



After having changed the treatment of heart failure with reduced ejection fraction: what are the latest evidences with sacubitril valsartan?

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1 Introduction

Sacubitril/valsartan (SV) is a first in class dual action molecule of the neprilysin (NEP) inhibitor prodrug sacubitril (AHU377) and the angiotensin II receptor (Ang-II) type I antagonist valsartan.^[1] It is the first angiotensin receptor-neprilysin inhibitor (ARNI) whose pharmacodynamic effects are consistent with a simultaneous stimulation of the natriuretic peptides system (via NEP inhibition) and the blockade of the renin-angiotensin-aldosterone system (valsartan effect) that finally results in systemic vasodilation, increased diuresis and natriuresis, reduction of plasmatic volume and diminution of peripheral vascular resistance.^[1,2]

During 2015, SV was approved by the European Medicine Agency for the treatment of symptomatic adults with a chronic heart failure and reduced ejection fraction (HFrEF), and by the United States Food and Drug Administration to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure (HF) in patients with chronic HFrEF (NYHA Class II–IV).^[3,4] Subsequently, the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure included SV with a class IB recommendation (patients who remain symptomatic despite optimal treatment),^[5] and more emphatically, the latest US guidelines, the 2017 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 recommended that patients in NYHA class II–III who tolerate an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) should be switched to SV in order to reduce morbidity and mortality risks linked to HF.^[6]

2 PARADIGM-HF

All these achievements are a consequence of the results

of the Prospective comparison of angiotensin–neprilysin inhibition with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF); the largest HF trial ever. This was a randomized, double-blind and event-driven trial designed to investigate the effect of SV compared with enalapril in patients with chronic and symptomatic HF. The trial enrolled 8442 ambulatory HF patients (NYHA class II–IV) previously treated with an ACEI (or ARB), beta-blockers, and/or a mineralocorticoid receptor antagonist, left ventricular ejection fraction (LVEF) $\leq 40\%$ ($\leq 35\%$ by amendment) and increased levels of brain natriuretic peptide (BNP) or N-terminal pro-B type natriuretic peptide (NT-proBNP).^[7]

Sacubitril/valsartan (200 mg, twice daily: equivalent to 97/103 mg twice daily) was compared (1:1 ratio) with enalapril (10 mg, twice daily) showing a clear 20% reduction ($P < 0.001$) in the primary endpoint which was a composite of death from CV causes or first hospitalization for HF. At median follow-up of 27 months, SV decreased the risk of death from any cause by 16% ($P < 0.001$), the risk of hospitalization from HF by 21% ($P < 0.001$) and logically, overall mortality (17.0% vs. 19.8%; $P < 0.001$). Symptomatic hypotension and non-serious angioedema were more common in the SV group but renal deterioration, cough and hyperkalemia occurred more frequently with enalapril; fewer patients in the SV arm needed to stop their medication due to an adverse event (10.7% vs. 12.3%, $P = 0.03$).^[7]

3 Inpatients administration

Taking into account that PARADIGM-HF population only involved ambulatory stable patients, the feasibility of prescribing SV for inpatients after and acute decompensation resulted necessary, and recently addressed by two trials whose results were known during 2018. In the open label TRANSITION study (NCT02661217), a comparison be-

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tween SV pre-discharge (≥ 24 hours after hemodynamic stabilization) versus its post-discharge initiation (initiated within days 1-14 after discharge) was performed and its primary endpoint was the proportion of patients achieving 200 mg SV twice daily (equivalent to 97/103 mg twice daily) at 10 weeks post-randomization. Secondary objectives included the amount of patients who reached and maintained a SV dose of 100 and/or 200 mg twice daily; or any dose for at least 2 weeks up to week 10 and the quantification of those who permanently discontinued SV during the same period (adverse events). A total of 1002 subjects were included (pre-discharge: 497/post discharge: 496) and at baseline, mean age was 67 years old (male 75%/mean LVEF 29%); 64% and 34% of patients were in NYHA class II and III, respectively.^[8] The proportion of patients achieving primary and secondary outcomes was similar in both arms; primary endpoint was met by 45% of patients in the pre-discharge arm and 50.4% in the post-discharge arm ($P = 0.092$). Patients able to keep either 100 or 200 mg of SV twice daily for at least two weeks and those capable to maintained any dose of SV were 62.5% vs. 68% ($P = 0.071$) and 86.4% vs. 88.8% ($P = 0.262$) in the pre-discharge and post-discharge arms, respectively. On the other hand, the rates of permanent SV discontinuation due to an adverse event were low (4.5% pre-discharge arm vs. 3.5% post-discharge arm; $P = 0.424$). Briefly, TRANSITION showed that about a half of patients stabilized after an acute HF decompensation were able to achieve the recommended SV target dose of 200 mg twice daily within 10 weeks and this clinically implies that SV initiation in hospitalized patients or shortly after discharge is feasible and well tolerated.^[8]

