ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 327–336
Published online 14 December 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12246

ORIGINAL RESEARCH ARTICLE

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

Domingo Pascual-Figal[1]*, Rolf Wachter[2], Michele Senni[3], Jan Belohlavek[4], Adele Noè[5], David Carr[5] and Dmytro Butylin[5]

[1]*Heart Failure and Heart Transplantation Unit, Cardiology Department, Virgen de la Arrixaca University Hospital, Universidad de Murcia, Ctra. Madrid-Cartagena s/n30120, Murcia, Spain;* [2]*Clinic and Policlinic for Cardiology, University Hospital Leipzig, Germany;* [3]*Cardiology Division, Cardiovascular Department, Hospital Papa Giovanni XXIII—Bergamo, Bergamo, Italy;* [4]*Complex Cardiovascular Centre, General Teaching Hospital, Charles University, Prague, Czech Republic;* [5]*Novartis Pharma AG, Basel, Switzerland*

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

Received: 12 June 2017; Revised: 28 September 2017; Accepted: 14 November 2017
**Correspondence to: Dr Domingo Pascual-Figal, Heart Failure and Heart Transplantation Unit, Cardiology Department, Virgen de la Arrixaca University Hospital, Universidad de Murcia, Ctra. Madrid-Cartagena s/n, 30120 Murcia, Spain. Tel: +34-8688163. Email: dpascual@um.es*
Clinical trial registration: unique identifier NCT02661217

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

increased by 65% over the period from 2000 to 2013.[4] One recent estimate placed the global annual cost of HF overall to be $US108bn,[5] and hospitalization represents a major component of this expenditure,[6] with hospital stays for AHF typically lasting for 5–10 days.[7] Moreover, as the population ages, the prevalence of HF is expected to increase markedly, with an associated impact on costs.[8,9]

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[10,11] at the time of hospital discharge[12,13] or shortly afterwards[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.[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.[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.[10] However, well-designed randomized trials substantiating a benefit for pre-discharge vs. post-discharge initiation are relatively rare.[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.[15] At 60 days post-discharge, significantly more patients in the pre-discharge initiation group were receiving a beta-blocker (91% vs. 73%, $P < 0.0001$), 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,[16] although a *post hoc* analysis of the EMPHASIS-HF study showed that eplerenone prescription shortly after hospital discharge is still beneficial.[14]

Recent registry data from Europe[17] and the USA[18] have shown an improvement in adherence to treatment guidelines[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.[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,[20] but during the first year after discharge, between 15% and 24% of patients die.[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 *de novo* AHF.[22]

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

The vulnerable phase after hospital discharge

The first months after hospitalization for AHF are termed the 'vulnerable phase'.[25] The risk of death and readmissions is greatest within the first 1–3 months after hospital discharge,[26] with the very highest rates observed in the first 30 days.[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.[28] Within the first 3 months post-discharge, 35–40% of patients will either die or be readmitted to hospital.[30] The most frequent causes of death in the first year after hospitalization for HF are pump failure and sudden cardiac death.[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.[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.[32] 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 neprilysin 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 neprilysin, 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.[39] 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.[40] 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,[38,41] 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 mortality[21,44] and hospital readmission,[21,23] 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,[52,53] remains to be determined.

Design of the TRANSITION study

Overview

TRANSITION is a multicentre, randomized, open-label, parallel-group study comparing pre-discharge and pos**T**-discharge t**R**eatment initiation with sacubitril/valsartan in he**A**rt failure patie**N**t**S** with reduced eject**I**on-frac**T**ion hosp**I**talised for an acute dec**O**mpensation eve**N**t (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

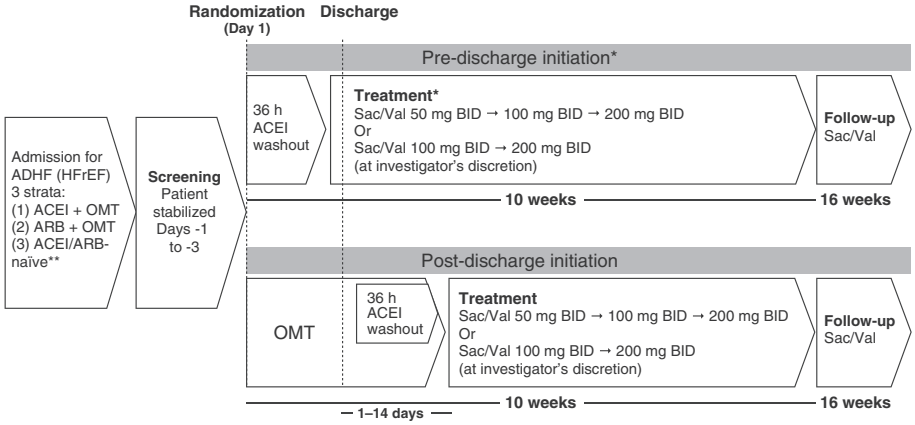
The primary objective of the study is to evaluate the proportion of patients in the pre-discharge and post-discharge treatment initiation groups who achieve the target sacubitril/valsartan dose of 200 mg twice daily at the end of Week 10 after randomization, regardless of any previous temporary dose 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

