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ORIGINAL ARTICLE

Influence of diabetes on sacubitril/valsartan titration and clinical outcomes in patients hospitalized for heart failure

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Abstract

Aims Diabetes mellitus is associated with worse outcomes and lower attainment of disease-modifying therapies in patients with heart failure with reduced ejection fraction (HFrEF). This post hoc analysis of TRANSITION compared the patterns of tolerability and uptitration of sacubitril/valsartan in patients with HFrEF stabilized after hospital admission due to acute decompensated HF depending on the presence or absence of diabetes as a co-morbidity.

Methods TRANSITION, a randomized, open-label study compared sacubitril/valsartan initiation pre-discharge vs. post-discharge (up to14 days) in 991 patients hospitalized for acutely decompensated HFrEF. The impact of diabetes status on tolerability and safety was studied at 10-week and 26-week post-randomization.

Results Among the 991 patients analysed at baseline, 460 (46.4%) had diabetes and exhibited a higher risk profile. At 10 weeks, sacubitril/valsartan target dose (97/103 mg bid) was achieved in a similar proportion of patients in each subgroup, when initiated pre-discharge or post-discharge respectively [diabetes subgroup: 47% (n = 105/226) vs. 50% (n = 115/228); relative risk ratio (RRR), 0.923; P = 0.412; non-diabetes subgroup: 45% (n = 119/267) vs. 51% (n = 133/261); RRR, 0.878; P = 0.155]. The proportions of patients achieving and maintaining either 49/51 mg or 97/103 mg bid [diabetes subgroup: 61.1% (n = 138/226) vs. 67.5% (n = 154/228); RRR, 0.909; P = 0.175; non-diabetes subgroup: 62.9% [n = 168/267] vs 69.3% [n = 181/261]; RRR, 0.906; P = 0.118] or any dose for ≥2 weeks leading to Week 10 [diabetes subgroup: 85% (n = 192/226) vs. 88.2% (n = 201/228); RRR, 0.966; P = 0.356; non-diabetes subgroup: 86.9% (n = 232/267) vs. 90.8% (n = 237/261); RRR, 0.963; P = 0.215] were also similar in each subgroup, when initiated pre-discharge or post-discharge, respectively. At 10 weeks, hypotension and renal dysfunction rates were similar, although hyperkalaemia was higher among patients with diabetes (15.9% vs. 9.5%). The rate of permanent discontinuation due to adverse events was similar in the diabetes and non-diabetes subgroups at 10 weeks, respectively: pre-discharge (7.5% vs. 7.1%) or post-discharge (5.7% vs. 4.2%). Similar patterns of uptitration and tolerability were observed at 26 weeks. Cardiac biomarkers including NT-proBNP ($P < 0.005$) and hs-TnT ($P < 0.005$) reduced significantly from baseline levels in both subgroups at Weeks 4 and 10; however, the response was greater among patients without diabetes. Mortality (diabetes vs. non-diabetes subgroups: 3.3% vs 4.0%; P = 0.438) and HF rehospitalization (diabetes vs. non-diabetes subgroups: 36.3% vs. 33.0%; P = 0.295) did not differ between the groups at 26 weeks.

Conclusions Despite a higher risk profile among patients with diabetes, sacubitril/valsartan initiation either before or shortly after discharge in hospitalized patients with HFrEF resulted in comparable rates of dose up-titration and tolerability as in those without diabetes.

Keywords Acute decompensated heart failure; Angiotensin receptor neprilysin inhibitor; Diabetes mellitus; Heart failure with reduced ejection fraction; N-terminal-pro-B-type natriuretic peptide; Sacubitril/valsartan

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Introduction

Around 30–40% of patients with heart failure (HF) have diabetes mellitus as a co-morbidity, and the presence of diabetes is associated with a higher risk of HF hospitalization and all-cause and cardiovascular (CV) mortality.[1]

Current recommendations for the management of heart failure with reduced ejection fraction (HFrEF) include therapies such as angiotensin receptor neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), and β-blockers to be up-titrated to the maximum tolerated or target doses in a timely manner.[2,3] However, in practice, the majority of patients do not achieve target doses.[4–7] One contributor to low rates of target dose achievement could be the presence of co-morbidities such as diabetes, which is associated with a higher frequency of adverse events (AEs), especially at older age. Clear evidence of potential to succeed and safety are required to support teams in optimizing the care of such patients with comorbidities, who are at highest clinical risk.[8] This situation is compounded in patients hospitalized due to an acute decompensated HF (ADHF) event as they present a higher risk of short-term AEs after discharge. The presence of diabetes further increases such clinical vulnerability.[9] On the other hand, hospitalization may provide a vital opportunity for the initiation and successful up-titration of guideline-recommended disease-modifying HF therapies.[10] Sacubitril/valsartan, a first-in-class ARNI, has demonstrated superiority over ACEi therapy in patients with HFrEF on important endpoints.[11,12] Thus, if treatment with sacubitril/valsartan can be initiated and up-titrated early in vulnerable populations, it could result in improved outcomes.[13] Hence, patients with diabetes admitted due to decompensated HF are an easily identifiable target population in whom in-hospital treatment initiation and further optimization are crucial as these may yield short-term and long-term benefits.

