



PERSPECTIVES IN CARDIOLOGY

Neurohormonal modulation: The new paradigm of pharmacological treatment of heart failure



J. Silva-Cardoso^{a,b,c,*}, D. Brás^d, F. Canário-Almeida^e, A. Andrade^f, L. Oliveira^g,
F. Pádua^h, C. Fonseca^{i,j}, N. Bragança^k, S. Carvalho^l, R. Soares^m, J. Ferreira Santosⁿ

^a *Unidade de Doenças Cardiovasculares, Faculdade de Medicina da Universidade do Porto, Portugal*

^b *Centro de Pesquisa em Tecnologias e Serviços de Saúde, Universidade do Porto, Portugal*

^c *Clínica de Insuficiência Cardíaca e Transplante do Serviço de Cardiologia do Centro Hospitalar de S. João, Porto, Portugal*

^d *Medical Advisor, Departamento Médico, Novartis Farma-Produtos Farmacêuticos S.A., Lisboa, Portugal*

^e *Serviço de Cardiologia do Hospital Senhora da Oliveira, Guimarães, Portugal*

^f *Clínica de Insuficiência Cardíaca, Serviço de Cardiologia do Centro Hospitalar do Tâmega e Sousa, Penafiel, Portugal*

^g *Serviço de Cardiologia do Centro Hospitalar Cova da Beira, Covilhã, Portugal*

^h *Hospital Dr. José Maria Grande (Unidade Local de Saúde do Norte Alentejano), Portalegre, Portugal*

ⁱ *Unidade de Insuficiência Cardíaca, Serviço de Medicina III e Hospital Dia, Hospital São Francisco Xavier – Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal*

^j *NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal*

^k *Serviço de Medicina III, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal*

^l *Serviço de Cardiologia do Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal*

^m *Serviço de Cardiologia do Hospital de Santa Marta, Lisboa, Portugal*

ⁿ *Serviço de Cardiologia do Hospital da Luz, Setúbal, Portugal*

Received 20 February 2018; accepted 29 October 2018

KEYWORDS

Heart failure with reduced ejection fraction;
Neurohormonal modulation;
Angiotensin-receptor neprilysin inhibitor;
Sacubitril/valsartan;
Cardiovascular mortality;

Abstract The current paradigm of medical therapy for heart failure with reduced ejection fraction (HFrEF) is triple neurohormonal blockade with an angiotensin-converting enzyme inhibitor (ACEI), a beta-blocker (BB) and a mineralocorticoid receptor antagonist (MRA). However, three-year mortality remains over 30%.

Stimulation of counter-regulatory systems in addition to neurohormonal blockade constitutes a new paradigm, termed neurohormonal modulation. Sacubitril/valsartan is the first element of this new strategy.

PARADIGM-HF was the largest randomized clinical trial conducted in HFrEF. It included 8442 patients and compared the efficacy and safety of sacubitril/valsartan versus enalapril. The primary endpoint was the composite of cardiovascular mortality and hospitalization due to HF, which occurred in 914 (21.8%) patients receiving sacubitril/valsartan and in 1117 (26.5%)

* Corresponding author.

E-mail address: silvacardoso30@gmail.com (J. Silva-Cardoso).

Hospitalization due to heart failure; PARADIGM-HF

patients receiving enalapril (HR 0.8, 95% CI 0.73-0.87, $p=0.0000002$; NNT 21). Sacubitril/valsartan reduced both primary endpoint components, as well as sudden cardiac death, death due to worsening HF, and death from all causes. Patients on sacubitril/valsartan reported less frequent deterioration of HF and of quality of life, and discontinued study medication less frequently because of an adverse event.

PARADIGM-HF demonstrated the superiority of sacubitril/valsartan over enalapril, with a 20% greater impact on cardiovascular mortality compared to ACEIs. Accordingly, in 2016, the European (ESC) and American (ACC/AHA/HFSA) cardiology societies simultaneously issued a class I recommendation for the replacement of ACEIs by sacubitril/valsartan in patients resembling PARADIGM-HF trial participants.

© 2019 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. All rights reserved.

PALAVRAS-CHAVE

Insuficiência cardíaca com fração de ejeção reduzida; Modulação neuro-hormonal; Inibidor da neprilisina e dos recetores da angiotensina (INRA); Sacubitril/valsartan; Mortalidade cardiovascular; Hospitalização por insuficiência cardíaca; PARADIGM-HF

Modulação neuro-hormonal: o novo paradigma do tratamento farmacológico da Insuficiência Cardíaca

Resumo O paradigma atual da terapêutica médica da insuficiência cardíaca com fração de ejeção reduzida (ICFEr) é o triplo bloqueio neuro-hormonal com inibidores da enzima convertora da angiotensina (IECA), bloqueadores beta-adrenérgicos (BB) e antagonistas dos recetores mineralocorticóides (ARM). Contudo, a mortalidade a três anos destes doentes mantém-se superior a 30%.

A estimulação de sistemas contra-reguladores em adição ao bloqueio neuro-hormonal enzye of ma constitui um novo paradigma designado por modulação neuro-hormonal. O sacubitril/valsartan é o primeiro passo desta nova estratégia.

O PARADIGM-HF foi o maior estudo aleatorizado realizado na ICFEr, tendo incluído 8442 doentes. Comparou a eficácia e segurança do sacubitril/valsartan *versus* enalapril. O objetivo primário foi o composto mortalidade cardiovascular/hospitalização por IC. Este ocorreu em 914 (21,8%) doentes sob sacubitril/valsartan e 1117 (26,5%) doentes sob enalapril (*hazard ratio* (HR) 0,8, IC95% [0,73-0,87], $p=0,0000002$, número de doentes necessário para prevenir um evento [NNT]=21). O sacubitril/valsartan reduziu ambos os componentes do objetivo primário. Diminuiu a morte súbita cardíaca, a devida a agravamento da IC e também a morte por todas as causas. Nos doentes sob sacubitril/valsartan ocorreu menos frequentemente agravamento da IC, deterioração da qualidade de vida e interrupção da medicação em consequência de um efeito adverso.

O PARADIGM-HF demonstrou superioridade do sacubitril/valsartan relativamente ao enalapril, sendo o seu efeito sobre a mortalidade cardiovascular 20% superior ao dos IECAs. Assim, as Sociedades Europeia (ESC) e Americanas (ACC/AHA/HFSA) de Cardiologia incluíram, simultaneamente, em 2016 uma recomendação de Classe I para substituição dos IECAs pelo sacubitril/valsartan em doentes com características semelhantes aos participantes do ensaio PARADIGM-HF.

