Rationale and design of TRANSITION: a randomized trial of pre-discharge vs. post-discharge initiation of sacubitril/valsartan

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Abstract

Aims  The prognosis after hospitalization for acute decompensated heart failure (ADHF) remains poor, especially <30 days post-discharge. Evidence-based medications with prognostic impact administered at discharge improve survival and hospital readmission, but robust studies comparing pre-discharge with post-discharge initiation are rare. The PARADIGM-HF trial established sacubitril/valsartan as a new evidence-based therapy in patients with heart failure (HF) and reduced left ventricular ejection fraction (<40%) (rEF). In common with other landmark studies, it enrolled patients who were ambulatory at the time of inclusion. In addition, there is also still limited knowledge of initiation and up-titration of sacubitril/valsartan in ACEi/ARB-naïve patients and in de novo HF with rEF patients.

Methods and results  TRANSITION is a multicentre, open-label study in which ~1000 adults hospitalized for ADHF with rEF are randomized to start sacubitril/valsartan in a pre-discharge arm (initiated ≥24 h after haemodynamic stabilization) or a post-discharge arm (initiated within Days 1–14 after discharge). The protocol allows investigators to select the appropriate starting dose and dose adjustments according to clinical circumstances. Over a 10 week treatment period, the primary and secondary objectives assess the feasibility and safety of starting sacubitril/valsartan in-hospital, early after haemodynamic stabilization. Exploratory objectives also include assessment of HF signs and symptoms, readmissions, N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T levels, and health resource utilization parameters.

Conclusions  TRANSITION will provide new evidence about initiating sacubitril/valsartan following hospitalization for ADHF, occurring either as de novo ADHF or as deterioration of chronic HF, and in patients with or without prior ACEi/ARB therapy. The results of TRANSITION will thus be highly relevant to the management of patients hospitalized for ADHF with rEF.

Keywords  Sacubitril/valsartan; LCZ696; Acute heart failure; Acute decompensated heart failure; Hospitalization; Discharge

Rationale for the TRANSITION study

The burden of acute heart failure

Acute heart failure (AHF) is a major public health issue. Approximately 1–2% of adults in developed countries have heart failure (HF), rising to ≥10% of those aged 70 years or older.1 HF is the most common cause of hospitalization for patients older than 65 years in developed countries,2 and the incidence of hospitalization for AHF in the USA is estimated to be 11.6 per 1000 persons aged 55 years or older.3 A study from Germany found that hospitalization for HF...
Evidence-based therapies in acute heart failure with reduced ejection fraction: impact, timing, and utilization

Among patients hospitalized for AHF, administration of evidence-based medications with prognostic impact\textsuperscript{10,11} at the time of hospital discharge\textsuperscript{2-13} or shortly afterwards\textsuperscript{14} has been associated with an improvement in survival and hospital readmission rates. A large observational analysis of outcomes associated with the performance measures recommended by the American College of Cardiology and the American Heart Association found that use of beta-blockers, or an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), at the time of discharge was associated with significant reductions in mortality and hospital readmission.\textsuperscript{12} For mineralocorticoid receptor antagonists (MRAs), observational studies have shown reduced death and readmissions for HF in patients with AHF discharged on spironolactone, with benefits seen within 30 days of initiation of therapy.\textsuperscript{13}

The European Society of Cardiology (ESC) guidelines advise that patients admitted to hospital for HF should receive evidence-based oral medication for at least 24 h before discharge.\textsuperscript{15} However, well-designed randomized trials substantiating a benefit for pre-discharge vs. post-discharge initiation are relatively rare.\textsuperscript{15} No such study has been undertaken regarding ARBs or ACEIs. For beta-blockade, the open-label IMPACT-HF trial in 2004 compared pre-discharge initiation of carvedilol with initiation of any beta-blocker >2 weeks after discharge in 363 patients hospitalized for AHF.\textsuperscript{15} At 60 days post-discharge, significantly more patients in the pre-discharge initiation group were receiving a beta-blocker (91\% vs. 73\%, \textit{P} < 0.0001), and there was a non-significant trend to a lower incidence of a combined endpoint of death or re-hospitalization vs. the delayed initiation group (hazard ratio 0.85; 95\% confidence interval [CI] 0.56–1.27). An observational, single-centre study of 685 consecutive patients discharged after admission for AHF suggested that delayed initiation of MRA therapy (30–90 days post-discharge) is associated with a significant increase in mortality vs. initiation in hospital,\textsuperscript{16} although a \textit{post hoc} analysis of the EMPHASIS-HF study showed that eplerenone prescription shortly after hospital discharge is still beneficial.\textsuperscript{14}

