



Changing the treatment of heart failure with reduced ejection fraction: clinical use of sacubitril-valsartan combination

Edgardo Kaplinsky

Cardiology Unit, Medicine Department, Hospital Municipal de Badalona. Via Augusta Av. 9-13 (08911), Badalona, Spain

Abstract

Despite significant therapeutic advances, patients with chronic heart failure (HF) remain at high risk of morbidity and mortality. Sacubitril valsartan (previously known as LCZ696) is a new oral agent approved for the treatment of symptomatic chronic heart failure in adults with reduced ejection fraction. It is described as the first in class angiotensin receptor neprilysin inhibitor (ARNI) since it incorporates the neprilysin inhibitor, sacubitril and the angiotensin II receptor antagonist, valsartan. Neprilysin is an endopeptidase that breaks down several vasoactive peptides including natriuretic peptides (NPs), bradykinin, endothelin and angiotensin II (Ang-II). Therefore, a natural consequence of its inhibition is an increase of plasmatic levels of both, NPs and Ang-II (with opposite biological actions). So, a combined inhibition of these both systems (Sacubitril / valsartan) may enhance the benefits of NPs effects in HF (natriuresis, diuresis, etc) while Ang-II receptor is inhibited (reducing vasoconstriction and aldosterone release). In a large clinical trial (PARADIGM-HF with 8442 patients), this new agent was found to significantly reduce cardiovascular and all cause mortality as well as hospitalizations due to HF (compared to enalapril). This manuscript reviews clinical evidence for sacubitril valsartan, dosing and cautions, future directions and its considered place in the therapy of HF with reduced ejection fraction.

J Geriatr Cardiol 2016; 13: 914–923. doi:10.11909/j.issn.1671-5411.2016.11.006

Keywords: Heart failure; LCZ696; Neprilysin; PARADIGM-HF; Sacubitril; Valsartan

1 Introduction

Neurohumoral stimulation is the basis of the pathophysiology of heart failure (HF) so in consequence, a combined targeting of renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) is indispensable to modify the evolution of HF with reduced ejection fraction (HF-rEF).^[1] In this context, different landmark studies have shown an improvement of morbidity and mortality using angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARBs), beta blockers and mineralocorticoid receptor antagonists (MRAs).^[2] However and even with this regular “gold standard” therapy, HF is still the most common cause of hospitalization in elderly patients (≥ 65 years) and its mortality rates remain approximately 50% within five years of diagnosis.^[3]

Therefore, factors like this among other have driven the search and the necessity for new therapies in order to achieve a better outcome.

2 Natriuretic peptides

Natriuretic peptides (NPs) counter regulates the harmful effects of the up-regulation of RAAS and SNS which are capital in HF-rEF pathophysiology.^[4] RAAS stimulation promotes vasoconstriction (via angiotensin II) and salt and water retention (via aldosterone) while SNS activation results in an increased heart rate, myocardial contractility and vasoconstriction. In addition, RAAS and SNS are strong inductors of myocardial hypertrophy and fibrosis, endothelial dysfunction and vascular remodeling.

NPs are composed by a family of peptides that work maintaining water and salt homeostasis and thereby, compensating the deleterious effect of fluid overload present in HF patients. Three distinct NPs have been identified; atrial natriuretic peptide (ANP) which is produced by cardiac atrial cells (28 amino acids), brain natriuretic peptide (BNP) which is mostly from a myocardial cell origin (32 amino acids) and C-type natriuretic peptide (CNP) that principally has an endothelial origin (22 amino acids).^[4] HF is the pathological condition in which the activation of these peptides is superlative and in this scenario, the increased cardiac wall stress (volume and/or pressure overload) is responsible of ANP and BNP synthesis and release. Their

Correspondence to: Edgardo Kaplinsky, MD, Cardiology Unit, Medicine Department, Hospital Municipal de Badalona, Via Augusta Av. 9-13 (08911), Badalona, Spain. E-mail: ejkaplinsky@gmail.com

Received: November 12, 2016 **Revised:** November 13, 2016

Accepted: November 21, 2016 **Published online:** November 28, 2016

major biological actions (all beneficial in HF) include direct vasodilatation, natriuresis and diuresis, brought about by the intracellular augment of cyclic guanosine monophosphate (cGMP) that acts as second messenger.^[5] CNP has a not completely understood autocrine and paracrine function (ossification process, vascular smooth, muscle proliferation, endothelial cell migration, etc).^[4]

In consequence and once the fact that NPS work to preserve homeostasis in HF, a novel pathway to target in HF management was natural to be considered.^[5]

3 Nephrylysin inhibition

The clearance of NPs takes place by two different processes such as a receptor-mediated-degradation and an enzymatic breakdown mainly executed by a zinc-dependent metalloproteinase called, Nephrylysin (NEP).^[5] Therefore, suppressing the activity of this enzyme could be an attractive option to increase NPs levels.^[6]

NEP is widely expressed in mammals (kidneys, lungs, cardiac myocytes, vascular wall, etc) but it is not only responsible of NPs degradation because it also cleaves other several peptides with vasoconstrictor effects like angiotensin II (Ang-II) and endothelin-1, among others.^[7,8] In consequence, inhibition of NEP would increase circulating levels of NPs which in turn stimulate the synthesis of cGMP promoting natriuresis, diuresis and vasodilation (beneficial in HF),^[5] but apart from this, it may increase levels of Ang-II whose over-activation contributes to vasoconstriction and sodium retention (harmful un HF).^[1] Therefore, the benefits of increasing the NPs system may be lost by increasing Ang-II, so a simultaneous suppression of the RAAS is necessary. In consequence this fact gave a clear pharmacological justification for agents that block both, NEP and Ang-II.^[6]

