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Review

Sacubitril/valsartan therapeutic strategy in HFpEF: Clinical insights and perspectives

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ABSTRACT

Sacubitril/valsartan represents the first of a new class of drugs able to act as a neprilysin inhibitor and as an angiotensin receptor blocker. This double inhibition has the advantage of concomitantly blocking a pro-fibrotic/pro-hypertrophic mechanism (angiotensin receptor blocker component) while stimulating an anti-fibrotic/anti-hypertrophic mechanism (neprilysin inhibitor component). Furthermore, the novel drug has natriuretic and diuretic properties, better preserves renal function, provides better blood pressure control as compared to renin angiotensin system inhibitors, and improves ventricular-arterial coupling. Consequently, sacubitril/valsartan provides greater target organ protection than angiotensin receptor blocker therapy alone, including cardiac, vascular, and renal protection. Up to now, this drug does not have an indication in patients with heart failure with preserved ejection fraction (HFpEF). However, its complex mechanism of action and previous experimental and clinical data seem to suggest its possible success in HFpEF. In this review we highlight and discuss the rationale, clinical insights, and perspectives behind the use of sacubitril/valsartan in HFpEF, specifically referring to its possible efficacy in pathophysiologic mechanisms, such as myocardial hypertrophy, fibrosis, and ischemia, renal dysfunction, impaired ventricular-arterial coupling, which are all tightly related to elevated left ventricular end diastolic pressure, a common hallmark for this multifaceted syndrome.

1. Introduction

Sacubitril/valsartan is a first in class angiotensin receptor-neprilysin inhibitor (ARNI) [1]. Following oral administration, sacubitril/valsartan delivers systemic exposure to a neprilysin inhibitor and valsartan. Neprilysin inhibition acts mainly through enhanced effects of biologically active natriuretic peptides (NPs). Additionally, neprilysin inhibition is known to increase plasma levels of other vasoactive peptides, including vasodilators ones such as adrenomedullin, calcitonin gene-related peptide, bradikynin, as well as vasoconstrictor peptides, including endothelin-1 and angiotensin I and II [2]. The final result of neprilysin inhibitor will rely also on different affinity of neprilysin to its substrates. The increased plasma levels of vasoconstrictors and in particular angiotensin I and II is the reason why the single neprilysin inhibition does not have a clinical benefit [3]. Conversely, sacubitril/valsartan, providing concomitant inhibition of neprilysin and the angiotensin AT1 receptor, has the advantage of concomitantly blocking a pro-fibrotic/pro-hypertrophic mechanism (angiotensin receptor blocker (ARB) component) while stimulating an anti-fibrotic/anti-hypertrophic mechanism (neprilysin inhibitor component). Consequently, sacubitril/valsartan provides greater target organ protection than ARB therapy alone, including cardiac, vascular, and renal protection. Indeed, cumulative evidence suggests that the novel drug is superior to renin angiotensin aldosterone system (RAAS) inhibitor therapy in stable symptomatic patients with heart failure (HF) with reduced ejection fraction (HFrEF) able to tolerate ACE (angiotensin converting enzyme) inhibitors or ARBs, with a better safety and efficacy profile [4–7].

2. Sacubitril/valsartan and HFpEF pathophysiology

Up to now, this drug does not have an indication in patients with HF with preserved ejection fraction (HFpEF). However, none of contemporary therapies is able to reduce HFpEF mortality. The failure of previous studies is believed to be related to an inadequate understanding of HFpEF pathophysiology. In fact, despite the burden related to HFpEF [8], its pathophysiologic mechanisms remain controversial and likely multifactorial [9–11]. As recently underscored, they might include both cardiovascular and non-cardiovascular mechanisms [9]. Amongst cardiovascular mechanisms, which in our view have a predominant pathophysiologic role, there are cardiac structural changes, such as left ventricular (LV) hypertrophy, stiffness, microvascular dysfunction, and cardiac energetic ones (i.e. mitochondrial dysfunction), finally leading to diastolic abnormalities. Other potential

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pathophysiologic mechanisms called into question include vascular stiffness, pulmonary hypertension, and renal mechanisms [12].