© 2019 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L.U. Todos os direitos reservados.

Cardiovascular disease

Cardiovascular disease, in particular heart disease, has a high prevalence worldwide.¹⁻³ In Europe in 2014, four million deaths (approximately 50% of all deaths on the continent) were due to cardiovascular disorders.²

In recent decades, care for heart failure (HF) patients in Europe has seen remarkable progress,^{1,3,4} and in Portugal alone mortality from HF decreased by 13% between 2005 and 2015.⁴ However, cardiovascular disease is still the leading cause of death in Portugal, accounting for approximately 30% of all deaths in 2014 and 2015.⁴

Heart failure

The high prevalence of cardiovascular risk factors in Portugal, Europe as a whole, and worldwide is responsible for the high incidence of cardiovascular disease which, in turn, is the cause of HF. This is of great epidemiological importance, and will be even more so in the coming decades,¹⁻⁵ since HF prevalence is expected to rise by 50-75% by 2030.⁵ The high prevalence, morbidity and mortality of HF represents an enormous economic and social burden.⁶

It is estimated that HF affects approximately 380 000 individuals in Portugal⁷ and approximately 26

million worldwide.⁸ Based on expected demographic changes, particularly the marked aging of the population, and assuming that current clinical practices are maintained, the prevalence of HF in mainland Portugal is estimated to increase by 30% by 2035 and by 33% by 2060, compared to 2011, resulting in 479 921 and 494 191 affected individuals in 2035 and 2060, respectively.⁹

In 2013 approximately 18 000 patients were hospitalized due to HF in Portugal.¹⁰ The number of HF hospitalizations and their mean duration increased between 2008 and 2013,¹⁰ with high in-hospital mortality (12.5% in 2014) and long-term rehospitalization and mortality rates.¹¹ Approximately 50-70% of HF-associated costs are due to hospitalizations.⁷

This serious impact on individuals and on society has prompted a decades-long effort dedicated to the development of new therapies which, acting on the pathophysiological mechanisms of the syndrome, are able to induce reverse remodeling and thus improve prognosis.¹² However, in spite of the notable advances achieved, the treatment of HF is far from perfect,¹³ and morbidity and mortality from the syndrome remain unacceptably high. Therefore, there is still a need to continue research in this area.¹⁴

The current paradigm: antagonism of regulatory systems (neurohormonal blockade)

Since proof emerged in the 1980s of the efficacy of enalapril in reducing mortality in patients with HF and reduced ejection fraction (HFrEF),^{15,16} angiotensin-converting enzyme inhibitors (ACEIs) have been the mainstay of treatment of this syndrome. Subsequently, it was demonstrated that further reductions in mortality and hospitalizations for HF in these patients could be obtained with the addition of beta-blockers (BBs) and mineralocorticoid receptor antagonists (MRAs) to ACEIs.^{17,18} This triple neurohormonal blockade is the current paradigm of medical therapy for HFrEF.¹⁹⁻²¹

This successful strategy is based on antagonism of regulatory systems, including the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). These systems induce not only vasoconstriction and sodium and water retention, but also hypertrophy, apoptosis and cardiac fibrosis, which form the basis of ventricular remodeling, and hence worsen prognosis.²²

However, despite the positive impact of this triple neurohormonal blockade, three-year mortality in these patients remains above 30%.²³

The new paradigm: stimulation of counter-regulatory systems (neurohormonal modulation)

A complementary approach to antagonism of regulatory systems is stimulation of counter-regulatory systems (the natriuretic peptide [NP] and other systems that counter the RAAS), the effects of which oppose the former.²⁰

The addition of stimulation of the NP counter-regulatory system to the traditional strategy of neurohormonal blockade is a significant step forward and constitutes a new

paradigm in the treatment of HF^{13,24-30} that is termed neurohormonal modulation. Sacubitril/valsartan (LCZ696) is the first element in this new therapeutic strategy.^{13,25}

Sacubitril/valsartan

Sacubitril/valsartan is a supramolecular sodium salt complex of the pro-drug sacubitril and the angiotensin receptor blocker (ARB) valsartan, in a molecular ratio of 1:1.³¹ Sacubitril (AHU377) is enzymatically metabolized to sacubitrilat, a neprilysin inhibitor. Neprilysin is a neutral endopeptidase that degrades a variety of endogenous vasoactive peptides,³² among them NPs. Inhibition of neprilysin by sacubitril increases natriuretic peptide levels, leading to an increase in cyclic GMP concentrations, promoting vasodilation, natriuresis and diuresis, inhibition of neurohormonal systems (central nervous system and RAAS), endothelin, and vasopressin, and antiapoptotic, antiproliferative and antifibrotic effects.¹⁷

However, if used in isolation, sacubitril will also increase serum levels of angiotensin II, which is also degraded by neprilysin. This may counteract the positive effects mentioned above. For this reason, in order to obtain the full benefit of the action of sacubitril, it must be combined with an ARB in order to block the stimulation of this receptor by elevated angiotensin II levels.¹⁸ Valsartan is an ARB that blocks the detrimental cardiovascular and renal effects of angiotensin II, and in addition inhibits the release of angiotensin II-dependent aldosterone. This blocks RAAS activity, including vasoconstriction and sodium and water retention, and also the cell proliferation, apoptosis, and fibrosis involved in cardiovascular remodeling.¹⁷

The above mechanisms are the reason that this new drug compound associates sacubitril with valsartan. From a pharmacological point of view it would not make sense to combine sacubitril with an ACEI, not only because it would be ineffective but also because this association would be dangerous, given the significantly increased risk of angioedema. Unlike ARBs, ACEIs do not bind to angiotensin II receptors; they inhibit the angiotensin-converting enzyme, which blocks the conversion of angiotensin I to angiotensin II, thus reducing the concentrations of this vasoactive peptide. They do not block the effect of sacubitril-induced elevated angiotensin II levels.

Sacubitril/valsartan: clinical studies

Hypertension

An eight-week study by Ruilope et al. published in 2010 in the *Lancet*³³ included 1328 patients with mild-to-moderate hypertension randomized to one of eight regimens: sacubitril/valsartan 100, 200 or 400 mg; valsartan 80, 160 or 320 mg; sacubitril 200 mg; or placebo.

The 200 mg and 400 mg doses of sacubitril/valsartan provided greater reductions in blood pressure than valsartan at doses of 160 mg and 300 mg, respectively.