In this setting, different NEP inhibitors were clinically checked; candoxatril the first pure NEP inhibitor result a failure since it concomitantly promoted natriuresis (via ANP) and systemic and pulmonary vascular resistances increase (via Ang-II).^[9] Ecadotril, a second agent but with similar mechanism of action was another failure because it showed no clinical benefits with a non-acceptable safety profile.^[10] Further on, a combined inhibition (ACE and NEP) was considered but it resulted in another negative experience. In the OVERTURE trial (omapatrilat versus enalapril randomized trial of utility in reducing events) a target dose of enalapril (10 mg twice daily) was compared with omapatrilat, an ACE-NEP inhibitor (40 mg once daily) which was found not superior to enalapril regarding the primary composite endpoint (death from any cause or HF hospitalization). In

addition, it was associated to a significant increase in an-gioedema favored by the augmented levels of bradykinin.^[11,12]

4 Angiotensin receptor blocker nephrylysin inhibitors

Next step in order to solve the failure of omapatrilat was the combination of an ARB and a NEP inhibitor. Sacubitril/valsartan (previously LCZ696) is a fused molecule that contains 1:1 molar ratio of sacubitril (prodrug), a NEP inhibitor and valsartan, an ARB.

It is a first-in-class medicine (ARNI) specifically designed to inhibit NEP (increasing NPs concentration) and simultaneously blocking the adverse effects of RAAS and reducing bradykinin enhancement (Figure 1).^[13]

During 2015, Sacubitril/valsartan was approved by the US Food and Drug Administration (FDA) to reduce the risk of cardiovascular (CV) death and HF hospitalization in patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction (EF),^[14] and a few months later, by the European Medicine Agency (EMA) with a similar indication; treatment of symptomatic chronic HF with reduced EF in adult patients.^[15]

5 Pharmacokinetics

After oral administration, the compound dissociates into

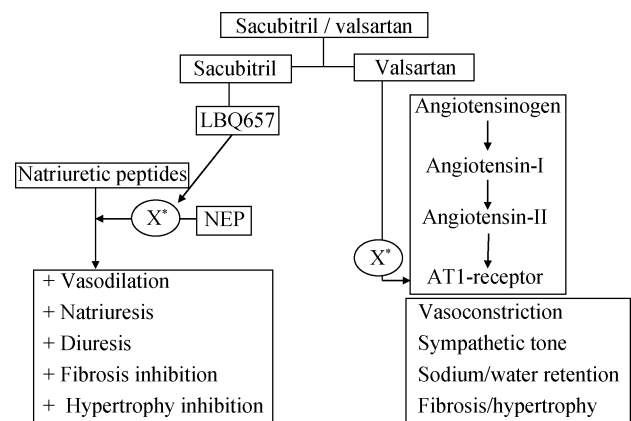


Figure 1. Sacubitril/valsartan: mode of action. *: dual concomitant inhibition (NEP and AT-1 receptor); #: enhance the benefits of NPs effects. The benefits of increasing the NPs system (NEP inhibition) may be lost by increasing angiotensin II, so a simultaneous suppression of the RAAS is necessary a simultaneous NEP inhibition (LBQ657) and AT1 receptor blockade (valsartan) is needed in order to maintain all the favourable biological action of NPs while the harmful effects of angiotensin II are avoided. +: enhance the benefits of NPs effects; AT1: subtype 1 angiotensin receptor; NEP: Nephrylysin; NPs: natriuretic peptides; RAAS: renin-angiotensin-aldosterone system.

sacubitril and valsartan. Sacubitril is a prodrug which is subsequently metabolized (by esterases) to LBQ657 which is the active form and since this metabolite does not inhibit aminopeptidase P, the risk of angioedema is minimized in comparison with omapatrilat. Peak plasma concentrations are reached between 1.5–2.2 h for valsartan, 0.5–1.1 h for sacubitril and 1.9–3.5 h in the case of LBQ657. Steady state levels are achieved in three days and concomitant administration with food does not alter Sacubitril / valsartan pharmacokinetics.^[13]

More consistent findings after oral intake are increased plasma and urine cGMP and a decrease of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (due to NEP inhibition) while blockade of AT1 receptor increases plasma renin activity, renin and Ang-II concentrations.^[16]

Sacubitril/valsartan was also designed to be prescribed twice daily in order to guarantee 24-h action and it is offered in tablets containing 24 mg of sacubitril and 26 mg of valsartan, 49 mg of sacubitril and 51 mg of valsartan and 97 mg of sacubitril and 103 mg of valsartan. Bioavailability of valsartan in this formulation is higher than valsartan given alone so 26 mg, 51 mg and 103 mg of valsartan in Sacubitril / valsartan are equivalent to 40 mg, 80 mg and 160 mg of valsartan in ordinary tablets. Sacubitril is principally eliminated in urine (52%–68%) while valsartan is mainly via feces (86%).^[13]

6 Sacubitril/valsartan in HFREF

The Prospective Comparison of ARNI with ACEi to determine Impact on Global Mortality and Morbidity in Heart failure Trial (PARADIGM-HF) was a double-blind, randomized and controlled trial. Its main intention was to compare head-to-head the effects of Sacubitril/valsartan with enalapril in adult patients with HFREF. The trial randomized 8442 patients (mean age 64 years and 22% female) to receive 10 mg twice daily of enalapril ($n = 4212$) or 200 mg twice daily of Sacubitril / valsartan ($n = 4187$) (Table 1).

Inclusion criteria were NYHA functional class II-IV, previously treated with an ACEi or ARB (equivalent to at least 10 mg of enalapril), left ventricular ejection fraction (LVEF) $\leq 40\%$ ($\leq 35\%$ by amendment) and raised NPs levels. Patients were required to have a plasma BNP level ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or, if they had been hospitalized for HF (within the previous 12 months), a BNP level ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL). Main exclusions included systolic blood pressure < 100 mmHg (screening), hyperkalemia or an estimated glomerular filtration rate (eGFR) < 30 mL/min per 1.73 m².

