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Early Initiation of Sacubitril/Valsartan in Patients With Acute Heart Failure and Renal Dysfunction: An Analysis of the TRANSITION Study

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ABSTRACT

Background: Treatment of patients with heart failure with reduced ejection fraction (HFrEF) and renal dysfunction (RD) is challenging owing to the risk of further deterioration in renal function, especially after acute decompensated HF (ADHF).

Methods and Results: We assessed the effect of RD (estimated glomerular filtration rate of ≥30 to <60 mL/min/1.73 m^2) on initiation, up-titration, and tolerability of sacubitril/valsartan in hemodynamically stabilized patients with HFrEF admitted for ADHF (RD, $n = 476$; non-RD, $n = 483$). At week 10, the target dose of sacubitril/valsartan (97/103 mg twice daily) was achieved by 42% patients in RD subgroup vs 54% in non-RD patients ($P < .001$). Sacubitril/valsartan was associated with greater estimated glomerular filtration rate improvements in RD subgroup than non-RD (change from baseline least squares mean 4.1 mL/min/1.73 m^2, 95% confidence interval 2.2–6.1, $P < .001$). Cardiac biomarkers improved significantly in both subgroups; however, compared with the RD subgroup, the improvement was greater in those without RD (N-terminal pro-brain natriuretic peptide, −28.6% vs −44.8%, high-sensitivity troponin T −20.3% vs −33.9%) ($P < .001$). Patients in the RD subgroup compared with those without RD experienced higher rates of hyperkalemia (16.3% vs 6.5%, $P < .001$), investigator-reported cardiac failure (9.7% vs 5.6%, $P = .029$), and renal impairment (6.4% vs 2.1%, $P = .002$).

Conclusions: Most patients with HFrEF and concomitant RD hospitalized for ADHF tolerated early initiation of sacubitril/valsartan and showed significant improvements in estimated glomerular filtration rate and cardiac biomarkers.

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Key Words: Acute decompensated heart failure, angiotensin receptor neprilysin inhibitor, heart failure with reduced ejection fraction, N-terminal-pro-B-type natriuretic peptide, renal dysfunction, sacubitril/valsartan.

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Patients with comorbid heart failure (HF) and renal dysfunction (RD) have a worse prognosis than HF patients without RD, with higher rates of hospitalization, mortality, and morbidity.[1] One of the additional challenges of management of patients with acute HF is the higher prevalence of RD (53%) compared with those with chronic HF (42%).[2] Not only are patients with both HF and RD at a higher risk of adverse outcomes during the vulnerable postdischarge phase after acute decompensated HF (ADHF) episodes, but HF treatment initiation and up-titration can be more challenging owing to differences in HF drugs' pharmacokinetics and pharmacodynamics.[3] This is especially the case for blockers of the renin−angiotensin−aldosterone system owing to the elevated risk of further deterioration in renal function and/or hyperkalemia.[3−5]

Sacubitril/valsartan (an angiotensin receptor neprilysin inhibitor [ARNI]) is the first agent that simultaneously inhibits neprilysin and the angiotensin receptor.[6] Current guidelines for the treatment of chronic HF give a Class 1 recommendation for sacubitril/valsartan in patients with HF with reduced ejection fraction (HFrEF) to decrease the risk of HF hospitalization and death.[7,8] In the PARADIGM-HF (A Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction) study, treatment with sacubitril/valsartan compared with the angiotensin-converting enzyme (ACE) inhibitor enalapril was associated with a lower risk of hyperkalemia and a slower decrease in renal function.[7,9,10] A recently conducted meta-analysis in 3460 patients with HF and RD suggested that treatment with sacubitril/valsartan results in significant increases in the estimated glomerular filtration rate (eGFR), with a decrease in blood pressure and improvements of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels[11]; however, there is limited evidence regarding the tolerability and feasibility of early in-hospital initiation and up-titration of sacubitril/valsartan in patients with HFrEF with RD hospitalized for ADHF.[12]

The current analysis of the TRANSITION (Comparison of Pre- and Post-discharge initiation of sacubiltryl/valsartan in HFrEF patients stabilised after Acute Decompensation Event) study aimed to compare the early initiation, up-titration success, and tolerability of sacubitril/valsartan among patients with HFrEF hospitalized owing to ADHF with concomitant RD (eGFR of ≥30 to <60 mL/min/1.73 m^2) compared with those without RD (eGFR of ≥60 mL/min/1.73 m^2) at baseline. This analysis also evaluated measures of renal function, biomarkers of cardiac injury and wall stress, and time to first all-cause and HF-related rehospitalizations in these two patient subgroups during the 26-week study duration.

Methods

Study Design and Patient Population

The study design and rationale of the TRANSITION (NCT02661217) study have been published previously.[13] In brief, TRANSITION was a randomized, open-label study that compared in-hospital initiation of sacubitril/valsartan with initiation early after discharge (1−14 days) in hemodynamically stabilized patients with HFrEF admitted for ADHF. The study included adult patients (aged ≥18 years) hospitalized for an episode of ADHF (de novo HF or deterioration of chronic HF) with a left ventricular ejection fraction of ≤40%, New York Heart Association functional class II−IV, and systolic blood pressure of ≥100 mm Hg at screening.

Eligible patients were randomized 1:1 to either in-hospital or postdischarge initiation of sacubitril/valsartan. Patients received treatment with sacubitril/valsartan for 10 weeks from randomization and were followed up for 16 more weeks. The current analysis compared up-titration success, safety, and tolerability of sacubitril/valsartan initiation in patients with RD as a comorbidity, as defined by an eGFR of ≥30 to <60 mL/min/1.73 m^2 at enrollment, with those without RD. Evaluation of eGFR was performed by the simplified Modification of Diet in Renal Disease formula at randomization. Patients with an eGFR of <30 mL/min/1.73 m^2 at baseline were excluded from the study.

TRANSITION was conducted in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice and with the ethical principles laid down in the Declaration of Helsinki.[14]. The trial protocol was approved by the ethics committees at all participating centers. All patients provided written informed consent.

End Points and Assessments

All end points and assessments were compared for patients with RD at baseline vs those without RD. The primary end point was the proportion of patients achieving the target dose of sacubitril/valsartan (97/103 mg twice daily) at 10 weeks after randomization, regardless of dose changes or interruptions, and in-hospital or postdischarge initiation of treatment. The secondary end points were (1) the proportion of patients who received and maintained any of two higher doses of sacubitril/valsartan 49/51 mg and/or 97/103 mg twice daily for ≥2 weeks leading up to week 10; (2) the proportion of patients who received and maintained any dose of sacubitril/valsartan for ≥2 weeks leading up to week 10; and (3) the rates of permanent study-drug discontinuations owing to adverse events (AEs) during the 10-week treatment initiation period.