Sacubitril/valsartan reduced systolic more markedly than diastolic blood pressure, thereby inducing reduced pulse pressure (PP) compared to valsartan. This is significant, given that reducing PP is beneficial owing to the

association of higher PP with arterial stiffness and risk of stroke, myocardial infarction, congestive heart failure and cardiovascular death.

Heart failure with preserved ejection fraction: the PARAMOUNT trial

The PARAMOUNT trial³⁴ assessed the efficacy and safety of sacubitril/valsartan in patients with HF and preserved ejection fraction (HFpEF). It included patients in New York Heart Association (NYHA) classes II and III, with left ventricular ejection fraction (LVEF) $\geq 45\%$ and N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 400 pg/ml. One hundred and forty-nine patients were randomized to sacubitril/valsartan and 152 to valsartan. Sacubitril/valsartan was titrated up to 200 mg twice daily and valsartan up to 160 mg twice daily. Patients were treated for 36 weeks. Reductions in NT-proBNP from randomization until week 12, the primary aim, were greater in the sacubitril/valsartan group than in the valsartan group ($p=0.005$). Sacubitril/valsartan was well tolerated and the occurrence of adverse events was similar in both study groups. Given the positive outcome of the PARAMOUNT trial in this area in which, until then, no drug had been able to show a reduction in mortality, the PARAGON trial (ClinicalTrials.gov identifier NCT01920711) was started with the aim of assessing the impact of sacubitril/valsartan on the composite endpoint of cardiovascular mortality and total hospitalizations due to HF.

Heart failure with reduced ejection fraction: the PARADIGM-HF trial

The PARADIGM-HF trial³⁵⁻³⁷ belongs, without a doubt, to the rare category of historic trials in medicine that definitively changed the way patients with HFrEF are treated. It was terminated early, in accordance with prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit of sacubitril/valsartan over enalapril had been crossed.

It is the largest trial conducted to date in the context of HFrEF, with 8442 patients. Eligibility requirements at screening included age at least 18 years, NYHA class II-IV, and LVEF $\leq 40\%$ (which was changed to $\leq 35\%$ by an amendment to the protocol on December 15, 2010). Patients were required to have a plasma B-type natriuretic peptide (BNP) level of at least 150 pg/ml (or NT-proBNP ≥ 60 pg/ml) or, if they had been hospitalized for HF within the previous 12 months, BNP of at least 100 pg/ml (or NT-proBNP ≥ 400 pg/ml). Patients taking any dose of an ACEI or ARB were considered for participation, but for at least four weeks before screening, patients were required to take a stable dose of a BB and an ACEI or ARB equivalent to at least 10 mg of enalapril daily. Exclusion criteria included symptomatic hypotension, systolic blood pressure (SBP) < 100 mmHg at screening or 95 mmHg at randomization, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m² of body surface area at screening or at randomization or a decrease in eGFR of more than 25% (amended to 35%) between screening and randomization, serum potassium > 5.2 mmol/l at screening (or > 5.4 mmol/l at randomization), or a history of angioedema

or unacceptable side effects during treatment with ACEIs or ARBs.³⁵

These patients were randomized to sacubitril/valsartan 200 mg twice daily, or enalapril 10 mg twice daily, in addition to recommended therapy.³⁵⁻³⁷

Primary outcome: cardiovascular mortality or hospitalization for heart failure

The primary outcome (cardiovascular death or first hospitalization due to heart failure) occurred in 914 (21.8%) patients receiving sacubitril/valsartan and in 1117 (26.5%) patients receiving enalapril in a median follow-up of 27 months (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.73-0.87, $p=0.0000002$, number needed to treat [NNT] 21).

In comparison with enalapril, sacubitril/valsartan had a positive impact on both components of the primary outcome: time to cardiovascular death (HR 0.80, 95% CI 0.71-0.89, $p<0.001$, NNT 32), and time to first hospitalization for HF (HR=0.79, 95% CI 0.71-0.89, $p<0.001$, NNT 36).³⁵

Mortality

Regarding impact on cardiovascular mortality, sacubitril/valsartan reduced sudden cardiac death in 20%, and death due to worsening of HF in 21%; together, these constituted the majority of cardiovascular deaths¹⁹ that occurred in the study. Sacubitril/valsartan also decreased all-cause mortality by 16%.³⁵

Hospitalizations

The reduction in first hospitalizations for HF with sacubitril/valsartan reached statistical significance after 30 days of treatment.²⁰ The total number of hospitalizations, including rehospitalizations, due to HF was lower in the sacubitril/valsartan group.²⁰ The drug also reduced cardiovascular hospitalizations by 16% and hospitalizations for any cause in 16%.²⁰ Rehospitalization at 30 and 60 days after discharge was less frequent in the sacubitril/valsartan arm.³⁸ These results are of great importance given the high prevalence and economic burden of hospitalizations due to HF.

Clinical progression

In patients treated with sacubitril/valsartan, admissions to the emergency department for HF decompensation were 30% lower than in those treated with enalapril. Additionally, there was less need for intensification of therapy with time and fewer reports of worsening NYHA functional class. Together, these findings demonstrate a lower risk of worsening of HF in patients treated with sacubitril/valsartan than in patients receiving enalapril.²⁰

Quality of life

The proportion of patients in whom there was a deterioration in quality of life of ≥ 5 points on the Kansas City Cardiomyopathy Questionnaire was higher with enalapril than with sacubitril/valsartan, the difference being statistically significant at four, eight and 12 months.²⁰

Table 1 Decreases in cardiovascular mortality in the SOLVD, CHARM and PARADIGM-HF trials.^{16,35,43}

Trial	Year of publication	No. of patients	Intervention	Follow-up	RRR of CV death	NNT
SOLVD Treatment	1991	2569	Enalapril 2.5-20 mg once daily vs. placebo	41.4 months (mean)	18%	23
CHARM-Alternative	2003	2028	Candesartan 4-32 mg once daily vs. placebo	33.7 months (median)	15%	31
PARADIGM-HF	2014	8442	Sacubitril/valsartan 200 mg twice daily vs. enalapril 10 mg twice daily	27 months (median)	20%	32

CV: cardiovascular; NNT: number needed to treat; RRR: relative risk reduction.