Figure 1 TRANSITION study design. Study visits take place at 2, 4, 6, 8, and 10 weeks and 14, 18, 22, and 26 weeks after randomization (or at the point of premature treatment or study discontinuation). ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; HFrEF, heart failure with reduced rejection fraction; OMT, optimized medical treatment as per treating physician; Sac/Val, sacubitril/valsartan.



* Initiated ≥12 hours before discharge and ≤7 days post-randomization
** No previous ACEI/ARB treatment, or no ACEI/ARB treatment in the 4 weeks prior to hospitalization for ADHF

Table 1 Objectives of the TRANSITION study

Primary objective	To evaluate the proportion of patients in the pre-discharge and post-discharge treatment initiation groups achieving the target sacubitril/valsartan dose of 200 mg twice daily at the end of Week 10 after randomization, regardless of previous temporary dose interruptions or down-titration
Secondary objectives	To assess the proportion of patients who achieve and maintain a sacubitril/valsartan dose of 100 and/or 200 mg twice daily for at least 2 weeks leading to Week 10 after randomization To assess the proportion of patients who achieve and maintain any dose of sacubitril/valsartan for at least 2 weeks leading to Week 10 after randomization To assess the proportion of patients who permanently discontinue the study drug owing to adverse events during the 10 week treatment period
Exploratory objectives	To evaluate: Patterns of NT-proBNP and hsTnT levels during the 10 week treatment period Patterns of HF signs and symptoms during the 10 week treatment period Median sacubitril/valsartan dose during the 10 week treatment period Number of patients re-hospitalized and time to first re-hospitalization Mean time to sacubitril/valsartan initiation (pre-discharge and post-discharge) Proportion of patients permanently discontinuing study drug for any reason at any time during the study Health resource utilization parameters assessed up to the end of study visit (i.e. including the follow-up period), including length of hospital stay during the index visit, number of emergency room visits without admission, number of readmissions after discharge, and type of discharge

HF, heart failure; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide.

II–IV and left ventricular ejection fraction $\leq$ 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 $\geq$ 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 $\geq$24 h. It is given $\geq$12 h before discharge and $\leq$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.[38] The dosing strategy follows the product licence.[33] 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 m^2) (*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 with consistent signs and symptoms	Hypersensitivity to sacubitril, valsartan, any ARBs, neprilysin inhibitors, or any of the sacubitril/valsartan excipients
Diagnosis of HFrEF NYHA Class II–IV and LVEF $\leq$ 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 intravenous inotropic therapy from the time of presentation for ADHF to randomization Stabilized (while in hospital) for $\geq$24 h prior to randomization[a]	End-stage renal disease at screening, or estimated GFR $<$ 30 mL/min/1.73 m^2 (MDRD formula) at randomization
	Serum potassium $>$ 5.4 mmol/L at randomization
On any dose of ACEI/ARB therapy at screening, or ACEI/ARB-naïve patients[b]	Known history of hereditary or idiopathic angioedema or angioedema related to 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