This analysis also assessed time to first all-cause and HF-related rehospitalizations during 26 weeks after discharge from index hospitalization. The patterns of change in biomarkers of cardiac wall stress and injury (NT-proBNP and high-sensitivity troponin T [hsTnT]) were assessed as a

predefined exploratory end point and were measured after hemodynamic stabilization at randomization, at discharge, and 4 and 10 weeks after randomization.[13,15]

Safety

Safety variables, specifically vital signs, laboratory evaluations, and AEs reported during the study, were evaluated in both subgroups. AEs were investigator reported and coded as per Medical Dictionary for Regulatory Activities preferred terms. Prespecified AEs of special interest included hypotension, hyperkalemia, RD, and angioedema.

Statistical Analyses

The current analysis included all randomized patients who received ≥1 dose of the study medication. The analyses of the primary and secondary end points were performed using the Cochran Mantel−Haenszel test stratified by response to ACE inhibitor stratum, angiotensin receptor blocker (ARB) stratum, or naïve patient stratum at randomization (except for the subgroup ACE inhibitor or ARB or naïve before admission). The incidence of AEs was summarized by preferred terms.

The NT-proBNP and hsTnT biomarkers were analyzed by fitting a repeated-measures mixed model to the log-transformed data with treatment group, visit, and, region as factors, log baseline biomarker as a covariate and treatment × visit and visit × log baseline interactions. Geometric least squares mean (LSM) were presented with 95% confidence intervals (CIs) for the change from baseline. *P* values of <.05, based on the log-transformed biomarker data, were considered statistically significant without adjusting for multiplicity.

Cumulative event rates of the composite of time to first all-cause rehospitalizations and HF-related rehospitalization after discharge from the index hospitalization were calculated using the Kaplan−Meier method and compared between the RD and non-RD subgroups. Patients without any hospitalizations were censored at the last date of the study. Treatment groups were compared using log-rank testing.

Results

In the TRANSITION study, a total of 1124 patients from 156 study sites across 19 countries were screened, of whom 1002 were randomized between February 2016 and December 2017 in a ratio of 1:1 to either predischarge or postdischarge initiation of sacubitril/valsartan. Of these 1002 patients, the current analysis included 959 patients who had an eGFR measured at baseline, categorized into RD ($n = 476$; median eGFR 46.7 mL/min/1.73 m^2, interquartile range [IQR] 39.4−54.0 mL/min/1.73 m^2) and non-RD ($n = 483$, median eGFR 75.0 mL/min/1.73 m^2, IQR 66.9−85.0 mL/min/1.73 m^2) subgroups. Patients with RD were older than those without RD (mean age 71.1 ± 10.2 years vs 62.5 ± 12.0 years) and exhibited a greater comorbidity burden with a higher prevalence of hypertension (83.8% vs 67.3%), diabetes (54.2% vs 39.1%), atrial fibrillation (52.7% vs 42.4%), prior myocardial infarction 38.0% vs 30.4%), and stroke (11.6% vs 7.7%). They presented with greater HF severity, were more likely to have a known history of HF (77.5% vs 64.8%), HF hospitalizations (55.0% vs 42.2%), and had significantly higher baseline levels of NT-proBNP (median 2235.0 pg/mL, IWR 1060.0−5050.0 pg/mL vs median 1411.0 pg/mL, IQR 638.5−2692.0 pg/mL), hsTnT (median 35.0 ng/L, IQR 23.0−53.0 ng/L vs median 23.0 ng/L, IQR 16.0−35.0 ng/L), and mean serum creatinine (126.3 vs 84.9 μmol/L), with all comparisons showing a *P* value of ≤.05 (Table 1).

Primary and Secondary End Points

The target dose of sacubitril/valsartan (97/103 mg twice daily) was achieved at week 10 by 41.9% of patients with RD and 54.3% of patients without RD ($P < .001$) (Fig. 1). Treatment initiation with sacubitril/valsartan in the hospital or shortly after discharge did not impact the rate of achievement of the target dose in either the RD subgroup (38.6% vs 45.3%, $P = .114$) or non-RD subgroup (52.5% vs 56.0%, $P = .400$) (Supplementary Fig. 1).

The proportion of patients with RD who achieved either an intermediate (49/51 mg twice daily) or target dose (97/103 mg twice daily) of sacubitril/valsartan and maintained it for ≥2 weeks leading to week 10 was 58.3% compared with 72.7% in patients without RD ($P < .001$) (Fig. 1). A similar pattern was observed for the end point of achieving any dose of sacubitril/valsartan and maintaining it for ≥2 weeks leading to week 10 (84.1% of patients with RD vs 92.1% of patients without RD, $P < .001$) (Fig. 1). Among patients with RD, 9.1% permanently discontinued sacubitril/valsartan owing to AEs during the first 10-week treatment period compared with 2.5% in the non-RD subgroup ($P < .001$) (Fig. 1).

The proportions of patients in both RD and non-RD subgroups achieving and maintaining sacubitril/valsartan 49/51 or 97/103 mg twice daily, or any dose of sacubitril/valsartan for ≥2 weeks leading to week 10 were comparable among patients initiated on sacubitril/valsartan in-hospital or after discharge but were numerically in favor of postdischarge initiation of sacubitril/valsartan in patients with RD (Supplementary Fig. 1).

Concomitant Medication Use

In the RD subgroup, at 10 weeks after initiation of sacubitril/valsartan, the proportion of patients receiving beta-blockers (BBs) increased from 55.2% before admission to 72.4%, diuretics from 62.1% to 88.6%, and those receiving mineralocorticoid receptor antagonists (MRAs) increased from 39.8% to 61.7% (Fig. 2). A similar trend was observed

Table 1 Baseline, demographic, and clinical characteristics (full analysis set).