TRANSITION showed that sacubitril/valsartan is well tolerated when initiated pre-discharge or shortly after discharge in a wide range of patients with HFrEF.[14] However, the evidence reflecting the tolerability and the feasibility of initiation and up-titration of sacubitril/valsartan in patients with diabetes hospitalized for ADHF is limited. This post hoc analysis aimed to assess the specific patterns of tolerability and success of uptitration of sacubitril/valsartan among patients with diabetes as a comorbidity at baseline, along with their predictors. This analysis also analysed trends in biomarkers and time to first HF and all-cause rehospitalizations.

Methods

Study design and population

TRANSITION (NCT02661217) was a randomized, international (19 countries), multicentre (156 sites), open-label study to compare the safety and tolerability of initiating sacubitril/valsartan in hospital vs. early after discharge in patients with stabilized ADHF and HFrEF. The study design, rationale, and a detailed description of population baseline characteristics and primary results have been published previously.[14,15] The study included male or female patients aged ≥18 years hospitalized for an episode of ADHF (de novo HF or deterioration in chronic HF) with a left ventricular ejection fraction (LVEF) ≤40%, New York Heart Association (NYHA) Class II–IV, and systolic blood pressure ≥100 mmHg at screening.[14] Of the 1124 patients screened between February 2016 and December 2017, 1002 patients were randomized. This post hoc analysis comprised all randomized study patients categorized into two subgroups: patients with diabetes based on the medical history and available medical records at baseline (n = 460; 46%) and those without known diabetes (n = 531; 54%) at baseline. In total, 982 patients (diabetes: n = 454 and non-diabetes: n = 528) received at least one dose of sacubitril/valsartan (safety analysis set). The treatment period comprised the initial 10 weeks after randomization and the follow-up period the next 16 weeks.

TRANSITION was conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and with the ethical principles laid down in the Declaration of Helsinki.[16] The trial protocol was approved by the ethics committees at all participating centres. All patients provided written informed consent.

Study endpoints and assessments

The primary endpoint of this analysis was the proportion of patients achieving the target dose of sacubitril/valsartan (97/103 mg twice daily [bid]) at 10 weeks post-randomization, regardless of dose changes or interruptions in pre-discharge and post-discharge groups between patients with and without diabetes. The pre-discharge group comprised patients who were initiated on sacubitril/valsartan in hospital, whereas post-discharge group included patients who were initiated on sacubitril/valsartan early after dis-

charge from the hospital. The three secondary end points were (i) the proportion of patients who received and maintained sacubitril/valsartan 49/51 mg and/or 97/103 mg bid dose for at least 2 weeks leading up to Week 10; (ii) the proportion of patients who received and maintained any dose of sacubitril/valsartan for at least 2 weeks leading up to Week 10; and (iii) the rates of permanent study drug discontinuations due to AEs during the 10-week treatment period in the diabetes and non-diabetes subgroups after an ADHF event.

In addition, patterns of cardiac biomarkers N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT) measured after haemodynamic stabilization at randomization and at 4-week and 10-week post-randomization[15,17] were assessed as a pre-defined exploratory endpoint.

Safety

Safety parameters, specifically, physical examination, vital signs, laboratory evaluations, electrocardiogram, and reported AEs during the course of the study, were evaluated in the diabetes and non-diabetes subgroups with a focus on the frequencies of prespecified AEs of special interest such as hypotension, hyperkalaemia, and renal dysfunction.

Statistical analysis

The full analysis set (FAS) consisted of all randomized patients except for those randomized inadvertently. Patients who did not start treatment within protocol-specified windows were excluded from FAS. The safety analysis set consisted of all patients included in the FAS who received at least one dose of study medication.

Primary and secondary objectives for the diabetes and non-diabetes subgroups were analysed by using the stratified Cochran–Mantel–Haenszel method. The probability of achieving the target dose at the end of Week 10 was estimated with a two-sided 95% confidence interval (CI) for each subgroup. The relative risk ratio (RRR) was estimated with a two-sided 95% CI. The incidence of AEs including death and AEs of special interest were summarized by primary system organ class and preferred term. A multivariable logistic regression model analysis was used to determine the baseline predictors of achieving the primary endpoint. Odds ratios and 95% CIs were evaluated to identify patients with a high possibility of achieving the target dose. Candidate predictors were identified from baseline and medical history variables and were filtered in a univariate analysis at a level of $P < 0.2$. In the final multivariable analysis model, only predictors with $P < 0.05$ (and treatment group) were maintained.