Recent registry data from Europe\textsuperscript{27} and the USA\textsuperscript{18} have shown an improvement in adherence to treatment guidelines\textsuperscript{10,11} at the point of hospital discharge, including ACEIs, ARB therapy, beta-blockers, and MRAs. Prescription rates for each of these drug classes increase during hospitalization as physicians improve treatment adherence prior to discharge.\textsuperscript{18,19}

Hospitalization for acute heart failure: outcomes after discharge

Despite prescription of evidence-based therapies after admission for AHF, the prognosis remains poor in terms of both disease progression, as indicated by readmission rates, and mortality. Patients can achieve a short-term symptomatic improvement with current medical treatment,\textsuperscript{20} but during the first year after discharge, between 15\% and 24\% of patients die.\textsuperscript{21} Patients hospitalized for acute decompensated HF (ADHF) have particularly poor outcomes. In a study of 1669 patients, there was a significantly higher risk of readmission (for any cause, for cardiovascular causes, or for HF) at 1 year after hospitalization owing to ADHF compared with \textit{de novo} AHF.\textsuperscript{22}

Readmission after hospitalization for AHF is frequent, occurring in 30–40\% of cases during the first-year post-discharge,\textsuperscript{21,23} and readmission is associated with more severe AHF and greater post-discharge mortality.\textsuperscript{23,24}

The vulnerable phase after hospital discharge

The first months after hospitalization for AHF are termed the ‘vulnerable phase’.\textsuperscript{25} The risk of death and readmissions is greatest within the first 1–3 months after hospital discharge,\textsuperscript{26} with the very highest rates observed in the first 30 days.\textsuperscript{21,27-29} Data from the ADHERE registry in the USA, based on 104 808 patients hospitalized owing to HF, showed a mortality data of 11.2\% and a readmission rate of 22.1\% at Day 30 after discharge.\textsuperscript{28} Within the first 3 months post-discharge, 35–40\% of patients will either die or be readmitted to hospital.\textsuperscript{30} The most frequent causes of death in the first year after hospitalization for HF are pump failure and sudden cardiac death.\textsuperscript{31}

On leaving hospital, the patient has very recently experienced intense neurohormonal over-activation with haemodynamic destabilization and undergone multiple acute interventions to manage the ADHF episode. Elevated filling pressures may still be present, which can lead to subacute or acute worsening of haemodynamics.\textsuperscript{31} In this high-risk condition, the patient moves from close supervision by the inpatient cardiology team to less intensive ambulatory management. This transition, with less frequent monitoring of blood pressure and well-being, more sporadic adjustment of HF medication and concomitant therapies, and an increased likelihood of non-adherence to the prescribed regimen,
compounds the risk for recurrent events. It is, clearly, a clinical priority to investigate options about how to manage the treatment regimen during this difficult transition period.

Sacubitril/valsartan in chronic heart failure with reduced ejection fraction

Sacubitril/valsartan is the first-in-class angiotensin receptor nephrilysin inhibitor. It is indicated for use in patients with chronic heart failure with reduced ejection fraction (HFrEF) of New York Heart Association (NYHA) Class II–IV and is recommended as a replacement for an ACEI or an ARB, usually in conjunction with a beta-blocker and an MRA.10,33 Sacubitril inhibits nephrilysin, which degrades vasoactive peptides including natriuretic peptides (NPs), bradykinin, and adrenomedullin.34–36 Enhanced levels of NPs exert physiologic effects through binding to NP receptors and the augmented generation of cyclic guanosine monophosphate, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling, countering the effect of renin–angiotensin–aldosterone over-stimulation. Simultaneous selective AT1-receptor blockade via valsartan reduces vasoconstriction, sodium and water retention, and myocardial hypertrophy.10,37

