

# Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study

**Rolf Wachter<sup>1\*</sup>, Michele Senni<sup>2</sup>, Jan Belohlavek<sup>3</sup>, Ewa Straburzynska-Migaj<sup>4</sup>, Klaus K. Witte<sup>5</sup>, Zhanna Kobalava<sup>6</sup>, Candida Fonseca<sup>7</sup>, Eva Goncalvesova<sup>8</sup>, Yuksel Cavusoglu<sup>9</sup>, Alberto Fernandez<sup>10</sup>, Said Chaaban<sup>11</sup>, Ellen Bøhmer<sup>12</sup>, Anne-Catherine Pouleur<sup>13</sup>, Christian Mueller<sup>14</sup>, Christophe Tribouilloy<sup>15</sup>, Eva Lonn<sup>16</sup>, Jehad A.L. Buraiki<sup>17</sup>, Jacek Gniot<sup>18</sup>, Maria Mozheiko<sup>19</sup>, Malgorzata Lelonek<sup>20</sup>, Adele Noè<sup>21</sup>, Heike Schwende<sup>21</sup>, Weibin Bao<sup>22</sup>, Dmytro Butylin<sup>21</sup>, and Domingo Pascual-Figal<sup>23</sup>, on behalf of the TRANSITION Investigators**

<sup>1</sup>Clinic and Policlinic for Cardiology, University Hospital Leipzig, and Clinic for Cardiology, University Medicine Göttingen and German Cardiovascular Research Center, Partner Site, Göttingen, Germany; <sup>2</sup>Cardiology Division, Cardiovascular Department, Papa Giovanni XXIII Hospital, Bergamo, Italy; <sup>3</sup>General Teaching Hospital, Charles University in Prague, Prague, Czech Republic; <sup>4</sup>First Department of Cardiology, University of Medical Sciences, Poznan, Poland; <sup>5</sup>Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK; <sup>6</sup>Peoples' Friendship University of Russia (RUDN University), Moscow, Russia; <sup>7</sup>Heart Failure Unit, Internal Medicine Department, Hospital de São Francisco Xavier, CHLO, NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal; <sup>8</sup>Odd. Srdcovehozlyhavanja a Transplantacie, Bratislava, Slovakia; <sup>9</sup>Eskişehir Osmangazi University Medical Faculty, Eskişehir, Turkey; <sup>10</sup>Sanatorio Modelo Quilmes, Buenos Aires, Argentina; <sup>11</sup>Hammoud Hospital University Medical Center, Saida, Lebanon; <sup>12</sup>Innlandet Hospital Trust, Lillehammer, Norway; <sup>13</sup>Cardiology Division, Cliniques Universitaires Saint-Luc, Brussels, Belgium; <sup>14</sup>University Hospital Basel, University of Basel, Basel, Switzerland; <sup>15</sup>Department of Cardiology, Amiens University Hospital, Amiens, France; <sup>16</sup>McMaster University and Hamilton Health Sciences, Hamilton, Canada; <sup>17</sup>King Faisal Specialist Hospital, Riyadh, Saudi Arabia; <sup>18</sup>SP ZOZ Szpital Specjalistyczny, Pulawy, Poland; <sup>19</sup>Yaroslavl Regional Hospital of Veterans of Wars, Yaroslavl, Russia; <sup>20</sup>Department of Noninvasive Cardiology, Medical University of Lodz, Lodz, Poland; <sup>21</sup>Novartis Pharma AG, Basel, Switzerland; <sup>22</sup>Novartis Pharmaceuticals, East Hanover, NJ, USA; and <sup>23</sup>Cardiology Department, Hospital Universitario Virgen de la Arrixaca, Universidad de Murcia, Murcia, Spain

Received 7 December 2018; accepted 24 April 2019; online publish-ahead-of-print 27 May 2019

## Aims

To assess tolerability and optimal time point for initiation of sacubitril/valsartan in patients stabilised after acute heart failure (AHF).

## Methods and results

TRANSITION was a randomised, multicentre, open-label study comparing two treatment initiation modalities of sacubitril/valsartan. Patients aged  $\geq 18$  years, hospitalised for AHF were stratified according to pre-admission use of renin–angiotensin–aldosterone system inhibitors and randomised ( $n = 1002$ ) after stabilisation to initiate sacubitril/valsartan either  $\geq 12$ -h pre-discharge or between Days 1–14 post-discharge. Starting dose (as per label) was 24/26 mg or 49/51 mg bid with up- or down-titration based on tolerability. The primary endpoint was the proportion

\*Corresponding author. Clinic and Policlinic for Cardiology, University Hospital Leipzig, Liebigstrasse 20, 04103 Leipzig, Germany. Tel: +49 341 9712650, Fax: +49 341 9712659, Email: rolf.wachter@medizin.uni-leipzig.de

A list of TRANSITION investigational site collaborators is provided in the online supplementary Appendix S1.

of patients attaining 97/103 mg bid target dose after 10 weeks. Median time of first dose of sacubitril/valsartan from the day of discharge was Day -1 and Day +1 in the pre-discharge group and the post-discharge group, respectively. Comparable proportions of patients in the pre- and post-discharge initiation groups met the primary endpoint [45.4% vs. 50.7%; risk ratio (RR) 0.90; 95% confidence interval (CI) 0.79–1.02]. The proportion of patients who achieved and maintained for  $\geq 2$  weeks leading to Week 10, either 49/51 or 97/103 mg bid was 62.1% vs. 68.5% (RR 0.91; 95% CI 0.83–0.99); or any dose was 86.0% vs. 89.6% (RR 0.96; 95% CI 0.92–1.01). Discontinuation due to adverse events occurred in 7.3% vs. 4.9% of patients (RR 1.49; 95% CI 0.90–2.46).

## Conclusions

Initiation of sacubitril/valsartan in a wide range of heart failure with reduced ejection fraction patients stabilised after an AHF event, either in hospital or shortly after discharge, is feasible with about half of the patients achieving target dose within 10 weeks.

Clinical Trial Registration: ClinicalTrials.gov ID: NCT02661217

## Keywords

Acute decompensated heart failure • Angiotensin receptor–neprilysin inhibitor • Heart failure • Hospitalisation • Sacubitril/valsartan

## Introduction

Acute heart failure (AHF) is the most common reason for hospitalisation in the Western world,<sup>1</sup> and 30–40% of patients are readmitted within 12 months.<sup>2</sup> During the vulnerable 2- to 3-month post-discharge period, early rehospitalisations can reach 25% during the first 30 days, and mortality can approach 10%.<sup>3</sup> Hospitalisation represents a window of opportunity for the initiation and successful up-titration of guideline-recommended therapies.

