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The role of sacubitril/valsartan therapy on renal function and glucose metabolism in chronic heart failure patients

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Abstract

Heart failure (HF) is a complex clinical syndrome characterized by abnormalities in cardiac structure and function, dynamic remodelling, and perturbations of the neurohumoral axis. Recently, the angiotensin receptor neprilysin inhibitor (ARNi) class has been successfully tested in chronic systolic HF, improving morbidity and mortality. This treatment approach represents a potential shift in the treatment of HF from partial neurohumoral system inhibition to an integrated composite neurohumoral system modulation. As a substantial number of chronic HF patients show co-morbidities, especially diabetes mellitus and kidney dysfunction, this review is mainly focused on the role of ARNi on renal function and glucose metabolism. Emerging data support that sacubitril/valsartan might enhance glycaemic control in patients with diabetes and heart failure with reduced ejection fraction (HFrEF); while it improves kidney function. This was attributed to the combined effects of angiotensin blockade and augmentation of other neprilysin substrates by neprilysin inhibition and down titration of diuretic therapy. An understanding of emerging novel therapeutic class may provide important insights into the expected on-target and off-target effects when this agent is more widely prescribed.

Introduction

It has been estimated that the prevalence of heart failure (HF) is approximately 2% of the total adult population; whereas, this rate increases up to 10% among older adults. Moreover, HF represents one of the main causes of hospitalization in the Western World [1]. The prognosis of HF patients is determined by several clinical, biochemical and electrophysiological factors. The study of people with HF, and the understanding of the mechanisms and factors that may prolong life and improve the quality of their life, are considered one of the most important issues in clinical cardiology. Pharmaceutical treatment plays an important role in the achievement of the latter goals, and particularly the introduction of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor antagonists, as well as advanced device therapies. The role of the combined angiotensin renin neprilysin inhibition (ARNI) sacubitril/valsartan for chronic HF with reduced ejection fraction, has received much attention in the very recent years [2,3]. Thus, the aim of the review was to present current scientific knowledge regarding the role of sacubitril, valsartan therapy on renal function and glucose metabolism, among HF patients.

HF management

Since the mid-1980s, studies like the VHeFTII, SOLVD-P, CONSENSUS and ATLAS, have firmly established the beneficiary effects of ACEIs and ARBs in HF patients [4]. More recently, the PARADIGM-HF trial has confirmed the belief that potent neurohumoral axis inhibition, coupled with concomitant activation of endogenous vasodilation and decongestion mechanisms, caused by the inhibition of natriuretic peptides degradation and the reciprocal increase in their circulatory levels can improve the clinical course of HF patients with moderate to severe functional impairment and without severely impaired renal function. Thus, the combined molecule of sacubitril/valsartan has been recognized as a Class I indication, (level of evidence B) in the recent European Society of Cardiology guidelines for the treatment of chronic symptomatic HF [5,6]. This indication was mainly based on the results of PARADIGM-HF clinical trial [7]. This Phase III active comparator trial conducted across 47 countries enrolled approximately 8,400 patients with New York Heart Association (NYHA) functional class II-IV HF, an ejection fraction ≤35% and elevated NT-pro beBrain Natriuretic Peptide (NT-BNP) levels, who were already on evidence-based treatment for HF. The investigators compared sacubitril/valsartan, under the code name of LCZ696, against enalapril, an ACE inhibitor with proven mortality benefits, with a primary end point of composite cardiovascular death or hospitalization for HF. The baseline characteristics of the cohort included a mean age of 63 years, left ventricular ejection fraction 29 ± 6%, background therapy of ACE/ARB (99%), beta-blockers (93%), mineralocorticoid receptor antagonists (56%), and predominantly NYHA Class II functional status (70%). 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 cardiovascular death or hospitalization for HF and a 16% relative risk improvement in all-cause mortality, with a number needed-to-treat of 35. The investigators also showed a significant 3 mmHg BP reduction, as well as higher quality of life scores, in the intervention arm at 8 months. Overall, 11% of the recruited patients withdrew due to adverse events, to either drug during the run-in period. Efficacy concerns revolved around the use of moder-

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Table 1. Key findings of selected trials, studied in the present literature review.

Study	Publication Year	Study and Sample characteristics	Key findings
PARADIGM-HF trial [7]	2017	phase III, multicentre, double-blind, parallel group, randomised active-controlled trial; New-onset of diabetes was a pre-specified exploratory outcome; the primary analysis was based on a subset of 3778 of the 8399 patients who reported a history of diabetes, had HbA_{1c} concentrations of 6.5% or more, or both	Patients with diabetes and heart failure with reduced ejection fraction who received sacubitril /valsartan had greater long-term reduction in HbA_{1c} *vs* enalapril.
PARAMOUNT trial [21]	2012	Phase II, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association class II–III HF, left ventricular ejection fraction 45% or higher, and NT-proBNP >400 pg/mL. Participants were randomly assigned (1:1) to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks.	LCZ696 reduced NT-proBNP to a greater extent than did valsartan at 12 weeks and was well tolerated

ate dose enalapril (20 mg/day) instead of its maximal dose (40 mg/day) against 400 mg/day LCZ 696 which delivered an equivalent valsartan dose of 320 mg/day (the maximal daily dose for valsartan). Hence, the supposed benefits may have simply been a result of more effective Renin Angiotensin Aldosterone System (RAAS) blockade conferred by the higher valsartan dose in the intervention arm. The dose of 20 mg enalapril is near the mean dose used in several HF studies (18 mg); while it is quite interesting how patients with systolic HF tolerate increased doses of valsartan; assuming that this combined drug shows compensated vasodilated, antifibrotic and anti-inflammatory effects. Additionally, it leads to improvement in ventricular diastolic function and arterio-ventricular coupling, as illustrated by the decrease in NT pro-BNP secretion [8-10].