Analysis of influence of patient characteristics at randomization

The superiority of sacubitril/valsartan proved to be independent of age,²⁶ severity of risk as assessed by the MAGGIC score,²⁹ time since the most recent hospitalization for HF,³⁹ LVEF,³⁹ NT-proBNP level,²⁰ presence of insulin resistance or diabetes,⁴⁰ and baseline treatment including MRAs.²⁸

Mean cumulative dose of sacubitril/valsartan and contraindicated concomitant medication

Sacubitril/valsartan was superior to enalapril in all cases, regardless of whether patients' clinical profile led to a mean cumulative dose of <100 mg twice daily, 100-200 mg twice daily or 200 mg twice daily, even in patients who could not tolerate the target dose.⁴¹ The target dose to be used is 200 mg twice daily unless this is not tolerated.^{22,42} Sacubitril/valsartan should not be administered concomitantly with ACEIs or within 36 hours of the last dose of an ACEI,^{21,41} or in patients with a history of angioedema.^{22,42} Combined treatment with an ARB is also contraindicated.²²

Neurohormonal modulation versus neurohormonal blockade

Comparing the results of the SOLVD (enalapril), CHARM (candesartan) and PARADIGM-HF trials, sacubitril/valsartan (neurohormonal modulation and neurohormonal blockade) had a two-fold greater effect than RAAS inhibitors^{16,35,43} (neurohormonal blockade only) on cardiovascular mortality (Table 1).

Compared to the placebo arm of SOLVD, sacubitril/valsartan in PARADIGM-HF reduced the relative risk of cardiovascular death or hospitalization for HF in 43%, of cardiovascular death in 34%, of all-cause mortality in 28% and of hospitalization for HF in 49%.⁴³

Concerning coronary disease and heart failure, sacubitril/valsartan may reduce the risk of myocardial ischemia through hemodynamic mechanisms, and may also have favorable effects on the coronary circulation by inhibiting the breakdown of C-type natriuretic peptide, which is involved in the regulation of coronary arterial tone and blood flow.⁴⁴ The benefits of sacubitril/valsartan in post-myocardial infarction patients with evidence of systolic

dysfunction and/or signs and symptoms of HF will shortly be addressed in the PARADISE-MI trial (ClinicalTrials.gov identifier NCT02924727).

Safety

In the sacubitril/valsartan arm of PARADIGM-HF fewer patients discontinued the study medication due to an adverse event than in the enalapril arm.³⁶

The sacubitril/valsartan group had a lower incidence of renal impairment, hyperkalemia and cough, although hypotension occurred more frequently. Sacubitril/valsartan was not associated with an increased risk of serious angioedema.³⁵

Co-administration of sacubitril/valsartan and an MRA is associated with a lower risk of severe hyperkalemia than co-administration of enalapril and an MRA.⁴⁵ In addition, in patients not treated with MRAs at the beginning of the study it was easier to start these drugs if the patient was receiving sacubitril/valsartan rather than enalapril.⁴⁵ MRAs were less often suspended in patients receiving sacubitril/valsartan than in those receiving enalapril.⁴⁵ Thus, replacing ACEIs with sacubitril/valsartan rather than enalapril may lead to safer use of MRAs, enabling patients to achieve the incremental benefits of these drugs with less risk of hyperkalemia.

Given that neprilysin is onmes that eliminate amyloid-beta peptides in the brain, there is a theoretical concern about the long-term effects of sacubitril/valsartan on cognition. A post-hoc analysis of PARADIGM-HF found no evidence of a higher incidence of dementia in the sacubitril/valsartan group than in the enalapril group during a median follow-up of 2.25 years (up to 4.3 years).²⁴ There is currently no evidence that sacubitril/valsartan has a deleterious effect on amyloid-beta levels in the brain.⁴⁶ The effects of the drug on cognitive function and amyloid plaque deposition are,⁴⁶ under investigation in an ongoing study with patients with HF_{rEF} (ClinicalTrials.gov identifier NCT02884206).

Although there are no published data on the effects of sacubitril/valsartan on the eye in humans, amyloid-beta deposits in the eye have been linked to age-related macular degeneration.⁴⁷

Limitations

A limitation sometimes mentioned is the low percentage of the study population with implanted cardioverter-defibrillators. However, PARADIGM-HF was carried out on a global scale, and this percentage reflects the practices of various countries. In the USA, for example, it is consistent with implantation rates in the country. It should be noted that in PARADIGM-HF the implantation rates of cardioverter-defibrillators were similar to those of other reference studies, such as EMPHASIS-HF²¹ and RED-HF,⁴⁸ and higher than those of the SHIFT trial.⁴⁹

Another limitation often alluded to is that enalapril was the ACEI chosen as comparator, and the dose of 10 mg twice daily has also been questioned. Enalapril was deliberately selected due to the US Food and Drug Administration's requirement that the study offer irrefutable evidence of the superiority of sacubitril/valsartan compared to the ACEI therapy used in studies that demonstrated a reduction in mortality in HFrEF with these drugs. In these studies^{15,16,50-52} the drug used was enalapril, and in PARADIGM-HF the dose of enalapril achieved by patients was the highest ever achieved in studies in HFrEF.

Conclusion

PARADIGM-HF unequivocally established the overwhelming therapeutic superiority of sacubitril/valsartan compared with enalapril in the treatment of patients with HFrEF.

This trial produced irrefutable evidence, based on a rigorous study design, a very large sample, for a clinically significant goal, and with strong statistical significance. The results were completely consistent across a wide range of studied subgroups.^{19,20,24,26-30,40}

Dose titration: the TITRATION study

The main aim of the TITRATION trial⁵³ was to assess the tolerability of sacubitril/valsartan in two titration regimens, with a follow-up period of 11 weeks.

The drug was titrated gradually, from an initial dose of 50 mg twice daily, up to the target dose of 200 mg twice daily. The initial dose of 50 mg twice daily was administered over a five-day open-label run-in. Patients who tolerated this phase were then randomized to one of two titration regimens up to 200 mg twice daily: a 'condensed' regimen, of 100 mg twice daily for two weeks followed by 200 mg twice daily, and a 'conservative' regimen, of 50 mg twice daily for two weeks, 100 mg twice daily for three weeks, followed by 200 mg twice daily. Tolerability criteria were hypotension, renal dysfunction, hyperkalemia, and angioedema. The analysis was stratified according to prior treatment with ACEIs/ARBs: high doses (>160 mg of valsartan or >10 mg enalapril, or equivalent) and low doses (\leq 160 mg of valsartan or \leq 10 mg enalapril, or equivalent).

Four hundred and ninety-eight patients with chronic HF, NYHA classes II-IV and LVEF \leq 35% were included. In 93% of cases patients were receiving ACEIs or ARBs before inclusion in the study; at admission, these drugs were replaced by sacubitril/valsartan according to the algorithm subsequently adopted by international guidelines.