The biomarkers NT-proBNP and hsTnT were analysed by fitting a repeated-measures mixed model on the log-transformed data with appropriate covariates. Geometric least square means along with 95% CIs were presented for the change from baseline. *P*-values of <0.05, 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 rehospitalization for HF and all-cause rehospitalization after discharge of index hospitalization were calculated using the Kaplan–Meier method and compared between the diabetes and non-diabetes subgroups. The Kaplan–Meier method was also used to estimate percentiles. Patients without any hospitalizations were censored at the last date of the study. The *P*-value to compare treatment groups was calculated using the log-rank test. SAS version 9.3 was used to perform all the statistical analyses.

Results

Study population

A total of 991 participants were analysed. The proportion of patients in the pre-discharge and post-discharge groups was similar in the diabetes (226 vs. 234) and non-diabetes subgroups (269 vs. 262). The baseline characteristics of the diabetes and non-diabetes subgroups are presented in *Table 1*. Patients in the diabetes subgroup were older compared with those in the non-diabetes subgroup and had higher body mass index (BMI), lower mean estimated glomerular filtration rate (eGFR), and higher LVEF. The proportion of patients with diabetes having a prior medical history of hypertension or myocardial infarction was markedly higher compared with those without diabetes. Otherwise, the percentages of patients with newly diagnosed (de novo) HF and ACEi/ARB-naïve (pre-trial use as per strata assignment) was lower in those with diabetes. Despite this, the use of HF-related and CV-related medications such as ACEi, ARBs, and β-blockers prior to admission was higher in those with diabetes. The time from discharge to the first dose of the study drug was similar between the diabetes and non-diabetes subgroups (*Figure S1*).

Uptitration at Week 10

The dose achievement endpoints by subgroup at Week 10 are shown in *Figure 1*. Despite the higher risk profile among patients with diabetes, a similar proportion of patients in each subgroup was able to achieve target dose of sacubitril/valsartan (97/103 mg bid) at Week 10 when initiated either at pre-discharge or post-discharge. In those with diabetes, 47% (n = 105/226) of patients in the pre-discharge group and 50% (n = 115/228) in the post-discharge group achieved

Table 1 Baseline characteristics

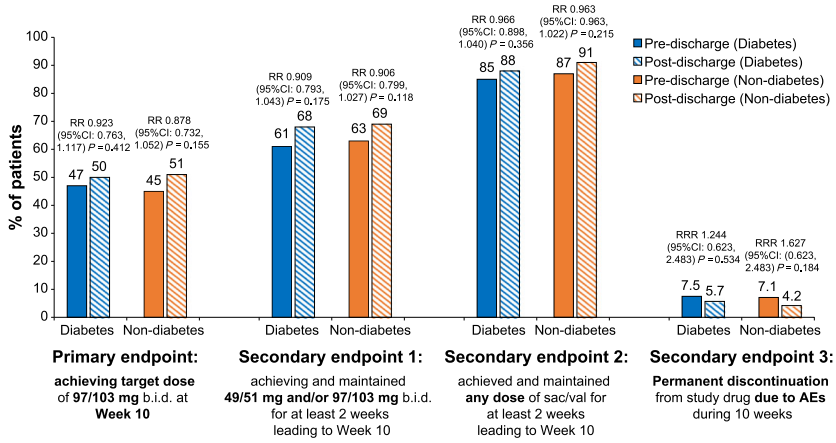
Parameters	Diabetes subgroup $n = 460$	Non-diabetes subgroup $n = 531$	P value[a]
Age, mean ± SD, years	68.5 ± 10.2	65.4 ± 13.2	<0.001
Male, *n* (%)	344 (74.8)	400 (75.3)	0.843
Caucasian, *n* (%)	443 (96.3)	520 (97.9)	0.187
BMI, median (min–max), kg/m^2	29.40 (18.1–48.5)	27.71 (17.1–58.8)	<0.001
LVEF, mean ± SD, %	29.7 ± 7.2	28.0 ± 7.8	<0.001
NYHA class, *n* (%)			0.321
I	3 (0.7)	0 (0.0)	
II	290 (63.0)	345 (65.0)	
III	159 (34.6)	180 (33.9)	
IV	6 (1.3)	5 (0.9)	
Missing	2 (0.4)	1 (0.2)	
SBP, mean ± SD, mmHg	125.6 ± 14.85	123.1 ± 13.02	0.005
Pulse rate at screening, mean ± SD, beats/min	74.0 ± 12.18	74.7 ± 13.49	0.359
eGFR[b], mean ± SD, mL/min/1.73 m^2	60.0 ± 21.66	63.9 ± 18.19	0.003
Ischaemic HF aetiology, *n* (%)	254 (55.2)	203 (38.2)	<0.001
Newly diagnosed (de novo) HF, *n* (%)	92 (20.0)	194 (36.5)	<0.001
Prior hospitalization for HF, *n* (%)	260 (56.5)	225 (42.4)	<0.001
NT-proBNP[b], median (min–max), pg/mL	1788.0 (32–35 000)	1693.0 (13–31,362)	0.825
hs-TnT, median (min–max), ng/L	31.0 (6–1090)	26.0 (3–920)	0.017
Medical history, *n* (%)			
Hypertension	403 (87.6)	342 (64.4)	<0.001
Atrial fibrillation	226 (49.1)	251 (47.3)	0.559
Myocardial infarction	190 (41.3)	149 (28.1)	<0.001
Stroke	48 (10.4)	49 (9.2)	0.524
Cardiac resynchronization therapy	46 (10.0)	42 (7.9)	0.249
Implantable cardioverter defibrillator	86 (18.7)	66 (12.4)	0.006
Medications by randomization strata, *n* (%)			
ACEi	246 (53.5)	257 (48.4)	<0.001
ARB	133 (28.9)	114 (21.5)	<0.001
ACEi/ARB-naïve	81 (17.6)	160 (30.1)	<0.001
Background medications prior to admission, *n* (%)[c]			
ACEi	234 (55.6)	232 (57.3)	
ARB	115 (27.3)	86 (21.2)	
β-Blockers	231 (54.9)	206 (50.9)	
Diuretics	270 (64.1)	230 (56.8)	
Loop diuretics	256 (60.8)	218 (53.8)	
MRA	176 (41.8)	170 (42.0)	

ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-TnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.
Values presented as mean ± SD unless specified.
[a]Fisher's exact test.
[b]Parameters were assessed at screening except for parameters with letter b that were assessed at randomization. Percentage calculated based on the patients with indication.
[c]Safety analysis set (diabetes $n = 454$ and non-diabetes $n = 528$).

the target dose of sacubitril/valsartan (RRR, 0.923; 95% CI, 0.763, 1.117; $P = 0.412$). Similarly, in the non-diabetes group, 45% ($n = 119/267$) vs. 51% ($n = 133/261$) of the patients achieved the target dose of sacubitril/valsartan (RRR, 0.878; 95% CI, 0.732, 1.052; $P = 0.155$). More than 60% of the patients in both the subgroups achieved and maintained either the 49/51 mg or the 97/103 mg bid dose of sacubitril/valsartan for ≥2 weeks leading to Week 10, when initiated pre-discharge or post-discharge, respectively [diabetes subgroup: 61.1% ($n = 138/226$) vs. 67.5% ($n = 154/228$); RRR, 0.909; 95% CI, 0.793; $P = 0.175$; non-diabetes subgroup: 62.9% ($n = 168/267$) vs. 69.3% ($n = 181/261$); RRR, 0.906; 95% CI, 0.799, 1.027; $P = 0.118$; *Figure 1*]. The proportion of patients who achieved and maintained any dose of sacubitril/valsartan for ≥2 weeks leading to Week 10 was also comparable across the two subgroups, when initiated pre-discharge or post-discharge, respectively [diabetes subgroup: 85% ($n = 192/226$) vs 88.2% [$n = 201/228$]; RRR, 0.966; 95% CI, 0.898, 1.040; $P = 0.356$; non-diabetes subgroup: 86.9% ($n = 232/267$) vs. 90.8% ($n = 237/261$); RRR, 0.963; 95% CI, 0.963, 1.022; $P = 0.215$; *Figure 1*].

Permanent discontinuation of sacubitril/valsartan due to AEs during 10-week treatment period was comparable between patients with and without diabetes. There were also no significant differences among the pre-discharge group compared with the post-discharge group, for patients with (7.5% and 5.7%; $P = 0.53$) and without diabetes (7.1% and 4.2%; $P = 0.18$).

Figure 1 Primary and secondary end points by diabetes status and treatment groups (safety analysis set). Safety analysis set (diabetes *n* = 454 and non-diabetes *n* = 528). AE, adverse event; bid, twice daily; RRR, relative risk ratio; sac/val, sacubitril/valsartan.