In the PIONEER-HF study (NCT02554890), hospitalized HFREF patients were randomly assigned (after hemodynamic stabilization) to receive SV (target dose 97/103 mg twice daily) or enalapril (target dose, 10 mg twice daily). The primary efficacy endpoint was the time-averaged proportional change in the NT-proBNP concentration from baseline through weeks four and eight, while safety outcomes included rates of worsening renal function, hyperkalemia, symptomatic hypotension and angioedema. Eligible candidates (LVEF $\leq 40\%$ and NT-proBNP ≥ 1600 pg/mL or BNP ≥ 400 pg/mL) were randomized no earlier than 24 hours and up to 10 days after acute decompensated HF meeting certain “stability criteria” (systolic blood pressure ≥ 100 mm Hg for the preceding 6 hours, no increase in the dose of intravenous diuretics and no use of intravenous vasodilators in the same lapse and no intravenous inotropes utilization during the previous 24 hours).^[9] A total of 881 patients (440 SV/441 enalapril) were enrolled with a median of 68 hours (48 to 98 hours) after hospitalization and strik-

ingly, still showing a high prevalence of congestive signs despite initial hemodynamic compensation (61.7% peripheral edema and 32.9%, pulmonary rales). Mean age was 61 ± 14 years (male: 72.1%) and median hospitalization duration was 5.2 days (4.09 to 7.2 days). At screening, median NT-proBNP concentration was 4812 pg/mL (3050 to 8745 pg/mL); while at randomization, median systolic blood pressure and LVEF (SV arm) were 118 mmHg (110 to 132 mmHg) and 24% (18%–30%), respectively. Sacubitril-valsartan reduced NT-proBNP to a greater degree than enalapril in patients hospitalized due to acute decompensated HF, and this reduction was noted as early as one week after drug initiation. The primary outcome (time-averaged reduction in NT-proBNP) for SV vs. enalapril was -46.7% vs. -25.3% (HR = 0.71, 95% CI: 0.63–0.81, $P < 0.001$). Side effects (SV vs. enalapril) including worsening renal function (13.6% vs. 14.7%, HR = 0.93, 95% CI: 0.67–1.28), hyperkalemia (11.6% vs. 9.3%, HR = 1.25, 95% CI: 0.84–1.84) and hypotension (15.0% vs. 12.7%, HR = 1.18, 95% CI: 0.85–1.64) were similar, while angioedema affected more patients receiving enalapril (0.2% vs. 1.4%, HR = 0.17, 95% CI: 0.02–1.38). There was a greater reduction of troponin T in the SV arm (-36.6% vs. -25.2% , HR = 0.85, 95% CI: 0.77–0.94), less death (2.3% vs. 3.4%, HR = 0.66, 95% CI: 0.30–1.48) and fewer rehospitalizations for HF (8.0% vs. 13.8%, HR = 0.56; 95% CI: 0.37–0.84).^[9]

In conclusion, initiation of SV in hospitalized patients due to an acute decompensated HF episode resulted in a significantly greater reduction in the NT-proBNP concentration (vs. enalapril) and in addition, rates of renal dysfunction, hyperkalemia, and symptomatic hypotension did not differ significantly between both groups. Very interestingly, in-hospital SV introduction was associated with fewer rehospitalizations for HF at eight weeks in comparison with enalapril therapy.^[9]