In this review we highlight and discuss the rationale, clinical insights, and perspectives behind the use of sacubitril/valsartan in HFpEF, specifically referring to the possible efficacy of ARNI in the aforementioned pathophysiologic mechanisms, which are all tightly related to elevated left ventricular end diastolic pressure (LVEDP), a common hallmark for this multifaceted syndrome.

3. Sacubitril/valsartan and its molecular/intra-cellular mechanism of action: beyond the RAAS inhibition

To understand the reasons for a possible success of ARNI in HFpEF treatment it is important to unveil existing data regarding its molecular and intra-cellular mechanism of action.

The upregulation of the RAAS has been identified as a key pathologic pathway contributing to fibrosis, cardiomyocyte abnormalities, inflammation, and endothelial dysfunction, all of which have been implicated in the progression of HFpEF. Pharmacologic inhibition of the RAAS has been shown in animal models of diastolic dysfunction and in clinical trials to reduce these deleterious processes and to improve diastolic function. Despite these data, clinical trials performed with RAAS inhibitors in patients with HFpEF have failed to demonstrate mortality benefits. However in CHARM Preserved trial a significant reduction of HF hospitalizations has been observed [13].

Aside the important inhibition of the RAAS through its valsartan component, the peculiarity of this drug is its capability to enhance many vasoactive peptides, the most important of which are the NPs (Fig. 1). NPs have potent natriuretic, diuretic and vasodilator actions, inhibit the activity of the RAAS, reduce sympathetic nervous system outflow, and have antiproliferative and antihypertrophic effects. The family of NPs comprise mainly the atrial-derived natriuretic peptides (ANP), B-type (brain) natriuretic peptides (BNP), and C-type natriuretic peptides (CNP). They play an important role in cardiovascular homeostasis through regulation of blood pressure (BP) and plasma volume. Sacubitril, a pro-drug further metabolized to the neprilysin inhibitor (LBQ657), inhibits neprilysin (neutral endopeptidase; NEP), which is a naturally occurring membrane-bound enzyme, responsible for the degradation of NPs and other vasoactive peptide hormones [14]. Neprilysin inhibition leads to increased NPs. Upon binding to its receptors (NPR-A, NPR-B), NP signal transduction leads to an increase in the second messenger cGMP, through membrane-bound particulate guanylate cyclase (pGC) which serves as a receptor for the conversion of guanosine-5′- triphosphate to cGMP. cGMP enhances the activity of the enzyme PKG, which is known to mediate phosphorylation of titin [15–19]. The expression of titin isoforms differs between patients with HFrEF and HFpEF, with a lower ratio of the compliant (N2BA) isoform to the stiff (N2B) isoform in patients with HFpEF. Phosphorylation of the N2B isoform by PKG decreases cardiomyocyte resting stiffness (Table 1).

4. The evidence for cGMP-PKG relevance in HFpEF pathophysiology

The cGMP-PKG pathway seems to play a central role in the derangements integral to HFpEF pathophysiology, possibly resulting from a wider pro-inflammatory state that is accompanied by widespread endothelial dysfunction and oxidative stress [20]. One study showed that 30% of HFpEF patients have diastolic dysfunction with no increase in