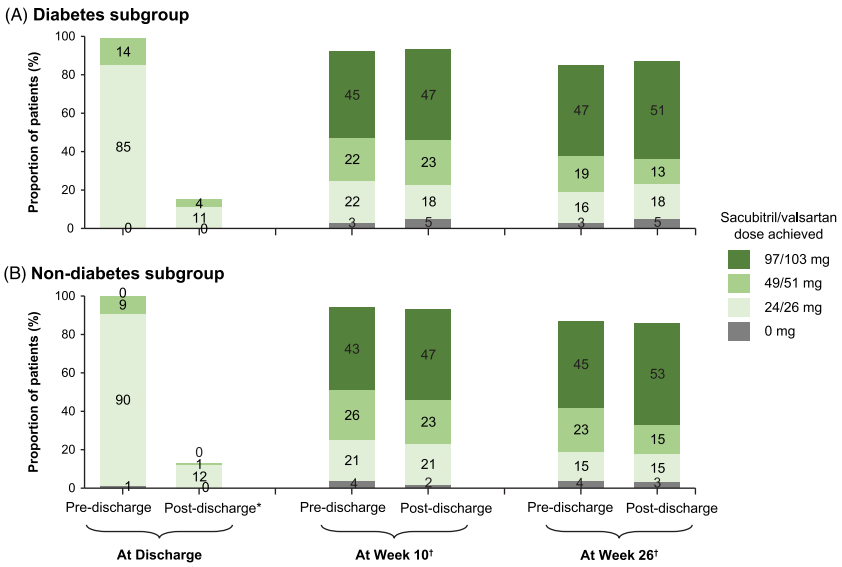
Persistence at Week 26

In the diabetes subgroup, the proportion of patients on target dose of sacubitril/valsartan (97/103 mg bid) increased to 46.5% vs. 51.3% by 26 weeks, in pre-discharge vs. post-discharge groups, respectively. Similarly, in the non-diabetes subgroup, the proportion at target dose increased to 44.6% vs. 53.3% by 26 weeks (*Figure 2A and 2B*).

Tolerability and safety

Hyperkalaemia, hypotension, and renal dysfunction were the most frequently reported AEs during the first 10 weeks in both the subgroups (*Figure S2A*). The proportion of patients with hyperkalaemia was higher in the diabetes (15.9%) than the non-diabetes (9.5%) subgroup (RRR, 1.67; 95% CI: 1.18, 2.36; *P* = 0.003) during the 10-week treatment period. In the pre-discharge and post-discharge groups, these values

Figure 2 Persistence of sacubitril/valsartan dosages at discharge, Week 10, and Week 26 by diabetes status (A: Diabetes subgroup; B: Non-diabetes subgroup) and pre-discharge or post-discharge treatment initiation groups. (A) Diabetes subgroup and (B) Non-diabetes subgroup. *Study medication was provided at discharge and patients initiated first dose of sacubitril/valsartan the next day after discharge. †At Week 10 and Week 26, only patients who reported as completed are included.



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were 15.0% and 14.5% in the diabetes subgroup vs. 8.2% and 8.8% in the non-diabetes subgroup. Similar to the findings during the 10-week treatment period, the proportion of patients with hyperkalaemia was higher in the diabetes subgroup during the 26-week treatment period (diabetes: 17.8% vs. non-diabetes: 11.7%; RRR, 1.53; 95% CI: 1.12; 2.09; P = 0.008). No significant differences were found in terms of hypotension and renal dysfunction (*Table S1*). The proportion of patients with hypotension was comparable among patients with and those without diabetes during the 10-week (12.8% and 10.5% vs. 12.7% and 8.8%) and 26-week treatment periods (14.6% and 14.0% vs. 16.5% and 13.8%) in the pre-discharge and post-discharge groups, respectively.

The proportion of patients with renal impairment among the diabetes vs. non-diabetes subgroups during the 10-week treatment period was 4.4% and 5.7% vs. 5.6% and 1.1%, in the pre-discharge and post-discharge groups, respectively. During the 26-week treatment period, the corresponding values were 6.6% and 7.9% vs. 7.9% and 3.4% in the pre-discharge and post-charge groups, respectively. The proportion of patients who permanently discontinued due to AEs at Week 10 was comparable in the diabetes and non-diabetes subgroups, respectively (pre-discharge: 7.5% vs. 7.1%; post-discharge: 5.7% vs 4.2%; *Figure S2B*). Similarly, no differences were observed between the diabetes and non-diabetes subgroups, respectively, during the entire 26-week (6-month) study period (pre-discharge: 11.5% vs. 11.2%; post-discharge: 8.8% vs. 8.4%). In the multivariable analysis, the presence of ischaemic heart disease was a significant ($P < 0.05$) predictor of permanent study drug discontinuation due to AEs in population with or without diabetes.