In the PARADIGM-HF trial, ambulatory patients with HFrEF (NYHA Class II–IV) were randomized to sacubitril/valsartan (200 mg twice daily, n = 4187) or to enalapril (10 mg twice daily, n = 4212) in addition to standard of care therapy with beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%).38 The trial was stopped prematurely because the primary outcome, a composite of death from cardiovascular causes or hospitalization for HF, showed highly significant superiority for sacubitril/valsartan compared with enalapril: 21.8% vs. 26.5% (P < 0.001). The benefit was seen to a similar extent for both cardiovascular death (13.3% vs. 16.5%, P < 0.001) and HF hospitalization (12.8% vs. 15.6%, P < 0.001), and, remarkably, the difference between treatment groups was significant as early as Day 30 after randomization.49 Both the rate of sudden death (6.0% vs. 7.4%, P = 0.008) and death due to worsening HF (3.5% vs. 4.4%, P = 0.034) were reduced with sacubitril/valsartan vs. enalapril.46 In addition to a mortality benefit, sacubitril/valsartan was also superior to enalapril in reducing symptoms and physical limitations associated with HF, as assessed by the Kansas City Cardiomyopathy Questionnaire. Fewer patients on sacubitril/valsartan experienced a worsening of NYHA functional class (≥1 class) from baseline to 8 months after starting treatment compared with those on enalapril (5.4% vs. 7.0%, P = 0.004).41 Sacubitril/valsartan was associated with a reduction in clinical progression in terms of worsening HF, hospital admissions, and recurrent readmissions, an effect that was particularly marked in patients previously hospitalized for HF.42 In both treatment groups, risk of the primary endpoint was lowest in patients who were up-titrated to the higher dose and remained on it, but the benefit of sacubitril/valsartan vs. enalapril was sustained even in the subgroup of patients receiving a submaximal dose of either drug.43

The safety profile of sacubitril/valsartan was comparable with that of enalapril, with a low rate of discontinuations due to adverse events in both arms.38 Renal impairment and hyperkalaemia, both hallmarks of disease progression in HF, were less frequent in the sacubitril/valsartan group. Thus, PARADIGM-HF showed that sacubitril/valsartan therapy in ambulatory HF patients provides highly significant reductions in mortality and hospitalization for HF, delays the clinical progression of HF, and is well tolerated.

Data gaps

AHF remains the most relevant clinical event in HF progression and is associated with high rates of mortality21,44 and hospital readmission, frequently occurring early after discharge.23 Nevertheless, there is a remarkable lack of evidence regarding the optimal management of patients after haemodynamic stabilization following hospitalization for AHF. The landmark studies in HF have predominantly recruited ambulatory patients with chronic ‘stable’ HF.45–50 The PARADIGM-HF trial established sacubitril/valsartan as a new evidence-based therapy in patients with chronic HF, but in common with other major studies, it enrolled patients who were ambulatory at the time of inclusion.38 The study population of the TITRATION study, which compared up-titration regimens of sacubitril/valsartan, included a small number of hospitalized HFrEF patients (56 out of 498 randomized patients).51 There is also still very limited knowledge of initiation and up-titration of sacubitril/valsartan in ACEI/ARB-naïve patients and in de novo HFrEF patients. Thus, evidence is required for the safety and tolerability of sacubitril/valsartan treatment initiated during hospitalization owing to AHF.

The TRANSITION study aims to provide evidence that it is feasible to start sacubitril/valsartan shortly after stabilization in patients hospitalized for AHF. In addition, it aims to investigate the following questions. Can the targeted dose be achieved more effectively using pre-discharge initiation compared with post-discharge initiation? Does an in-hospital strategy offer clinical benefits vs. initiation shortly after hospital discharge, especially in terms of early readmissions, and regarding health resource utilization? Lastly, the effect of sacubitril/valsartan on N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hsTnT) concentrations, both of which are widely accepted prognostic biomarkers after hospitalization for AHF, remains to be determined.
Design of the TRANSITION study

Overview

TRANSITION is a multicentre, randomized, open-label, parallel-group study comparing pre-discharge and post-discharge treatment initiation with sacubitril/valsartan in heart failure patients with reduced ejection fraction hospitalised for an acute decompensation event (ClinicalTrials.gov identifier: NCT02661217) (Figure 1). It is being conducted at ~180 centres in 19 countries, with a planned population of ~1000 randomized patients. The purpose of the trial is to compare pre-discharge and post-discharge initiation of sacubitril/valsartan in patients with HFrEF following haemodynamic stabilization after an episode of ADHF. ADHF can either be de novo HF (i.e. their first presentation) or due to deterioration of chronic HF. Following screening and randomization, the study comprises a 10 week treatment period followed by a 16 week follow-up phase during which clinical and laboratory data will continue to be collected.