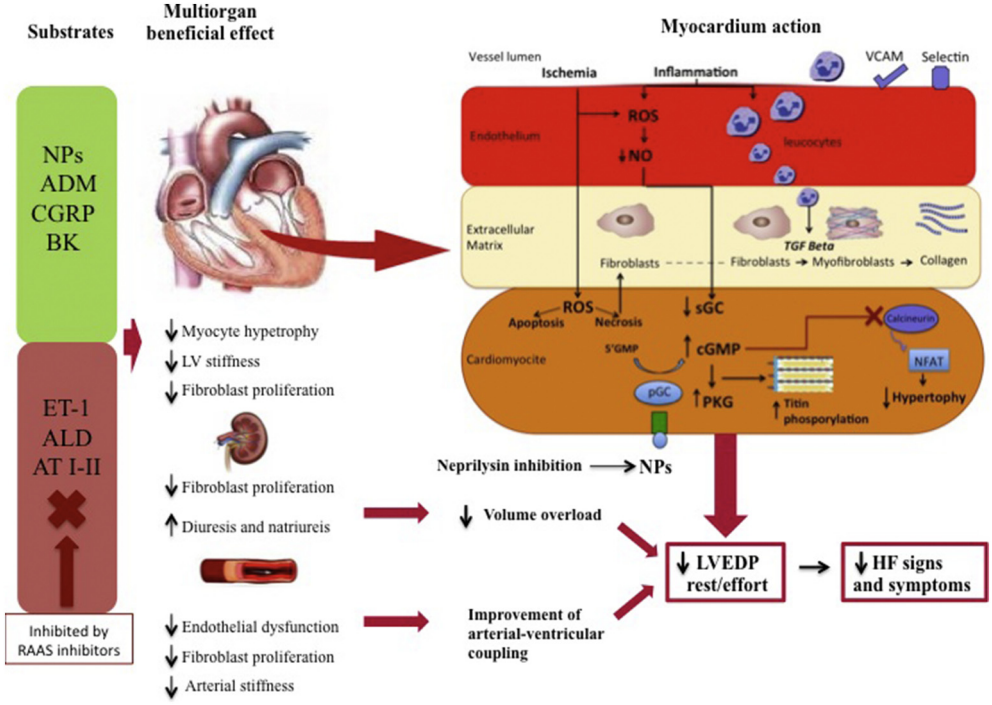

Fig. 1. Sacubitril/valsartan mechanisms of action in HFpEF. Neprilysin catalyzes the degradation of vasodilator peptides, including NPs, ADM, CGRP, BK, as well as vasoconstrictor peptides, including ET-1, ALD, AT I and AT II, which are inhibited by RAAS inhibitors. The net effect of neprilysin inhibition will depend on whether the predominant substrates degraded are vasodilators or vasoconstrictors. Sacubitril/valsartan's action affect the myocardium, the kidney and the vessels to a different extent with beneficial effects related to reduction of myocyte hypertrophy and LV stiffness, increase of diuresis and natriuresis, reduction of fibroblast proliferation, endothelial dysfunction, and arterial stiffness. Myocardial remodeling and hypertrophy begins with coronary endothelial microvascular inflammation evident from endothelial expression of adhesion molecules such as VCAM and E-Selectin. These molecules attract leukocytes secreting TGF-β, which converts fibroblasts to myofibroblasts with consequent production of interstitial collagen. Endothelial inflammation causes the presence of ROS, which reduce NO, leading to a reduction of sGC activity, and cGMP. Neprilysin inhibition contrasts this inflammation pathway acting through NPs receptors, with activation of pGC. By converting 5′GMP in cGMP, pGC enhances cGMP and PKG, with a reduction of cardiomyocyte stiffness and hypertrophy by contrasting calcineuring/NFAT signaling. Abbreviations: NPs: natriuretic peptides; ADM: adrenomedullin; CGRP: calcitonin gene related protein; BK: bradikinin; ET: endothelin; ALD: aldosterone; AT I: angiotensin I; AT II: angiotensin II; RAAS: renin angiotensin aldosterone system; LV: left ventricle; VCAM: vascular cell adhesion molecule; ROS: reactive oxygen species; NO: nitric oxide; TGF: transforming growth factor; sGC: soluble guanylate cyclase; cGMP: cycling guanosine monophosphate; PKG: protein Kinase G; pGC: particulate guanylyl ciclase; NFAT: nuclear factor of activated T cell; LVEDP: left ventricle end diastolic pressure; HF: heart failure.

Table 1
Experimental trial on different substrates in Heart Failure with Preserved Ejection Fraction.