Effect on biomarkers of wall stress and cardiac injury

Initiation of sacubitril/valsartan was associated with significantly marked and sustained reductions from baseline in NT-proBNP ($P < 0.05$) and hs-TnT ($P < 0.05$) levels in both the diabetes and the non-diabetes subgroups. However, the magnitude of both reductions was greater in the non-diabetes subgroup. Both groups exhibited a rapid reduction of hs-TnT concentrations, already significant at discharge, followed by a more pronounced reduction in the non-diabetes subgroup at Week 4 (least square mean: 1.155; 95% CI: 1.085–1.229; $P < 0.001$) and Week 10 (least square mean: 1.222; 95% CI: 1.140–1.310; $P < 0.001$; *Figure 3A*). Similarly, a rapid reduction in NT-proBNP was observed in both subgroups; however, the reductions were higher in patients with non-diabetes, which became significant at Week 4 (least square mean: 1.132; 95% CI: 1.037–1.236; P = 0.006) and was sustained until Week 10 (least square mean: 1.214; 95% CI: 1.084–1.359; $P < 0.001$; *Figure 3B*).

First HF rehospitalization and all cause rehospitalization

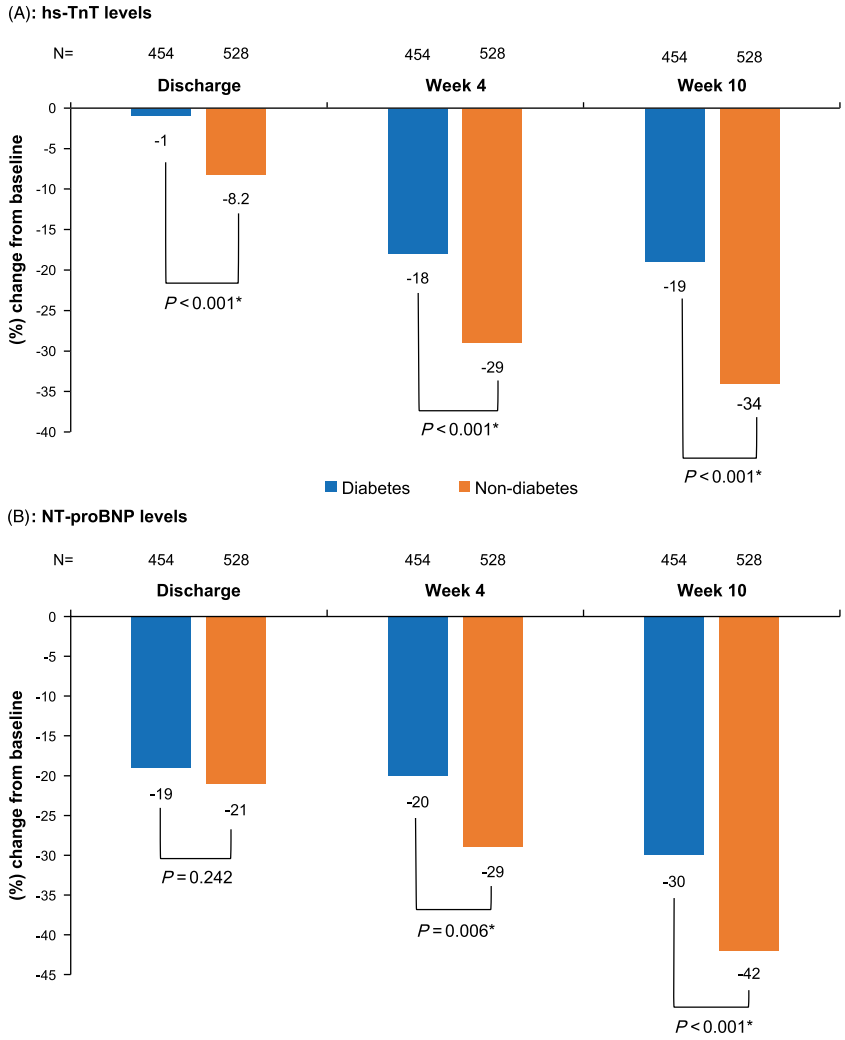
The Kaplan–Meier analysis demonstrated that the time-to-first HF rehospitalization (*Figure S3A*) and all-cause rehospitalization (*Figure S3B*) after discharge from index admission due to an ADHF event was similar between the two subgroups (P = 0.4725 and P = 0.3317, respectively). Over the 26-week duration of the study, 165/454 (36.3%) of patients with diabetes and 174/528 (33%) of patients without diabetes had HF-related rehospitalizations. The incidence of all-cause death during the 26-week duration was low and similar between the diabetes (3.3%) and non-diabetes (4.0%) subgroups (P = 0.438).

