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Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation

The PARADIGM-HF Trial

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ABSTRACT

OBJECTIVES This study assessed whether the benefit of sacubtril/valsartan therapy varied with clinical stability.

BACKGROUND Despite the benefit of sacubitril/valsartan therapy shown in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, it has been suggested that switching from an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker should be delayed until occurrence of clinical decompensation.

METHODS Outcomes were compared among patients who had prior hospitalization within 3 months of screening (n = 1,611 [19%]), between 3 and 6 months (n = 1,009 [12%]), between 6 and 12 months (n = 886 [11%]), >12 months (n = 1,746 [21%]), or who had never been hospitalized (n = 3,125 [37%]).

RESULTS Twenty percent of patients without prior HF hospitalization experienced a primary endpoint of cardiovascular death or heart failure (HF) hospitalization during the course of the trial. Despite the increased risk associated with more recent hospitalization, the efficacy of sacubitril/valsartan therapy did not differ from that of enalapril according to the occurrence of or time from hospitalization for HF before screening, with respect to the primary endpoint or with respect to cardiovascular or all-cause mortality.

CONCLUSIONS Patients with recent HF decompensation requiring hospitalization were more likely to experience cardiovascular death or HF hospitalization than those who had never been hospitalized. Patients who were clinically stable, as shown by a remote HF hospitalization (>3 months prior to screening) or by lack of any prior HF hospitalization, were as likely to benefit from sacubitril/valsartan therapy as more recently hospitalized patients. (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF]; NCT01035255) (J Am Coll Cardiol HF 2016;4:816–22) © 2016 by the American College of Cardiology Foundation.

The angiotensin receptor neprilysin inhibitor sacubitril/valsartan (LCZ696) (1) reduced both death and heart failure (HF) hospitalizations in patients with New York Heart Association (NYHA) functional classes II to IV HF and ejection fraction compared with enalapril in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (2). The benefits of sacubitril/valsartan therapy were consistent across

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all pre-specified subgroups, robust across the spectrum of HF on the basis of comprehensive risk score (3), and were unrelated to the severity of left ventricular dysfunction (4). Nevertheless, selection of the appropriate patients for transition from angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) to sacubitril/valsartan has been the subject of debate. Some clinicians have suggested that only patients with exacerbation of symptoms or hospitalization despite ACE inhibitors or ARBs be switched (5). Hospitalization for HF is a reflection of clinical instability as well as a predictor of poor subsequent outcome. Prior HF hospitalization was a strong predictor of risk of cardiovascular (CV) death and HF hospitalizations in the CHARM (Candesartan in Heart failure - Assessment of moRtality and Morbidity) program, and this risk declined with time from the event (6). To determine whether clinically stable patients with HF and reduced ejection fraction would benefit more from treatment with sacubitril/valsartan therapy than from enalapril, we used the occurrence of and time from a prior hospitalization for HF as the measure of clinical stability and related this outcome to subsequent outcomes and the efficacy of sacubitril/valsartan.

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METHODS

STUDY DESIGN AND PATIENT SELECTION. PARADIGM-HF was a double-blind, randomized, active controlled trial designed to compare the impact of the angiotensin receptor neprilysin inhibitor sacubitril/valsartan with that of enalapril on CV mortality and HF hospitalizations in patients with left ventricular ejection fraction (LVEF) ≤40% and NYHA functional classes II to IV HF. Patients with acute decompensated HF were excluded. Details of inclusion and exclusion and the study design have been reported previously (7). 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.

Eligible subjects had at least mildly elevated natriuretic peptide levels (patients not hospitalized within 12 months were required to have slightly higher natriuretic peptide levels) and were treated with stable doses of ACE inhibitors or ARBs and beta-adrenergic receptor blockers for at least 4 weeks prior to trial enrollment. Patients with symptomatic hypotension, or an estimated glomerular filtration rate <30 ml/min/1.73 m^2, or potassium concentration >5.2 mmol/l at screening, or history of angioedema were excluded.