First author	Publication year	Type of experiment	Primary Endpoint	Follow up time	Results
Hamdani [16]	2013	Four groups of rats (Wistar-Kyoto, n = 11; lean ZSF1, n = 11; obese ZSF1, n = 11, and obese ZSF1 with high-fat diet, n = 11)	To elucidate the mechanisms underlying myocardial dysfunction in metabolic risk-related HFpEF	20 months	Cardiac titin hypophosphorylation was associated with high myocardial stiffness and HFpEF in an obese ZSF1 rat model with high metabolic risk
Tokudome [26]	2005	Guanylyl cyclase A knock-out mice	To determine the role of calcineurin in cardiac remodeling	–	Activation of cardiac GCA by locally secreted natriuretic peptides protects the heart from excessive cardiac remodeling by inhibiting the calcineurin-NFAT pathway
Rademaker [50]	2002	8 sheep with HF	Changes in arterial pressure, LA pressure, peripheral resistance, cardiac output, urinary volume, sodium, creatinine, and cAMP excretion	3 h	Cotreatment with ADM and an endopeptidase inhibitor has beneficial hemodynamic and renal effects in HF beyond those of either agent separately
Machado J (53)	2016	Experimental rats	In vitro and in vivo anti-proteolytic effect	–	CGRP exerts a direct inhibitory action on autophagic-lysosomal proteolysis in control and denervated rat skeletal muscle by recruiting cAMP/PKA signaling
Cruden NL (57)	2004	Randomized double-blind placebo-controlled crossover trial (14 patients)	Control of bradykinin-mediated vasodilatation and net tissue plasminogen activator release	6 weeks	BK, ANP, and sodium nitroprusside caused dose-dependent increases in forearm blood flow ($P < 0.0001$)

Abbreviation: HFpEF: heart failure with preserved ejection fraction; HF: heart failure; ADM: Adrenomedullin; LA: left atrium; cAMP: cycling adenosine monophosphate; CGRP: calcitonin gene related protein; PKA: protein kinase A; BK: bradykinin; ANP: atrial natriuretic peptide

LV collagen [21], but with increased cardiomyocyte stiffness attributed to titin hypophosphorylation due to cGMP-PKG deterioration [17]. Indeed, as compared to patients with aortic stenosis or HFrEF, HFpEF patients show reduced myocardial PKG activity and lower cGMP concentrations [17]. Other data demonstrated that inhibition of the breakdown of cGMP by the enzyme PDE5A facilitated increased myocardial PKG activity and contributed to counteract slow LV relaxation and high diastolic LV stiffness in HFpEF [15–17]. Another interesting finding was that the accumulation of comorbidities and risk factors typically encountered in HFpEF, such as ageing, hypertension, diabetes, obesity, and physical inactivity, limit NO bioavailability decreasing PKG activity in adjacent cardiomyocytes, which has been mechanistically linked to concentric LV remodeling and cardiomyocyte stiffening due to titin hypophosphorylation [18–22]. Furthermore, a reduced bioavailability of NO was demonstrated in an animal model of HFpEF and in HFpEF patients, suggesting that impaired cGMP-PKG signaling in HFpEF may be related to the low myocardial NO bioavailability resulting from high oxidative stress [23]. cGMP has also an antiinflammatory role by inhibiting P-selectin expression and leukocyte recruitment (Fig. 1) [24].

Additionally, cGMP antagonizes pathological signaling leading to hypertrophy, endothelial dysfunction, and fibrosis, such as the calcineurin pathway. Calcineurin, a Ca^{2+} sensor in the cytoplasm of the cardiomyocyte, is a serine/threonine phosphatase that is regulated through the adaptor protein calmodulin. In the canonical calcineurin pathway, a cardiac specific isoform CnAb2 acts on nuclear factor of activated T cells (NFAT). NFAT dephosphorylation allows its nuclear translocation and transcriptional activation of prohypertrophic genes. The conventional wisdom is that calcineurin is essential for pathological hypertrophy development [25]. Of note, the calcineurin/NFAT appears to be one of the most relevant pathways underlying the antihypertrophic and antifibrotic effects of NPs (Table 1) [26]. Thus, NPs signaling directly inhibits the calcineurin/NFAT system and may act as an autocrine antihypertrophic system within the heart. Interestingly, a recent study demonstrated for the first time that another unique calcineurin pathway, calcineurin splice variant CnAb1, is protective to myocardium, playing a novel and counterintuitive noncanonical role in the heart by activating cardioprotective pathways involved in serine and one-carbon metabolism along with upregulation of antioxidant enzymes that enhance mitochondrial function [27]. Whether NPs may influence also this pathway is unknown and merit further investigation.