Parameters	RD subgroup (n = 476)	Non-RD subgroup (n = 483)	P Value*
Age (years)	71.1 ± 10.2	62.5 ± 12.0	<.001
≥75	205 (43.1)	76 (15.7)	<.001
Male	327 (68.7)	394 (81.6)	<.001
Race			.822
Caucasian	465 (97.7)	466 (96.5)	
Black	5 (1.1)	8 (1.7)	
Asian	4 (0.8)	6 (1.2)	
Native American	1 (0.2)	0 (0.0)	
Pacific Islander	0 (0.0)	1 (0.2)	
BMI (kg/m^2)	28.1 (25.2–31.7)	28.5 (25.5–33.2)	.136
LVEF (%)	29.6 ± 7.4	27.9 ± 7.6	<.001
NYHA functional class (at randomization)			.562
I	2 (0.4)	1 (0.2)	
II	297 (62.4)	319 (66.0)	
III	169 (35.5)	159 (32.9)	
IV	7 (1.5)	4 (0.8)	
SBP (mm Hg)	124.5 ± 14.2	123.9 ± 13.7	.512
Pulse rate (beats/min)	73.3 ± 12.2	75.6 ± 13.4	.006
Ischemic HF etiology	240 (50.4)	203 (42.0)	.008
Prior HF	369 (77.5)	313 (64.8)	<.001
Prior HF hospitalization	262 (55.0)	204 (42.2)	<.001
Biomarkers (at randomization)			
NT-proBNP (pg/mL)	2235.0 (1060.0–5050.0)	1411.0 (638.5–2692.0)	<.001
hsTnT (ng/L)	35.0 (23.0–53.0)	23.0 (16.0–35.0)	.001
Serum creatinine (μmol/L)	126.3 ± 25.6	84.9 ± 14.2	<.001
Medication strata			.005
Prior ACE inhibitor use	249 (52.3)	245 (50.7)	
Prior ARB use	131 (27.5)	102 (21.1)	
ACE inhibitor/ARB naïve	96 (20.2)	136 (28.2)	
Medical history			
Hypertension	399 (83.8)	325 (67.3)	<.001
Diabetes	258 (54.2)	189 (39.1)	<.001
AF	251 (52.7)	205 (42.4)	.001
MI	181 (38.0)	147 (30.4)	.013
Stroke	55 (11.6)	37 (7.7)	.041
Cardiac resynchronization therapy	52 (10.9)	36 (7.5)	.063
Implantable cardioverter defibrillator	88 (18.5)	60 (12.4)	.009

Note: RD was defined as eGFR (MDRD formula) ≥30 to <60 mL/min/1.73 m^2 determined at randomization. Values are mean ± standard deviation, number (%), or median (interquartile range).

*Subgroup comparisons were performed by using a chi-squared test for the categorical variables (or a Fisher's exact test in case of small cell size) and using a t-test for the continuous variables.ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; hsTnT, high-sensitivity troponin T; IQR, interquartile range; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; n, number of patients; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RD, renal dysfunction; SBP, systolic blood pressure.

among patients in the non-RD subgroup, with the proportion of patients receiving BBs increasing from 51.1% to 71.7%, diuretics from 58.5% to 89%, and 43.7% to 67.8% for patients receiving MRAs (Fig. 2).

Biomarkers of Renal Function

Treatment with sacubitril/valsartan was associated with an early increase in the eGFR from baseline to week 4 in both the RD and non-RD subgroups (eGFR slope 1.0 mL/min/1.73 m^2, 95% CI 0.3–1.7 mL/min/1.73 m^2 vs eGFR slope 0.8 mL/min/1.73 m^2, 95% CI 0.1–1.5 mL/min/1.73 m^2, P = .637, respectively). This improvement in eGFR at week 4 in the RD subgroup patients was significantly greater than those in the non-RD subgroup (treatment difference LSM 3.2, 95% CI 1.6–4.9, P < .001). The increase in eGFR from baseline was sustained throughout the 26-week study duration of in the RD subgroup (change from baseline LSM 3.9, 95% CI 2.3–5.4), whereas in the non-RD group, the eGFR values remained stable and close to baseline levels up to week 18, with a minor decrease observed between week 22 and week 26 (change from baseline LSM −1.2, 95% CI −2.7 to 0.2) (P [treatment difference RD vs non-RD] < .001) (Fig. 3).

Initiation of sacubitril/valsartan in-hospital or after discharge in patients with RD was associated with an early increase in eGFR, with a more pronounced early increase by week 4 among patients initiated shortly after discharge (treatment difference in LSM −2.3, 95% CI −4.4 to 0.3, P = .027), and this trend was sustained throughout the 26-week study duration (Supplementary Fig. 2a). Among