Participants underwent sequential single blind run-in phases with enalapril at a dose of at least 10 mg twice daily for 2 weeks followed by sacubitril/valsartan, first given at 100 mg twice daily (sacubitril/valsartan 49 mg/51 mg twice daily), then 200 mg twice daily (sacubitril/valsartan, 97 mg/103 mg twice daily) for 4 to 6 weeks. They were subsequently randomized to receive enalapril, 10 mg twice daily, or sacubitril/valsartan, 200 mg twice daily, and were followed for a median of 27 months. History of HF hospitalization and date of that hospitalization were recorded on case report forms.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

HF = heart failure

NYHA = New York Heart Association

STATISTICAL METHODS. For this analysis, we used presence of and time from a prior hospitalization for HF as the measure of clinical stability. We divided patients into 5 categories: those with prior HF hospitalization within 3 months of screening; those with a remote HF hospitalization defined as one of the following 3 categories: a HF hospitalization between 3 and 6 months prior to screening; between 6 and 12 months prior to screening; >1 year prior to screening; and those patients defined as most stable without prior HF hospitalization. Patients with very recent hospitalizations represented the least stable patients. Trends in baseline characteristics across groups were compared using linear regression and the Cuzick nonparametric trend test and chi-squared test for linear trend for continuous normally distributed data, continuous non-normally distributed data, and binary/categorical data, respectively. Primary outcome was the composite of CV death or HF hospitalization, but we also assessed the outcomes CV death and all-cause mortality. We assessed the relationships among these 5 categories and risk for events, regardless of treatment, using both unadjusted and adjusted Cox models. We tested for interactions between the treatment and the prior hospitalization group with respect to these outcomes. No correction was made for multiple testing. The continuous relationship between time since previous HF hospitalization and the treatment effect (sacubitril/valsartan-to-enalapril incidence rate ratio) for the primary outcome was assessed among patients with previous hospitalization. We considered modeling time since previous HF both linearly and non-linearly by using restricted cubic splines with up to 7 knots. We also considered log-transformation of the time variable. We chose the model (linear with log transformation), which yielded the minimum Akaike information criterion value. A p value <0.05 was

TABLE 1 Baseline Characteristics According to Prior Heart Failure Hospitalization

	<3 Months (n = 1,611)	3-6 Months (n = 1,009)	6-12 Months (n = 886)	>12 Months (n = 1,746)	No Prior HF Hospitalization (n = 3,125)	p Value
Age, yrs	62 ± 12	63 ± 11	63 ± 11	65 ± 11	65 ± 11	<0.001
Females	335 (21)	212 (21)	211 (24)	345 (20)	724 (23)	0.12
Body mass index, kg/m^2	28.2 ± 5.7	28.6 ± 5.4	28.3 ± 5.6	28.5 ± 5.4	27.8 ± 5.4	0.001
NYHA functional class at randomization						<0.001
1	77 (5)	45 (4)	37 (4)	60 (3)	167 (5)	
2	1,085 (67)	680 (67)	581 (66)	1,209 (69)	2,351 (75)	
3	438 (27)	270 (27)	254 (29)	459 (26)	591 (19)	
4	8 (0)	13 (1)	13 (1)	15 (1)	11 (0)	
LVEF	29 ± 6	29 ± 6	30 ± 6	29 ± 6	30 ± 6	0.004
History of hypertension	1,214 (75)	732 (73)	639 (72)	1,236 (71)	2,101 (67)	<0.001
Race						0.08
White	1,035 (64)	654 (65)	608 (69)	1,277 (73)	1,958 (63)	
Black	104 (6)	66 (7)	49 (6)	87 (5)	119 (4)	
Asian	329 (20)	187 (19)	142 (16)	252 (14)	592 (19)	
Other	143 (9)	102 (10)	87 (10)	130 (7)	456 (15)	
Region						<0.001
North America	82 (5)	61 (6)	68 (8)	178 (10)	208 (7)	
Latin America	259 (16)	173 (17)	144 (16)	197 (11)	660 (21)	
Western Europe plus other	217 (13)	220 (22)	204 (23)	561 (32)	845 (27)	
Central Europe	729 (45)	377 (37)	330 (37)	565 (32)	819 (26)	
Asia-Pacific	324 (20)	178 (18)	140 (16)	245 (14)	593 (19)	
SBP, mm Hg	122 ± 15	121 ± 15	122 ± 16	121 ± 15	122 ± 16	0.78
Diabetes	533 (33)	357 (35)	332 (37)	657 (38)	1,017 (33)	0.62
Heart rate, beats/min	74 ± 13	72 ± 12	73 ± 12	72 ± 12	71 ± 12	<0.001
Ischemic cardiomyopathy	854 (53)	601 (60)	557 (63)	1,082 (62)	1,925 (62)	<0.001
Prior MI	589 (37)	440 (44)	429 (48)	815 (47)	1,353 (43)	<0.001
History of AF	644 (40)	372 (37)	320 (36)	717 (41)	1,032 (33)	<0.001
History of stroke	132 (8)	67 (7)	79 (9)	186 (11)	259 (8)	0.23
ICD	105 (7)	142 (14)	149 (17)	416 (24)	428 (14)	<0.001
CRT	53 (3)	83 (8)	80 (9)	194 (11)	164 (5)	0.036
ACE	1,292 (80)	788 (78)	689 (78)	1,364 (78)	2,380 (76)	0.003
ARB	323 (20)	225 (22)	195 (22)	389 (22)	757 (24)	0.002
Diuretics	1,381 (86)	818 (81)	744 (84)	1,421 (81)	2,359 (75)	<0.001
Beta-blockers	1,512 (94)	936 (93)	829 (94)	1,634 (94)	2,878 (92)	0.05
Digoxin	540 (34)	304 (30)	266 (30)	528 (30)	894 (29)	0.002
MRA	1,095 (68)	648 (64)	491 (55)	948 (54)	1,479 (47)	<0.001
Serum creatinine, mg/dl	1.09 ± 0.28	1.12 ± 0.29	1.12 ± 0.30	1.17 ± 0.31	1.11 ± 0.30	0.002
NT-proBNP, pg/ml	1,884 [923-4,035]	1,554 [824-3,256]	1,439 [683-3,024]	1,670 [957-3,070]	1,565 [911-3,003]	0.025
BNP, pg/ml	272 [153-579]	249 [132-465]	221 [128-463]	254 [168-442]	251 [161-446]	0.16