Discussion

Diabetes mellitus is a co-morbidity in 30–40% of all patients with HFrEF and considerably worsens the prognosis. It is associated with worse renal function, worse side effect profile, greater symptoms for a given degree of cardiac impairment, and higher hospitalization and mortality rates.[18–20] Partly as a result of this higher underlying risk, the benefits of optimal medical therapy are greater in patients with Type 2 diabetes mellitus,[21] and the drive to achieve optimization is more pressing. Despite this, the gap in HFrEF treatment optimization is similar in patients with and without diabetes. Initiation and titration of HF therapies in patients with diabetes are more challenging due to a higher rate of side effects, including renal dysfunction and hyperkalaemia.[1,22] Although hospitalization is associated with poor prognosis, and adversely affects quality of life, it may also serve as an opportunity to optimize medical therapy including uptitration.

TRANSITION confirmed that initiating sacubitril/valsartan in de novo HFrEF patients or switching from an ACEi/ARB to sacubitril/valsartan in HFrEF patients following stabilization after an ADHF event, either in hospital or shortly after discharge is feasible and well tolerated.[14] Early and sustained improvements in biomarkers of cardiac wall stress and myocardial injury were associated with in-hospital initiation of sacubitril/valsartan, indicating pathophysiological benefits of the prompt optimization of HF therapies during the in-hospital admission or early after discharge.[13,23] In PIONEER.HF, the in-hospital initiation of sacubitril/valsartan was associated with a greater reduction in NT-proBNP level compared with enalapril. There was no significant difference in the sacubitril/valsartan and enalapril groups with regard to key safety outcomes such as rates of worsening renal function, symptomatic hypotension, hyperkalaemia, and angioedema.[12] In both the PIONEER-HF and TRANSITION trials, sacubitril/valsartan demonstrated similar efficacy and safety in patients who were naïve to ACEi/ARB treatment

Figure 3 Change in biomarkers of wall stress in patients with and without diabetes (safety set). (A): hs-TnT levels; (B): NT-proBNP levels. *Change from baseline is P < 0.05; mixed model with repeated measures. hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.



prior to initiation of sacubitril/valsartan (PIONEER-HF: 53% patients were ACEi/ARB-naïve; TRANSITION: 24% patients were ACEi/ARB-naïve).[12,14]

Recent guidelines for treatment of HFrEF recommend the initiation of ARNI in patients hospitalized with acute HFrEF before discharge in the absence of contraindications.[2,24] The present analysis was designed to assess whether an approach to begin this process of optimization during hospitalization was successful and safe in patients at highest underlying risk, namely, those with diabetes as a co-morbidity. The results reveal that sacubitril/valsartan initiation in HFrEF patients with diabetes hospitalized for ADHF either before or shortly after discharge achieves comparable rates of up-titration to target or highest tolerated dose levels, tolerability, and dose maintenance than in patients without diabetes. This was achieved despite a higher risk of hyperkalaemia restricted to the first 10 weeks. In addition, despite an apparent lower response in terms of meaningful cardiac biomarker reduction in those with diabetes, the rate of clinical outcomes was similar in both subgroups.

A subanalysis of the PARADIGM-HF study in ambulatory, chronic, stable HFrEF patients with prediabetes or diabetes indicated that sacubitril/valsartan is superior to ACEi (enalapril), irrespective of the diabetes status at baseline. AEs, such as renal dysfunction and hyperkalaemia, were more prevalent among patients with diabetes mellitus in the enalapril group compared with that in the sacubitril/valsartan group. Although hypotension episodes were more common with sacubitril/valsartan than with enalapril, the increment in these episodes was smaller in patients with diabetes. Additionally,

patients in the sacubitril/valsartan group demonstrated a lower decline in renal function than those in the enalapril group.[25]

In our analysis, patients with diabetes were more likely to experience hyperkalaemia although overall discontinuation rates of sacubitril/valsartan due to AE and all-cause death over 26 weeks were low and comparable in patients with and without diabetes. It is important to emphasize that the majority of these common AEs during the vulnerable post-ADHF post-discharge time could be managed by the temporary down-titration of sacubitril/valsartan or adjustment of concomitant diuretic doses.

Almost 90% of the study population remained on sacubitril/valsartan until the end of the 26-week (6-month) time point, re-confirming the safety and tolerability profile of sacubitril/valsartan initiated early after an ADHF event. Similar trends over the short-term, 8-week follow-up, double-blind comparison of ARNI to ACEi were observed in the PIONEER-HF study.

