Internal and Emergency Medicine

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--Manuscript Draft--

Manuscript Number:	IAEM-D-19-00440
Full Title:	The nephroprotective effect of Sacubitril/Valsartan in Heart Failure: insights from the real life clinical setting
Article Type:	Commentary
Section/Category:	IM - COMMENTARY
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The nephroprotective effect of sacubitril/valsartan in heart failure: insights from the real life clinical setting

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The authors have no conflict of interest to declare

The authors report no specific funding in relation to the preparation of this paper.

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Sacubitril/valsartan represents the first agent in a new class of drugs developed for heart failure (HF) treatment and termed angiotensin receptor neprilysin (NEP) inhibitors (ARNIs). It is a fixed dose combination compound containing molecular moieties of valsartan, an angiotensin type I receptors (AT1)-inhibitor, and the NEP inhibitor sacubitril in a 1:1 molar ratio [1]. Sacubitril is a prodrug that, following oral administration, is rapidly metabolized to the biologically active molecule sacubitrilat. This inhibits the NEP, which is a ubiquitous endopeptidase that is responsible for the breakdown of many vasoactive peptides, including the biologically active natriuretic peptides (NPs), adrenomedullin, substance P, bradykinin, vasoactive intestinal polypeptide, calcitonin gene-related peptide, and enkephalins. Inhibition of NEP increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling in patients with HF [1]. The NPs are structurally related but genetically different hormones or paracrine factors, that protect the cardiovascular (CV) system from volume overload. The mammalian NP system comprises of mainly 3 NPs: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). In the kidney, more specifically distal tubular cells, expression of ANP precursor produces a subtype called urodilatin, which helps ANP to regulate renal sodium and water excretion through inhibition of antidiuretic hormone and, Angiotensin II/aldosterone-dependent sodium and water re-absorption [2]. In addition, NPs are known to oppose RAS and have anti-proliferative and anti-hypertrophic effects. As the clinical stage of HF progresses, the responsiveness to NPs, in particular ANP and BNP, decreases. This can be due to down-regulation of NPs receptors, increased clearance of BNP by NEP or the NPR-C receptor, or decreased downstream signaling. Blocking NEP with sacubitril/valsartan (S/V) results in greater level of NPs and in increased generation of myocardial cGMP. In this way it is possible to overcome natriuretic resistance, resulting from any one of the above described mechanisms, thus producing favourable clinical outcomes in patients with HF [2]. Indeed, S/V is the most remarkable pharmacological innovation concerning the treatment of patients with chronic HF and reduced ejection fraction

(HFrEF) [3]. In “The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure” (PARADIGM-HF) trial, this drug was studied in 8442 patients with HFrEF, clearly showing superiority above treatment with ACE-inhibitor enalapril [4]. The outcomes of the trial were so overwhelmingly positive that it was stopped early by its data monitoring committee. With a median follow-up of 27 months, the investigators demonstrated a 20% relative risk reduction in the composite of CV death or hospitalization for HF and a 16% relative risk improvement in all-cause mortality, with a number needed-to-treat of 35 [4]. Additionally, S/V is also promising in HF with preserved ejection fraction (HFpEF), because it leads to improvement in ventricular diastolic function.

The large ongoing “Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Global Outcomes in HFpEF” (PARAGON-HF) trial) is testing the hypothesis that S/V would be superior to valsartan in reducing morbidity and mortality in patients with HFpEF [5].

Following the publication of the results of the PARADIGM-HF study, updated guidelines of many cardiologic scientific societies, including the European Society of Cardiology, recommend S/V instead of an ACE -inhibitor or ARB in patients falling within the profile of the PARADIGM-HF study [6]. However, in patients with drug indication, renal function is often reduced and may worsen during treatment with renin –angiotensin-aldosterone system (RAAS) blockers. It is recognized that renal haemodynamic reserve is impaired even in early stages of left ventricular (LV) systolic dysfunction. [7] The activation of the RAAS preserves the glomerular filtration rate (GFR) when renal blood flow decreases and renal perfusion pressure declines. In early stages of CHF, kidney function is maintained due to compensatory increases in filtration fraction; while in patients with more advanced stages of HF, GFR depends on afferent arteriolar flow by the stimulation of haemodynamic and hormonal pathways, while the fall in effective renal blood flow is relatively more pronounced [7] .