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

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralcorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure.

considered significant. All analyses were conducted using Stata version 14.1 software (College Station, Texas).

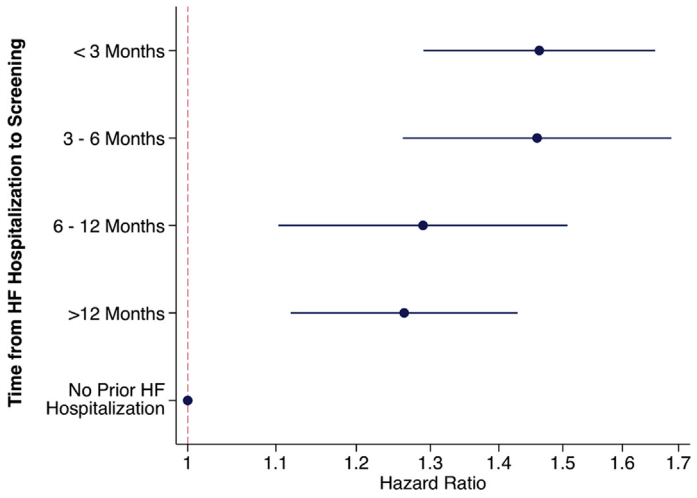
RESULTS. Of 8,399 validly randomized subjects, 5,274 patients (63%) had a prior HF hospitalization, which occurred <3 months from screening in 1,611 patients (19%); between 3 and 6 months prior to randomization in 1,009 patients (12%); between 6 and 12 months prior to randomization in 886 patients (11%); and >12 months prior to randomization in 1,746 patients (21%). A total of 3,125 patients (37%) had never been hospitalized for HF. Prior HF hospitalization dates were not available for 6 patients and were incorrectly or incompletely recorded for 16 patients. Baseline characteristics by prior HF hospitalization status and time are shown in Table 1. Participants with more recent HF hospitalizations

were younger, had a more advanced NYHA functional class at baseline, had slightly lower LVEF, were more likely to have a history of hypertension or atrial fibrillation but were less likely to have had a prior MI, and were more likely to have been treated with a mineralocorticoid receptor antagonist and to have had higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Regardless of treatment, the risk for the primary outcome (CV death or HF hospitalization) was higher in patients with more recent hospitalization than for those with no prior hospitalization in adjusted models (<3-month hazard ratio [HR]: 1.46; 95% confidence interval [CI]: 1.29 to 1.66; 3- to 6-month HR: 1.46; 95% CI: 1.26 to 1.69; 6- to 12-month HR: 1.29; 95% CI: 1.10 to 1.51; and >12-month HR: 1.26; 95% CI: 1.12 to 1.43; $p < 0.001$ for trend) (Figure 1). In the least stable patients, those with a HF hospitalization within 3 months of screening, 29% had a primary event, and 19% died during the course of the trial. In the most stable patients, those without prior HF hospitalization, 20% of patients had a primary event, and 17% died during the course of the trial. In 51% of those most stable patients who died during the study, the primary event was CV death with no preceding HF hospitalization, and 60% of those CV deaths were sudden cardiac deaths.