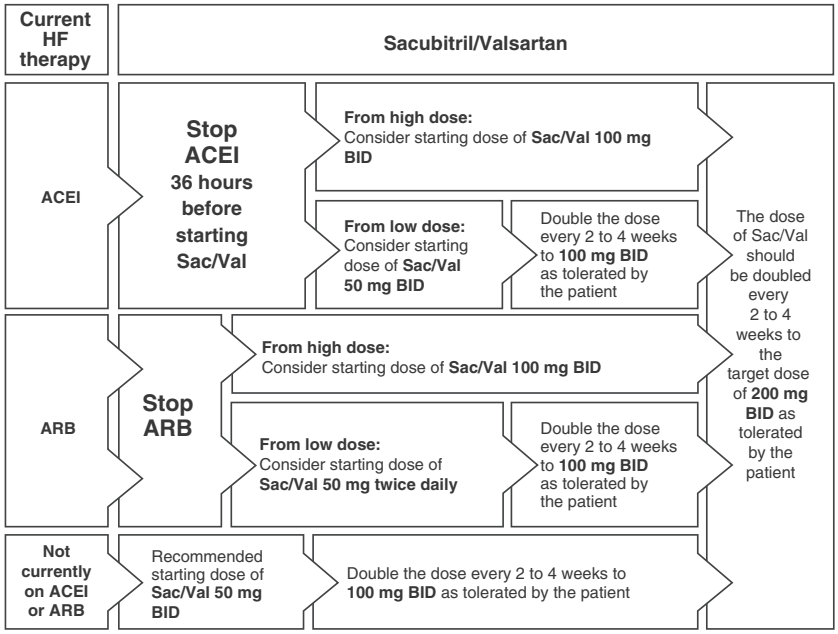
ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; ECG, electrocardiogram; GFR, glomerular filtration rate; HFrEF, HF and reduced rejection fraction; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; NHYA, New York Heart Association; SBP, systolic blood pressure; VAD, ventricular assistance device.
[a]Defined as no requirement for intravenous diuretics in the previous 24 h prior to signing the informed consent form, with SBP $\geq$ 110 mmHg for $\geq$6 h prior to randomization.
[b]ACEI/ARB-naïve defined as not on ACEI or ARB for $\geq$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 prematurely 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.

Figure 2 Dosing schedule for sacubitril/valsartan (Sac/Val) in the TRANSITION study. ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HF, heart failure.



* Regardless of ACEI dose, a Sac/Val starting dose of 50 mg BID is recommended in moderate renal impairment (eGFR 30–60 mL/min/1.73m^2) or moderate hepatic function (Child Pugh B classification) or with AST/ALT values >2 times upper limit of normal

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).[10] 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.

Acknowledgements

The manuscript was drafted by a freelance medical writer (C. Dunstall) based on a written brief from the authors, with funding from Novartis Pharma AG, Basel, Switzerland.

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.

Jan Belohlavek has been a member of advisory boards for Novartis and AcelRX, and has received a research grant from Novartis and speaker's honoraria from Novartis, Servier, AstraZeneca, and Maquet.

Adele Noè, David Carr, and Dmytro Butylin are employees of Novartis Pharma AG.

Author contributions

Adele Noè, 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.

Funding

The TRANSITION study is initiated and funded by Novartis Pharma AG, Basel, Switzerland.

References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines. ES Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**: 1787–1847.
2. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011; **8**: 30–41.
3. Chang PP, Chambless LE, Shahar E, Bertoni AG, Russell SD, Ni H, He M, Mosley TH, Wagenknecht LE, Samdarshi TE, Wruck LM, Rosamond WD. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol* 2014; **113**: 504–510.
4. 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.
5. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol* 2014; **171**: 368–376.
6. Maggioni AP, Orso F, Calabria S, Rossi E, Cinconze E, Baldasseroni S, Martini N, Observatory ARNO. The real-world evidence of heart failure: findings from 41 413 patients of the ARNO database. *Eur J Heart Fail* 2016; **18**: 402–410.
7. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Siswanto BB, Sliwa K, Filippatos G. Heart failure: preventing disease and death worldwide. 2014. **https://www.escardio.org/static_file/Escardio/Subspecialty/HFA/WHFA-whitepaper-15-May-14.pdf (2 March 2017).**
8. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG, American Heart Association Advocacy Coordinating Committee, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013; **6**: 606–619.
9. Tran DT, Ohinmaa A, Thanh NX, Howlett JG, Ezekowitz JA, McAlister FA, Kaul P. The current and future financial burden of hospital admissions for heart failure in Canada: a cost analysis. *CMAJ Open* 2016; **4**: E365–E370.
10. 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, Authors/Task Force Members. 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 Heart J* 2016; **37**: 2129–2200.
11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016

ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2016; **68**: 1476–1488.
12. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy C, Young JB, OPTIMIZE-HF Investigators and Hospitals. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA* 2007; **297**: 61–70.
13. Maisel A, Xue Y, van Veldhuisen DJ, Voors AA, Jaarsma T, Pang PS, Butler J, Pitt B, Clopton P, de Boer RA. Effect of spironolactone on 30-day death and heart failure rehospitalization (from the COACH Study). *Am J Cardiol* 2014; **114**: 737–742.
14. Girerd N, Collier T, Pocock S, Krum H, McMurray JJ, Swedberg K, Van Veldhuisen DJ, Vincent J, Pitt B, Zannad F. Clinical benefits of eplerenone in patients with systolic heart failure and mild symptoms when initiated shortly after hospital discharge: analysis from the EMPHASIS-HF trial. *Eur Heart J* 2015; **36**: 2310–2317.
15. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade 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.
16. Rossi R, Crupi N, Coppi F, Monopoli D, Sgura F. Importance of the time of initiation of mineralocorticoid receptor antagonists on risk of mortality in patients with heart failure. *J Renin Angiotensin Aldosterone Syst* 2015; **16**: 119–125.
17. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene 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.
18. Allen LA, Fonarow GC, Liang L, Schulte PJ, Masoudi FA, Rumsfeld JS, Ho PM, Eapen ZJ, Hernandez AF, Heidenreich PA, Bhatt D, Peterson ED, Krumholz HM. American Heart Association's Get With The Guidelines Heart Failure (GWTG-HF) Investigators. Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures. *Circulation* 2015; **132**: 1347–1353.
19. Krantz MJ, Ambardekar AV, Kaltenbach L, Hernandez AF, Heidenreich PA, Fonarow GC, Get With the Guidelines Steering Committee and Hospitals. Patterns and predictors of evidence-based medication continuation among hospitalized heart failure patients (from Get With the Guidelines-Heart Failure). *Am J Cardiol* 2011; **107**: 1818–1823.
20. Follath F, Yilmaz MB, Delgado JF, Parissis JT, Porcher R, Gayat E, Burrows N, McLean A, Vilas-Boas F, Mebazaa A. Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of StandardTreatment (ALARM-HF). *Intensive Care Med* 2011; **37**: 619–626.
21. Crespo-Leiro MG, Anker SD, AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A, Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016; **18**: 613–625.
22. Senni M, Gavazzi A, Oliva F, Mortara A, Urso R, Pozzoli M, Metra M, Lucci D, Gonzini L, Cirrincione V, Montagna L, Di Lenarda A, Maggioni AP, Tavazzi L, IN HF Outcome Investigators. In-hospital and 1-year outcomes of acute heart failure patients according to presentation (de novo vs. worsening) and ejection fraction. Results from IN-HF Outcome Registry. *Int J Cardiol* 2014; **173**: 163–169.
23. Hernandez AF, Greiner MA, Fonarow GC, Hammill BG, Heidenreich PA, Yancy CW, Peterson ED, Curtis LH. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA* 2010; **303**: 1716–1722.
24. Davison BA, Metra M, Senger S, Edwards C, Milo O, Bloomfield DM, Cleland JG, Dittrich HC, Givertz MM, O'Connor CM, Massie BM, Ponikowski P, Teerlink JR, Voors AA, Cotter G. Patient journey after admission for acute heart failure: length of stay, 30-day readmission and 90-day mortality. *Eur J Heart Fail* 2016; **18**: 1041–1050.
25. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol* 2015; **12**: 220–229.
26. Marti CN, Fonarow GC, Gheorghiade M, Butler J. Timing and duration of interventions in clinical trials for patients with hospitalized heart failure. *Circ Heart Fail* 2013; **6**: 1095–1101.
27. Kociol RD, Liang H, Hernandez AF, Curtis LH, Heidenreich PA, Yancy CW, Fonarow GC, Peterson ED. Are we targeting the right metric for heart failure? Comparison of hospital 30-day readmission rates and total episode of care inpatient days. *Am Heart J* 2013; **165**: 987–994.
28. Kociol RD, Hammill BG, Fonarow GC, Klaskala W, Mills RM, Hernandez AF, Curtis LH. Generalizability and longitudinal outcomes of a national heart failure clinical registry: Comparison of Acute Decompensated Heart Failure National Registry (ADHERE) and non-ADHERE Medicare beneficiaries. *Am Heart J* 2010; **160**: 885–892.
29. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007; **116**: 1482–1487.
30. Writing group members, Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Roger VL, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010; **121**: e46–e215.
31. Greene SJ, Fonarow GC, Solomon SD, Subacius H, Maggioni AP, Böhm M, Lewis EF, Zannad F, Gheorghiade M1 ASTRONAUT Investigators and Coordinators. Global variation in clinical profile, management, and post-discharge outcomes among patients hospitalized for worsening chronic heart failure: findings from the ASTRONAUT trial. *Eur J Heart Fail* 2015; **17**: 591–600.
32. Fermann GJ, Levy PD, Pang P, Butler J, Ayaz SI, Char D, Dunn P, Jenkins CA, Kampe C, Khan Y, Kumar VA, Lindenfeld J, Liu D, Miller K, Peacock WF, Rizk S, Robichaux C, Rothman RL, Schrock J, Singer A, Sterling SA, Storrow AB, Walsh C, Wilburn J, Collins SP. Design and rationale of a randomized trial of a care transition strategy in patients with acute heart failure discharged from the