In the PARADIGM-HF trial,<sup>4</sup> the angiotensin receptor–neprilysin inhibitor (ARNI) sacubitril/valsartan was compared to enalapril in ambulatory patients with heart failure (HF) and reduced ejection fraction (HFrEF), showing that it reduced the combined endpoint of cardiovascular death or HF hospitalisation by 20%, overall safety and tolerability was comparable to enalapril<sup>5</sup> and showed statistically significant reduction in HF hospitalisations detectable as early as 30 days following randomisation.<sup>6</sup>

Data from the Get With The Guidelines-Heart Failure (GWTG-HF) registry suggest that during the initial 12 months following Food and Drug Administration approval, only 2.3% of HFrEF patients hospitalised for AHF in the US were prescribed sacubitril/valsartan at discharge, although nearly 70% of hospitalised patients would have been eligible for the drug.<sup>7</sup> One possible reason might be the absence of data showing the benefit and safety of in-hospital initiation of sacubitril/valsartan in this vulnerable patient population. PIONEER-HF was the first study in post-acute decompensated HF (ADHF) patients, conducted entirely in the US, to show that in-hospital initiation of sacubitril/valsartan reduced the time-averaged N-terminal pro B-type natriuretic peptide (NT-proBNP) concentration by 29%, compared to enalapril.<sup>8</sup> The TRANSITION study, conducted in 19 countries, sought to investigate whether in-hospital initiation of sacubitril/valsartan in haemodynamically stabilised HF patients is as well tolerated as its initiation early after discharge on an outpatient basis.

## Methods

### Study population and therapies

TRANSITION (NCT02661217) was a randomised, multicentre, open-label study performed in 19 countries and 156 hospitals worldwide. The study design and rationale have been previously published.<sup>9</sup> The study included male or female patients aged  $\geq 18$  years who were hospitalised for an episode of ADHF (*de novo* HF or due to exacerbation of chronic HF), with New York Heart Association (NYHA) class II–IV, blood pressure  $\geq 100$  mmHg and left-ventricular ejection fraction (LVEF)  $\leq 40\%$ . The study was conducted in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice and with the ethical principles of the Declaration of Helsinki.<sup>10</sup> Trial protocol was approved by ethics committees at participating centres.

All patients provided written informed consent 24 h after haemodynamic stabilisation [no need for intravenous diuretics in the 24 h prior to signing informed consent, and systolic blood pressure (SBP)  $\geq 110$  mmHg for  $\geq 6$  h prior to randomisation]. At screening, patients were stratified based on their pre-admission renin–angiotensin–aldosterone system (RAAS)-inhibitor therapy [angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and ACEI/ARB treatment-naïve patients] and, within each stratum, were randomised 1:1 to start sacubitril/valsartan either pre- or post-discharge. HFrEF patients in the pre-discharge group received the first dose of sacubitril/valsartan no later than 12 h before discharge and  $\leq 7$  days after randomisation. Patients in the post-discharge group received the first dose of sacubitril/valsartan at any time between Days 1 and 14 post-discharge.

The TRANSITION study protocol instructions for initiation and up-titration of sacubitril/valsartan reflected the label recommendations in the participating countries. In short, patients receiving ACEI therapy went through a 36 h washout period before starting sacubitril/valsartan administration. ARB therapy was stopped before sacubitril/valsartan administration. The starting dose (24/26 mg or 49/51 mg bid) was chosen by the investigator as per label recommendations. Up-titration was based on the label recommendations and the patient's tolerability, allowing the dose to be doubled every 2–4 weeks at the treating physician's discretion, up to the target dose. Concomitant HF therapies were optimised along with the initiation

and up-titration of sacubitril/valsartan. Down-titration or temporary discontinuation of study medication was allowed at any time in line with label recommendations. Additional information is provided in the online supplementary *Methods S1*. The study design has two parts: starting with 10-week treatment, and continuing with 16-week follow-up treatment, counting from randomisation. In this paper, the focus is on the initial 10-week treatment.<sup>9</sup>

## Follow-up and outcomes measures

The study visits took place every 2 weeks after randomisation. The primary endpoint assessed the proportion of patients who achieved the target dose of 97/103 mg bid at the end of Week 10 after randomisation, regardless of dose changes or interruptions. Secondary endpoints were: (i) the proportion of patients who achieved and maintained a sacubitril/valsartan dose of 49/51 or 97/103 mg bid for  $\geq 2$  weeks leading to Week 10 after randomisation; (ii) the proportion of patients who maintained any dose of sacubitril/valsartan for  $\geq 2$  weeks leading to Week 10; (iii) rates of permanent study drug discontinuations owing to adverse events (AEs) during the 10-week period.

## Safety

Safety parameters were assessed throughout the study in all patients, by physical examination, vital signs, laboratory evaluations, electrocardiogram (ECG) and reported AEs. A Data Monitoring Committee performed interim analyses of tolerability and safety parameters for the first 300 and 600 patients who completed the Week 10 visit. Adverse events are presented as MedDRA dictionary preferred terms.

## Statistical methods

The full analysis set (FAS) consisted of all randomised patients with the exception of those randomised inadvertently. The safety analysis set consisted of all patients included in the FAS who received at least one dose of study medication.

The primary and secondary endpoints were analysed in the safety analysis set using the stratified Cochran–Mantel–Haenszel method with treatment group and stratification variable (ACEI, ARB, or treatment-naïve) as stratification factors. The risk ratio (RR, ratio of the probability of achieving the target dose at the end of Week 10 in the pre-discharge to the probability in the post-discharge initiation group) was estimated with a two-sided 95% confidence interval (CI) along with the estimated probability and 95% CI for each treatment group. The primary endpoint was also analysed as a supportive analysis in the FAS. As the frequency of AEs was expected to be higher in the pre-discharge group due to the longer duration of exposure in a well-monitored hospital setting, AEs were analysed in the FAS from randomisation to the end of 10 weeks following the intent-to-treat principle.

A multivariable logistic regression model analysis was performed to identify baseline predictors of successful up-titration to sacubitril/valsartan 97/103 mg bid target dose at the end of Week 10. Odds ratios (OR) and 95% CIs were constructed to identify those patients with a high likelihood 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.

## Results

### Study population

Between February 2016 and December 2017, in total 1124 patients were screened and 1002 patients were randomised (*Figure 1*). Thirteen patients discontinued prior to randomisation, one of whom died during the screening period. A total of 111 patients did not meet the screening criteria. Thus, 500 patients were randomised to pre-discharge initiation and 502 to post-discharge initiation. Of these, 493 (99%) patients in the pre-discharge group and 489 (97%) patients in the post-discharge group received study medication.

The median time from admission to first dose of study drug was 7 days in the pre-discharge group and 10 days in the post-discharge group. Median time from randomisation to the first dose was 0 days [interquartile range (IQR) 0–1 days] and 3 days (IQR 2–6 days) in pre-discharge and post-discharge groups, respectively. The median time from discharge to the first dose was –1 day in the pre-discharge group (IQR –2 to –1 days) and 1 day in the post-discharge group (IQR 1–4 days) (*Figure 2*).

Baseline characteristics (*Table 1*) show that two-thirds of patients (64%) were in NYHA class II and 34% in NYHA class III at randomisation, as patients were expected to be stabilised after the acute event. Twenty-nine percent of patients were newly diagnosed (*de novo*) HF ( $n = 286$ ), and 24% ( $n = 241$ ) of the patients were ACEI/ARB-naïve prior to the ADHF event (as per strata assignment), and 49% ( $n = 485$ ) had a prior hospitalisation for HF.