The tolerability of the two titration regimens, 'condensed' and 'conservative', was similar: there was no

statistically significant differences between the study arms in the incidence of hypotension (9.7% vs. 8.4%), renal dysfunction (7.3% vs. 7.6%), hyperkalemia (7.7% vs. 4.4%), or angioedema (0% vs. 0.8%).

In the group receiving low-dose ACEIs/ARBs before the study began, the 'condensed' titration of sacubitril/valsartan led to a higher rate of hypotension than the 'conservative' titration. In patients receiving high-dose ACEIs/ARBs before the study began, the tolerability of the two titration regimens was similar.

Cost-effectiveness

A study by Gaziano et al. published in *JAMA Cardiology* assessed the cost-effectiveness of sacubitril/valsartan compared with enalapril in the USA.⁵⁴ In eligible patients with HFrEF, a Markov model showed that sacubitril/valsartan would increase life expectancy with an incremental cost-effectiveness ratio comparable to that of other high-value accepted cardiovascular interventions. Sensitivity analyses showed that sacubitril/valsartan would remain cost-effective vs. enalapril.

Since sacubitril/valsartan is a non-generic drug, the cost to the patient compared to ACEIs/ARBs may, for some patients, be a hurdle. However, in view of the magnitude of the prognostic gain associated with sacubitril/valsartan, policy-makers may decide to adopt the same policy regarding this drug as that adopted for anti-diabetics, making it essentially free, at least for less well-off patients.

Potential impact on mortality

A study by Fonorow et al. published in *JAMA Cardiology* in 2016 concluded that the use of sacubitril/valsartan in the USA could prevent about 28 500 deaths per year among patients with HFrEF.⁵⁵ Extrapolation of these calculations for Europe could mean the prevention of about 85 500 deaths annually.

The new paradigm: transposition to clinical practice

Recommendations of the European and American cardiology societies

In view of the importance of the PARADIGM-HF trial results, in 2016 the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA)^{22,42} simultaneously issued a class I recommendation that in patients with chronic symptomatic HFrEF, in NYHA class II or III, who have tolerated an ACEI or an ARB, these drugs should be replaced by sacubitril/valsartan, with the goal of further reducing morbidity and mortality.

The new paradigm of neurohormonal modulation is thus confirmed in the HFrEF treatment algorithm from the most important cardiology societies.

According to the Summary of Product Characteristics for Entresto, approved by the European Medicines Agency and the Portuguese National Authority for Medicines and Health Products (INFARMED), "Sacubitril/valsartan is indicated in

adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction".⁵⁶

Despite the firm evidence of the benefit of this new class of drug, its widespread use is far from desirable. Clinical practitioners tend to underestimate the intrinsic risk for HF-related morbidity and mortality in apparently stable HF patients, and resist changing their therapeutic strategy in patients who seem to be doing well.⁵⁷ The value of sacubitril/valsartan is unquestionable even in minimally symptomatic HF patients, given their high short-term mortality. This may be due to the occurrence of arrhythmic sudden death or to the vulnerability of HF patients to factors inducing hemodynamic decompensation that is trivial to healthy individuals but extremely important for the HF population, who, even if not seriously symptomatic, are unable to adapt to hemodynamic overload. This has been shown in PARADIGM-HF and other trials.

Dosage and substitution rules

Sacubitril/valsartan is available in three doses: 50 mg (24 mg/26 mg), 100 mg (49 mg/51 mg) and 200 mg (97 mg/103 mg).

Co-administration of sacubitril/valsartan with an ACEI is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan should only be started after 36 hours of washout of ACEIs.^{22,42,56}

Given that valsartan is an ARB, sacubitril/valsartan should not be co-administered with another ARB.²¹ However, a washout period of a previously administered ARB is not necessary, and sacubitril/valsartan can be initiated at the time of the next dose.

During the process of titration, blood pressure and serum creatinine and potassium should be monitored.

Condensed titration: Patients who previously took high doses of ACEI (enalapril >10 mg/day or equivalent) or ARB (valsartan >160 mg/day or equivalent) can start sacubitril/valsartan at a dose of 100 mg (49 mg/51 mg) twice daily and after 3-4 weeks increase to 200 mg (97 mg/103 mg) twice daily.

Conservative titration: Patients who were not previously treated with ACEIs or ARBs, or those who previously took low doses of ACEI (enalapril ≤10 mg/day or equivalent) or ARB (valsartan ≤160 mg/day or equivalent), or who have SBP >100 and ≤110 mmHg, moderate to severe renal impairment, or moderate hepatic impairment, can begin sacubitril/valsartan at a dose of 50 mg (24 mg/26 mg) twice daily. After 3-4 weeks, the dose can be increased to 100 mg (49 mg/51 mg) twice daily and, if this dose is tolerated, can be increased further after 3-4 weeks to 200 mg (97 mg/103 mg) twice daily.⁵⁶

Adverse events

The most frequently reported adverse reactions to sacubitril/valsartan compared to enalapril in the PARADIGM-HF trial³⁶ were hypotension (16.7% vs. 10.6% of participants), hyperkalemia (20.4% vs. 22.9%), and renal dysfunction (4.8% vs. 6.5%). However, in most cases, these adverse events were classified as non-serious; hypotension was a serious

adverse event in 1.4% of patients and renal failure in 1.02%. Angioedema occurred in 0.5% of these patients.

Another important point to take into consideration is that patients in clinical practice are often frailer and have more severe disease than the PARADIGM-HF study population. In fact, although the intrinsic risk of adverse events in real-world patients may be higher, this may actually result in a larger benefit of sacubitril/valsartan in absolute terms. This should be taken into account by physicians who are hesitating to begin or up-titrate sacubitril/valsartan in these patients.

Special warnings and precautions for use

Hypotension and hyperkalemia: Treatment should not be initiated if SBP < 100 mmHg or serum potassium > 5.4 mmol/L. If hypotension occurs during treatment, dose adjustment of diuretics and/or vasodilators and treatment of other causes of hypotension (e.g. hypovolemia) should be considered.