PIONEER-HF also demonstrated that in-hospital initiation of sacubitril/valsartan was feasible, safe, and markedly decreased NT-proBNP levels. Moreover, the approach was associated with a significant 39% reduction in HF rehospitalizations compared with enalapril in patients stabilized after an ADHF event. There were no differences in the rates of renal insufficiency, hyperkalaemia, and symptomatic hypotension between both treatment groups.[12,13,26]

The sacubitril/valsartan-induced reductions in NT-proBNP and hs-TnT in ambulatory HF patients as well as in patients admitted with ADHF are associated with a lower risk of HF hospitalization and mortality, as well as disease progression.[12,27,28]

The present analysis showed that initiation of sacubitril/valsartan was associated with sustained reductions in NT-proBNP and hs-TnT levels that were more pronounced in patients without diabetes. Furthermore, the rates of HF and all-cause rehospitalization were also low and similar between the subgroups in our analysis. A post hoc analysis of the PARADIGM-HF trial suggested that patients with HFrEF and diabetes treated with sacubitril/valsartan had a greater long-term reduction in glycated haemoglobin compared with those treated with ACEi. In addition, the initiation of oral anti-hyperglycaemic therapy and new use of insulin were lower in patients receiving sacubitril/valsartan compared with patients receiving ACEi. These results suggest that replacing ACEi or ARBs with sacubitril/valsartan in patients with HFrEF and diabetes might be associated with additional benefit.[29] The approach is in alignment with the recent guideline update.[29,30]

In conclusion, the results of this analysis demonstrate that irrespective of the presence of diabetes as a co-morbidity, the initiation of sacubitril/valsartan in a wide range of patients with HFrEF hospitalized for ADHF either before or shortly after discharge is feasible, safe, and well tolerated.

Limitations

There are several limitations to this analysis. First, this is a post hoc evaluation of the TRANSITION study, which was not initially designed or powered to compare the outcomes between HFrEF patients with and without diabetes. Second, the TRANSITION trial was completed before the widespread dissemination of the ESC 2019 guidelines for DM. Hence, HbA1c measurement was not required to establish a diagnosis of DM. Third, this analysis was conducted before the introduction of sodium-glucose co-transporter 2 (SGLT2) inhibitors in the 2021 ESC guidelines for the treatment of patients with HFrEF.

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Conflict of interest

K.K.W. received personal fees from Novartis as investigator in TRANSITION and has received speaker and consultancy fees from Novartis. He has also received consultancy and speaker fees from Medtronic, Abbott Medical, Cardiac Dimensions, Astra Zeneca, Boehringer Ingelheim, and Bayer. R.W. received grants from Boehringer Ingelheim during the conduct of the study; personal fees and/or investigator fees from Bayer, Berlin-Chemie, Boehringer Ingelheim, Medtronic, Novartis, Servier, Bristol-Myers Squibb, Pfizer, Sanofi, and CVRx and Boston Scientific, Gilead, Johnson & Johnson, Relypsa outside the submitted work. M.S. reports personal fees from Novartis during the conduct of the study and personal fees from Bayer, Abbott, Merck, AstraZeneca, Vifor Pharma, and Boehringer Ingelheim outside the submitted work. J.B. received personal fees from Novartis during the conduct of the study and grants and/or personal fees from Novartis, AstraZeneca, and Servier outside the submitted work. E.S.M. received personal fees and/or non-financial support from Servier, Pfizer, Boehringer Ingelheim, Berlin Chemie/Menarini Polska, Astra Zeneca, and Bayer outside the submitted work. C.F. received personal fees as TRANSITION investigator and national coordinator and personal fees, non-financial support, and/or investigator fees from Amgen, Bayer, Boehringer Ingelheim, Novartis, Orion, Roche, Servier, and Vifor Pharma outside the submitted work. E.L. received grants from AstraZeneca, Merck, and Eli Lilly and grants and/or personal fees from Bayer,

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Multivariate analysis for comparison between diabetes and non-diabetes subgroups with adjustments for predictive baseline characteristics in AEs of special interest for the 26-week study duration (safety set; N = 982).

Figure S1. Time from discharge to first dose of sacubitril/valsartan in diabetes and non-diabetes subgroups

Day 0 is the day of discharge; 2 days in both subgroups: diabetes (range 1–16 days; interquartile range (IQR): 1.5–4.0 days) and non-diabetes subgroup (range 1–17 days; IQR: 2.0–4.0 days).

Figure S2. AEs of special interest and permanent discontinuations due to AEs in the diabetes versus non-diabetes subgroups (safety analysis set)

*P = 0.003; indicates statistical significance (two-sided) at 0.05 level, analysis is performed with the Cochran Mantel–Haenszel test; (A): AEs of special interest during the 10-week treatment period and the 16-week follow-up period; (B): Permanent discontinuations due to AEs during the 10-week treatment period and 26 weeks of study period.

Figure S3. Time-to-first rehospitalization in the diabetes versus non-diabetes subgroups (safety analysis set)

(A): Time-to-first HF rehospitalization due to an ADHF event; (B): time-to-first all-cause rehospitalization after discharge of index hospitalization.

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