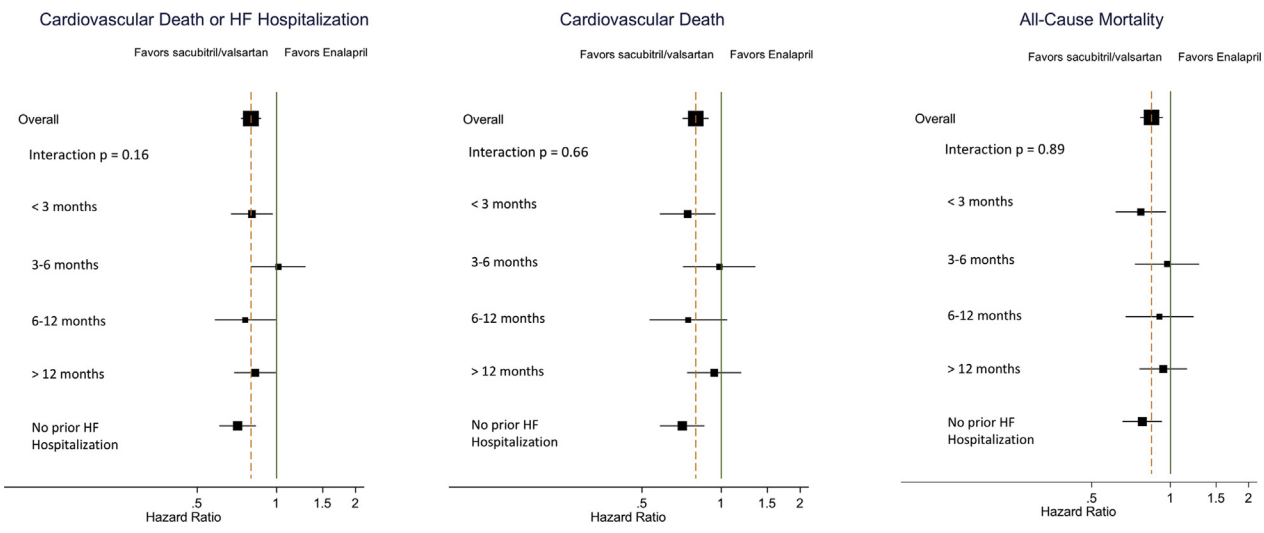
The efficacy of sacubitril/valsartan therapy was not significantly different from that of enalapril based on presence or timing of prior hospitalization for HF (Figure 2, interaction p values = 0.16, 0.66, and 0.89 for primary outcome, CV death, and all-cause death, respectively). Specifically, compared to patients in the enalapril group, patients in the

FIGURE 1 Hazard Ratio for Primary Endpoint



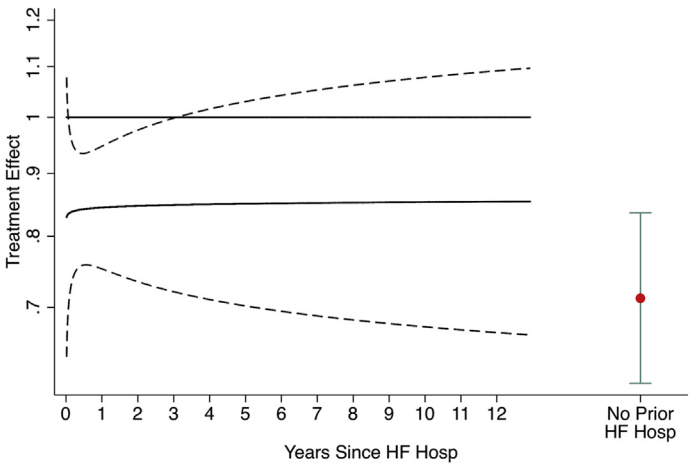
Hazard ratio for primary endpoint (cardiovascular death or HF hospitalization) based on the presence of and time from a HF hospitalization prior to screening, adjusted for baseline characteristics which significantly differed across groups. HF = heart failure.