Table 1. PARADIGM-HF: characteristics of the patients at baseline.^[17]

Characteristic	Sacubitril/valsartan ($n = 4187$)	Enalapril ($n = 4212$)
Age, yrs / Female sex	63.8 \pm 11.5 / 879 (21%)	63.8 \pm 11.3 / 953 (22.6%)
SBP, mmHg / HR, beats/min	122 \pm 15 / 72 \pm 12	121 \pm 15 / 73 \pm 12
NYHA functional class, %	I, II, III, IV (4.3 / 71.6 / 23.1 / 0.8)	I, II, III, IV (5.0 / 69.3 / 24.9 / 0.6)
Cr - mg/dL / LVEF, %	1.13 \pm 0.3 / 29.6 \pm 6.1	1.12 \pm 0.3 / 29.4 \pm 6.3
Median BNP, pg/mL	255 (155–474)	251 (153–465)
Median NT-proBNP, pg/mL	1631 (8815–3154)	1594 (886–3305)
Ischemic cardiomyopathy	2506 (59.9%)	2530 (60.1%)
Atrial fibrillation	1517 (36.2%)	1574 (37.4%)
Hypertension / diabetes	2969 (70.9%) / 1451 (34.7%)	2971 (70.5%) / 1456 (34.6%)
Hospitalization for HF	2607 (62.3%)	2667 (63.3%)
Pre-trial use ACEi or ARB, %	78%/22.2%	77.5%/22.9%
Beta blocker / MRA	93.1 / 54.2	92.9 / 57

Data are presented as n (%), mean \pm SD, or mean (IQR). In both groups white and black races were 66% and 5.1%, respectively. Body-mass indexes were 28.1 ± 5.5 Kg/m² (Sacubitril/valsartan) and 28.2 ± 5.5 Kg/m² (enalapril). Pre-use of implantable cardioverter-defibrillators or resynchronization devices were as follow (%): 14.9/7 (Sacubitril/valsartan), 14.7/6.7 (enalapril). ACEi: ngiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers; BNP: brain natriuretic peptide; Cr: serum creatinine; HF: heart failure; IQR: interquartile range; LVEF: left ventricular ejection fraction; MRAs: mineralocorticoid receptor antagonists; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; SBP: systolic blood pressure.

The trial consisted of a screening period; a single-blind run-in period (all patients received enalapril 10 mg twice daily); it was followed by an additional single-blind run in period during which all patients who tolerated enalapril received Sacubitril/valsartan (100 mg twice daily and then 200 mg twice daily); and finally, a double-blind treatment period in two study groups. The single dose of 200 mg delivers the equivalent of 160 mg of valsartan and mean \pm SD administered doses of Sacubitril/valsartan and enalapril were 375 ± 71 mg and 18.9 ± 3.4 mg, respectively.

Primary endpoint was a composite of death from CV causes or first hospitalization for heart failure (HFH) while secondary outcomes were time to death from any cause, change from baseline at 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ), time to new onset of atrial fibrillation and time to first declination of renal function. The study was interrupted early (March 2014) due to

an overwhelming performance in the Sacubitril / valsartan arm after a median follow-up of 27 months.

At the time of trial stopping, 21.8% of the Sacubitril/valsartan group and 26.5% of the enalapril one had reached the primary endpoint (HR: 0.80; 95% CI: 0.73–0.87; $P < 0.001$). Compared with patients randomized to enalapril, the use of Sacubitril/valsartan reduced the risk of death from any cause by 16% ($P < 0.001$) and the risk of hospitalization from HF by 21% ($P < 0.001$). Overall mortality was also lower in the Sacubitril/valsartan arm (17.0% vs. 19.8%, HR: 0.84, 95% CI: 0.76–0.93, $P < 0.001$). Regarding the KCCQ, its mean change from baseline to month 8 was a reduction of 2.99 points and 4.63 points in the Sacubitril/valsartan and enalapril arms, respectively ($P = 0.001$). New onset atrial fibrillation was detected in 84 patients in the Sacubitril/valsartan group and in 83 patients taking enalapril ($P = 0.84$) while protocol defined worsening renal function, affected 94 patients of the Sacubitril/valsartan group and 108 of the enalapril one ($P = 0.28$) (Table 2).

During the run-in period, 2079 patients (12%) discontinued the study due to side effects (657 subjects in enalapril

and 605 in Sacubitril/valsartan). Hypotension, cough, hyperkalemia and renal dysfunction were the more commons with a higher rate in the enalapril group. This 12% dropout is important to take into account because it implies a limit of PARADIGM-HF results generalization since only patients that tolerated the run-in period were randomized. During trial, the most common adverse event was symptomatic hypotension which was more present in the Sacubitril /valsartan group (14% vs. 9.2%, $P < 0.001$). Patients in the enalapril arm were more likely to have hyperkalemia (serum potassium ≥ 6.0 mmol/L; 5.6 vs. 4.3%, $P = 0.007$), renal deterioration (creatinine level ≥ 2.5 mg/dL; 4.5% vs. 3.3%, $P = 0.007$) and cough (14.3% vs. 11.3%, $P < 0.001$). A non-significant incidence of non-serous angioedema affected more patients taking Sacubitril/valsartan ($P = 0.13$).