4 Sacubitril-valsartan: hemodynamic effects and beyond

As it was previously described, SV is a dual action molecule that splits into the NEP inhibitor sacubitril and the ARB valsartan. This last one inhibits all the negative effects mediated by Ang-II (vasoconstriction, fluid retention, cardiac hypertrophy, and fibrosis) while sacubitril prevents the degradation of endogenous natriuretic peptides and in consequence, augmenting their beneficial actions (vasodilation, natriuresis, diuresis, fibrosis and hypertrophy inhibition).^[1,2] Apart from all these primary hemodynamic effects, there is growing evidence indicating that SV could be beneficial in the HF context for other different reasons. A

post-hoc analysis of the PARADIGM-HF trial suggests that SV might enhance glycemic control in HF patients.^[10] In total, 3778 (45%) of the 8399 subjects included in PARADIGM-HF also had diabetes; and between screening and the 1-year follow-up, glycated hemoglobin decreased by 0.16% \pm 1.4% in the enalapril group and by 0.26% \pm 1.25% in the SV one ($P = 0.013$). Additionally, new use of antidiabetic drugs and new onset insulin were 23 % and 29% respectively lower in patients treated with SV.^[10] This effect of SV on glycemic control is considered among other factors, probably related to the increase of glucagon-like peptide-1 (GLP-1) concentration secondary to NEP inhibition.^[11] This peptide has a strong antihyperglycaemic effect which is for example potentiated, by the antidiabetic drugs of the dipeptidyl peptidase-4 (DPP-4) inhibitor family.^[12]

The recently published PRIME study (Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation / NCT02687932) showed that SV was able to reduce mitral regurgitation (MR) to a greater extent than valsartan alone in patients with HFrEF and chronic functional MR.^[13] A total of 118 patients (mean age: 63 years, 61% men) were included and the primary outcome was change in the effective regurgitant orifice area (EROA) of functional MR at 12 months. Changes in regurgitant volume, left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV) and incomplete mitral leaflet closure were considered secondary endpoints.

The decrease in EROA was significantly greater in the SV group compared to valsartan (-0.058 ± 0.095 vs. -0.018 ± 0.105 cm², $P = 0.032$), and regurgitant volume was as well significantly decreased in the SV group (mean difference: -7.3 mL, 95% CI: -12.6 to -1.9 , $P = 0.009$). Reduction of LVEDV index was also greater in the SV group (mean difference: -7 mL/m², 95% CI: -13.8 to -0.2 , $P = 0.044$) and there were no significant differences regarding changes in incomplete mitral leaflet closure area, LVESV and blood pressure.^[13] Left ventricular reverse remodeling response to SV was studied in a single-center, prospective echocardiographers-blinded study (median follow-up: 118 days) in 125 HFrEF patients (66 ± 10 years, NYHA class II-IV). Left ventricular EF improved ($29.6\% \pm 6\%$ to $34.8\% \pm 6\%$; $P < 0.001$) in a dose-dependent manner ($P < 0.001$), and a reduction of both LVEDV (206 ± 71 to 197 ± 72 mL, $P = 0.027$) and LVESV (147 ± 57 to 129 ± 55 mL; $P < 0.001$) was also documented. Additionally, a declination in the degree of MR [1.59 ± 1.0 to 1.11 ± 0.8 , $P < 0.001$, (scale from: 0–4)] and in the E/A-wave ratio (1.75 ± 1.13 to 1.38 ± 0.88 ; $P = 0.002$) was observed. Furthermore, diastolic filling time resulted prolonged ($48\% \pm 9\%$ to $52\% \pm 1\%$, $P = 0.005$) and the percent of patients with a restrictive

mitral filling pattern felt from 47% to 23% ($P = 0.004$).^[14]

In this context, the results of the ongoing PROVE-HF study (Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes-NCT02887183) will be very enlightening. PROVE-HF is a 52-week, multicenter, open-label, single-arm study that will include approximately 830 patients with HFrEF to be treated with SV. Primary efficacy endpoints include the changes in NT-proBNP concentrations and cardiac remodeling from baseline to one year while secondary endpoints comprise changes in NT-proBNP concentrations and remodeling to six months and changes in patient-reported outcomes using the Kansas City Cardiomyopathy Questionnaire from baseline to one year. In addition, some other relevant biomarkers like high-sensitivity troponin, urinary cGMP, ANP, BNP, proBNP adrenomedullin and sST2 will be also measured as well as the incidence of CV events.^[15]