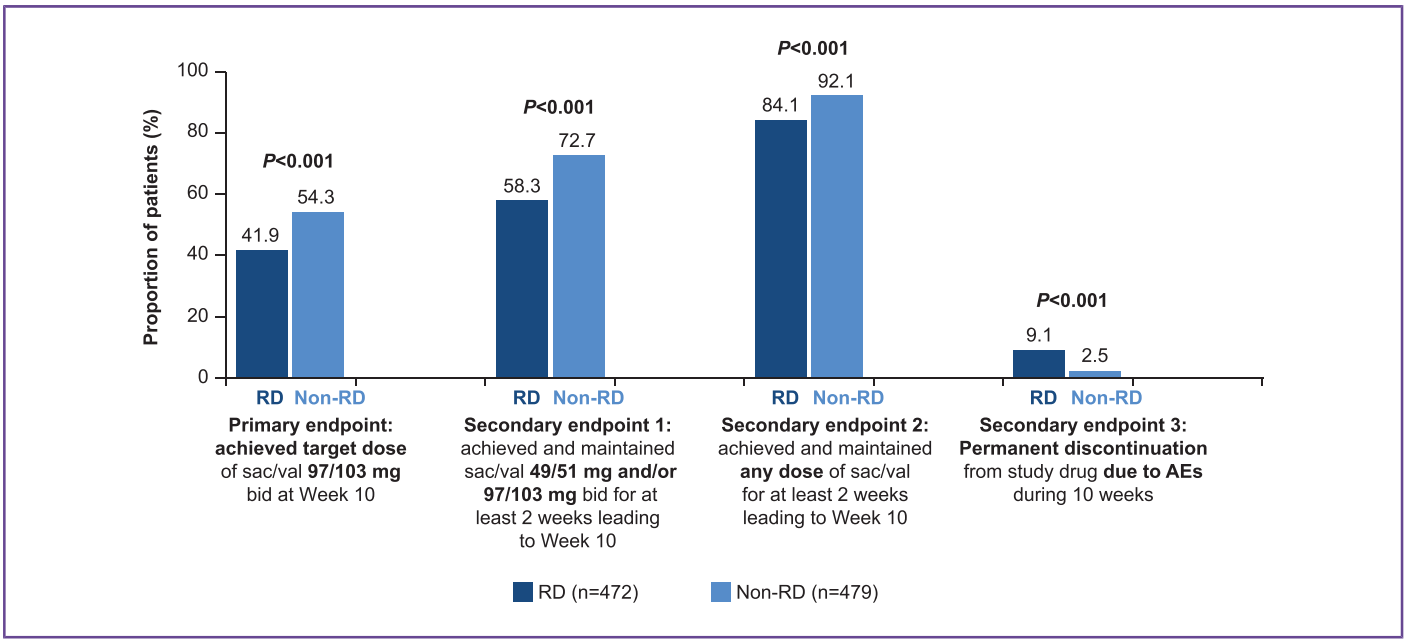


Fig. 1. Primary and secondary end points by presence or absence of RD (safety analysis set). AE, adverse event; bid, twice daily; RD, renal dysfunction; sac/val, sacubitril/valsartan.

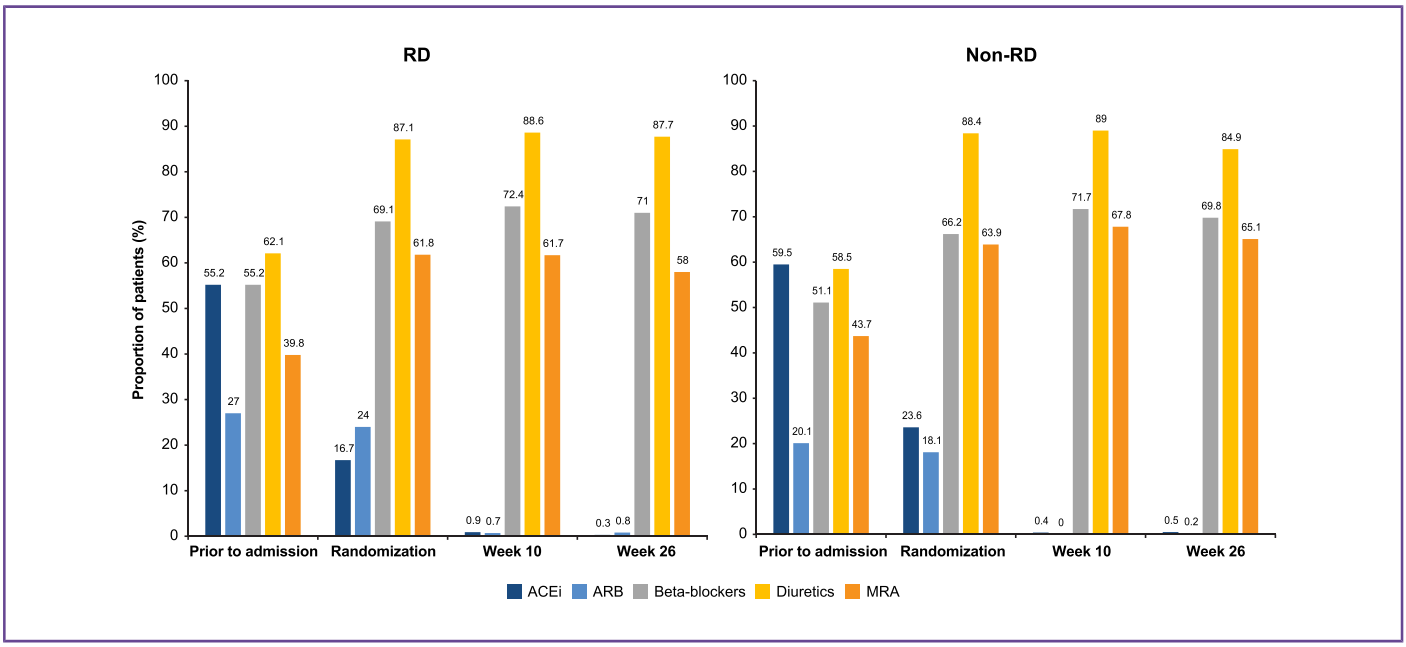
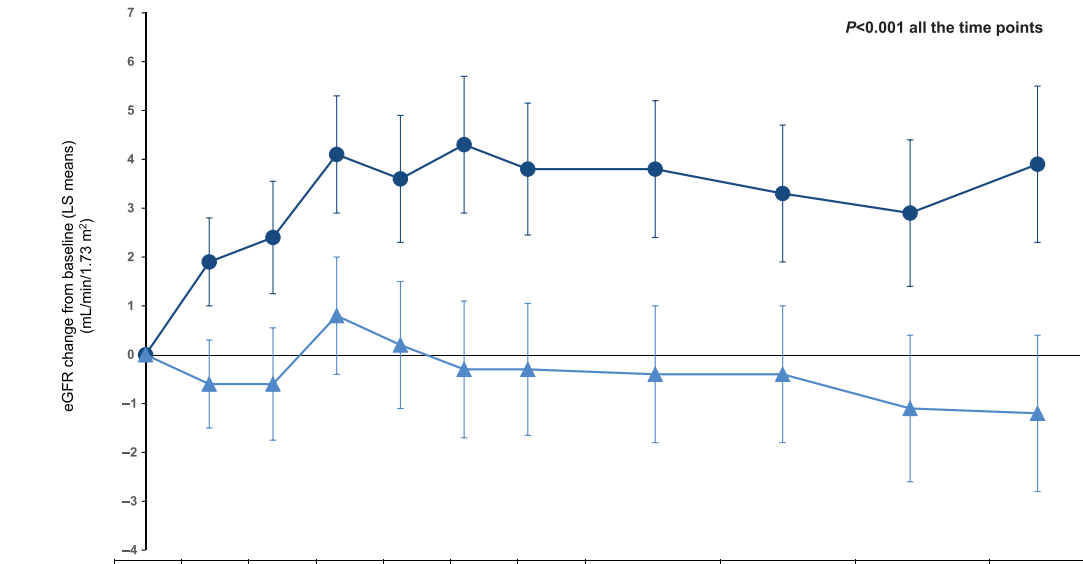


Fig. 2. Concomitant medication use by presence or absence of renal dysfunction (safety analysis set). ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

patients without RD, there was no significant difference in eGFR improvements by 4 weeks between patients who initiated sacubitril/valsartan in-hospital or after discharge (treatment difference in LSM 0.7, 95% CI −1.9 to 3.3; $P = .595$), and this trend was sustained throughout the 26-week study duration (Supplementary Fig. 2b).