Altogether these findings do suggest a possible therapeutic role in HFpEF for drugs able to improve PKG activity, due to improved diastolic function. Furthermore, cGMP is associated with positive effects on the pulmonary vasculature, which may also contribute to success of cGMP modulation in HFpEF (Fig. 1) [28]. Importantly, sacubitril/valsartan has been demonstrated to enhance urinary cGMP concentrations as compared to enalapril in the PARADIGM-HF study (Table 2) [29]. In a dose escalation study in healthy volunteers, there was a significant increase in cGMP at all doses of valsartan/sacubitril compared with baseline [1].

5. Alternative means to enhance cGMP-PKG signaling

The amount of data regarding the importance of cGMP-PKG signaling has formed the basis for several therapeutic interventions that activate this pathway, besides NPs action, such as enhancement of NO production, stimulation/activation of sGC activity, or via inhibition of cGMP degrading enzymes. Up to now, none of these alternative strategies has shown clear benefits on surrogate endpoints in small randomized studies in HFpEF patients. Thus, a successful therapeutic strategy probably needs to act on this as well as others signaling pathways.

Nitroxyl donors might have positive inotropic and lusitropic effects on the heart through the direct action of nitroxyl on myofilaments, ryanodine receptor 2 (RyR2), and sarco/endoplasmic reticulum Ca^{2+}-ATPase [30]. In addition, NO signaling has anti-fibrotic and anti-hypertrophic actions, and might induce earlier LV relaxation [31,32]. Concordantly, in patients with chest pain but without coronary lesions, intracoronary infusion of sodium nitroprussiade slightly decreased LV peak systolic pressure and acutely increased LV end-diastolic capacitance [33].

However, patients with HF develop a rapid tolerance phenomenon, leading to an impaired NO bioactivation associated to increased vascular oxidative stress [34]. Additionally, chronic administration of isosorbide mononitrate did not improve quality of life or submaximal exercise capacity as compared to placebo [35]. Finally, preliminary results (not yet published) of the INDIE-HFpEF trial showed no benefit of inorganic nitrite delivery to HFpEF patients on aerobic capacity [36].

Soluble guanylate cyclase (sGC) is the only known receptor for nitric oxide (NO) and is completely intracellular. This enzyme is involved in vasodilatation through enhanced levels of cGMP. The responsiveness of sGC to NO and its subsequent ability to generate cGMP is impaired

Table 2
Clinical Trial in HFpEF and HFrEF related to neprilysin inhibition.

Trial author	Publication year	LVEF (%)	NTproBNP (pg/ml)	Type of trial (n pts)	Primary endpoint	Secondary endpoint	Follow-up time	Results
PARAMOUNT HF Solomon SD (72)	2012	≥45	>400	Randomized 1:1 double bind (301)	Change in NTproBNP from baseline to 12 weeks	-Change in LA size -Change in NHYA class	36 weeks	LCZ696 group had 23% reduction in NT pro-BNP compared to valsartan ($P = 0.005$), 7% reduction of LA volume ($P = 0.003$), 9% improvement in NHYA class ($P = 0.051$)
PARAMOUNT HF (post hoc analysis) Voors AA (69)	2015	≥45	>400	Randomized 1:1 Double Bind (301)	Change in renal function (creatinine, eGFR, cystatin C, and UACR)		12 and 36 weeks	LCZ696 for 36 weeks was associated with preservation of eGFR compared with valsartan therapy, but an increase in UACR
PARADIGM HF McMurray JJ [4]	2014	<40	>600	Multicenter, randomized, double-blind, (8442)	Composite of death from CV causes or hospitalization for HF	Time to death from any cause; Change in KCCQ; Time to a new onset of AF; Time to the first occurrence of a decline in renal function	27 months	LCZ696 group had a significant reduction of death from CV causes or hospitalization for HF compared to enalapril (21.8% vs 26.5, $P < 0.001$)
PARADIGM HF (post hoc analysis) Packer [29]	2015	<40	>600	Multicenter, randomized, double-blind, (8442)	Change in NHYA class Change in KCCQ Change in symptoms requiring increase of diuretic dose or hospitalization	Changes in biomarkers reflecting cardiac injury, wall stress, and the effects of neprilysin inhibition	50 months	LCZ696 group had 23% fewer hospitalizations for worsening HF ($P < 0.001$), less necessity to receive intensive care (18% rate reduction, $P = 0.005$), intravenous positive inotropic agents (31% risk reduction, $P < 0.001$), and to have implantation of a HF device or cardiac transplantation (22% risk reduction, $P = 0.07$).
TITRATION Senni [5]	2016	≤35		Multicenter Randomized Double Bind (429)	To assess the tolerability of initiating/uptitrating sacubitril/valsartan (LCZ696) from 50 to 200 mg twice daily over 3 and 6 weeks	Treatment success Tolerability success	3 and 6 weeks	Initiation/uptitration of LCZ696 from 50 to 200 mg twice daily had a tolerability profile in line with other HF treatments.
PARAGON HF Solomon SD (73)	2017	≥45	>300 no AF, >900 AF	Multicenter, randomized, double-blind, parallel group (4800)	Composite endpoint of CV mortality and total hospitalizations for worsening HF		57 months	Ongoing
PARALLAX	–	≥45	>220 no AF, >600 AF	Randomized, double-blind, multi-center, parallel group (2200 estimated)	Reducing NT-proBNP Improving HF symptoms and functional capacity		24 weeks	Ongoing
PERSPECTIVE	–	>40	>125	Multicenter, randomized, double-blind, active-controlled (520)	Change from baseline in the CogState Global cognitive composite score		3 years	Ongoing
PARAMETER Williams B (62)	2017	–	–	Randomized double bind (454)	To assess the effects of LCZ696 versus olmesartan on central aortic pressures in elderly patients (aged ≥60 years) with systolic hypertension and pulse pressure >60 mm Hg	–	52 weeks	BP parameters were similar between treatments ($P < 0.002$); more patients required add-on antihypertensive therapy with olmesartan (47%) versus LCZ696 (32%; $P < 0.002$)