If hypotension is not corrected by these measures, or serum potassium falls below 5.4 mmol/L, discontinuation or temporary dose reduction of sacubitril/valsartan should be considered.⁵⁶

Of note, PARADIGM-HF enrolled a large number of patients with low SBP, and those in the lowest SBP category (including those with SBP < 100 mmHg) attained the same relative magnitude of benefit from sacubitril/valsartan as patients in the trial overall.⁵⁸ Because such patients are at higher risk of adverse clinical outcomes, the same relative risk reduction with sacubitril/valsartan is expected to give a greater absolute risk reduction. Using a conservative up-titration regimen, the majority of patients are able to tolerate the target dose of sacubitril/valsartan, and even using a lower dose patients will still derive benefit compared with enalapril.⁵⁹ These observations are reassuring and support the use of sacubitril/valsartan in patients with low SBP, even less than 100 mmHg. Therefore, physicians should not avoid prescribing this potentially life-saving treatment in HF patients. Titration should be conservative and may not achieve the target dose, but it should be attempted.^{60,61}

Renal impairment and diabetes: In patients with mild renal impairment (eGFR 60-90 ml/min/1.73 m²) there is no need to adjust dosage. In patients with moderate (eGFR 30-60 ml/min/1.73 m²) or severe (eGFR < 30 ml/min/1.73 m²) renal impairment a conservative titration should be performed. There is limited clinical experience in patients with eGFR < 30 ml/min/1.73 m² and these patients may be at greater risk of hypotension and hyperkalemia. Sacubitril/valsartan is not recommended in patients with end-stage renal disease.

If patients present clinically significant worsening of renal function during the use of sacubitril/valsartan, a temporary dose reduction or discontinuation should be considered.⁵⁶

Sacubitril/valsartan, compared with enalapril, slowed the rate of decrease in eGFR and had favorable effects on cardiovascular and renal outcomes in patients with and without chronic kidney disease.⁶² The observed increase in the urinary albumin/creatinine ratio results from a block in the reabsorption of protein in the proximal renal tubule and is

not related to an increased rate of decline in glomerular filtration, as it usually is with the use of RAAS inhibitors.⁶³ This finding is important and has therapeutic implications, since conventional RAAS blockers are often withheld or withdrawn in patients with heart failure and renal dysfunction.

Diabetes is another frequent comorbid condition in HFrEF. In diabetic patients, sacubitril/valsartan has been shown to have additional benefits beyond its cardiovascular impact, attenuating the rate of decline in renal function and improving glycemic control.^{63,64}

NYHA class IV: Clinical experience is very limited in this population.⁵⁶ The HFN-LIFE trial will provide valuable insight into the practical use of sacubitril/valsartan in patients with advanced HF, prospectively comparing its effectiveness with valsartan alone, in a randomized, double-blind trial of approximately 400 subjects with NYHA class IV heart failure (ClinicalTrials.gov identifier NCT02816736).

Hepatic impairment: In patients with mild hepatic impairment (Child-Pugh class A) dose adjustment is not necessary. In patients with moderate hepatic impairment (Child-Pugh class B) or with aspartate aminotransferase/alanine aminotransferase values twice the upper limit of normal, caution and conservative titration are recommended. Sacubitril/valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh class C).⁵⁶

Drug interactions: Sacubitril/valsartan may increase the serum concentration of atorvastatin, resulting in significantly greater blood pressure reduction if co-administered with phosphodiesterase type 5 inhibitors, including sildenafil, and may increase the risk of worsening of renal function if co-administered with non-steroidal anti-inflammatory drugs. Caution is recommended in these circumstances.⁵⁶

Use of NT-proBNP to monitor therapy with sacubitril/valsartan for heart failure

Neprilysin hydrolyzes BNP but not NT-proBNP.⁶⁵ Therapy with sacubitril/valsartan thus induces an increase in BNP levels as a result of neprilysin inhibition. NT-proBNP is therefore a useful biomarker to assess therapeutic effect and prognosis in patients treated with neprilysin inhibitors.⁶⁵ However, currently available commercial assays for detection of NT-proBNP and BNP actually measure a mixture of the two peptides. Furthermore, it remains unclear whether degradation or oligomerization of either BNP or NT-proBNP impairs the accuracy of commercial assays used for their detection.⁶⁶

Conclusion

Stimulation of counter-regulatory systems such as the NPs, which counter the effects of the RAAS, in addition to neurohormonal blockade (antagonism of regulatory systems such as the RAAS and SNS), constitutes a new paradigm, termed neurohormonal modulation. Sacubitril/valsartan is the first element of this new strategy.

The PARADIGM-HF trial demonstrated the overwhelming superiority of sacubitril/valsartan compared to enalapril, with a two-fold greater effect on cardiovascular mortality compared to ACEIs. Accordingly, in 2016, the ESC and

ACC/AHA/HFSA simultaneously issued a class I indication for the replacement of ACEIs by sacubitril/valsartan in these patients, with the goal of further reducing hospitalization and death due to HF.

Considering the high prevalence, morbidity and mortality of HF and the enormous economic burden that it represents in Portugal, sacubitril/valsartan is unquestionably an important addition to the therapeutic armamentarium of HFrEF in our population.

Finally, the forthcoming PIONEER-HF (ClinicalTrials.gov identifier NCT02554890) and TRANSITION (ClinicalTrials.gov identifier NCT02661217) trials should answer the question of inpatient vs. outpatient initiation of angiotensin receptor-neprilysin inhibitors in acute HF.

The Portuguese team of investigators of the PARADIGM-HF trial: Serviço de Cardiologia do Centro Hospitalar de S. João – J. Silva-Cardoso (Principal Investigator), S. Amorim, M. Campelo, B. Moura, A. Gomes, A. Lebreiro, E. Martins, M. Paiva, A. Sousa; Serviço de Cardiologia do Centro Hospitalar do Alto Ave – F. Canário-Almeida (Principal Investigator), J. Guardado, V. Hugo; Serviço de Cardiologia do Centro Hospitalar do Tâmega e Sousa – A. Andrade (Principal Investigator), C. Queirós, N. Moreno; Serviço de Cardiologia do Centro Hospitalar Cova da Beira – L. Oliveira (Principal Investigator), E. Dias, A. Peixeiro; Hospital Dr. José Maria Grande (Unidade Local de Saúde do Norte Alentejano) – F. Pádua (Principal Investigator), J. Segurado; Serviço de Medicina III do Hospital São Francisco Xavier, Lisboa – C. Fonseca (Principal Investigator), P. Sarmiento, I. Araújo, F. Marques; Serviço de Medicina III do Hospital Prof. Doutor Fernando Fonseca – N. Bragança (Principal Investigator), T. Cruz, A. Ricardo; Serviço de Cardiologia do Centro Hospitalar de Trás-os-Montes e Alto Douro – S. Carvalho (Principal Investigator), P. Magalhães, I. Moreira; Serviço de Cardiologia do Hospital de Santa Marta – R. M. Soares (Principal Investigator), J. Feliciano, L. Cardona, F. Ferreira; Serviço de Cardiologia do Hospital de São Bernardo – J. Ferreira Santos (Principal Investigator), L. Mendes, I. Silvestre, O. Simões, R. Rodrigues.