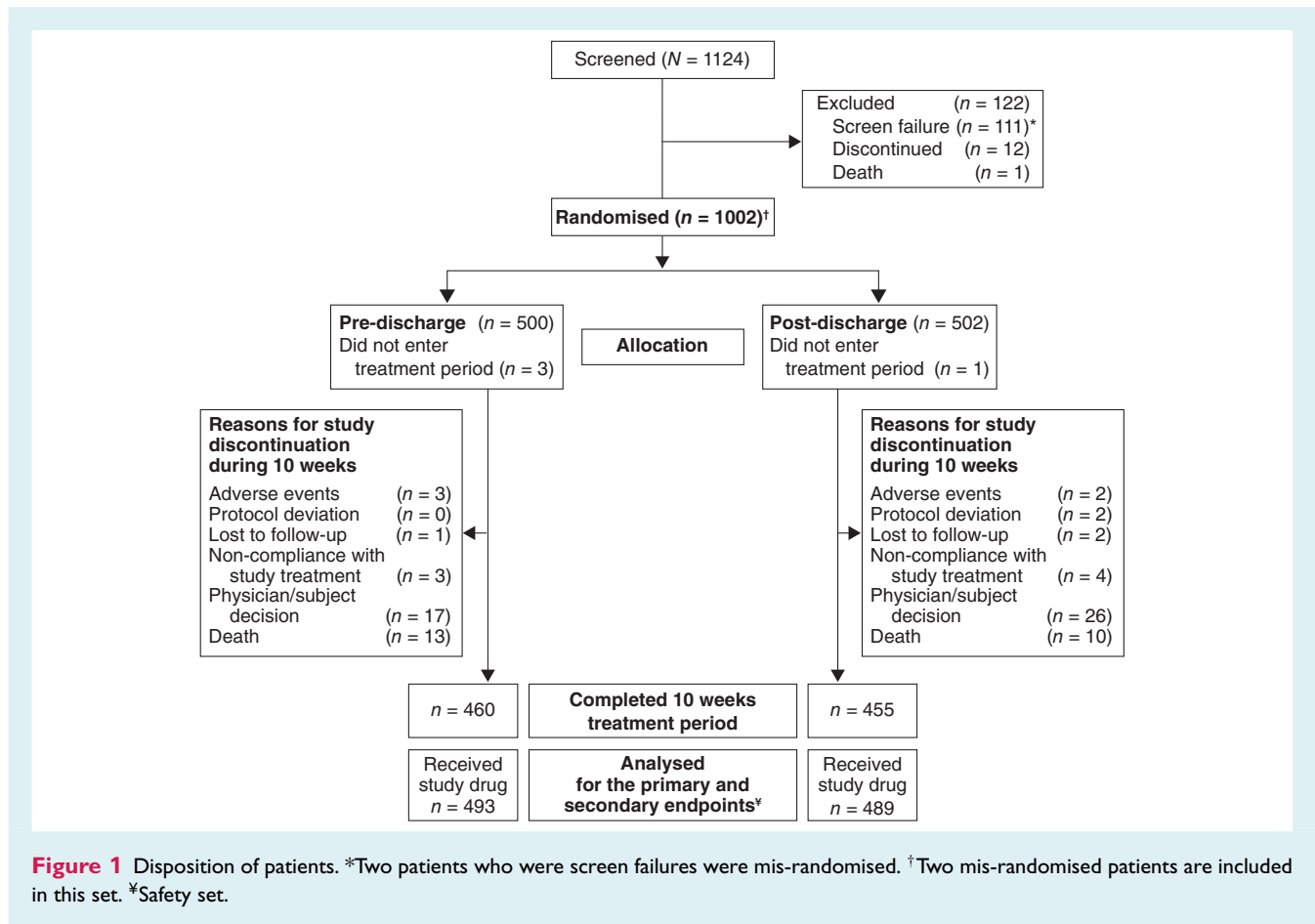
### Initial starting dose of sacubitril/valsartan

A lower 24/26 mg bid starting dose was chosen by the investigators in 436 (88.4%) patients in the pre-discharge, and in 413 (84.5%) patients in the post-discharge group. The higher starting dose of 49/51 mg bid was used in the remaining patients.

### Primary and secondary endpoints

The target dose of 97/103 mg bid sacubitril/valsartan at Week 10 after randomisation in the SAF was attained by 224 (45.4%) patients in the pre-discharge group and 248 (50.7%) in the post-discharge group, regardless of previous dose interruption or down-titration (relative RR 0.90; 95% CI 0.79–1.02) (*Figure 3*). Similar results were obtained in the FAS (relative RR 0.91; 95% CI 0.80–1.04). The 49/51 mg or 97/103 mg bid dose of sacubitril/valsartan was maintained for  $\geq 2$  weeks leading to Week 10 after randomisation by 62.1% of patients in the pre-discharge and by 68.5% of patients in the post-discharge group (relative RR 0.91; 95% CI 0.83–0.99). The proportion of patients who achieved and maintained any dose of sacubitril/valsartan for  $\geq 2$  weeks leading to Week 10 were comparable (86.0% and 89.6% in the pre-discharge and post-discharge groups, respectively; relative RR 0.96; 95% CI 0.92–1.01) (*Figure 3*).

In the analysis of the third secondary endpoint, 7.3% of patients in the pre-discharge group and 4.9% of patients in the post-discharge group permanently discontinued sacubitril/valsartan due to an AE (relative RR 1.49; 95% CI 0.90–2.46).



There were no significant differences in the proportion of patients who met the primary endpoint between the ACEI or ARB strata, compared to those who were naïve (relative RR 1.01; 95% CI 0.88–1.16). The analysis of the secondary endpoints confirmed a comparable tolerability of sacubitril/valsartan in both strata (online supplementary Figure S1).

### Predictors of up-titration success

In a multivariable analysis, significant ( $P < 0.05$ ) predictors of target-dose attainment within 10 weeks were age  $< 65$  years, SBP  $\geq 120$  mmHg at baseline, history of hypertension, *de novo* HF, no atrial fibrillation at baseline, estimated glomerular filtration rate  $\geq 60$  mL/min/1.73 m<sup>2</sup> at randomisation, and a sacubitril/valsartan starting dose of 49/51 mg bid. Assignment to pre- or post-discharge initiation of sacubitril/valsartan was not significant (OR 1.21; 95% CI 0.93–1.59), nor was prior use of an ACEI or ARB a significant predictor of up-titration success (OR 1.04; 95% CI 0.75–1.45) (Figure 4).