Cardiac Biomarkers

The percentage changes in NT-proBNP and hsTnT from baseline are presented in Fig. 4. At week 10, treatment with sacubitril/valsartan was associated with sustained decreases in NT-proBNP levels from baseline in patients in both RD (LSM 0.7, 95% CI 0.6−0.8) and non-RD subgroups (LSM 0.6, 95% CI 0.5−0.6), although the decrease was greater in those without RD (ratio of LSM [RD vs non-RD] 1.3, 95% CI 1.2−1.4, $P < .001$). A similar trend was observed in change of hsTnT from baseline (ratio of LSM [RD vs non-RD] 1.2, 95% CI 1.1−1.3, $P < .001$). The magnitude of change in both biomarkers was greater in patients in the non-RD subgroup at week 10 (NT-proBNP −28.6% RD subgroup vs −44.8% non-RD subgroup;



	Baseline	Discharge	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 14	Wk 18	Wk 22	Wk 26
RD	0	1.9	2.4	4.1	3.6	4.3	3.8	3.8	3.3	2.9	3.9
Non-RD	0	−0.6	−0.6	0.8	0.2	−0.3	−0.3	−0.4	−0.4	−1.1	−1.2

Fig. 3. eGFR change from baseline (LS means) and treatment difference during the 26-week study duration by presence or absence of RD (safety analysis set). eGFR, estimated glomerular filtration rate; LS, least-square; RD, renal dysfunction.

hsTnT −20.3% RD subgroup vs −33.9% non-RD subgroup) (Fig. 4).

All-cause Rehospitalizations and HF-related Rehospitalizations

Comparison of event rates during the entire 26-week study duration between patients with and without RD indicates that patients with RD had a higher rate of all-cause rehospitalization (number of events 180 RD subgroup vs 143 non-RD subgroup, relative risk 1.3, 95% CI 1.1−1.,; $P = .003$) and HF-related rehospitalization (number of events 68 RD subgroup vs 40 non-RD subgroup, relative risk 1.6, 95% CI 1.1−2.4, $P = .002$) (Fig. 5).

Safety and Tolerability

Hyperkalemia, hypotension, and cardiac failure were the most frequently reported AEs during the first 10 weeks after initiation of sacubitril/valsartan in both RD and non-RD subgroups (Supplementary Table 1). RD at baseline was associated with an increased occurrence of hyperkalemia (16.3% vs 6.5%, $P < .001$) and cardiac failure (9.7% vs 5.6%, $P = .029$). However, there were no major differences observed for these AEs between the in-hospital vs postdischarge initiation groups in either the RD or non-RD subgroup (Supplementary Table 2).

During the 10-week treatment period, investigators more often reported kidney-related AEs in the RD subgroup compared with the non-RD subgroup, renal impairment (6.4% vs 2.1%, $P = .002$), renal failure (3.6% vs 0.6%, $P = .002$), and acute kidney injury (2.8% vs 0.4%, $P = .002$). However, a lower proportion of patients in the RD subgroup compared with non-RD experienced a >50% increase from baseline in serum creatinine (1.7% vs 3.5%, $P = .07$) (Supplementary Table 1).

Discussion

RD is a common comorbidity in patients with HF and is usually associated with a worse prognosis and underuse/underdose of guideline-recommended-HF treatments, such as ARNI, ACE inhibitors, ARBs, BBs, and MRAs.[16,17] In the pivotal PARADIGM-HF trial, which demonstrated superiority of sacubitril/valsartan over ACE inhibitor (enalapril) in decreasing the risk of death and HF hospitalization in patients with HFrEF,[18] >30% of the study population (2745 patients out of the 8399 overall study population) had concomitant RD (eGFR <60 mL/min/1.73 m^2) at enrollment. Among chronic patients with HFrEF with RD, treatment with sacubitril/valsartan compared with enalapril was associated with improved cardiovascular (CV) outcomes, slower rates of eGFR decline, and superior clinical benefits, including decreased all-cause or CV deaths and HF hospitalization, irrespective of baseline eGFR levels.[10]

The TRANSITION study demonstrated that in-hospital initiation of sacubitril/valsartan is feasible in patients with HFrEF stabilized after an ADHF event, with