Abbreviation: LVEF: Left ventricle ejection fraction, NTproBNP: N terminal pro Brain Natriuretic Peptide; LA: left atrium, NHYA: New York Heart Association; CV: cardiovascular; HF: heart failure; AF: atrial fibrillation; KCCQ: Kansas City Cardiomyopathy Questionnaire; BP: blood pressure; eGFR: estimated glomerular filtration rate; UACR urinary albumin to creatinine ratio

by oxidation. sGC activators and stimulators represent two distinct compounds that modulate sGC activity.

sGC activators are ideal substitutes for NO under conditions of increased oxidative stress [37]. Up to now, this class of drugs has been successfully tested in a preclinical HFrEF canine model with the sGC activator cinaciguat, and in early clinical data on acute decompensated HF [37]. However, the phase IIb COMPOSE trial, performed in acute decompensated HF, was terminated early because of excessive hypotension in the cinaciguat arm [38].

sGC stimulators reduce cardiac and renal organ damage in experimental models [39]. Recently, a phase II clinical study in patients with LV systolic dysfunction and pulmonary hypertension found that the sGC stimulator riociguat failed to reduce pulmonary artery pressure, but did cause an increment in stroke volume, without changing wedge pressure, thus with possible improvement of diastolic function [40]. Another oral sGC stimulator, vericiguat, was recently investigated in a phase II trial on HFpEF patients (SOCRATES-PRESERVED) [41]. Vericiguat did not change NT-proBNP and left atrial volume at 12

weeks compared with placebo, but was associated with improvements in quality of life. Given these results, the effects of vericiguat in patients with HFpEF are evaluated in an ongoing phase IIB trial (VITALITY trial).

Inhibitors of cGMP degrading enzymes, such as PDE5A, improved cardiac muscle relaxation via PKG mediated phosphorylation of titin [15–17,22,42]. In experimental settings, inhibition of cGMP degradation by sildenafil enhanced NO mediated vasodilation, restored LV relaxation kinetics, and increased LV compliance [43,44]. Similar effects have been observed in patients with HFpEF with pulmonary hypertension [45]. These data provided the rationale to perform the RELAX trial, a 24-week trial of sildenafil in patients with HFpEF [46]. The study failed to raise plasma cGMP or to ameliorate diastolic LV dysfunction. These unexpected results might have been related to the lower values of pulmonary pressure as compared to earlier studies. Another possible explanation is that PDE5A was shown to be up-regulated in the LV of end-stage HFrEF patients, but not in HFpEF patients. A recent study has now shifted attention to the PDE9A isoform [42], which seems to control a pool of cGMP that is produced by the ANP-pGC pathway, is independent of NO, and is increased in HFpEF patients [42]. Besides the RELAX trial, in another HFpEF population sildenafil did not improve invasive right ventricular hemodynamics [47].