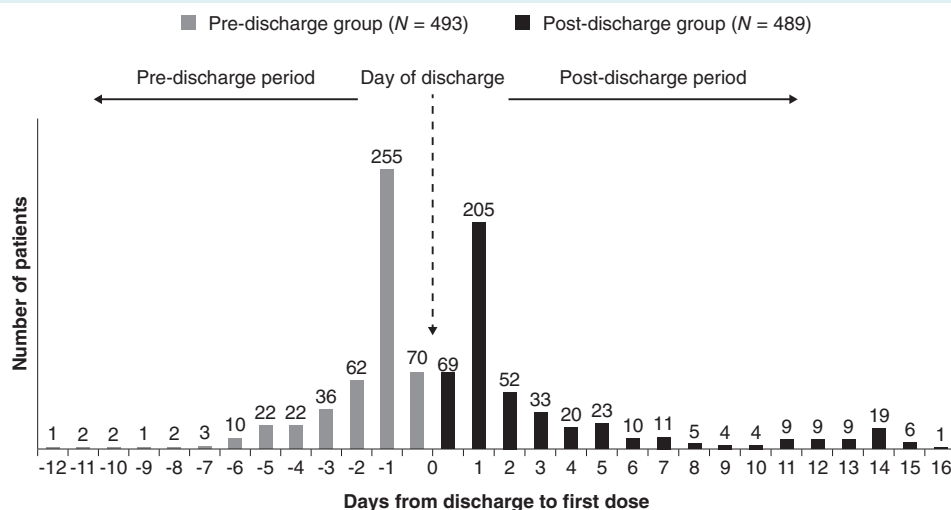
### Safety

Rates of permanent discontinuation of study drug due to AEs were low in both treatment groups: 7.1% in the pre-discharge and 5.6%

in the post-discharge group (relative RR 1.25; 95% CI 0.77–2.03). In the total study population, 67.3% of patients reported at least one AE, and 18.4% at least one serious AE (SAE). Rates of AEs, SAEs and temporary and permanent treatment discontinuations during 10 weeks did not show major differences between the two groups, although a non-significant higher incidence of treatment discontinuations was observed in the pre-discharge group (Table 2).

The most frequently reported AEs in the pre-discharge vs. post-discharge groups were hyperkalaemia (11.3% vs. 11.3%), hypotension (12.7% vs. 9.5%), cardiac failure (7.1% vs. 8.5%), dizziness (5.7% vs. 4.2%), and renal impairment (5.1% vs. 3.2%) (online supplementary Table S1). An independent adjudication committee confirmed three reported cases of angioedema (two patients in the pre- and one patient in the post-discharge group) during the 10 weeks. All three cases were treated pharmacologically and none required hospitalisation or had compromised airways. Overall, the most common AEs leading to permanent study treatment discontinuation were hypotension (0.7%), cardiac failure (0.6%), acute kidney injury (0.6%), and hyperkalaemia (0.6%) (online supplementary Figure S2).

Cardiac failure was the most common SAE reported in 5.1% and 5.8% of patients in pre- and post-discharge groups, respectively; followed by acute cardiac failure reported in 1.4% and 1.8%; and acute kidney injury, reported with the same incidence of 1.2% in



**Figure 2** Time from discharge to first dose of sacubitril/valsartan in both treatment groups. Day 0 is the day of discharge. Patients in both study arms could receive the first dose of study medication on the day of discharge: pre-discharge arm patients could take the first dose still in the hospital and were discharged the same day; post-discharge arm patients could take the first dose in the evening of the discharge day.

both groups. Hypotension and hyperkalaemia SAEs occurred at rates < 1% in both treatment groups (online supplementary Table S2).

Mortality rates were low in both treatment groups: 13 patients (2.6%) died in the pre-discharge group and 10 (2.0%) in the post-discharge group (relative RR 1.30; 95% CI 0.58–2.94) (Table 2). No deaths were attributed to the study treatment by the investigators.

## Discussion

Hospitalisation due to AHF allows an opportunity for the initiation and successful up-titration of guideline-recommended therapies, to improve outcomes in the vulnerable period after hospitalisation and in the longer term. TRANSITION compared two treatment modalities of sacubitril/valsartan initiation in HFrEF patients recruited in 19 countries from Western and Eastern Europe, North and South America, and the Middle East pre- vs. post-discharge, following haemodynamic stabilisation. The approach to up-titration was based on tolerability as per label, and close to clinical practice.

Tolerability of early initiation, measured as proportion of patients reaching the guideline-recommended target dose of sacubitril/valsartan in 10 weeks after randomisation, was comparable in both groups, and was achieved in almost half the population.

In comparison with trials that initiated sacubitril/valsartan in ambulatory patients (PARADIGM-HF, TITRATION),<sup>5,11</sup> TRANSITION had no run-in period and the study population presented with a more severe clinical profile at baseline owing to the enrolment of hospitalised patients. In particular, patients in TRANSITION were older and with a higher prevalence of co-morbidities. The baseline characteristics of the TRANSITION population were similar to those observed in previous trials of in-hospital treatment initiation of beta-blockers<sup>12</sup> or aliskiren.<sup>13</sup> Prior to hospital

admission, TRANSITION patients, on average, were less well medicated compared to PARADIGM-HF, which could be attributed to the high proportion of patients with *de novo* HF. In addition, PARADIGM-HF patients had to be on a stable dose of an ACEI or ARB, and a beta-blocker to qualify for recruitment.<sup>5</sup>

It is important to put the present findings in context of PIONEER-HF, a recently published randomised trial in a similar patient population, but comparing two different drugs. PIONEER-HF randomised 882 patients with AHF and elevated levels of natriuretic peptides to receive either enalapril or sacubitril/valsartan. By Week 8, sacubitril/valsartan had reduced NT-proBNP by 29% in comparison to enalapril.<sup>8</sup> Data from the PIONEER-HF extension phase was recently presented at the American College of Cardiology conference.<sup>14</sup> Patients randomised to the enalapril group who switched in the open-label extension phase to sacubitril/valsartan showed a greater reduction in NT-proBNP levels than patients who were already on sacubitril/valsartan, resulting in similar NT-proBNP levels at Week 12 in both groups. However, the reduction in serious clinical outcomes in favour of the sacubitril/valsartan arm that was seen at Week 8 persisted at Week 12, suggesting a strategy of in-hospital initiation is superior. Compared to PIONEER-HF, patients enrolled in TRANSITION were, on average, 6 years older and suffered more from diabetes, coronary artery disease, previous myocardial infarction and atrial fibrillation, but less from hypertension (online supplementary Tables S3 and S4). Median NT-proBNP at randomisation was lower in TRANSITION compared to PIONEER-HF, owing to differences in the respective trial protocols.<sup>8,9</sup> The differences in prior HF treatments received by patients in PIONEER-HF and TRANSITION are explained by higher proportion of ACEI/ARB-naïve patients recruited in PIONEER-HF and the general lower use of mineralocorticoid receptor antagonists in the US.<sup>15</sup>