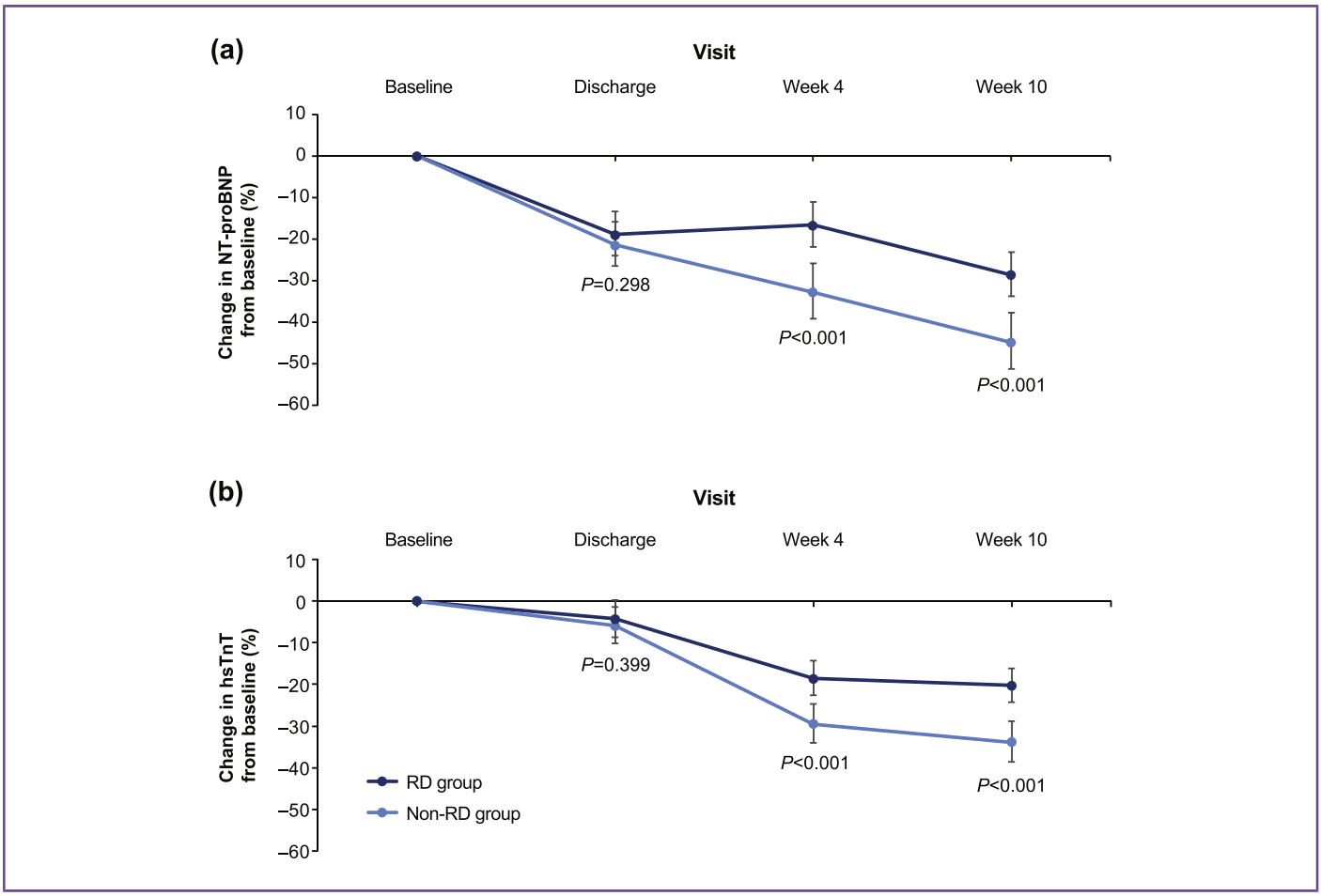


Fig. 4. Percentage change from baseline in (a) NT-proBNP and (b) hsTnT owing to initiation of sacubitril/valsartan during the 10-week treatment period by presence or absence of RD (safety analysis set). Note: RD was defined as eGFR (MDRD formula) ≥30 to <60 mL/min/1.73 m^2 determined at randomization. The graphs present pooled data from pre-discharge and postdischarge groups. eGFR, estimated glomerular filtration rate; hsTnT, high-sensitivity troponin T; MDRD, Modification of Diet in Renal Disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RD, renal dysfunction.

approximately 50% of patients achieving the target dose (97/103 mg twice daily) within the first 10 weeks.[19] Although HF treatment guidelines consistently recommend up-titration of medications to the target doses defined in clinical trials, comorbidities often limit the ability of patients to achieve these.[20] Many patients with HFrEF are not prescribed all 4 recommended HF therapy classes, or receive subtarget doses of guideline-directed medical therapies (GDMT). In the ESC-HF Long-Term Registry, among outpatients with chronic HF, the target doses of ACE inhibitor were achieved in only 29.3% patients, 24.1% for ARB, 17.5% for BBs, and 30.5% for MRA.[17] Data from the CHAMP-HF registry from the United States show that only 17% of patients received target doses of ACE inhibitor/ARBs, 14% ARNIs, and 28% BBs.[16] A systematic review based on 37 studies on patients with HFrEF indicated that worsening renal function is associated with non-use or subtarget dosing of GDMT for HFrEF.[21] In light of these data, the current finding that it is feasible and safe to reach a target dose of sacubitril/valsartan in ≤42% of patients with RD just recently stabilized after an ADHF event in TRANSITION, a trial that was designed to be close to real-world clinical practice, is of significant clinical importance.

This analysis is the first to study the influence of RD on sacubitril/valsartan initiation and up-titration in patients with HFrEF stabilized from ADHF and confirms that RD at baseline was associated with a lower proportion of patients achieving the target dose of 97/103 mg twice daily of sacubitril/valsartan at week 10. Despite this anticipated observation, 84% of patients with HFrEF with RD were able to initiate and maintain any dose of sacubitril/valsartan within the vulnerable first 10 weeks after an ADHF event. Initiation of sacubitril/valsartan in patients with RD early after an ADHF event was generally well-tolerated. Patients with RD at enrollment experienced higher incidence rates of hyperkalemia, cardiac failure, and renal failure compared with patients without RD, which could be attributed to the overall higher risk profile of these comorbidities in the postacute HF vulnerable time and setting. There were approximately 9% of patients with RD who permanently discontinued sacubitril/valsartan owing to AEs in this study.