6. Sacubitril/valsartan: beyond the RAAS and NP system

Sacubitril/valsartan is known to enhance other vasoactive peptides with recognized beneficial effects on LV remodeling, such as adrenomedullin, calcitonin gene-related peptide (CGRP), and bradykinin (Table 1).

Adrenomedullin (ADM) is a 52 amino acid peptide mainly expressed by vascular endothelium and is present in the circulation. ADM acts on a specific receptor, the so-called calcitonin gene-related peptide receptors, elevates intracellular cAMP, and increases intracellular calcium, which, in turn, activates NO synthase and intracellular NO [48]. Infusion of ADM in the renal arteries of dogs causes increased renal blood flow, natriuresis, and diuresis [49]. Neprilysin inhibition potentiated ADM-induced natriuresis and diuresis in this model. In a sheep HF model, neprilysin inhibition potentiated the vasodilator response to intravenous ADM, while preserving natriuresis and diuresis [50]. ADM has also been shown to reduce myocyte hypertrophy, collagen synthesis, fibroblast proliferation, and aldosterone secretion. ADM infused into normal subjects showed it to be a potent vasodilator. In patients with HF, it reduced both pulmonary and systemic blood pressures, concomitantly increasing cardiac performance, urinary output, and sodium excretion [51]. Additionally, elevation of circulating ADM was found to be an independent predictor of prognosis in HF patients [52]. Thus, it would seem that ADM enhancement could be beneficial in patients with HF.

CGRP is a 37-aminoacid neuropeptide generated by differential splicing of calcitonin gene [53]. This neuropeptide is present in a wide variety of neurons in the central and peripheral nervous systems and in neuromuscular junction, where it potentiates muscle contraction. Machado et all showed that CGRP in vitro and in vivo inhibited muscle protein breakdown in basal and atrophic conditions. Furthermore, a long acting analogue of the CGRP induced positive metabolic effects and secretion of the glucagon-like peptide-1 [54]. Other studies have shown that CGRP might protect against the onset and development of angiotensin II–induced hypertension, attenuate cardiac remodeling, and have identified protective mechanisms at the vascular level [55,56].

Finally, bradykinin is a peptide made up of nine amino acids that increases vascular permeability and acts as a potent vasodilator through stimulation of specific endothelial B2 receptors and of endothelial NO, and an inhibitor of pathological growth, actions potentially useful in HF [57].

7. Sacubitril/valsartan in HFpEF: other ancillary mechanisms

7.1. Blood pressure control and aortic stiffness

Since hypertension is a leading cause of remodeling and a predominant cardiovascular risk factor in HFpEF, a first milestone in the path to an ARNI in the treatment of HFpEF is represented by the results of many studies which have demonstrated a superior blood pressure lowering effect with sacubitril/valsartan, especially as compared to ARB, in hypertensive patients [58,59].

Noteworthy, vascular stiffness, which is also a common finding with ageing in HFpEF, is associated with raised systolic blood pressure, pulse pressure, and pulse wave velocity, which are all independent predictors of adverse cardiac events [60]. Of note, it has been demonstrated that omapatrilat was superior over enalapril in reducing both central aortic and peripheral arterial pulse pressures, reflecting a reduced stiffness of the aorta [61]. In a study of hypertensive subjects, sacubitril/valsartan reduced both ambulatory systolic and pulse pressures more than did valsartan, a finding compatible with a reduction of aortic stiffness [59]. Accordingly, the PARAMETER study (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin Receptor Blocker Measuring Arterial Stiffness in the Elderly), for the first time, demonstrated superiority of sacubitril/valsartan versus olmesartan in reducing clinic and ambulatory central aortic and brachial pressures in elderly patients with systolic hypertension and stiff arteries (Table 2) [62]. A direct linear relationship between the degree of blood pressure lowering and the extent of reduction in separate components of arterial and LV systolic stiffness has been shown. Hence we could expect that sacubitril/valsartan improve ventricular-arterial coupling a key component in patients with HFpEF (Fig. 1) [63].