**Table 1** Baseline characteristics

| Characteristic   | Pre-discharge initiation<br>(n = 495) | Post-discharge initiation<br>(n = 496) | Total population<br>(n = 991) |
|--|---------------------------------------|--|-------------------------------|
| Age, mean, years   | 66.7                                  | 66.9                                   | 66.8                          |
| Male sex, n (%)  | 371 (74.9)                            | 373 (75.2)                             | 744 (75.1)                    |
| Caucasian ethnicity, n (%)                                     | 483 (97.6)                            | 480 (96.8)                             | 963 (97.2)                    |
| BMI, median (min–max), kg/m <sup>2</sup> *                     | 27.9 (17.6–58.8)                      | 28.8 (17.1–53.8)                       | 28.4 (17.1–58.8)              |
| LVEF, mean ± SD, %   | 28.6 ± 7.5                            | 29.0 ± 7.6                             | 28.8 ± 7.6                    |
| NYHA class, n (%) <sup>*</sup>                                 |                                       |  |                               |
| I  | 0 (0.0)                               | 3 (0.6)                                | 3 (0.3)                       |
| II   | 320 (64.6)                            | 315 (63.5)                             | 635 (64.1)                    |
| III  | 166 (33.5)                            | 173 (34.9)                             | 339 (34.2)                    |
| IV   | 7 (1.4)                               | 4 (0.8)                                | 11 (1.1)                      |
| SBP, mean ± SD, mmHg   | 124 ± 13.8                            | 124 ± 14.1                             | 124 ± 14.0                    |
| Pulse, mean ± SD, bpm  | 73.8 ± 13.6                           | 74.9 ± 12.2                            | 74.4 ± 12.9                   |
| eGFR, mean ± SD, mL/min/1.73 m <sup>2</sup> *                  | 61.6 ± 20.5                           | 62.5 ± 19.4                            | 62.0 ± 20.0                   |
| Ischaemic HF aetiology, n (%)                                  | 218 (44.0)                            | 239 (48.2)                             | 457 (46.1)                    |
| De novo HF, n (%)  | 148 (29.9)                            | 138 (27.8)                             | 286 (28.9)                    |
| Prior hospitalisation for HF, n (%)                            | 236 (47.7)                            | 249 (50.2)                             | 485 (48.9)                    |
| NT-proBNP, median (IQR), pg/mL <sup>*</sup>                    | 1902 (945–3847)                       | 1669 (706–3599)                        | 1744 (846–3719)               |
| hs-TnT, median (IQR), ng/L <sup>*</sup>                        | 29 (18–45)                            | 28 (17–44)                             | 29 (18–44)                    |
| Medical history, n (%)   |                                       |  |                               |
| Hypertension   | 372 (75.2)                            | 375 (75.6)                             | 747 (75.4)                    |
| Diabetes   | 226 (45.7)                            | 234 (47.2)                             | 460 (46.4)                    |
| Atrial fibrillation  | 243 (49.1)                            | 237 (47.8)                             | 480 (48.4)                    |
| Myocardial infarction  | 168 (33.9)                            | 171 (34.5)                             | 339 (34.2)                    |
| Stroke   | 51 (10.3)                             | 46 (9.3)                               | 97 (9.8)                      |
| Cardiac resynchronisation therapy                              | 38 (7.7)                              | 50 (10.1)                              | 88 (8.9)                      |
| Implantable defibrillator insertion                            | 73 (14.7)                             | 79 (15.9)                              | 152 (15.3)                    |
| Medications by randomisation strata, n (%)                     |                                       |  |                               |
| ACEI   | 250 (50.5)                            | 253 (51.0)                             | 503 (50.8)                    |
| ARB  | 123 (24.8)                            | 124 (25.0)                             | 247 (24.9)                    |
| ACEI/ARB naïve   | 122 (24.6)                            | 119 (24.0)                             | 241 (24.3)                    |
| Other HF- and CV-related medications prior to admission, n (%) |                                       |  |                               |
| Beta-blocker   | 213 (43.0)                            | 233 (47.0)                             | 446 (45.0)                    |
| MRA  | 169 (34.1)                            | 181 (36.5)                             | 350 (35.3)                    |
| Diuretic   | 248 (50.1)                            | 261 (52.6)                             | 509 (51.4)                    |
| Loop diuretics   | 238 (48.1)                            | 245 (49.4)                             | 483 (48.7)                    |
| Thiazide diuretics   | 15 (3.0)                              | 13 (2.6)                               | 28 (2.8)                      |
| Cardiac glycosides   | 63 (12.7)                             | 45 (9.1)                               | 108 (10.9)                    |
| Nitrates   | 31 (6.3)                              | 45 (9.1)                               | 76 (7.7)                      |

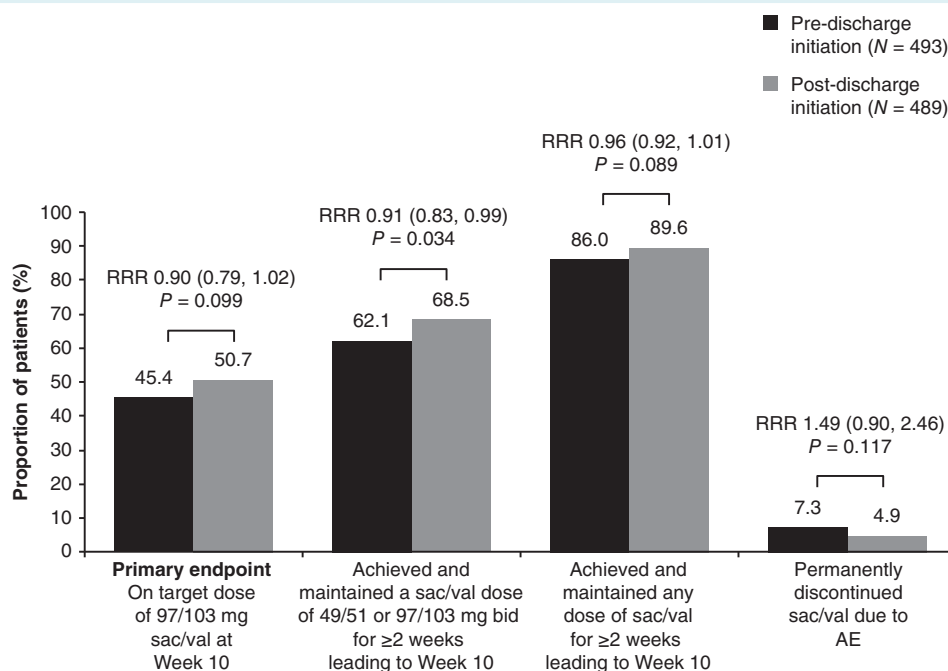
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-TnT, high-sensitivity troponin T; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

Parameters were assessed at screening except for parameters with an \* that were assessed at randomisation.