Basically, PARADIGM-HF showed that over a median of 27 months, Sacubitril/valsartan led to a highly statically significant 20% reduction in the combined primary endpoint (CV death and HFH) and a 16% reduction in the risk of death for any cause.^[17]

Table 2. PARADIGM-HF: primary and secondary outcomes.^[17]

Outcomes	Sacubitril/ valsartan (n = 4187)	Enalapril (n = 4212)	Hazard Ratio (95% CI)	P value
Primary composite outcome				
Death from CV cause / first HFH	914 (21.8%)	1117 (26.5%)	0.80 (0.73–0.87)	< 0,001
Death from CV cause	558 (13.3%)	693 (16.5 %)	0.80 (0.71–0.89)	< 0,001
First HFH	537 (12.8%)	658 (15.6 %)	0.79 (0.71–0.89)	< 0,001
Secondary outcomes				
Death from any cause	711 (17%)	835 (19,8%)	0,84 (0,76–0,93)	<0,001
Change in KCCQ	-2.99 ± 0.36	-4.63 ± 0.36	1,64 (0,63–2,65)	0,001
New-onset atrial fibrillation	84 (3.1%)	83 (3.1%)	0,97 (0,72–1,31)	0,83
Renal function deterioration	94 (2.2%)	108 (2.6%)	0,86 (0,65–1,13)	0,28

Data are presented as n (%) or mean ± SD. KCCQ at 8 months: range from 0–100 (higher scores showing fewer limitations). Renal function declination was defines as end stage renal disease or a decrease $\geq 50\%$ in the estimated glomerular filtration rate form the randomization value or a decrease > 30 mL/min per 1.73 m², to less than 60 mL/min per 1.73 m². CV: cardiovascular; HFH: heart failure hospitalization; KCCQ: Kansas City Cardiomyopa-
thy Questionnaire.

7 Analyses after PARADIGM-HF

7.1 Age

Older patients in PARADIGM-HF were more often female, white (enrolled in Western Europe and North America) with higher systolic blood pressure and NPs levels. In addition, they were more likely to be in NYHA functional class III/IV than I/II with a worse renal function or to have ischemic heart disease or atrial fibrillation. Efficacy and safety outcomes according to age were examined in the following categories (years): < 55 ($n = 1624$), $55–64$ ($n = 2655$), $65–74$ ($n = 2655$), and ≥ 75 ($n = 1563$) and even the above mentioned differences, the effect of Sacubitril/valsartan was similar across all the spectrums. Overall hazard ratio (HR) was 0.80 (95% CI: 0.73–0.87; $P < 0.001$) and adverse events increased with age, being hypotension more frequent in patients taking Sacubitril/valsartan while renal impairment and hyperkalemia affected more the enalapril arm.^[18]

7.2 Geographical variation

In PARADIGM-HF, 622 patients (8%) were recruited in North America (NA), 1680 (20%) in Western Europe (WE), 2762 (33%) in Central-Eastern Europe & Russia (CEER), 1413 (17%) in Latin America (LA) and 1487 (18%) in Asia-Pacific (AP). There were as expected, many regional differences and more notable were: WE patients were about 10 years older than those from AP (68 vs. 58 years) and women were more present in LA cohort than in the NA one

(27% vs. 17%). Coronary artery disease affected more NA patients (62%) than patients recruited in LA (43%).

Patients from CEER, showed more hypertension (87%) and atrial fibrillation (52%) than those from AP (48% and 17%, respectively) but a eGFR < 60 mL/min per 1.73 m² was more frequent in NA patients (51%) than in those from AP (27%).

In this wide and heterogeneous context, rates of the primary composite outcome (per 100 patient-years) varied among regions (from lowest to highest): WE 9.6 (95% CI: 8.6–10.6), LA 11.2 (10.0–12.5), 12.5 (11.3–13.8), CEER 12.3 (11.4–13.2) and NA 13.5 (11.7–15.6). After adjustment values (using NA as reference region), WE exhibited the lowest risk (HR 0.84, 95% CI: 0.70–1.01) vs. AP with the highest one (HR 1.36, 95% CI: 1.05–1.76). Risk of CV death was higher in LA and AP with a lowest risk for HFH in WE; hospitalization duration was shortest in NA and WE and longest in CEER. In any case and despite all these regional differences, the clinical benefit of Sacubitril / valsartan was not affected.^[19]

7.3 LVEF

For analysis, LVEF was divided into the following categories: < 17.5% (*n* = 339), ≥ 17.5% to < 22.5% (*n* = 930), ≥ 22.5% to < 27.5% (*n* = 1500), ≥ 27.5% to < 32.5% (*n* = 2486) and ≥ 32.5% (*n* = 3143). Patients with lower EF were younger and more likely to be male and to be in NYHA functional class III/IV (than I/II) with a higher serum creatinine. In addition, they were less likely to have history of hypertension, myocardial infarction, or atrial fibrillation. LVEF was documented as a significant and independent predictor of all outcome (risk increased with the decrease of LVEF); each 5-point in its reduction was associated with a 9% increased risk of the combined primary endpoint (HR: 1.09; 95% CI: 1.05–1.13; *P* < 0.001), a 9% increased for CV death (HR: 1.09; 95% CI: 1.04–1.14), a 9% increased risk in HFH (HR: 1.09; 95% CI: 1.04–1.14), and a 7% in-

creased risk in all-cause mortality (HR: 1.07; 95% CI: 1.03–1.12). Sacubitril/valsartan was effective across the whole spectrum without any heterogeneity for the primary endpoint (*P*_{interaction} = 0.87), CV death (*P*_{interaction} = 0.55), HFH (*P*_{interaction} = 0.78) and all cause mortality (*P*_{interaction} = 0.93),^[20] (Table 3).