7.2. Renal disease

Nowadays ACE-inhibitors and ARBs represent drugs of choice to slow progression of chronic kidney disease [64]. However, previous data might suggest a similar efficacy of sacubitril/valsartan in this setting. Specifically, the NEP-inhibitor candoxatrilat has been shown to be associated with natriuresis in patients with moderate renal dysfunction [65]. Studies in partially nephrectomized rats and in rats with diabetic nephropathy have demonstrated that omapatrilat, a vasopeptidase inhibitor, was superior to an ACE-inhibitor in delaying the progression of renal injury in the remaining renal tissue [66]. In both the IMPRESS and OVERTURE trials, omapatrilat was less frequently associated with worsening renal function than the ACE-inhibitor comparator [67,68]. Similar findings were observed with sacubitril/valsartan in the PARAMOUNT trial, despite a greater blood pressure lowering effect and a modest increase in albuminuria [69]. Additionally, in the PARADIGM-HF trial fewer patients on sacubitril/valsartan developed a serum creatinine level ≥2.5 mg/dl than did patients on enalapril [4] and the overwhelming benefits of sacubitril/valsartan were confirmed in patients with impaired renal function at baseline (Damman K Gori M et al. JACC:HF 2018, in press). These data are relevant, since it has been shown that in patients with HFpEF with RAAS inhibitors induced worsening renal function there is an increased mortality risk, in contrast to patients with HFrEF [70]. Altogether these information suggest that sacubitril/valsartan might be superior to ACE-inhibitors and ARBs on renal function (Table 2). This is being tested prospectively in the UKHARP (UK Heart and Renal Protection) III trial, comparing sacubitril/valsartan with irbesartan in patients with an eGFR ≥20 and <60 ml/min/1.73 m2 and proteinuric renal disease [71].

8. The PARAMOUNT-HF study and ongoing trials in HFpEF patients

A recently published phase II study, the PARAMOUNT-HF trial, gave promising results on the potential effectiveness of the novel compound [72]. This was a 36-week trial to evaluate the efficacy, safety, and

tolerability of sacubitril/valsartan compared to valsartan in 301 patients with HFpEF, NYHA class II-III, left ventricular ejection fraction ≥45%, and elevated NTproBNP. The primary endpoint was change in NTproBNP from baseline to 12 weeks. The 36-week treatment effect assessment focused on structural changes. The study achieved its primary objective and demonstrated a statistically significant greater reduction in NT proBNP from baseline to Week 12 for sacubitril/valsartan compared to valsartan, with a difference between groups of 23% ($P = 0.005$). Notably at 36 weeks, there was a greater reduction in left atrial size (both left atrial dimension and left atrial volume index) with sacubitril/valsartan compared to valsartan. NYHA classification at Week 36 showed greater improvement in the sacubitril/valsartan than in the valsartan group. These data show for the first time a reverse remodeling effect of a drug in HFpEF and, together with the revolutionary results of the PARADIGM-HF trial [4], represented the strong rationale to perform the ongoing trials in HFpEF patients, such as the PARALLAX and the PARAGON-HF (Table 2).

The PARALLAX is a 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of sacubitril/valsartan on NT-proBNP, symptoms, exercise function, and safety compared to individualized medical management of comorbidities in patients with HFpEF. Conversely, the Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF) trial is an ongoing double blind randomized trial evaluating whether sacubitril/valsartan will be able to reduce morbidity and mortality in patients with HFpEF [73]. Finally, the PERSPECTIVE trial will evaluate the efficacy and safety of sacubitril/valsartan compared to valsartan on cognitive function in patients with HFpEF, due to concerns regarding the possible effect of neprilysin inhibition on amyloid deposits into the brain.

In conclusion, HFpEF is a major public health problem that lacks effective evidence-based therapies. However, experimental and clinical data do support the idea that sacubitril/valsartan will be effective in the HFpEF multifaceted arena, characterized by many comorbidities, older age, and highly prevalent hypertension. Specifically, the drug might be successful on different mechanisms, such as vascular stiffness, and renal function, but in particular on the target HFpEF domain, represented by the heart and diastolic dysfunction.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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