The target dose of sacubitril/valsartan was reached in about 48% of patients in TRANSITION, which is slightly lower than the 55% of patients in PIONEER-HF who achieved target dose in 8 weeks. Possible reasons are younger age of patients, lower burden of co-morbidities and more patients with *de novo* HF in PIONEER-HF, which we identified as predictors of up-titration success in TRANSITION, as well as different up-titration methods. The proportions of patients who reached the target dose at 8 weeks or 10 weeks in both PIONEER-HF and TRANSITION were lower than the 76% of patients at 12 weeks in the TITRATION study. This difference

is likely attributable to the stricter up-titration schedule, prevalence of the ambulatory settings, initiation in stable patients, and small number of in-hospital patients at baseline (56 out of 498 randomised) in TITRATION.<sup>11</sup>

A higher proportion of patients in the post-discharge arm achieved and maintained  $\geq 49/51$  mg bid dose of sacubitril/valsartan. The difference reached statistical significance; however, sources of bias to the disadvantage of the pre-discharge arm need to be considered. Patients in the pre-discharge arm were started sooner after the ADHF event on the study drug;



**Figure 3** Primary and secondary endpoints during pre-discharge and post-discharge initiation of sacubitril/valsartan. AE, adverse event; bid, twice daily; RRR, relative risk ratio; sac/val, sacubitril/valsartan.

potentially, because of this, more patients (4%) started on the lowest 24/26 mg bid dose in the pre-discharge compared to the post-discharge group.

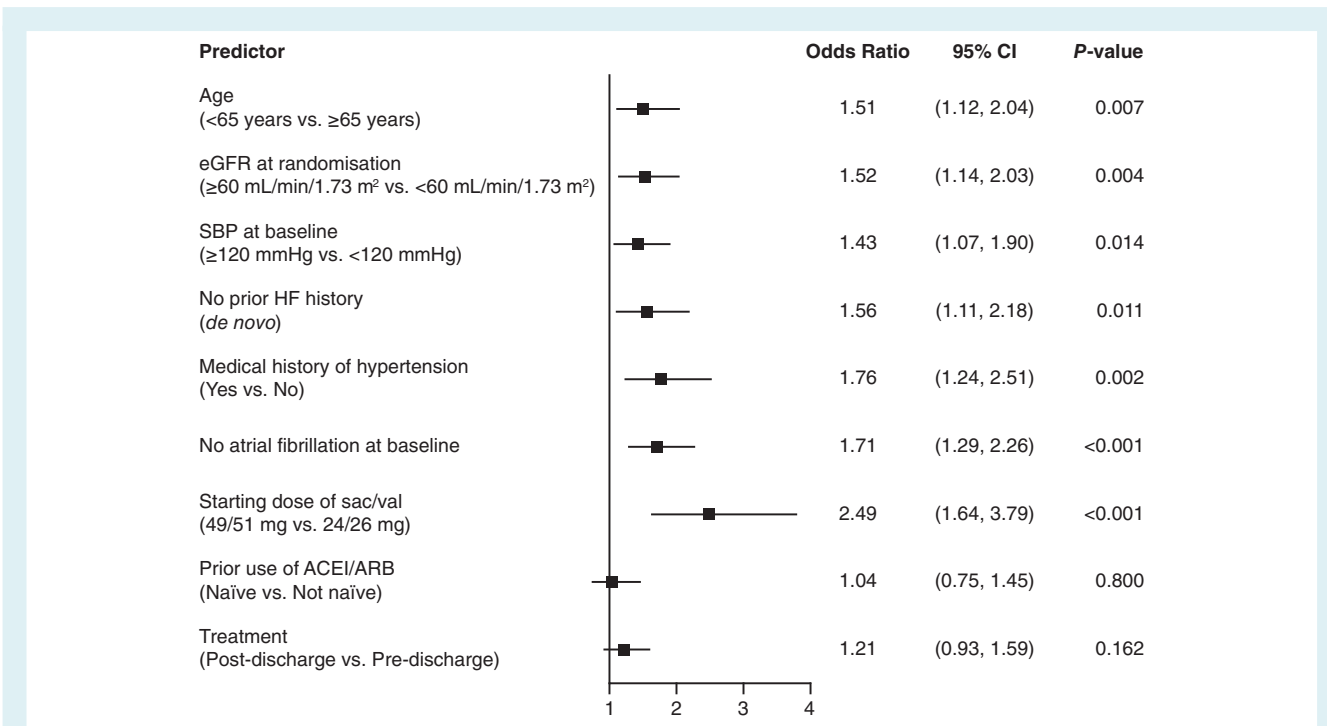
The finding that 62% of the patients up-titrated to 49/51 or 97/103 mg bid of sacubitril/valsartan are relevant when compared to registry data, showing only 43% of patients receiving more than 24/26 mg bid of sacubitril/valsartan in an outpatient setting.<sup>16,17</sup> This gap between data from controlled trials and daily practice requires further study, and gives room for future improvement in HF therapy.<sup>18–20</sup> The results of TRANSITION provide support to continuing the efforts of up-titration after discharge. Reaching target dose is feasible in many patients with initiation and up-titration following label recommendations.

The incidence of permanent discontinuation of sacubitril/valsartan due to AEs in TRANSITION was 7.1% in the pre-discharge group during 10 weeks and it compares well with the rates of patients discontinued due to AEs during 8 weeks in PIONEER-HF (10.1% enalapril, and 11.5% sacubitril/valsartan). Although a slightly higher proportion of patients in PIONEER-HF were able to achieve the target dose of sacubitril/valsartan than in TRANSITION, discontinuation rates were higher in PIONEER-HF. The aforementioned difference in up-titration methods between the studies might have contributed to this finding.<sup>5</sup>

The identified predictors of up-titration success in TRANSITION indicate less advanced HF with fewer co-morbidities (younger age, new diagnosis of HF, intact renal function, normal or elevated SBP, absence of atrial fibrillation, and a starting dose of 49/51 mg bid sacubitril/valsartan). These are in line with findings from other HF trials with ACEI, ARBs and beta-blockers.<sup>21</sup> Prior

RAAS inhibitor exposure or initiating sacubitril/valsartan before or shortly after discharge were not predictors of up-titration success. A higher baseline SBP predicted higher up-titration success. Low SBP is often a limitation for the initiation and up-titration of evidence-based HF medications. Although only seven patients (0.7%) in TRANSITION permanently discontinued treatment due to hypotension, six were in the pre-discharge group, indicating the importance of achieving haemodynamic stabilisation before starting treatment with sacubitril/valsartan. Similar to ACEI or ARB management, slow up-titration to target dose in the highly vulnerable post-ADHF phase is recommended. In a *post-hoc* analysis of TITRATION, > 80% of patients with SBP  $\geq$  100 mmHg achieved and maintained the target dose of sacubitril/valsartan if the treatment was titrated gradually.<sup>22</sup> We observed that ACEI/ARB-naïve patients were similar to patients on an ACEI or ARB able to initiate, up-titrate and maintain sacubitril/valsartan. These findings address a key question that had remained unanswered in the PARADIGM-HF study.<sup>23</sup>

Tolerability to sacubitril/valsartan in TRANSITION appears comparable to that reported for beta-blockers and ACEIs/ARBs under real-life conditions.<sup>2</sup> During the sacubitril/valsartan initiation and up-titration phase in the PARADIGM-HF run-in (median drug exposure 29 days), 5.8% of patients discontinued permanently because of an AE,<sup>5</sup> which is comparable to the 6.4% overall discontinuation due to AEs in TRANSITION, considering the challenging scenario of a recent ADHF episode. The 2.3% mortality rate over 10 weeks in TRANSITION seems low compared to other reports<sup>12,13</sup> but is likely due to the strict inclusion and exclusion criteria of the trial. PIONEER-HF reported similarly low mortality



**Figure 4** A multivariable logistic regression model was used to determine predictors for successful sacubitril/valsartan dose up-titration to 97/103 mg bid during the 10-week study period for the entire population. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bid, twice daily; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; SBP, systolic blood pressure.