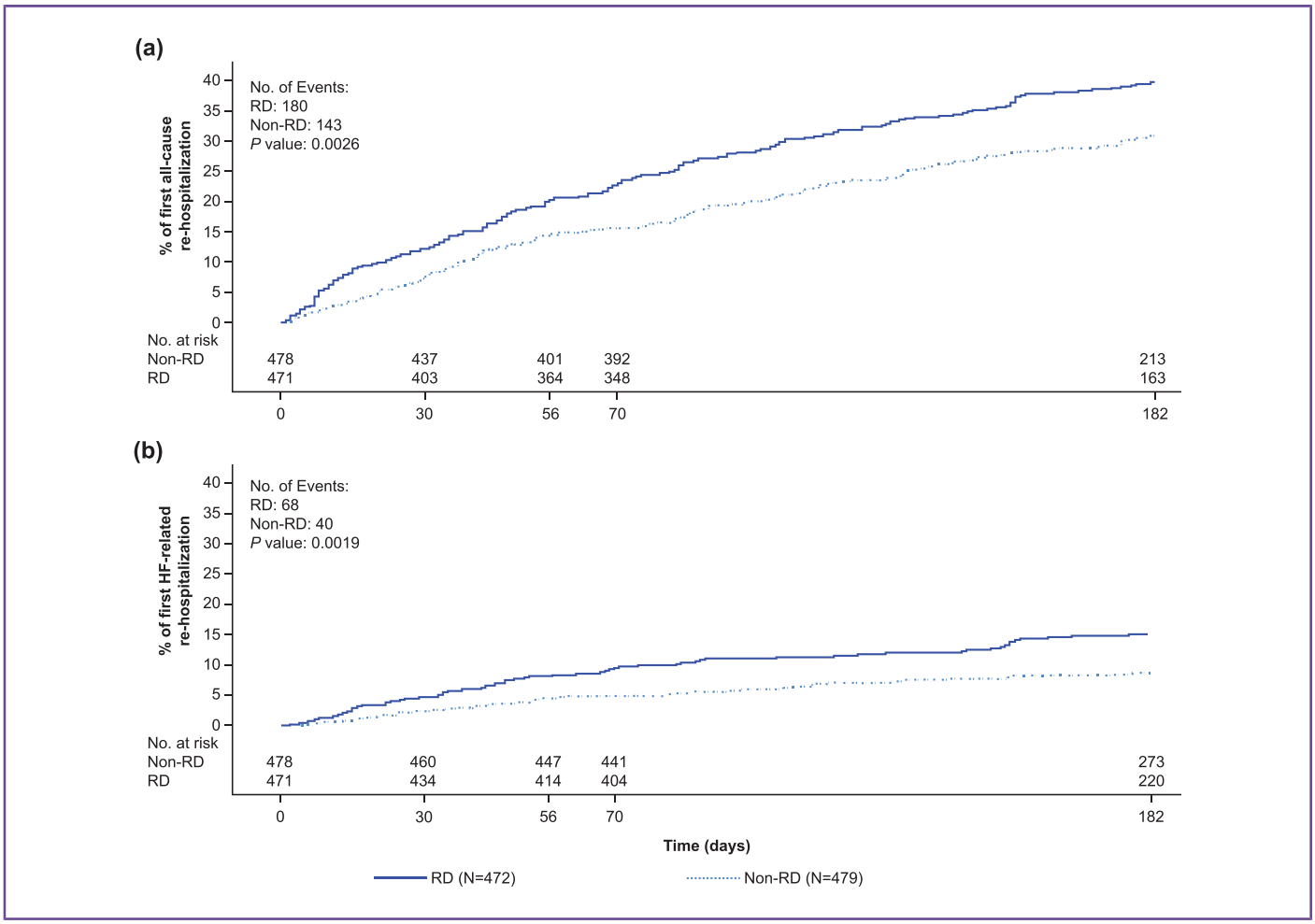


Fig. 5. Time to (a) first all-cause rehospitalization and (b) first HF-related rehospitalization during the 26-week study duration by presence or absence of RD (safety analysis set). Note: The graphs present pooled data from pre-discharge and postdischarge groups. The 95% CIs were estimated by using the Wilson method. CI, confidence interval; HF, heart failure; RD, renal dysfunction.

Supportive evidence from the TITRATION (A Multicenter, Randomized, Double-blind, Parallel Group Study to Assess the Safety and Tolerability of Initiating Sacubitryl/Valsartan in Heart Failure Patients Comparing Two Titration Regimens) study, in which one-third of the study population had RD (eGFR <60 mL/min/1.73 m^2) at baseline, indicates that more patients on a low ACE inhibitor/ARB dose before entering the study achieved and maintained the sacubitril/valsartan target dose if they were up-titrated more gradually. This difference was owing to fewer hypotension-, hyperkalemia-, and RD-related AEs with gradual up-titration over 6 weeks instead of an expedient 3-week up-titration regimen.[22] These findings support a slower up-titration approach for patients with RD. An approach to individualize initiation and up-titration of treatment among high-risk patients with HF, such as those with concomitant RD (eGFR >30 mL/min/1.73 m^2), may be considered based on the patient's clinical profile. Such an approach primarily targets the main neurohormonal systems associated with pathogenesis of HFrEF by initiating the patients on ARNI (sacubitril/valsartan) or an ACE inhibitor, followed by BBs. An MRA or sodium-glucose transport protein 2 inhibitor and diuretics can be added later in the regimen based on the physician's decision.[23]

In the present analysis, it was observed that the initiation and up-titration of sacubitril/valsartan in patients with or without RD did not affect optimization of other HF GDMT treatments, because use of BBs, MRAs, and diuretics increased by approximately 20% at 10 weeks after hospitalization. Additionally, results from recent studies indicate that patients with HFrEF simultaneously treated with ARNI and an sodium-glucose transport protein 2 inhibitor experience more pronounced improvement in cardiac function and a decreased risk of CV death or hospitalization compared with ARNI or sodium-glucose transport protein 2 inhibitor alone.[24,25] This finding is encouraging, especially considering recent HF guideline recommendations to initiate low doses of all 4 foundational HFrEF therapies within a short time frame instead of sequential initiation followed by full up-titration of one drug.[7,8] Hence, efforts should be made to initiate ARNIs in a wider range of patients with HFrEF and concomitant

RD (eGFR 30−60 mL/min/1.73 m^2) in parallel with the optimization of other GDMT.

In the current analysis, treatment with sacubitril/valsartan was associated with rapid, significant, and sustained improvement in NT-proBNP and hsTnT levels among patients with HFrEF with RD, although greater improvements were observed in those without RD. As might be expected, patients with RD had lower baseline eGFR levels, which improved significantly after 4 weeks of treatment initiation with sacubitril/valsartan and was sustained throughout the study duration, whereas patients without RD had baseline eGFR levels in the normal range that remained stable throughout. A recently conducted meta-analysis (n = 16456) of 10 randomized clinical trials (including PARADIGM-HF [A Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction], PARAGON-HF [Angiotensin—Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction], EVALUATE-HF [A Multicenter, Randomized, Double-blind, Double-dummy, Parallel Group, Active-controlled, Forced-titration, 12-week Comparison of Combined Angiotensin-neprilysin Inhibition With Sacubitril and Valsartan Versus Enalapril on Changes in Central Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction], PIONEER-HF [A Multicenter, Randomized, Double-blind, Double dummy, Parallel Group, Active-controlled 8-week Study to Evaluate the Effect of Sacubitril and Valsartan (LCZ696) Versus Enalapril on Changes in NT-proBNP and Safety and Tolerability of In-hospital initiation of LCZ696 Compared to Enalapril in HFrEF Patients who have been Stabilized Following Hospitalization for Acute Decompensated Heart Failure (ADHF)], PARAMOUNT-HF [A 36-week, Randomized, Double-blind, Multi-center, Parallel Group, Active Controlled Study to Evaluate the Efficacy, Safety and Tolerability of LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction], and UK HARP-III [United Kingdom Heart and Renal Protection-III], among others) demonstrated that treatment with sacubitril/valsartan in patients with HFrEF and RD was associated with a reduction in CV outcomes and renal impairment.[26] Results of a previously conducted analysis from PIONEER-HF showed consistent reductions in CV death and HF-related rehospitalizations with in-hospital initiation of sacubitril/valsartan compared with enalapril in HF patients with and without RD.[27] Moreover, maintenance of the highest tolerable doses of ARNI has been shown to be beneficial compared with an ACE inhibitor-based regimen.[28,29] The benefit of sacubitril/valsartan treatment among patients with HF and RD is further supported by real-world evidence from studies conducted in multiple geographical locations.[30−32]