emergency department: GUIDED-HF (Get With the Guidelines in Emergency Department Patients With Heart Failure). *Circ Heart Fail* 2017; **10**:pii: e003581.
33. Entresto prescribing information. Novartis AG. Last updated August 2015
34. Cruden NL, Fox KA, Ludlam CA, Johnston NR, Newby DE. Neutral endopeptidase inhibition augments vascular actions of bradykinin in patients treated with angiotensin-converting enzyme inhibition. *Hypertension* 2004; **44**: 913–918.
35. Rademaker MT, Charles CJ, Espiner EA, Nicholls MG, Richards AM, Kosoglou T. Neutral endopeptidase inhibition: augmented atrial and brain natriuretic peptide, haemodynamic and natriuretic responses in ovine heart failure. *Clin Sci (Lond)* 1996; **91**: 283–291.
36. Wilkinson IB, McEniery CM, Bongaerts KH, MacCallum H, Webb DJ, Cockcroft JR. Adrenomedullin (ADM) in the human forearm vascular bed: effect of neutral endopeptidase inhibition and comparison with proadrenomedullin NH2-terminal 20 peptide (PAMP). *Br J Clin Pharmacol* 2001; **52**: 159–164.
37. Volpe M. Natriuretic peptides and cardio-renal disease. *Int J Cardiol* 2014; **176**: 630–639.
38. McMurray JJV, 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.
39. Desai AS, Claggett BL, Packer M, Zile MR, Rouleau JL, Swedberg K, Shi V, Lefkowitz M, Starling R, Teerlink J, McMurray JJ, Solomon SD, PARADIGM-HF Investigators. Influence of sacubitril/valsartan (LCZ696) on 30-day readmission after heart failure hospitalization. *J Am Coll Cardiol* 2016; **68**: 241–248.
40. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, Gong J, Rizkala AR, Brahimi A, Claggett B, Finn PV, Hartley LH, Liu J, Lefkowitz M, Shi V, Zile MR, Solomon SD. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J* 2015; **36**: 1990–1997.
41. Packer M, McMurray JJV, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile M, Andersen K, Arango JL, Arnold JM, Bělohlávek J, Böhm M, Boytsov S, Burgess LJ, Cabrera W, Calvo C, Chen CH, Dukat A, Duarte YC, Erglis A, Fu M, Gomez E, Gonzàlez-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.
42. Solomon SD, Claggett B, Packer M, Desai A, Zile MR, Swedberg K, Rouleau J, Shi V, Lefkowitz M, McMurray JJ. Efficacy of sacubitril/valsartan relative to a prior decompensation: the PARADIGM-HF trial. *JACC Heart Fail* 2016; **4**: 816–822.
43. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, Teerlink JR, Desai AS, Lefkowitz M, Shi V, McMurray JJ, Solomon SD. Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. *Eur J Heart Fail* 2016; **18**: 1228–1234.
44. Lassus JP, Siirilä-Waris K, Nieminen MS, Tolonen J, Tarvasmäki T, Peuhkurinen K, Melin J, Pulkki K, Harjola VP, FINN-AKVA study group. Long-term survival after hospitalization for acute heart failure—differences in prognosis of acutely decompensated chronic and new-onset acute heart failure. *Int J Cardiol* 2013; **168**: 458–462.
45. The CONSENSUS Trial Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Group. *N Engl J Med* 1987; **316**: 1429–1435.
46. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353**: 9–13.
47. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**: 709–717.
48. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; **364**: 11–21.
49. McMurray JJ, Krum H, Abraham WT, Dickstein K, Køber LV, Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnesby G, Massie BM, ATMOSPHERE Committees Investigators. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med* 2016; **374**: 1521–1532.
50. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, Investigators SHIFT. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; **376**: 875–885.
51. Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, Andreka 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, randomized comparison of two uptitration regimens. *Eur J Heart Fail* 2010; **18**: 1193–1202.
52. Leto L, Testa M, Feola M. The predictive value of plasma biomarkers in discharged heart failure patients: role of plasma NT-proBNP. *Minerva Cardioangiol* 2016; **64**: 157–164.
53. Perna ER, Címbaro Canella JP, Coronel ML, Macin SM. The predictive value of plasma biomarkers in discharged heart failure patients: role of troponin I/T. *Minerva Cardioangiol* 2016; **64**: 165–180.