**Table 2** Adverse events and treatment interruptions during the 10-week treatment period

|   | Pre-discharge<br>(n = 495) | Post-discharge<br>(n = 496) | Total<br>(n = 991) | Relative risk ratio<br>(95% CI) |
|---|----------------------------|-----------------------------|--------------------|---------------------------------|
| Patients with ≥ 1 AE, n (%)                 | 342 (69.1)                 | 325 (65.5)                  | 667 (67.3)         | 1.054 (0.97, 1.15)              |
| Patients with ≥ 1 SAE, n (%)                | 93 (18.8)                  | 89 (17.9)                   | 182 (18.4)         | 1.047 (0.81, 1.36)              |
| Deaths, n (%)                               | 13 (2.6)                   | 10 (2.0)                    | 23 (2.3)           | 1.303 (0.58, 2.94)              |
| Temporary treatment interruptions, n (%)    |                            |                             |                    |                                 |
| Due to AEs                                  | 61 (12.3)                  | 48 (9.7)                    | 109 (11.0)         | 1.273 (0.89, 1.82)              |
| Due to SAEs                                 | 19 (3.8)                   | 16 (3.2)                    | 35 (3.5)           | 1.190 (0.62, 2.29)              |
| Due to non-SAEs                             | 47 (9.5)                   | 36 (7.3)                    | 83 (8.4)           | 1.308 (0.86, 1.98)              |
| Permanent treatment discontinuations, n (%) |                            |                             |                    |                                 |
| Due to AEs                                  | 35 (7.1)                   | 28 (5.6)                    | 63 (6.4)           | 1.253 (0.77, 2.03)              |
| Due to SAEs                                 | 17 (3.4)                   | 14 (2.8)                    | 31 (3.1)           | 1.217 (0.61, 2.44)              |
| Due to non-SAEs                             | 19 (3.8)                   | 15 (3.0)                    | 34 (3.4)           | 1.269 (0.65, 2.47)              |

AE, adverse event; CI, confidence interval; SAE, serious adverse event.

rates of 2.3% in the sacubitril/valsartan group and 3.4% in the enalapril group.

The overall rates of hypotension (11.1%), hyperkalaemia (11.3%) and renal impairment (4.1%) reported during the 10 weeks in TRANSITION were lower than the corresponding rates over the 8-week follow-up in PIONEER-HF for the sacubitril/valsartan group (18.0%, 12.5%, and 8.2%, respectively). The initiation during a more stabilised period in TRANSITION, after discontinuation

of intravenous diuretics, could account for this difference. The corresponding rates observed in PARADIGM-HF for the sacubitril/valsartan group (17.6%, 11.6%, and 10.1%, respectively) are attributable to the longer follow-up in PARADIGM-HF (median, 27 months).<sup>5</sup> The numerically higher rate of hypotension and renal impairment in the pre-discharge group compared to the post-discharge group may indicate an increased vulnerability of these patients, but the longer observation period for the



pre-discharge arm, in a well-monitored hospital setting, might also have contributed to the group differences. Of note, most often these AEs did not lead to treatment discontinuation and were not considered serious in the vast majority of cases.

The TRANSITION study has several limitations: first, we used an estimation approach to define the sample size. Although the difference in the primary endpoint was not significant, we cannot rule out that a difference of 5–7% between both study arms exists. Similarly, despite overall low rates of permanent discontinuations due to AEs, the group difference might have reached statistical significance with a larger sample size. Second, the study was open-label to provide flexibility to investigators to follow their clinical practice of treatment initiation and modifications in ADHF patients, such as choosing the time point of treatment initiation flexibly within the protocol-defined windows. However, this flexibility unexpectedly reduced the differentiation between the two groups: patients in the pre-discharge arm received the first dose in the very late phase of their hospitalisation (median time of the first dose relative to discharge was –1 day) whereas in the post-discharge group patients started study drug very early after discharge (median time of the first dose relative to discharge was +1 day). Third, several sources of bias exist (less time for stabilisation, but more time for up-titration in the pre-discharge arm, closer monitoring for AEs in the hospital).

Despite these limitations, the study provides important quantitative information to physicians about the tolerability and safety of sacubitril/valsartan in the 10 weeks after an ADHF event in a large patient population with a high, unmet need and limited data to date. The European Society of Cardiology guidelines recommend initiation of disease-modifying treatments in *de novo* HF patients early after haemodynamic stabilisation.<sup>24</sup> PIONEER-HF and TRANSITION are the first two randomised studies to provide data in this vulnerable population. TRANSITION adds data from patients recruited in 19 countries that were not presented in PIONEER-HF, with a trial protocol reflecting daily clinical practice of using the drug according to label instructions. The two studies also provide data about the use of the 24/26 mg bid starting dose of sacubitril/valsartan in the vulnerable phase after ADHF in elderly and co-morbid HFrEF patients as well as data on the use of this drug in ACEI/ARB-naïve patients. They also provide tolerability data in a patient population that did not go through a run-in period, thereby providing information that is closer to clinical practice of the use of sacubitril/valsartan.

In summary, about half of HFrEF patients stabilised after an acute HF decompensation event achieved the recommended target dose of sacubitril/valsartan within 10 weeks, and 86% or more were able to maintain any dose of sacubitril/valsartan for more than 2 weeks, following label recommendations for initiation and up-titration. Adverse events and permanent treatment discontinuations were low, considering the extremely vulnerable post-ADHF population. Findings from the randomised TRANSITION study complement those from the PIONEER-HF study showing that early initiation of sacubitril/valsartan in a wide range of HFrEF patients recently admitted for ADHF is feasible either in hospital or shortly after discharge.

## Supplementary Information

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

**Appendix S1.** TRANSITION investigational site collaborators.

**Methods S1.** Supplementary methods.

**Figure S1.** Primary and secondary endpoints in patients with pre-study use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and ACEI/ARB-naïve patients.

**Figure S2.** Most common adverse events ( $\geq 2$  events in any treatment group) leading to permanent discontinuation of sacubitril/valsartan during the 10-week treatment period.

**Table S1.** Most common adverse events ( $\geq 2\%$  of patients in any group), during the 10-week treatment period regardless of study drug relationship.

**Table S2.** Most common serious adverse events  $\geq 0.5\%$  in any group.

**Table S3.** Baseline characteristics of patients in the PIONEER-HF and the TRANSITION studies.

**Table S4.** Medical history of patients in the PIONEER-HF and the TRANSITION studies.

## Acknowledgement

Following an outline of the study results developed by the authors, a first draft of the manuscript was written by Pelle Stolt, Magliarotta. Subsequent drafts and the final version of the manuscript were the sole work of the authors.