Impaired renal function has consistently been found to be an independent risk factor for CV disease

outcomes and all-cause mortality in a broad spectrum of patients with CHF. Additionally, patients with albuminuria, even if mild, bear a near doubling of cardiovascular mortality risk [7-8].

The initiation of treatment with RAAS inhibitors may deteriorate renal function due to the inhibition of the adaptive constriction of the efferent renal arteriole, that serves as a renal compensation mechanism for preserving GFR [9]. Worsening renal function has become the main barrier to the use of therapies known to prolong survival in HF, including ACE inhibitors, angiotensin II-receptor antagonists and aldosterone blockers.

Treating patients with ARNIs offers the exciting prospect of not only improving CV risk, but also preserving renal function [1, 4-5, 10-12].

Experimental investigations using renal mesangial cells [11] and studies based on 5/6 nephrectomy models [12] suggested that S/V reduces histological markers of kidney damage [11-12] and delays the progression of renal disease [12] more than RAAS inhibition alone.

In the PARADIGM-HF study lower incidences of renal impairment-related adverse effects leading to study drug discontinuation were reported for S/V-treated patients compared with enalapril-treated patients. Additionally, categorical changes in eGFR and serum creatinine showed lower rates in the S/V group *vs* the enalapril group [4]. A more recent post-hoc analysis of the same trial documented that the protective effect on GFR of S/V was greater in patients with versus those without diabetes [13]. This difference was independent of blood pressure (BP) changes over time and of glycaemic control [13].

These findings might be a consequence of both increased neprilysin activity and diminished responsiveness to endogenous NPs described in patients with type 2 diabetes [13].

The beneficial effect on renal function of S/V, along with the improved CV outcomes, as compared to the Enalapril arm, was also observed in a more recent subanalysis of the PARADIGM-HF trial, focusing on the renal effects of angiotensin-neprilysin inhibition [14] (table 1). The overall risk for the post hoc assembled composite renal endpoint of reaching ESRD or $\geq$ 50% reduction in estimated GFR (eGFR) from baseline was lower in patients undergoing S/V therapy than in those

treated with enalapril. This result was demonstrated in subjects with or without baseline chronic kidney disease (CKD: eGFR ≥ 60 ml/min/1.73 m2) [14]. In a subgroup of the study population, including 1872 patients, in which urinary albumin/ creatinine ratio (UACR) was available, the subjects with greater levels of albuminuria experienced, as expected, an enhanced risk for developing the composite renal endpoint. Intriguingly, however, even if a rise in UACR was more common in the S/V arm than in the group assigned to enalapril, worsening of albuminuria was associated with an unfavourable renal prognosis only in the latter group [14].

The results concerning the renal effects of S/V were replicated also in the PARAMOUNT study, in which 301 patients with HFpEF were randomised to valsartan or S/V [15]. Mean eGFR at baseline was 65.4±20.4mL/min per 1.73m2. It declined less in the S/V group than in the valsartan group (table 1). Over 36 weeks, the geometric mean of UACR increased in the S/V group, whereas it remained stable in the valsartan group [15]. The mechanisms underlying this albuminuria increase, already described in the PARADIGM-HF study, remain to be elucidated. A relative vasodilation of the afferent arteriole or changes in the contractile state of mesangial cells (or podocytes), induced by the increased availability of NPs may putatively explain this effect on UACR [16] . Whatever the reason of the UACR increase, it seems not to be associated with worsening of renal function or other adverse events. The multivariate analyses performed in the PARADIGM-HF study demonstrated that the beneficial effects of S/V on the CV outcomes remain significant even after taking into account the rise of albuminuria [14] . Interestingly, this effect on UACR was not reported in patients with hypertension, where indeed a slight but significant reduction in albuminuria was observed [17-18].

It is important to note that patients with an eGFR <30 ml/min/ 1.73 m2 were excluded from the PARADIGM-HF study. Thus, the tolerability and efficacy of this drug in patients with more advanced CKD remains uncertain, although S/V was noted to be effective in those with eGFR 30 to 60 ml / min / 1.73 m2 (35% of patients in PARADIGM-HF) (14).