7.4 HF severity

This analysis was done in order to examine the spectrum of risk in PARADIGM-HF and the effect of Sacubitril/valsartan across that spectrum. Baseline risk for each patient in PARADIGM-HF was calculated using the MAGGIC risk score (Meta-Analysis Global Group in Chronic Heart Failure) whose median value was 20 (IQR: 16 to 24). Each 1-point increase in score was associated with a 6% higher risk for the primary composite endpoint (*P* < 0.001) and a 7% increased risk for CV death (*P* < 0.001). The benefit of Sacubitril/valsartan was similar across the spectrum of risk (*P* = 0.159) although the absolute benefit was greater for patients at the highest risk. Treating 100 patients for two years with Sacubitril / valsartan as an alternative of enalapril led to seven fewer patients in the highest quintile of risk facing primary outcomes (compared with three in the lowest quintile).^[21]

7.5 Disease progression

Sacubitril/valsartan was more effective than enalapril preventing clinical deterioration. Less patients in the Sacubitril/valsartan arm (vs. enalapril) required to intensify their HF treatment including, the need of intravenous positive inotropic support or the necessity to visit an emergency department due to worsening HF. In addition, patients treated with Sacubitril/valsartan were less likely to be hospitalized for HF (once or multiple times) and this diminution was already patent within the first 30 days after randomization (Table 4). Regarding biomarkers, patients treated with Sacubitril/valsartan had significantly lower levels of

Table 3. PARADIGM-HF: outcomes incidence rates by LVEF (100 patient/year).^[20]

Outcomes	< 17.5% (<i>n</i> = 339)	17.5%–22.5% (<i>n</i> = 930)	22.5%–27.5% (<i>n</i> = 1500)	≥ 27.5%–32.5% (<i>n</i> = 2486)	≥ 32.5% (<i>n</i> = 3143)
CV death/HFH	18.7 (15.6–24.5)	15.2 (13.5–17.1)	13.2 (12.0–14.6)	11.9 (10.9–12.9)	9.7 (9.0–10.4)
CV death	10.9 (8.6–13.6)	9.1 (7.8–10.5)	7.3 (6.4–8.3)	6.8 (6.1–7.5)	5.5 (5.0–6.1)
HFH	11.9 (9.4–14.9)	8.7 (7.5–10.2)	7.6 (6.7–8.7)	7.3 (6.6–8.1)	5.5 (5.0–6.1)
All-cause death	12.5 (10.1–15.4)	11.1 (9.7–12.6)	8.6 (7.6–9.7)	8.3 (7.6–9.1)	7.2 (6.6–7.8)

LVEF ranged from 5% to 42% (mean: 29.5% ± 6.2%) and echocardiography was the predominant method for assessment (96%). Median time between LVEF determination and screening was 27 days (range: 2–73). Incidence of all outcomes was greatest at the lower end of LVEF spectrum and patients in this situation were preferably younger (mostly men) and more likely to be in NYHA functional class III/IV (than I/II) showing lower systolic blood pressure and higher values of serum creatinine. CV: cardiovascular; HFH: heart failure hospitalization; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Table 4. PARADIGM-HF: clinical progression of surviving patients.^[22]

Nonfatal clinical deterioration: prespecified measures	Enalapril (n = 4212)	Sacubitril/valsartan (n = 4187)	HR (95% CI)/ P Value
Outpatient therapy intensification	604 (14.3%)	520 (12.4%)	0.84 (0.74–0.94) / 0.003
ED visit for HF	150 (3.6%)	102 (2.4%)	0.66 (0.52–0.85) / 0.001
Patients hospitalized for HF	658 (15.6%)	537 (12.8%)	0.79 (0.71–0.89) / < 0.001
HFH	1079	851	0.77 (0.67–0.89)* / < 0.001
Patients receiving IV inotropic drugs	229 (5.4%)	161 (3.9%)	0.69 (0.57–0.85) / < 0.001
Patients requiring CRT, VAD or HT	119 (2.8%)	94 (2.3%)	0.78 (0.60–1.02) / 0.07

Data are presented as n (%) or n. *: rate ratio estimated from a negative binomial model; ratios without an asterisk are hazard ratios derived by using the Cox proportional hazards model. Sacubitril/valsartan prevented more efficiently clinical progression of surviving patients with heart failure than enalapril. In addition, it led an early and sustained reduction in biomarkers of both, myocardial wall stress and injury. CI: confidence interval; CRT: cardiac resynchronization therapy; ED: emergency department; HFH: heart failure hospitalization; HR: hazard ratio; HT: heart transplantation; IV: intravenous; VAD: ventricular assist device.

plasma NT-proBNP and troponin (as an expression myocardial wall stress and injury reduction) while levels of urinary cGMP and plasma BNP are increased (reflecting NEP inhibition).^[22]

7.6 Mode of death

During the trial, 1546 patients died (all cause mortality) including 711 (17%) in the Sacubitril/valsartan arm and 833 patients (19.8 %) in the enalapril one (HR 0.84, 95% CI: 0.76–0.93). Majority of death (80.9%) were linked to CV causes with 558 cases in patients taking Sacubitril / valsartan (13.3%) and 693 (16.5%) in the enalapril group (HR 0.80; 95% CI: 0.72–0.89; P < 0.001). Sudden death accounted for 44.8% of CV death while pump failure was considered in 26.5% and both, were reduced by Sacubitril/valsartan (vs. enalapril). Non-CV death and other causes of CV death like myocardial infarction or stroke did not differ between both groups (Figure 2).^[23]

The significant quantity of SD in PARADIGM-HF was relatively similar to other trials in which the majority of

included patients had mild to moderate symptoms (V-HEFT II, MERIT HF, etc),^[24,25] while other trials that enrolled more severe patients, exhibited a larger proportion of death due to progressive HF (CONSENSUS, RALES).^[26,27]

7.7 Lower vs. target doses

In this intent to treat analysis, patients (n = 4850) who received the maximal dose (200 mg Sacubitril/valsartan or 10 mg enalapril twice daily) along the trial were compared with those (n = 35,649) who required any dose reduction to lower doses (100/50/0 mg of Sacubitril/valsartan and 5/2.5/0 mg of enalapril twice daily. A total of 43% in the enalapril arm and 42% in the Sacubitril/valsartan one reduced their dose at any time after randomization (median time to dose reduction were 255 days for enalapril and 249 days for Sacubitril/valsartan; P = 0.54). Subjects in both groups who needed a dose reduction were older, had worse NYHA functional class, higher serum creatinine levels and NT-proBNP values at baseline. In this context, any dose reduction regardless of treatment assignment was associated