## Funding

This work was supported by Novartis. The medical writing service was funded by Novartis.

**Conflict of interest:** 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; 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 outside the submitted work. J.B. received personal fees from Novartis during the conduct of the study; 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 and Bayer outside the submitted work. K.K.W. received payment as investigator in TRANSITION from Novartis. C.F. received personal fees, non-financial support and/or investigator fees from Amgen, Novartis, Servier, Vifor, Bayer, Orion, and grants from Merck Serono. E.G. received personal fees, consultancy fees, non-financial support from Novartis, outside the submitted work. Y.C. received grants and personal fees from Novartis; speaker fees, honoraria, consultancy, advisory board fees, and investigator fees from Novartis, Servier, Roche, Actelion, Sanofi, Bayer and Otsuka. A.-C.P. received personal fees from Novartis. C.M. received grants and personal fees from Novartis during

the conduct of the study; grants, personal fees and non-financial support from several diagnostic and therapeutic companies outside the submitted work. C.T. received personal fees and non-financial support from Novartis during the conduct of the study; personal fees from BMS outside the submitted work. E.L. received grants from AstraZeneca, Merck, Eli Lilly, grants and/or personal fees from Bayer, Boehringer Ingelheim, Amgen, Novartis, Sanofi, Novo Nordisk, The Medicines Company and Resvirologix outside the submitted work. J.G. received payment as investigator in TRANSITION from Novartis. A.N., H.S. and D.B. are employed by Novartis Pharma AG. W.B. is an employee and stock holder of Novartis Pharmaceutical Inc. D.P.-F. received personal fees and non-financial support from Novartis during the conduct of the study. The other authors have nothing to disclose.

## References

- Christ M, Störk S, Dörr M, Heppner HJ, Müller C, Wachter R, Riemer U, Trend HF Germany Project. Heart failure epidemiology 2000–2013: insights from the German Federal Health Monitoring System. *Eur J Heart Fail* 2016;**18**:1009–1018.
- Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozd J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavaliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L; Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013;**15**:1173–1184.
- Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghide M. The vulnerable phase after hospitalisation for heart failure. *Nat Rev Cardiol* 2015;**12**:220–229.
- McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Committees and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail* 2013;**15**:1062–1073.
- McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
- Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JM, Böhlhåvek J, Böhm M, Boytsov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Erglis A, Fu M, Gomez E, González-Medina A, Hagège AA, Huang J, Katova T, Kiatchoosakun S, Kim KS, Kozan Ö, Llamas EB, Martinez F, Merkely B, Mendoza I, Mosterd A, Negrusz-Kawecka M, Peuhkurinen K, Ramires FJ, Refsgaard J, Rosenthal A, Senni M, Sibulo AS Jr, Silva-Cardoso J, Squire IB, Starling RC, Teerlink JR, Vanhaecke J, Vinereanu D, Wong RC; PARADIGM-HF Investigators and Coordinators. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation* 2015;**131**:54–61.
- Ambrosy AP, Mentz RJ, Fiuzat M, Cleland JGF, Greene SJ, O'Connor CM, Teerlink JR, Zannad F, Solomon SD. The role of angiotensin receptor-neprilysin inhibitors in cardiovascular disease-existing evidence, knowledge gaps, and future directions. *Eur J Heart Fail* 2018;**20**:963–972.
- Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;**380**:539–548.
- Pascual-Figal D, Wachter R, Senni M, Belohlavek J, Noè A, Carr D, Butylin D. Rationale and design of TRANSITION: a randomised trial of pre-discharge vs. post-discharge initiation of sacubitril/valsartan. *ESC Heart Fail* 2018;**5**:327–336.
- World Medical Association. WMA declaration of Helsinki - Ethical principles for medical research involving human subjects. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (11 March 2019).
- Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, Andreaka P, Shehova-Yankova N, Anand I, Yilmaz MB, Gogia H, Martinez-Selles M, Fischer S, Zilahi Z, Cosmi F, Gelev V, Galve E, Gómez-Doblas JJ, Nociar J, Radomska M, Sokolova B, Volterrani M, Sarkar A, Reimund B, Chen F, Charney A. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomised comparison of two uptitration regimens. *Eur J Heart Fail* 2016;**18**:1193–1202.
- Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghide M; IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol* 2004;**43**:1534–1541.
- Gheorghide M, Böhm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, Gimpelewicz CR, Jaumont X, Lesogor A, Maggioni AP; ASTRONAUT Investigators and Coordinators. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomised trial. *JAMA* 2013;**309**:1125–1135.
- DeVore A. PIONEER-HF: results of the open-label extension. Science News from ACC 2019. [https://professional.heart.org/professional/EducationMeetings/EducationMeetings/UCM\\_503744\\_Science-News-from-ACC-2019.jsp](https://professional.heart.org/professional/EducationMeetings/EducationMeetings/UCM_503744_Science-News-from-ACC-2019.jsp) (9 April 2019).
- Kristensen SL, Martinez F, Jhund PS, Arango JL, Böhlhåvek J, Boytsov S, Cabrera W, Gomez E, Hagège AA, Huang J, Kiatchoosakun S, Kim KS, Mendoza I, Senni M, Squire IB, Vinereanu D, Wong RC, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJ. Geographic variations in the PARADIGM-HF heart failure trial. *Eur Heart J* 2016;**37**:3167–3174.
- Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams F, Hernandez AF, Fonarow GC. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol* 2018;**72**:351–366.
- Wachter R, Fonseca AF, Balas B, Kap E, Engelhard J, Schlienger R, Klebs S, Wirta SB, Kostev K. Real-world treatment patterns of sacubitril/valsartan: a longitudinal cohort study in Germany. *Eur J Heart Fail* 2019;**21**:588–597.
- Desai AS. The three-phase terrain of heart failure readmissions. *Circ Heart Fail* 2012;**5**:398–400.
- Chun S, Tu JV, Wijeyesundera HC, Austin PC, Wang X, Levy D, Lee DS. Lifetime analysis of hospitalisations and survival of patients newly admitted with heart failure. *Circ Heart Fail* 2012;**5**:414–421.
- Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghide M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Dosing of beta-blocker therapy before, during, and after hospitalisation for heart failure (from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). *Am J Cardiol* 2008;**102**:1524–1529.
- Ouwkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Metra M, Zwinderman AH. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J* 2017;**38**:1883–1890.
- Senni M, McMurray JJ, Wachter R, McIntyre HF, Anand IS, Duino V, Sarkar A, Shi V, Charney A. Impact of systolic blood pressure on the safety and tolerability of initiating and up-titrating sacubitril/valsartan in patients with heart failure and reduced ejection fraction: insights from the TITRATION study. *Eur J Heart Fail* 2018;**20**:491–500.
- Andries G, Yandrapalli S, Aronow WS. Benefit-risk review of different drug classes used in chronic heart failure. *Expert Opin Drug Saf* 2019;**18**:37–49.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.