Definitely lower eGFR values (20-60 ml/min/1.73 m2) are found only in the population recruited in

the United Kingdom Heart and Renal Protection (UK HARP)-III trial, which compared S/V and irbesartan, in CKD patients with the primary end point represented by the variation of the GFR level [19]. This trial demonstrated after 12 months that S/V and irbesartan did not differ regarding the effects on renal function (table 1) and albuminuria, but S/V has the additional effect of lowering BP and cardiac biomarkers in people with CKD [19].

In the current issue of *Internal and Emergeny Medicine,* Spannella and colleagues published a paper which provides a new piece of evidence in the field of the renal effects of ARNIs [20]. They conducted a longitudinal observational study in 54 outpatients with HFrEF in order to evaluate the influence of S/V on renal function in a real-life clinical setting. Patients were evaluated at baseline and after 6 and 12 months after initiating S/V and compared with a group of 30 historical controls. In agreement with the results obtained in the randomized clinical trials performed in patients with HF, the eGFR improved after 12 months compared to historical controls (p for interaction<0.001), despite a reduction in BP values [20]. The greater protective effect on renal funcion was detected in the 25 subjects aged <65 years and in the 25 patients with CKD. A modest, but statistically significant increase, in serum potassium was also observed. No cases of symptomatic hypotension occurred [20].

The beneficial effect of S/V was observed also in subjects older than 65 years, but only after one year, probably for the lower dosage of the drug used in this subset of the study population and their greater renal damage at baseline [20].

The interesting study of Spanella et al needs to be interpreted in the context of its limitations. Besides the intrinsic weakness due to its obsevational design, other study limitations need to be highlighted. The first one is its small sample size that makes the study underpowered in order to detect the possible influence of potential confounding factors on the temporal evolution of renal function. The second one is due to the lacking information about proteinuria, a well-known predictor of adverse CV and renal outcomes. Moreover, the renal function of the enrolled patients was generally good at baseline and only 25 participants had a moderate reduction of the GFR,

leaving substantially unexplored the effect of S/V in subjects with more severe renal function impairment. Even with these limitations, the study of Spannella and colleagues adds significant information regarding the effects of S/V on the GFR of subjects with chronic HF, indicating that the preservation of renal function obtained with angiotensin/neprilysin inhibitors in the context of the RCT, may be observed also in the real-life clinical setting.

Further studies are warranted in order to better evaluate the renal effects of S/V and their underlying pathophysiological mechanisms in subjects with and without HF, as well as in those with severe kidney dysfunction.

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Table 1: Randomized controlled studies investigating the effect of sacubitril/valsartan on glomerular filtration rate

Study	Ref	Year	Population	N° of patients	Estimated glomerular filtration rate (ml/min/1.73 m^2)					
					Sacubitril/Valsartan			Comparator		
					Baseline	Reduction at the end of the study	Yearly reduction	Baseline	Reduction at the end of the study	Yearly reduction
PARADIGM-HF	[14]	2018	HFrEF patients with and without CKD	8399	70 ± 20	-7.8	-1.61*	70 ± 20	- 10.2	-2.04
PARAMOUNT-HF	[15]	2015	HFpEF patients	301	67 ± 19	-1.5	-0.2**	64 ± 21	-5.2	-2.0
UK HARP-III trial	[19]	2018	CKD patients	414	35 ± 11	-3.4	-3.4 ^{NS}	35 ± 11	-3.9	-3.9

HFrEF; heart failure with reduced ejection fraction; HFpEF; heart failure with preserved ejection fraction; CKD: chronic kidney disease

* $p < 0.001$ VS comparator (enalapril); ** $p = 0.002$ vs comparator (valsartan);

^{NS} no statistically significant difference with the comparator (irbesartan)

SBP: systolic blood pressure; DBP: diastolic blood pressure

a) 2.2/1.9 mm Hg, when allowing for publication bias,

b) assessed at 6 months; at 12 months the BP reductions were not statitistically significant (1.5/0.8 mmHg)

c) individual data meta-analysis

66.5±19.4 64.3±21.3

Conflict of Interest Disclosure Form

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I certify that there is no actual or potential conflict of interest in relation to this article.

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