FIGURE 2 Treatment Effect of Sacubitril/Valsartan Therapy



Forest plot shows treatment effects of sacubitril/valsartan (hazard ratio with 95% confidence interval) based on the presence of and time from a heart failure hospitalization prior to screening on the outcomes of cardiovascular death or heart failure hospitalization **(left)**, cardiovascular death **(middle)**, and all-cause mortality **(right)**.

FIGURE 3 Treatment Effect on Primary Outcome



Linear regression model showing the treatment effect of sacubitril/valsartan (incidence rate ratio with 95% confidence interval) continuously as a function of time from a heart failure hospitalization prior to screening for the outcome of cardiovascular death or heart failure hospitalization **(left)**. The patients with no prior HF hospitalization are included on the far right for comparison. Abbreviations as in Figure 1.

sacubitril/valsartan group had a reduction of 19% or greater in risk of a primary endpoint and a reduction of 25% or greater in the risk of CV death, when patients were in the most stable subgroup (no prior hospitalization) or in the least stable subgroup (hospitalization within 3 months). Figure 3 demonstrates the continuous relationship between time since previous HF hospitalization and the treatment effect with respect to the primary outcome. There was no evidence of differential treatment effect across the spectrum of time since hospitalization ($p = 0.90$ for interaction).

The relative incidence of adverse events of interest, including symptomatic hypotension, elevation in serum creatinine >2.5 mg/dl, or elevation in serum potassium >6.0 mmol/l, was similar among patients with a recent, remote, or no prior HF hospitalization, with no significant interactions with treatment (Table 2). The percentage of patients for whom the study drug was discontinued and the percentage of patients with any dose reduction and the average daily dose did not differ among patients with a recent, remote, or no prior HF hospitalization (Table 2). We also saw no evidence that timing from prior hospitalization affected the likelihood of reaching target dose of enalapril and sacubitril/valsartan during the run-in phase of the trial ($p = 0.67$).

DISCUSSION

We found that patients enrolled in PARADIGM-HF who had never had a prior HF hospitalization or had a remote HF hospitalization, arguably the most clinically stable patients enrolled, still had high absolute rates of CV death and of HF hospitalization during the course of the trial. In these stable patients, 51% of the first events experienced were CV death, and 60% of these deaths were sudden cardiac deaths. With respect to the risk of the primary endpoint and of CV death, the patients with no prior HF hospitalization or a remote HF hospitalization derived at least as much benefit from treatment with sacubitril/valsartan as with enalapril as did patients who were regarded as clinically less stable. These findings indicate that

TABLE 2 Adverse Events of Interest According to Prior HF Hospitalization

		Symptomatic Hypotension	Elevated Serum Creatinine, >2.5 mg/dl	Elevated Serum Potassium, >6.0 mmol/l	Drug Discontinuation Not Due To Death	Any Dose Reduction	Average Daily Dose (% of Target)*
<3 months	Enalapril	61 (7.9)	28 (3.6)	51 (6.8)	164 (21.2)	334 (43.1)	85 ± 27
	Sacubitril/valsartan	95 (11.5)	23 (2.8)	38 (4.6)	124 (14.8)	316 (37.8)	88 ± 24
3–6 months	Enalapril	43 (8.2)	32 (6.2)	39 (7.5)	84 (16.0)	222 (42.4)	87 ± 25
	Sacubitril/valsartan	77 (15.9)	15 (3.1)	18 (3.8)	83 (17.1)	202 (41.6)	87 ± 24
6–12 months	Enalapril	45 (10.0)	11 (2.5)	24 (5.4)	81 (18.1)	176 (39.3)	88 ± 24
	Sacubitril/valsartan	59 (13.5)	12 (2.8)	21 (4.8)	82 (18.7)	191 (43.6)	86 ± 26
>12 months	Enalapril	96 (10.6)	47 (5.2)	45 (5.0)	193 (21.3)	408 (45.1)	85 ± 26
	Sacubitril/valsartan	145 (17.2)	40 (4.8)	30 (3.6)	191 (22.7)	396 (47.0)	85 ± 26
No prior HF hospitalization	Enalapril	142 (9.2)	67 (4.4)	75 (4.9)	307 (19.9)	648 (41.9)	86 ± 25
	Sacubitril/valsartan	210 (13.3)	49 (3.1)	74 (4.7)	264 (16.7)	647 (40.9)	87 ± 25
p value for interaction		0.72	0.68	0.07	0.40	0.22	0.11