Study objectives

The primary objective of the study is to evaluate the proportion of patients in the pre-discharge and post-discharge treatment initiation groups who achieve the target sacubitril/valsartan dose of 200 mg twice daily at the end of Week 10 after randomization, regardless of any previous temporary dose interruption or down-titration (Table 1). Secondary objectives are to assess the proportion of patients who achieve and maintain (i) a sacubitril/valsartan dose of 100 and/or 200 mg twice daily or (ii) any dose of sacubitril/valsartan for at least 2 weeks leading to Week 10 after randomization, and also (iii) the proportion of patients who permanently discontinue sacubitril/valsartan owing to adverse events during the 10 week treatment period. Over the 10 week treatment period, exploratory objectives include assessment of HF signs and symptoms, the number of patients re-hospitalized, the time to first re-hospitalization, and levels of the biomarkers NT-proBNP and hsTnT (both measured centrally). Additionally, levels of serum creatinine and potassium, as well as vital parameters, will be assessed at all study visits. Health resource utilization parameters will be evaluated up to the end of study visit, i.e. including the 16 week follow-up period.

The biomarker and safety data collected in TRANSITION will complement information from the ongoing PIONEER-HF trial (Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode; NCT02554890). PIONEER-HF compares in-hospital initiation of sacubitril/valsartan vs. enalapril in patients who have been stabilized following hospitalization for ADHF with HFrEF. The primary endpoint of PIONEER-HF is the change in NT-proBNP levels over an 8 week treatment period, with results expected in 2018.

Study population

The study population comprises male or female patients aged ≥18 years hospitalized for an episode of ADHF (de novo HF or due to deterioration of chronic HF), with HFrEF (NYHA Class
II–IV and left ventricular ejection fraction ≤ 40%). The key inclusion and exclusion criteria for the study are summarized in Table 2. Patients can be receiving ACEI, ARB, or no ACE/ARB therapy at the time of admission, and, based on previous reports, it is expected that ACE/ARB treatment-naïve patients will represent at least 7% of the study population.

Randomization

Randomization does not take place until at least 24 h after documented haemodynamic stabilization (i.e. no requirement for intravenous diuretics in the previous 24 h and systolic blood pressure ≥ 110 mmHg for at least 6 h prior to randomization). Eligible patients are stratified prior to randomization based on the pre-admission therapy, i.e. (i) receiving any dose of ACEI, (ii) receiving any dose of ARB, or (iii) ACEI/ARB treatment-naïve patients, defined as no previous treatment with ACEI or ARB therapy or no ACEI or ARB therapy for at least 4 weeks before admission to hospital. Within each stratum, patients are randomized (1:1) to start sacubitril/valsartan either pre-discharge or post-discharge. The randomization procedure is performed using interactive response technology.

Study treatment

Patients randomized to the pre-discharge arm receive their first dose of sacubitril/valsartan during hospitalization, once the investigator has assessed their condition as stable for ≥ 24 h. It is given ≥ 12 h before discharge and ≤ 7 days after randomization. Patients randomized to the post-discharge arm continue to receive optimized standard of care HF medication, with the first dose of sacubitril/valsartan given at any time between the day after discharge and Day 14 post-discharge (Figure 1).

Patients in both groups are expected to be continuously treated with optimized standard of care HF therapy, except that sacubitril/valsartan is intended to replace ACEI or ARB therapy. For both groups, an ACEI wash-out period of at least 36 h is required before sacubitril/valsartan treatment is started in any patient receiving ACEI therapy, owing to the potential risk of angioedema if the two therapies are administered concomitantly. ARB therapy must be stopped before sacubitril/valsartan is started.