In PARADIGM-HF, the majority of causes of death were of CV origin (80.9% of total) being more numerous in the enalapril group than in the SV one (16.5% vs. 13.3%, HR = 0.80, 95% CI: 0.72–0.89, $P < 0.001$). In this setting, 44.8% were considered sudden death and 26.5% pump failure-related, and both, were more reduced by SV compared with enalapril (HR = 0.80, 95% CI: 0.68–0.94; $P = 0.008$ and HR = 0.79, 95% CI: 0.64–0.98, $P = 0.034$, respectively).^[7] The precise mechanism by which SV reduce sudden cardiac death in patients with HFrEF is not clear but a possible multifactorial anti-arrhythmic effect is considered.^[16] In a recent study, a total of 120 patients with an implantable cardioverter-defibrillator (ICD), LVEF $\leq 40\%$ (HYHA \geq II) and remote monitoring were evaluated before and after SV introduction. During nine months, all these patients received ACEI (or ARB), beta-blockers and a mineralocorticoid receptor antagonist; and subsequently, the ACEI (or ARB) was changed for SV and followed for another nine months.^[17] SV (vs. ACEI/ARBs) was associated with a reduced number of non-sustained ventricular tachycardia episodes (5.4 ± 0.5 vs. 15 ± 1.7 , $P < 0.002$), sustained ventricular tachycardia and appropriate ICD shocks (0.8% vs. 6.7%, $P < 0.02$) and less premature ventricular contractions per hour (33 ± 12 vs. 78 ± 15 , $P < 0.0003$), which was associated with an increased biventricular pacing percentage (from $95\% \pm 6\%$ to $98.8\% \pm 1.3\%$; $P < 0.02$).^[17]

Finally, a secondary intention-to-treat analysis of PARADIGM-HF suggests that SV also helps to preserve kidney function based on the determination of the change in the estimated glomerular filtration rate (eGFR) over a 44-month follow-up period in patients with ($n = 3784$) and without ($n = 4615$) diabetes.^[18] Non-diabetic patients on SV showed an eGFR decrease of -1.1 mL/min per 1.73 m² per year (95%

CI: 1.0–1.2) compared to -2.0 mL/min per 1.73 m² per year (95% CI: 1.9–2.1) for diabetic patients ($P < 0.0001$). Compared to patients on enalapril, the rate of kidney function declination was slower with SV (-1.3 mL/min per 1.73 m² per year vs. -1.8 mL/min / 1.73 m² per year, $P < 0.0001$) and the impact of this benefit was stronger in diabetic patients versus non-diabetic patients (difference: 0.6 mL/min per 1.73 m², 95% CI: 0.4 – 0.8 vs. 0.3 mL/min per 1.73 m², 95% CI: 0.2 – 0.5 per year, $P_{\text{interaction}} = 0.038$).^[18]

5 Experimental data: what is promisory?

On the other hand, some interesting data coming from non-clinical studies have shown that SV is capable to attenuate cardiac fibrosis and cardiac hypertrophy after an experimental myocardial infarction (MI) in rats in a greater degree than a NEP inhibitor or an ARB used alone.^[19] In the same direction but in a rabbit experimental MI model, SV was found to be more effective (vs. valsartan or placebo) in reducing infarct size and plasma cardiac troponin release, while left ventricular function resulted less affected.^[20] In another rabbit model of ischemic HFrEF, SV was superior than valsartan given alone or placebo in attenuating left ventricular scar size and improving LVEF.^[21] In a HF rat model created by pressure overload, SV and sacubitril elevated beta-endorphin levels fact that was linked to an improvement of exercise tolerance whereas valsartan and placebo did not.^[22] A recent *post hoc* secondary analysis of PARADIGM-HF revealed that SV significantly improved nearly all Kansas City Cardiomyopathy Questionnaire physical and social activities compared with enalapril, with the biggest responses in sexual activities and household chores,^[23] may beta-endorphin levels play a role here?^[24]

6 Conclusions

Sacubitril/valsartan represents an undeniable therapeutic advance in the clinical field of HFrEF, and its benefits are going beyond its hemodynamic effects which are mainly based on an effectively counterbalance of the triggered renin-angiotensin-aldosterone system by boosting the natriuretic peptides system.

Recent clinical evidence suggests that SV could be safety initiated in hospitalized and decompensated patients reaching target or almost target doses. At the same time, SV utilization would provide some other benefits such as reduction of MR severity, the promotion of inverse remodeling while furthermore; it may also present antiarrhythmic, nephroprotective and antidiabetic effects. In addition, promisory preclinical data would extend its benefits towards the

limitation of infarct scars size (potential clinical implications), and the improvement of exercise tolerance probably connected with the augmentation of beta-endorphin levels.

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