Values are n (%) or mean ± SD. *Average daily dose during double-blind period was divided by 20 mg for the enalapril arm and 400 mg for the sacubitril/valsartan arm.
HF = heart failure.

physician perceptions of clinical stability are not a reliable approach to identifying patients who are likely to benefit from the use of an angiotensin receptor neprilysin inhibitor as a replacement for an ACE inhibitor.

As was shown previously, we confirmed that a recent HF hospitalization, a marker of clinical instability, portends increased risk for major adverse CV events in patients with HF, and this risk declines over time (6). Patients with no history of HF hospitalization or only a remote history of HF hospitalization are generally considered the most stable (particularly if they have only Class II symptoms, as was the case in most of the patients enrolled in the PARADIGM-HF trial). Accordingly, clinicians may be least likely to alter therapeutic regimens in these patients, a phenomenon that has been termed "therapeutic inertia" (8,9). Indeed, one review recently suggested that switching from an ACE inhibitor or ARB to sacubitril/valsartan was warranted only "if there are persistent symptoms with recent exacerbations or hospitalization while on…optimized treatment." (5) Our data, which demonstrate not only high event rates but a superior response to sacubitril/valsartan in these stable patients, suggest that the perception of "stability" in these patients is not a reliable indicator for selecting patients who would benefit from intensified treatment. This is particularly true as sudden cardiac death is frequently the first (and last) manifestation of instability in patients with HF who are identified as being clinically stable.

STUDY LIMITATIONS. Several limitations of this analysis should be noted. Results of this analysis are most applicable to those patients who fulfilled the inclusion and exclusion criteria of the PARADIGM-HF trial. Indeed, patients were required to have some elevation in natriuretic peptide levels to be enrolled, and thus, these results cannot be interpreted as directly applicable to HF patients without natriuretic peptide elevation. Nevertheless, we saw no evidence of heterogeneity in the relationship between prior HF hospitalization and treatment effect in patients in the lowest tertile of NT-proBNP (p interaction = 0.49). Although the overlapping 95% CIs and lack of statistically significant interaction with randomized therapy are suggestive of a consistent treatment benefit across a spectrum of patients, these observations do not prove that no differences in effectiveness exist, as the PARADIGM-HF study was not designed with power to test for such differences. Furthermore, our analyses were not corrected for multiple testing, increasing the likelihood of false positive findings, and therefore all statistically significant findings must be interpreted in this context. Although these were post-hoc analyses and thus need to be interpreted with caution, these results are consistent with 2 previous analyses in which we showed that other metrics of severity of illness in HF, the comprehensive MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score and LVEF, also did not influence the magnitude of the superiority of sacubitril/valsartan therapy relative to that of enalapril (3,4). These metrics, however, are more likely to reflect clinical severity than clinical stability.

CONCLUSIONS

We found that the patients deemed to be most clinically stable by virtue of never having had a prior HF hospitalization or having had only a remote HF hospitalization prior to randomization in PARADIGM-HF benefited at least as much from sacubitril/valsartan therapy as less stable patients with a recent history of clinical decompensation. These findings do not support recommendations to wait for evidence of clinical decompensation or instability as a rational strategy for switching patients from a conventional inhibitor of the renin-angiotensin system to sacubitril/valsartan.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our findings address whether clinically stable patients would benefit from sacubitril/valsartan. We find that while the more remote a HF hospitalization, the lower the overall risk, there was no evidence that these most stable patients benefit less than the least stable patients. These results should help inform clinicians who might consider switching patients with HF from standard RAS inhibitors to sacubitril/valsartan.

TRANSLATIONAL OUTLOOK: While large HF trials are often designed to assess the effectiveness and safety of therapies in a broad group of patients, the spectrum of patients in clinical practice can be broader still. Further research on broader populations incorporating patients who may not have been eligible for PARADIGM-HF is necessary to fully appreciate the safety and efficacy of sacubitril/valsartan in the full spectrum of HF patients.

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