Conflicts of interest

Author José Silva Cardoso was the national coordinator of the PARADIGM-HF study and has been a consultant for Novartis, AstraZeneca Pharmaceuticals, Orion, Pfizer, Servier and Vifor (companies that develop and market treatments for heart failure). He has participated in the Steering Committees of clinical studies sponsored by Novartis, Orion and Pfizer. He has received honoraria as a speaker in sessions on heart failure, or research fellowships from Novartis, Abbott, AstraZeneca Pharmaceuticals, Bial, Boehringer Ingelheim, Menarini, Merck Serono, Merck Sharp & Dohme, Orion, Pfizer, Sanofi, Servier and Vifor. Author Daniel Brás is an employee of Novartis Farma, Portugal. Author Filipa Canário-Almeida has received honoraria for lectures in the area of HF from Servier and Orion. Author Aurora Andrade was the principal investigator of a Portuguese center of the PARADIGM-HF study; she has received honoraria on lectures and other scientific sessions on heart failure from Servier, Orion Pharma and Roche. Author Luís Oliveira was the principal

investigator of a Portuguese center of the PARADIGM-HF, PARADIGM-HF extension and TRANSITION studies. He has been a consultant of Orion and Merck Sharp & Dohme. He has received honoraria as a speaker in clinical sessions of Tecmede, Menarini, AstraZeneca, Merck Sharp & Dohme, Pfizer, Delta, Servier, Boehringer Ingelheim and Sanofi. Author Fernando Pádua has no conflicts of interest. Author Cândida Fonseca has received consulting fees related to the area of HF, participation in Steering Committees of clinical studies, lectures at congresses and other scientific sessions from Novartis, Servier, Orion, Roche, Bayer and Vifor (companies that develop and market tests and/or treatments in the area of heart failure). Author Nuno Bragança has been a consultant of BMS. He has received honoraria as a speaker in sessions in the areas of HT, dyslipidemia, diabetes, vitamin D, pain, platelet antiaggregation and anticoagulation from MSD, Menarini, JABA, Merk, Generis, BMS, Pfizer, Bial, Tecmede and Sanofi. Authors S. Carvalho and R. M. Soares have no conflicts of interest. Author José Ferreira Santos was the principal investigator of a Portuguese center of the PARADIGM-HF study and has been a consultant of AstraZeneca Pharmaceuticals, Bayer, GlaxoSmithKline, Vitória Laboratories and MSD. He has received honoraria as a speaker in sessions on heart failure from Servier, Orion Pharma, Novartis Farma and Merck Serono.

References

1. Ceia F, Fonseca C, Mota T, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail.* 2002;4:531–9.
2. Nichols M, Townsend N, Scarborough P, et al. Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J.* 2014;35:2950–9.
3. Pereira M, Peleteiro B, Capewell S, et al. Changing patterns of cardiovascular diseases and cancer mortality in Portugal, 1980–2010. *BMC Public Health.* 2012;12:1126.
4. Direção Geral de Saúde. Programa nacional para as doenças cérebro-cardiovasculares. In: Portugal. 2017.
5. Silva D, Gomes-Sanches MA. Heart failure: a new epidemic of cardiovascular disease. *Acta Med Port.* 2016;29:10–1.
6. Silva Cardoso J, Fonseca C, Rebocho MJ, et al. Heart transplantation in Portugal: current status and future perspectives. *Rev Port Cardiol.* 2002;21:1077–97.
7. Fonseca C, Brito D, Cernadas R, et al. For the improvement of Heart Failure treatment in Portugal – consensus statement. *Rev Port Cardiol.* 2017;36:1–8.
8. Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. *ESC Heart Fail.* 2014;1:4–25.
9. Fonseca C, Bras D, Araujo I, et al. Heart failure in numbers: estimates for the 21st century in Portugal. *Rev Port Cardiol.* 2018;37:97–104.
10. Direção Geral de Saúde. Doenças cérebro-cardiovasculares em números – 2015. In: Portugal. 2015.
11. Pinho-Gomes AC, Silva Cardoso J, Azevedo LF, et al. Characterization of acute heart failure hospitalizations in a Portuguese cardiology department. *Rev Port Cardiol.* 2013;32:567–75.
12. Amorim S, Campelo M, Martins E, et al. Prevalence, predictors and prognosis of ventricular reverse remodeling in idiopathic dilated cardiomyopathy. *Rev Port Cardiol.* 2016;35:253–60.
13. Kitai T, Tang WW. Recent advances in treatment of heart failure. *F1000Res.* 2015;4.
14. Silva Cardoso J. LCZ696, an angiotensin–neprilysin inhibitor versus enalapril in heart failure – summary of PARADIGM-HF results. *Eur J Arrhythm Electrophysiol.* 2016;2:14–7.
15. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med.* 1987;316:1429–35.
16. Yusuf S, Pitt B, Davis CE, et al., The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325:293–302.
17. Gu J, Noe A, Chandra P, et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor–neprilysin inhibitor (ARNi). *J Clin Pharmacol.* 2010;50:401–14.
18. Maric C, Zheng W, Walther T. Interactions between angiotensin II and atrial natriuretic peptide in renomedullary interstitial cells: the role of neutral endopeptidase. *Nephron Physiol.* 2006;103:149–56.
19. Desai AS, McMurray JJ, Packer M, et al. Effect of the angiotensin-receptor–neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J.* 2015;36:1990–7.
20. Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation.* 2015;131:54–61.
21. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 2011;364:11–21.
22. Ponikowski P, Voors AA, Anker SD, et al. 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 Heart J.* 2016;37:2129–200.
23. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J.* 2012;33:1750–7.
24. Cannon J, Boytsov S, Senni M, et al. Dementia-related adverse effects in 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.* 2015;17 Suppl. 1:5–441 (P242).
25. Gordin JS, Fonarow GC. New medications for heart failure. *Trends Cardiovasc Med.* 2016;26:485–92.
26. Jhund PS, Fu M, Bayram E, et al. Efficacy and safety of LCZ696 (sacubitril–valsartan) according to age: insights from PARADIGM-HF. *Eur Heart J.* 2015;36:2576–84.
27. McMurray JJ, Jhund PS, Fu M, et al. Effect of the angiotensin receptor neprilysin inhibitor LCZ696 compared with enalapril according to age in PARADIGM-HF. *Eur J Heart Fail.* 2015;17 Suppl. 1:5–441 (P689).
28. Okumura N, Jhund P, Gong J, et al. Consistent benefit of sacubitril/valsartan over enalapril, irrespective of background therapy in IN PARADIGM-HF. *J Am Coll Cardiol.* 2016;67:1456.
29. Simpson J, Jhund PS, Silva Cardoso J, et al. Comparing LCZ696 with enalapril according to baseline risk using the MAGGIC and EMPHASIS-HF risk scores: an analysis of mortality and morbidity in PARADIGM-HF. *J Am Coll Cardiol.* 2015;66:2059–71.
30. Solomon SD, Claggett B, Desai AS, et al. Influence of ejection fraction on outcomes and efficacy of sacubitril/valsartan (LCZ696) in heart failure with reduced ejection fraction: The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial. *Circ Heart Fail.* 2016;9:e002744.

31. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC Heart Fail.* 2014;2:663–70.
32. Cruden NL, Fox KA, Ludlam CA, et al. Neutral endopeptidase inhibition augments vascular actions of bradykinin in patients treated with angiotensin-converting enzyme inhibition. *Hypertension.* 2004;44:913–8.
33. Ruilope LM, Dukat A, Bohm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet.* 2010;375:1255–66.
34. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet.* 2012;380:1387–95.
35. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371:993–1004.
36. McMurray JJ, Packer M, Desai AS, et al. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail.* 2014;16:817–25.
37. McMurray JJ, Packer M, Desai AS, et al. 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;15:1062–73.
38. Desai AS, Claggett BL, Packer M, et al. Influence of sacubitril/valsartan (LCZ696) on 30-day readmission after heart failure hospitalization. *J Am Coll Cardiol.* 2016;68:241–8.
39. Solomon SD, Claggett B, Packer M, et al. Efficacy of sacubitril/valsartan relative to a prior decompensation: the PARADIGM-HF trial. *JACC Heart Fail.* 2016;4:816–22.
40. Kristensen SL, Preiss D, Jhund PS, et al. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. *Circ Heart Fail.* 2016;9:e002560.
41. Vardeny O, Claggett B, Packer M, et al. 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;18:1228–34.
42. Yancy CW, Jessup M, Bozkurt B, et al. 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;68:1476–88.
43. McMurray JJ, Packer M, Desai A, et al. A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure. *Eur Heart J.* 2015;36:434–9.
44. Mogensen UM, Kober L, Kristensen SL, et al. The effects of sacubitril/valsartan on coronary outcomes in PARADIGM-HF. *Am Heart J.* 2017;188:35–41.
45. Desai AS, Vardeny O, Claggett B, et al. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF trial. *JAMA Cardiol.* 2017;2:79–85.
46. Langenickel TH, Tsubouchi C, Ayalasomayajula S, et al. The effect of LCZ696 (sacubitril/valsartan) on amyloid- β concentrations in cerebrospinal fluid in healthy subjects. *Br J Clin Pharmacol.* 2016;81:878–90.
47. Singh JSS, Burrell LM, Cherif M, et al. Sacubitril/valsartan: beyond natriuretic peptides. *Heart.* 2017;103:1569–77.
48. McMurray JJ, Anand IS, Diaz R, et al. Baseline characteristics of patients in the reduction of events with Darbeoetin alfa in Heart Failure trial (RED-HF). *Eur J Heart Fail.* 2013;15:334–41.
49. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875–85.
50. Remme WJ, Riegger G, Hildebrandt P, et al. The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction. The carvedilol and ACE-inhibitor remodelling mild heart failure evaluation trial (CARMEN). *Cardiovasc Drugs Ther.* 2004;18:57–66.
51. Yusuf S, Pitt B, Davis CE, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med.* 1992;327:685–91.
52. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med.* 1991;325:303–10.
53. Senni M, McMurray JJ, Wachter R, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail.* 2016;18:1193–202.
54. Gaziano TA, Fonarow GC, Claggett B, et al. Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction. *JAMA Cardiol.* 2016;1:666–72.
55. Fonarow GC, Hernandez AF, Solomon SD, et al. Potential mortality reduction with optimal implementation of angiotensin receptor neprilysin inhibitor therapy in heart failure. *JAMA Cardiol.* 2016;1:714–7.
56. European Medicines Agency. Summary of product characteristics: Entresto; 2015. https://www.ema.europa.eu/en/documents/product-information/entresto-epar-product-information_en.pdf
57. Luo N, Fonarow GC, Lippmann SJ, et al. Early adoption of sacubitril/valsartan for patients with heart failure with reduced ejection fraction: insights from get with the guidelines-heart failure (GWTG-HF). *JACC Heart Fail.* 2017;5:305–9.
58. Bohm M, Young R, Jhund PS, et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. *Eur Heart J.* 2017;38:1132–43.
59. Vardeny O, Claggett B, Kachadourian J, et al. Incidence, predictors, and outcomes associated with hypotensive episodes among heart failure patients receiving sacubitril/valsartan or enalapril: the PARADIGM-HF trial (prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin-converting enzyme inhibitor to determine impact on global mortality and morbidity in heart failure). *Circ Heart Fail.* 2018;11:e004745.
60. Senni M, McMurray JJ, Wachter R, et al. Impact of systolic blood pressure on the safety and tolerability of initiating and uptitrating sacubitril/valsartan in patients with heart failure and reduced ejection fraction: insights from the TITRATION study. *Eur J Heart Fail.* 2018;20:491–500.

61. Bruno RM, Taddei S. Sacubitril/valsartan and low blood pressure in heart failure with reduced ejection fraction. *Eur Heart J*. 2017;38:1144–6.
62. Damman K, Gori M, Claggett B, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail*. 2018;6:489–98.
63. Packer M, Claggett B, Lefkowitz MP, et al. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin–angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol*. 2018;6:547–54.
64. Seferovic JP, Claggett B, Seidelmann SB, et al. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol*. 2017;5:333–40.
65. Langenickel TH, Dole WP. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. *Drug Discov Today: Therapeut Strat*. 2012;9:e131–9.
66. Martinez-Rumayor A, Richards AM, Burnett JC, et al. Biology of the natriuretic peptides. *Am J Cardiol*. 2008;101:3–8.