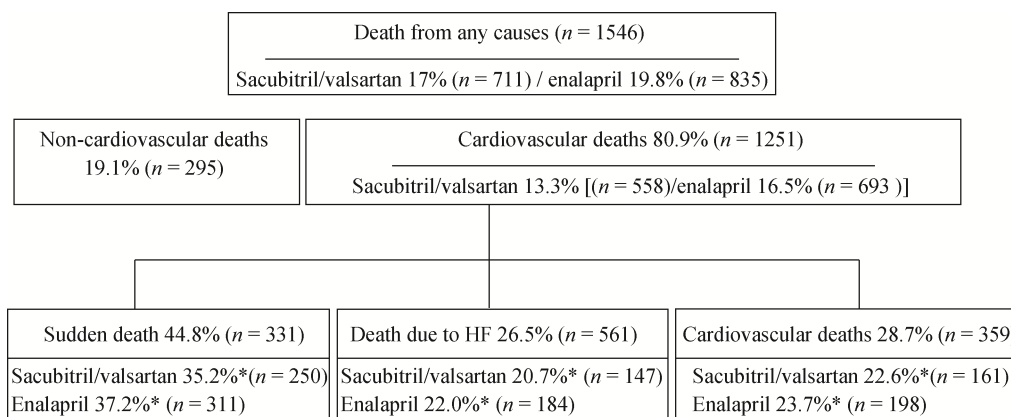


Figure 2. Causes and rates of death according to treatment in PARADIGM-HF. *Percentage of deaths. In PARADIGM-HF, the majority of cardiovascular deaths were categorized as sudden (44.8%) or heart failure related (26.5%) and in both cases, the hazard ratio was significantly reduced by Sacubitril/valsartan vs. enalapril. Deaths linked to other cardiovascular causes (myocardial infarction and stroke), were infrequent and distributed uniformly between both groups, as were non-cardiovascular deaths. HF: heart failure.

with a higher subsequent risk of the primary event (HR 2.5, 95% CI: 2.2–2.7). However, the treatment benefit of Sacubitril/valsartan over enalapril following a dose reduction was similar (HR 0.80, 95% CI: 0.70–0.93; $P < 0.001$) to that observed in patients who had not experienced any dose of reduction (HR 0.79, 95% CI: 0.71–0.88; $P < 0.001$). This analysis suggest that those patients who were unable to tolerate target doses of Sacubitril/valsartan or enalapril still benefited from lower doses of Sacubitril/valsartan in comparison with lower doses of enalapril.^[28]

8 Place in therapy

Less than a year after regulatory approvals, Sacubitril / valsartan got a strong class I recommendation in both, US and European HF guidelines (May, 2016). In the EU guidelines,^[29] Sacubitril/valsartan obtained a recommendation IB which denotes class I (is recommended) and level of evidence B (data derived from one single trial). It implies that Sacubitril/valsartan is recommended as an ACEi replacement to further reduce the risk of HFH and death in ambulatory patients with HF and reduced EF who remains symptomatic (NYHA class II to IV) despite optimal treatment with an ACEi, a beta-blocker and an MRA. For European authors a reduced LVEF is $\leq 35\%$ and values of BNP ≥ 150 pg/mL or NT-proBNP ≥ 600 pg/mL or BNP ≥ 100 pg/mL and NT-proBNP ≥ 400 pg/mL with a HFH in the previous year 12 months are helpful to make the decision.

In the case of US guidelines,^[30] Sacubitril/valsartan got a recommendation I-BR that signifies a class of recommendation I “strong” and level of evidence BR “moderate quality” (evidence based in only one study). In consequence, an ARNI should be recommended to further reduce morbidity and mortality in patients with chronic symptomatic HF, reduced EF, NYHA class II or III and who tolerate an ACEi or ARB (replacement). Therefore, Sacubitril/valsartan is integrated into the standard therapy for HF with reduced EF as an alternative to an ACEi or an ARB, given together with a beta blocker and an MRA. For US authors, there is not any specific cutting level of EF needed to indicate Sacubitril/valsartan (only reduced EF) and/or the necessity of a prior MRA utilization.

In conclusion, key indications for Sacubitril/valsartan introduction seems to be patients with chronic NYHA class II to IV and reduced EF ($\leq 35\%$) currently being treated with a beta blocker (at recommended target doses) and an ACEi (dose equivalent to 10 mg twice daily) or an ARB. A preferential treatment with an MRA can also be considered but taking into account that more than 40% of patients recruited in PARADIGM did not receive any MRA. An episode of

HFH in the previous year and/or elevated values of BNP or NT-proBNP could be helpful.

9 Sacubitril/valsartan: dosing and cautions

The recommended starting dose for HF treatment is Sacubitril/valsartan 49/51 mg twice a day (with or without food). This dose has to be doubled after a period of 2–4 weeks to Sacubitril/valsartan 97/103 mg twice daily (target maintenance dose). The starting dose should be reduced to Sacubitril/valsartan 24/26 mg twice daily for patients not currently taking an ACEi or an ARB or who were taking a low dose of these agents, for patients with severe renal impairment (GFR < 30 mL/min per 1.73m^2) and for patients with moderate hepatic insufficiency. Dose adjustment as required and tolerated by the patients has to be done in 2–4 weeks.^[31]