The target dose of sacubitril/valsartan in both groups is 200 mg twice daily, the dose studied in the PARADIGM-HF trial. The dosing strategy follows the product licence. The recommended starting dose of sacubitril/valsartan is 100 mg twice daily, doubled every 2–4 weeks to the target dose, as tolerated by the patient. An initial dose of 50 mg twice daily, doubled every 2–4 weeks to 100 mg twice daily and then to 200 mg twice daily, as tolerated by the patient, is to be considered in patients taking low doses of an ACEI or ARB or with no ACEI or ARB therapy, or in patients with moderate hepatic impairment or moderate renal impairment (estimated glomerular filtration rate 30–60 mL/min/1.73 m²) (Figure 2). Up-titration steps and dose adjustments are defined in the protocol as tolerated by the patient, including specific guidance on interventions in response to adverse events and the circumstances in which the sacubitril/valsartan dose may be reduced, with a particular focus on hyperkalaemia, symptomatic hypotension, and clinically significant changes in renal or hepatic function. Development of end-stage renal disease, severe hepatic impairment, or angioedema-like events triggers immediate and permanent discontinuation of sacubitril/valsartan therapy. During the follow-up phase, open-label sacubitril/valsartan therapy is continued. Concomitant use of any ACEI, ARB, or direct renin inhibitors (e.g. aliskiren) is
Table 2  Key eligibility criteria for the TRANSITION study

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Hospitalized owing to ADHF episode as primary diagnosis and                       | Hypersensitivity to sacubitril, valsartan, any ARBs, neprilysin                      |
| with consistent signs and symptoms                                                | inhibitors, or any of the sacubitril/valsartan excipients                            |
| Diagnosis of HFrEF NYHA Class II–IV and LVEF ≤ 40% at screening                  | Symptomatic hypotension and/or SBP < 110 or > 180 mmHg prior to randomization         |
| Did not receive any intravenous vasodilators, except nitrates, and/or any         | End-stage renal disease at screening, or estimated GFR < 30 mL/min/1.73 m² (MDRD    |
| intravenous inotropic therapy from the time of presentation for ADHF to           | formula) at randomization                                                            |
| randomization                                                                       | Serum potassium > 5.4 mmol/L at randomization                                         |
| Stabilized (while in hospital) for ≥ 24 h prior to randomization³                 | Known history of hereditary or idiopathic angioedema or angioedema related to       |
| On any dose of ACEI/ARB therapy at screening, or ACEI/ARB-naïve patients³         | previous ACEI or ARB therapy                                                        |
|                                                                                  | History or current diagnosis of ECG abnormalities indicating significant risk of      |
|                                                                                  | safety for patients participating in the study                                       |
|                                                                                  | Acute coronary syndrome, stroke, transient ischaemic attack, cardiac, carotid, or    |
|                                                                                  | other major cardiovascular surgery, percutaneous coronary intervention, or carotid    |
|                                                                                  | angioplasty within the 3 months prior to screening                                    |
|                                                                                  | Coronary or carotid artery disease likely to require surgical or percutaneous        |
|                                                                                  | intervention within the 3 months after screening                                      |
|                                                                                  | Implantation of a pacemaker, implantable cardioverter                               |
|                                                                                  | defibrillator, cardiac resynchronization therapy pacemaker/defibrillator, or        |
|                                                                                  | upgrade of an existing device or revision of device leads within 1 month of         |
|                                                                                  | screening                                                                           |
|                                                                                  | Heart transplant or VAD or intent to transplant (on transplant list) or implant a    |
|                                                                                  | VAD                                                                                 |
|                                                                                  | History of severe pulmonary disease (i.e. treatment with oral steroid for their     |
|                                                                                  | pulmonary disease, or with inhaled oxygen on an outpatient basis)                   |
|                                                                                  | Diagnosis of peripartum or chemotherapy-induced cardiomyopathy within the 12 months  |
|                                                                                  | prior to screening                                                                   |
|                                                                                  | Presence of haemodynamically significant mitral and/or aortic valve disease, except  |
|                                                                                  | mitral regurgitation secondary to left ventricular dilatation                         |
|                                                                                  | Presence of other haemodynamically significant obstructive lesions of left ventricular|
|                                                                                  | outflow tract, including aortic and sub-aortic stenosis                              |
|                                                                                  | Severe hepatic impairment, biliary cirrhosis, and cholestasis                        |

ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; ECG, electrocardiogram; GFR, glomerular filtration rate; HFrEF, HF and reduced rejection fraction; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; NYHA, New York Heart Association; SBP, systolic blood pressure; VAD, ventricular assistance device.

³Defined as no requirement for intravenous diuretics in the previous 24 h prior to signing the informed consent form, with SBP ≥ 110 mmHg for ≥ 6 h prior to randomization.

