1.27 (1.05-1.54)	2.51	1.23 (0.99-1.53)	1.89	1.27 (1.09-1.47)	3.08
Use of Beta-blocker (at the beginning of runin period)	0.87 (0.70-1.09)	-1.22	0.72 (0.56-0.92)	-2.62	0.79 (0.66-0.94)	-2.65
History of Hypertension	0.71 (0.50-0.99)	-1.99	0.76 (0.48-1.19)	-1.22	0.71 (0.53-0.95)	-2.28

Potassium per 1 mmol/L increase	1.03 (0.83-1.28)	0.25	1.46 (1.13-1.89)	2.88	1.21 (1.01-1.44)	2.13

Logistic regression models were used to identify the predictors of study discontinuation during either run-in period. Covariates used in this logistic regression models were selected by forward stepwise regression models from following candidate variables using cut-off p-value of 0.05; age, sex, race, region, body mass index, systolic and diastolic BP, heart rate, smoking status, NYHA functional class (III and IV vs II), history of HF hospitalization, hypertension, diabetes, angina pectoris, myocardial infarction, atrial fibrillation, stroke, percutaneous coronary intervention, coronary artery bypass grafting, pacemaker or implantable cardioverter defibrillator, duration of HF, ischemic etiology of HF, hemoglobin, sodium, potassium, estimated glomerular filtration rate, left ventricular ejection fraction and log-transformed NT-proBNP (all measured at screening); and pretrial use of an ACE inhibitor or ARB, use of diuretics, beta-blocker, calcium channel blocker, mineral corticoid receptor antagonist assessed at the beginning of the valsartan run-in. Adjusted odds ratio was shown with 95% CI. The number of patients who were not included in multivariable logistic models were 160. Goodness of fit tested by Hosmer-Lemeshow: P=0.22. Variance inflation factor of each covariate was less than 2.2. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; Sac/Val, sacubitril/valsartan.

Figure 1. Estimated effects of sacubitril/valsartan compared with valsartan on safety and efficacy outcomes in PARAGON-HF in models weighted according to the inverse probability of run-in completion

	Incidence (100 PY)	RR (95% CI)
Primary Endpoint		
Observed: Run-in completers	13.7	0.87 (0.75-1.01)
Estimated: Run-in failures	18.8	0.83 (0.69-1.00)
Estimated: All patients	14.6	0.86 (0.74-1.00)
Total HF Hospitalizations		**RR (95% CI)**
Observed: Run-in completers	10.7	0.85 (0.72-1.00)
Estimated: Run-in failures	14.9	0.81 (0.66-0.99)
Estimated: All patients	11.4	0.84 (0.71-0.99)
Cardiovascular Death		**HR (95% CI)**
Observed: Run-in completers	3.0	0.95 (0.79-1.16)
Estimated: Run-in failures	3.8	0.93 (0.73-1.19)
Estimated: All patients	3.1	0.94 (0.78-1.15)
All-cause Death		**HR (95% CI)**
Observed: Run-in completers	5.0	0.97 (0.84-1.13)
Estimated: Run-in failures	6.2	0.87 (0.72-1.05)
Estimated: All patients	5.2	0.94 (0.81-1.09)
Renal Composite Outcome		**HR (95% CI)**
Observed: Run-in completers	0.7	0.50 (0.33-0.77)
Estimated: Run-in failures	0.8	0.42 (0.26-0.69)
Estimated: All patients	0.7	0.47 (0.30-0.72)
Drug Discontinuation due to AE		**HR (95% CI)**
Observed: Run-in completers	6.1	0.93 (0.80-1.07)
Estimated: Run-in failures	7.9	0.83 (0.70-0.99)
Estimated: All patients	6.4	0.90 (0.78-1.04)
Drug Discontinuation for Any Reasons		**HR (95% CI)**
Observed: Run-in completers	10.0	0.93 (0.83-1.04)
Estimated: Run-in failures	12.4	0.84 (0.73-0.97)
Estimated: All patients	10.4	0.90 (0.81-1.01)