Renal function and serum potassium should be checked as for any other RAAS inhibitor or blocker. Sacubitril/valsartan is not recommended to be started in patients with a systolic blood pressure < 100 mmHg or serum potassium levels > 5.4 mmol/L. The necessity of adjusting the dosing of other agents (diuretics, antihypertensive drugs, etc) should be considered facing the development of hypotension, renal impairment or hyperkalemia. Sacubitril/valsartan utilization should be quickly stopped in case of angioedema appearance and it is very important to remark the total necessity of stopping any previous ACEi treatment for 36 h before initiating Sacubitril / valsartan.^[31]

Sacubitril/valsartan can cause fetal damage (as any drug acting on the RAAS system) so it is contraindicated in pregnancy and during lactation. Concurrent use with a potassium-sparing diuretic may increase serum potassium levels so if this association is needed, serum potassium levels should be checked regularly. Simultaneous utilization of Sacubitril/valsartan with non-steroidal anti-inflammatory drugs and lithium may increase the risk of renal failure development and lithium toxicity, respectively.^[31]

Finally, it is important to clarify that BNP is not an appropriate biomarker of HF severity in patients taking Sacubitril/valsartan since it is a NEP substrate; NT-proBNP is more useful since its levels are in this case, a real reflex of wall stress reduction.^[32]

10 NEP inhibition: unaddressed issues

There is a risk of angioedema with Sacubitril / valsartan and prior to its initiation; patients should discontinue therapy with an ACEi at least 36 hours before.^[31] Black Americans have a natural increased risk of angioedema (ACEi

associated)^[33] and their presence in PARADIGM-HF population, were very low (5%).^[17]

There were 54 confirmed angioedema cases during PARADIGM-HF duration (run-in period 25 and double-blind period 29) with 25 events in the enalapril arm and 29 in the Sacubitril/valsartan one. The majority of events were of mild severity (no treatment or antihistamines) with only five patients (two enalapril, three Sacubitril/valsartan) requiring hospitalization (no mechanical airway support was needed). Regarding black patients, there were four cases (two Sacubitril/valsartan) within the 25 run-in confirmed angioedema ones and six cases (five Sacubitril/valsartan) in the 29 events during the randomization phase.^[34]

Therefore, it seems that black patients were at higher risk of angioedema events with both treatments so in order to assess if Sacubitril/valsartan is really safe in this population, an observational US study will be held in this kind of population.^[35] In addition, this issue as well others (hypotension, hyperkalemia, renal impairment, hepatotoxicity, etc) will be addressed in a post-authorization European study focused in HF patients newly starting treatment with Sacubitril / valsartan.^[35]

Amyloid- β (A β) is generated in the brain through sequential cleavage of amyloid precursor protein (β and γ secretases),^[36] and it is removed by multiple processes, including transport into cerebrospinal fluid, the bloodstream, and enzymatic degradation.^[37] NEP is one of multiple enzymes degrading A β ^[38] so its inhibition by Sacubitril / valsartan may increase its levels with the consecutive brain accumulation. Senile plaques composed by A β aggregation are found in the brain of patients with Alzheimer's disease.^[39] So in consequence, a theoretical risk may exist between Sacubitril/valsartan administration and Alzheimer's disease development.

Although, no signals of an increase in dementia or cognitive impairment were seen in the PARADIGM-HF trial,^[17] the effects of Sacubitril/valsartan on cognitive function will be assessed in the ongoing PARAGON-HF trial (NCT01920711)^[35] In addition, a multicenter, randomized, double-blind, active-controlled study is planned in order to specifically evaluate cognitive impairment and brain amyloid plaque deposition (PET imaging) comparing Sacubitril/valsartan vs. valsartan.^[35]

11 Sacubitril/valsartan in HF: looking ahead

In the next years, clinical impact of Sacubitril/valsartan will be investigated in different HF scenarios like, preserved EF (NCT00887588), real life setting (NCT02690974), biomarkers (NCT02554890), pediatrics (NCT02678312),

Japanese population (NCT02468232), ischemic functional mitral regurgitation (NCT02687932), post acute decompensation (NCT02661217) or asymptomatic patients with elevated natriuretic peptide and left atrial volume index (NCT02682719).

In this context, the previously mentioned PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction) has a transcendental importance since our current lack of proven clinical benefits in patients with HF and preserved EF. This trial is designed to compare the effects of Sacubitril/valsartan and valsartan alone in reducing CV death or total HFH in patients with the following entry criteria: LVEF \geq 45%, NYHA class II-IV, histories of HFH within 9 months or elevated NPs, and evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement)

Therefore and considering PARADIGM results (largest HF trial ever) it seems that Sacubitril / valsartan has come to change the present and future cornerstone of HF treatment in all these different scenarios.

12 Conclusions

ACEi have been the cornerstone of HFrEF for more than 25 years since enalapril was found to improve survival.^[26,40] Sacubitril/valsartan represents a striking innovation in this field as an effective and safe alternative to ACEi because of its significant improvements in survival and reduced rates of HFH in comparison with enalapril. Hence and taking into account PARADIGM results, Sacubitril/valsartan can be considered over an ACEi or an ARB for the first-line management of patients with HFrEF. Very valuable information on different settings (real life, pediatrics, elderly, HF with preserved EF, acute decompensated HF, etc.) will be provided by planned and ongoing studies in the next years.

In consequence, it is almost sure that our future daily clinical practice treating HF patients will be modified by a complete displacement of ACEi and ARBs in favor of Sacubitril/valsartan. Therefore, the hot question expressed in this same journal in 2015 "PARADIGM-HF trial: will LCZ696 change the current treatment of systolic heart failure?"^[41] has now a clear answer: "yes".