²ACEI/ARB-naïve defined as not on ACEI or ARB for ≥ 4 weeks prior to screening

strictly prohibited while the patient is receiving sacubitril/valsartan. Concomitant administration of bile acid sequestering agents (e.g. cholestyramine and colestipol) is also prohibited, to avoid interference with study drug absorption.

Statistical methods

The primary endpoint will be compared between treatment groups using the stratified Cochran–Mantel–Haenszel method for 2 × 2 tables with the stratification variable at randomization (i.e. treatment with ACEI, ARB, or no ACEI/ARB) as stratification factor. The ‘risk ratio’, defined as the ratio of the probability to achieve the target sacubitril/valsartan dose of 200 mg twice daily at the end of Week 10 after randomization in the pre-discharge initiation arm over the corresponding probability in the post-discharge initiation arm, will be estimated with a two-sided 95% CI along with the estimated probability and 95% CI for each treatment arm. No imputation will be used for any patients who discontinue sacubitril/valsartan therapy owing to adverse events or abnormal laboratory values, or who premature discontinue the study. The secondary endpoints (Table 1) will be analysed in an identical fashion to the primary variable. Other results will be presented descriptively.
The planned sample size of ~1000 randomized patients provides reasonable precision for estimation of the treatment effect size on the primary variable. For instance, if 80% of patients in both the pre-discharge and post-discharge initiation groups achieve the target sacubitril/valsartan dose of 200 mg twice daily by Week 10, this sample size will provide an estimated risk ratio and 95% CI of 1.00 (0.94, 1.06).

**Trial status**

Patient recruitment started in February 2016, and results of the study are expected in 2018.

**Translational outlook**

Sacubitril/valsartan is an established component of the therapeutic armamentarium for chronic HFrEF. It is recommended in the ESC Heart Failure guidelines as disease-modifying therapy for ambulatory HFrEF patients who remain symptomatic despite optimal treatment with an ACEI, a beta-blocker, and an MRA (Class IB recommendation), and also for HFrEF with ventricular arrhythmias to reduce the risk of sudden death (Class 1A recommendation). Additional information is required, however, regarding the initiation and titration of sacubitril/valsartan in patients hospitalized for ADHF with newly diagnosed or pre-existing HFrEF. The TRANSITION trial has been designed to address this question. Specifically, it will determine whether starting sacubitril/valsartan before or after hospital discharge in patients stabilized after admission for ADHF is more successful in achieving the target dose of 200 mg twice daily after 10 weeks of therapy. The protocol takes into account the needs of the practising cardiologist, allowing investigators to select the appropriate starting dose and dose adjustments according to clinical circumstances. Additionally, TRANSITION will provide new evidence about the resource utilization of novel disease-modifying HFrEF therapy in the setting of ADHF, and in particular the impact of starting it before hospital discharge. The results will thus be highly relevant to the management of patients stabilized after hospital admission for ADHF with HFrEF.

In conclusion, TRANSITION will provide new data concerning the initiation and up-titration of sacubitril/valsartan after haemodynamic stabilization in patients hospitalized for ADHF occurring as either de novo ADHF or deterioration of chronic HF, and in patients with or without prior ACEI or ARB therapy. By determining whether sacubitril/valsartan treatment initiated closer to the event is safe and well tolerated, the trial may help to improve the clinical course after ADHF.
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Conflict of interest

Domingo Pascual-Figal is a member of advisory boards and/or has received research grants and/or speaker’s honoraria from Novartis, Servier, Vifor, Roche, and bioMérieux.

Rolf Wachter is a member of advisory boards and/or has received speaker’s honoraria from Boehringer Ingelheim, Bayer, CVRx, Medtronic, Novartis, Pfizer, Sanofi, and Servier. He has received research grants from Boehringer Ingelheim, the European Union, and Bundesministerium für Bildung und Forschung.

Michele Senni is a member of advisory boards and/or has received research grants and/or speaker’s honoraria from Novartis, Bayer, Merck/MSD, and Abbott Vascular.

Author contributions

Adele Noé, David Carr, and Dmytro Butylin designed and wrote the TRANSITION study protocol. Domingo Pascual-Figal, Rolf Wachter, Michele Senni, and Jan Belohlavek are national principal investigators of the study and collect data. All authors drafted the manuscript or made critical revision of the manuscript for important intellectual content, and approved the final version for submission.

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