The presence of RD as a comorbidity in patients with HF is a known predictor of a worse prognosis associated with a significantly increased risk of further deterioration in renal function.[1,27,33] Consistent with this finding, in the current analysis, patients with RD had clinical markers of a more severe HF syndrome and higher levels of other risk factors, such as older age, elevated levels of cardiac biomarkers, and more frequently had a history of HF/prior HF-related hospitalizations, hypertension, diabetes, atrial fibrillation, myocardial infarction, and stroke. Therefore, the adverse clinical phenotype would explain the observed higher risk of rehospitalization in the presence of RD, despite a significant improvement in eGFR. Similar trends were observed in ambulatory HF patients at baseline in PARADIGM-HF, in which 30% of HF patients with RD experienced the primary outcome of CV death or HF hospitalization despite an overall improvement in eGFR compared with 21% patients without RD.[10] Findings of this analysis support further investigation of the potential benefits of sacubitril/valsartan in preserving renal function in patients with HF and concomitant RD.

Limitations

Patients in the RD and non-RD subgroups in the TRANSITION study received open-label sacubitril/valsartan, but the treatment benefit was not assessed against a comparator. However, the early clinical benefits of sacubitril/valsartan treatment compared with enalapril have been illustrated in patients with ADHF, irrespective of the presence or absence of renal impairment, in PIONEER-HF.[27]

The analysis excluded patients with an eGFR of <30 mL/min/1.73 m^2, who are at even higher risk of kidney failure and a worse overall prognosis. Moreover, variability of eGFR laboratory measurements early after an ADHF event may be affected by more intensive in-hospital management and concomitant comorbidities, which might have contributed to some potential misclassification of patients in the RD group and vice versa. It is noteworthy that the 26-week follow-up in the TRANSITION study did not allow assessment of the long-term impact of renal impairment on CV outcomes; however, longer term benefits have already been reported from the 27-month median follow-up duration in PARADIGM-HF. Further, considering the increase in the concomitant use of BBs, MRAs, and diuretics in the study, the potential additive treatment benefit of these drugs with sacubitril/valsartan in improving cardiac parameters in at least some patients cannot be disregarded.

In addition, the limitations of the overall randomized, however, open-label study design of the TRANSITION study, and some potential biases, such as earlier initiation of sacubitril/valsartan after an ADHF event, more time for treatment up-titration for the predischarge group, and closer laboratory monitoring of AEs while in hospital compared with postdischarge settings, need to be considered. Overall, results from the current analysis must be interpreted with caution considering the inherent limitations of a post hoc analysis.

Lay Summary

- Renal dysfunction (RD) is a common comorbidity in patients with heart failure (HF) and is usually associated with a worse prognosis and underuse/underdose of guideline-recommended HF treatments, such as sacubitril/valsartan (angiotensin receptor neprilysin inhibitors), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists.
- The efficacy of sacubitril/valsartan over ACE inhibitors in reducing adverse clinical outcomes has already been demonstrated in clinical trials; however, sacubitril/valsartan is not initiated and/or up-titrated in most patients with both HF with reduced ejection fraction (HFrEF) and concomitant RD.
- The current study shows that majority of patients with HFrEF and concomitant RD hospitalized for ADHF tolerated early initiation of sacubitril/valsartan and showed significant improvements in estimated glomerular filtration rate and cardiac biomarkers. A higher susceptibility to hyperkalemia and a more fragile status should be considered in patients with concomitant RD who may require slower, gradual up-titration during the vulnerable postdischarge phase after a decompensation event.

Brief Lay summary

Treatment with sacubitril/valsartan is not initiated and/or a low dose is prescribed among most patients with both heart failure and kidney disease. This study shows that treatment with sacubitril/valsartan is feasible in the majority of patients with heart failure and kidney disease who were hospitalized for worsening cardiac symptoms, and early initiation of sacubitril/valsartan improved markers of kidney and cardiac function in these patients. Some of these patients may have a higher susceptibility to adverse renal outcomes; hence, a gradual approach to increasing the dosage of sacubitril/valsartan should be followed, especially just after being discharged from the hospital.

Conclusions

Early initiation of sacubitril/valsartan after hospitalization owing to an ADHF event was tolerated by the majority of patients with HFrEF with RD, and it was associated with early and significant improvements in eGFR from baseline to week 4 and through the 26-week study duration. Considering the proven benefits of ARNI in patients with HFrEF, concomitant RD should not discourage physicians from initiating sacubitril/valsartan early after hemodynamic stabilization following an ADHF event and up-titrating to the highest tolerable dose. However, a higher susceptibility to hyperkalemia and a more fragile status should be considered in patients with concomitant RD who may require slower, gradual up-titration during the vulnerable postdischarge phase following a decompensation event.

EWA STRABURZYNSKA-MIGAJ

Declaration of Competing Interest

E. Straburzynska-Migaj received consultancy fees and/or honoraria from Novartis, Boehringer Ingelheim, Pfizer, Abbott, Servier, AstraZeneca, and Bausch Health. M. Senni received consultancy fees and/or speaker's honoraria from Novartis, Bayer, Abbott, Merck, AstraZeneca, Vifor Pharma, and Boehringer Ingelheim. R. Wachter is a member of advisory boards and/or received speaker's honoraria from Boehringer Ingelheim, Bayer, CVRx, Medtronic, Novartis, Pfizer, Sanofi, and Servier, and research grants from Boehringer Ingelheim, European Union, and Bundesministerium für Bildung und Forschung. C. Fonseca received consultancy fees, grants and speaker's honoraria from Astra Zeneca, Bayer, Boehringer Ingelheim, Novartis, Roche, Sanofi, Servier, and Vifor Pharma.

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Lawrence are employees of Novartis. B. Suryawanshi is an employee of IQVIA, India. D. Pascual-Figal declares research grants from Roche, Novartis, AstraZeneca, Medtronic, and Pfizer; and consultancy or educational honoraria from AstraZeneca, Novartis, Servier, Pfizer, Vifor Pharma, Rovi, and Abbott.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2023.08.021.

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