References

- 1 Goldsmith SR. Interactions between the sympathetic nervous system and the RAAS in heart failure. *Curr Heart Fail Rep* 2004; 1: 45–50.
- 2 Hunt SA, Abraham WT, Chin MH, *et al.* 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. *Circula-*

- tion 2009; 119: e391–e479.
- 3 Go AS, Mozaffarian D, Roger VL, *et al.* Heart disease and stroke statistics–2013 update: a report from the American Heart Association. *Circulation* 2013; 127: 143–152.
 - 4 Krupicka J, Janota T, Kasalova Z, *et al.* Natriuretic peptides – physiology, pathophysiology and clinical use in heart failure. *Physiol Res* 2009; 58: 171–177.
 - 5 Volpe M, Rubattu S, Burnett J. Jr. Natriuretic peptides in cardiovascular diseases: current use and perspectives. *Eur Heart J* 2014; 35: 419–442.
 - 6 Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC Heart Fail* 2014; 2: 663–670.
 - 7 Erdős EG, Skidgel RA. Neutral endopeptidase 24.11 (enkephalinase) and related regulators of peptide hormones. *FASEB J* 1989; 3: 145–151.
 - 8 Maguer-Satta V, Besançon R, Bachelard- Cascales E. Concise review: neutral endopeptidase (CD10): a multifaceted environment actor in stem cells, physiological mechanisms, and cancer. *Stem Cells* 2011; 29: 389–396.
 - 9 Kentsch M, Otter W, Drummer C, *et al.* Neutral endopeptidase 24.11 inhibition may not exhibit beneficial haemodynamic effects in patients with congestive heart failure. *Eur J Clin Pharmacol* 1996; 51: 269–272.
 - 10 Cleland JG, Swedberg K. Lack of efficacy of neutral endopeptidase inhibitor ecdotril in heart failure. *Lancet* 1998; 351: 1657–1658.
 - 11 Packer M, Califf RM, Konstam MA, *et al.* Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002; 106: 920–926.
 - 12 Fryer RM, Segreti J, Banfor PN, *et al.* Effect of bradykinin metabolism inhibitors on evoked hypotension in rats: rank efficacy of enzymes associated with bradykinin-mediated angioedema. *Br J Pharmacol* 2008; 153: 947–955.
 - 13 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: 401–414.
 - 14 U.S. Department of Health and Human Services website. www.fda.gov/NewsEvents/Newsroom/PressAnnouncement/ucm453845.html. (Accessed July 7, 2015).
 - 15 New medicine to treat heart failure recommended for approval. The European Medicines Agency website. www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/09/news_detail_002401.jsp&mid=WC0b01ac058004d5c1. (Accessed Jan 16, 2016).
 - 16 Kobalava Z, Averkov O, Meray I, *et al.* Natriuretic peptide inhibition in the presence of angiotensin receptor blockade following short term treatment with LCZ696 in heart failure patients: effect on ANP, BNP, NTproBNP and cGMP. *Eur Heart J* 2011; 32(suppl): 784–785.
 - 17 McMurray JJ, Packer M, Desai AS, *et al.* Angiotensin- neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371: 993–1004.
 - 18 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: 2576–2584.
 - 19 Kristensen SL, Martinez F, Jhund PS, *et al.* Geographic variations in the PARADIGM-HF heart failure trial. *Eur Heart J*. Published Online First. 28 Jun. 2016. doi:10.1093/eurheartj/ehw326
 - 20 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.
 - 21 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: 2059–2071.
 - 22 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.
 - 23 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: 1990–1997.
 - 24 Cohn JN, Tognoni G. A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; 345: 1667–1675.
 - 25 Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF) MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure. *Lancet* 1999; 353: 2001–2007.
 - 26 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987; 316: 1429–1435.
 - 27 Pitt B, Zannad F, Remme WJ, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341: 709–717.
 - 28 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*. Published Online First. 10 Jun. 2016. doi: 10.1002/ejhf.580.
 - 29 Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. Published Online First. 20 May 2016. doi:10.1093/eurheartj/ehw128.
 - 30 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*. Published Online First. 17 May 2016. doi:10.1016/j.jacc.2016.05.011.
- 31 Cada DJ, Baker DE, Leonard J. Sacubitril/Valsartan. *Hosp Pharm* 2015; 50: 1025–1036.
- 32 Mair J, Lindahl B, Giannitsis E, *et al*. Will sacubitril-valsartan diminish the clinical utility of B-type natriuretic peptide testing in acute cardiac care? *Eur Heart J Acute Cardiovasc Care* Published Online First. Accessed pii: 2048872615626355.
- 33 Brown NJ, Ray WA, Snowden M, *et al*. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema *Clin Pharmacol Ther*. 1996; 60: 8–13.
- 34 Kaplan A, Streefkerk H, Thorburn C, *et al*. Comparison of angioedema in heart failure patients treated with Sacubitril / valsartan or enalapril in the PARADIGM-HF Study. *J Card-fail* 2016; 22 (8 Suppl): S66–S67.
- 35 EMA. Summary of the Risk Management Plan (RMP) for Entresto (Sacubitril/Valsartan). EMA website. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Risk-management-plan_summary/human/004062/WC500194315.pdf. (12 January 2016. July 24, 2016)
- 36 Haass C, Kaether C, Thinakaran G, *et al*. Trafficking and proteolytic processing of APP. *Cold Spring Harb Perspect Med* 2012; 2: a006270.
- 37 Saido T, Leissring MA. Proteolytic degradation of amyloid β -protein. *Cold Spring Harb Perspect Med* 2012; 2: a006379.
- 38 Takaki Y, Iwata N, Tsubuki S, *et al*. Biochemical identification of the neutral endopeptidase family member responsible for the catabolism of amyloid β peptide in the brain. *J Biochem* 2000; 128: 897–902.
- 39 Hersh LB, Rodgers DW. Neprilysin and amyloid beta peptide degradation. *Curr Alzheimer Res* 2008; 5: 225–231.
- 40 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.
- 41 Kaplinsky E. PARADIGM-HF Trial: will LCZ696 change the current treatment of systolic heart failure? *J Geriatr Cardiol* 2015; 12: 470–473.