An important issue that should be discussed is the management of a stable patient. *Why should we change medications in a stable patient?* Although most patients in the overall PARADIGM-HF population had mild symptoms, in stage II of NYHA classification; the implementation of a Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score revealed that many of those were at high risk for adverse outcomes and obtained a large absolute benefit from the angiotensin receptor neprilysin inhibitor LCZ696, compared with enalapril, over a relatively short time period [11]. Furthermore, the definition of stability needs to be more clarified as in the guidelines stable patient is considered the one that has no hospitalization and remains in unchanged clinical condition the last 4 weeks.

Renal function

In daily clinical practice, serum sodium, urea and creatinine levels, have shown a significant prognostic value for the clinical severity of HF [12]. However, most of the clinical studies on HF therapy have excluded patients with advanced kidney dysfunction, estimated as a glomerular filtration rate (GFR) <30 ml/min or even participants with serum creatinine >220 μmol/L (2.5 mg/dL), although those patients show worse prognosis and are met in high numbers in "real" clinical world [13]. Especially, in specific groups such as hypertensive individuals, elderly subjects, patients with recent stroke, survivors of myocardial infarction, and patients after open heart surgery, elevated serum creatinine may be an independent predictor of all-cause and cardiovascular disease mortality [14,15]. It is now established that the association between renal function and prognosis is linked by neurohumoral activation, as the activation of the RAAS preserves GFR when renal blood flow decreases and renal perfusion pressure declines [16]. In early stages of congestive heart failure (CHF), kidney function is maintained due to compensatory increases in filtration fraction; while in patients with more advance 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 and therefore disproportional to the reduction in cardiac output [17,18]. Nowadays, it is recognized that renal haemodynamic reserve is impaired even in early stages of left ventricular systolic dysfunction [19].

Kidney dysfunction and cardiovascular disease

Patients with chronic kidney disease have an excess risk of developing cardiovascular complications as a result of substantial changes in their internal milieu [13]. Numerous studies have demonstrated progressively increasing cardiovascular risk, with a worsening GFR. Additionally, patients with albuminuria, even if mild, bear a near doubling of cardiovascular mortality risk [14]. Treating this cohort of patients with ARNIs offers the exciting prospect of not only improving cardiovascular risk, but also delaying the progression to renal replacement therapy [19]. The PARAMOUNT trial showed no significant difference in new-onset renal dysfunction, hyperkalaemia, or >50% reduction in GFR between the LCZ696 and valsartan arms. In fact, there was a higher degree of change in estimated GFR (eGFR) in the valsartan group (LCZ 696, -1.6 mL/min/1.73 m^2 *vs* valsartan, -5.2 mL/min/1.73 m^2; p=0.007) [20].

The analysis from PARADIGM-HF was also with no significant difference in protocol-defined decline in renal function or progression to end-stage renal disease [7]. In contrast, increased diuretic use and inadequate response to high doses of diuretic therapy, often described in patients with renal impairment, diabetes mellitus, atherosclerotic disease, and acute HF de-compensation, seem to independently predict worse outcomes [8]. In a recent meta-analysis of the role of RAAS inhibition in CHF patients on worsening renal function (WRF) and clinical outcomes, although more participants developed WRF in the RAAS inhibitor group than in the placebo group, the benefit of those medications in WRF is greater than in the no WRF group, indicative of their cardioprotective role [9]. However, the initiation of RAAS therapy 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; although GFR reduction usually do not exceed 15 - 20% of initial values [9,17].

Concerning neprilysin inhibition, previous studies have shown that with the initiation of omapatrilat, another neprilysin inhibitor, there was greater reduction in blood pressure, increased urinary atrial natriuretic peptide, improved functional status, increased natriuresis, diuresis and GFR, compared with treatment with ACE-I alone [10], which, as it was shown in animal model, may deteriorate glomerulosclerosis and tubulointerstitial fibrosis [21,22]. Unfortunately, despite pharmacodynamic studies that suggested twice daily dosing as appropriate, in the Overture trial ompatrilat was administered once daily failing to improve primary end point (death or hospitalization); while cases of angioedema were more frequent in the treatment arm [23]. The new combined medication of valsartan/sacubitril in an

'putative placebo' analysis yielded a remarkable reduction in total mortality and HF events in patients with significant HF upon oral administration, sacubitril/valsartan provides exposure to sacubitril (AHU377), a pro-drug that is rapidly metabolized to the biologically active neprilysin inhibitor sacubitrilat (LBQ657) and to the AT1-receptor blocker valsartan. These active drugs augment neprilysin substrates such as natriuretic peptides while inhibiting AT1-receptor-mediated responses with reduced ejection fraction [24]. Additionally, natriuretic peptide (NP) system which is released represents a group of structurally related but genetically different hormones or paracrine factors, having actions focusing at protecting the cardiovascular 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), all of which share a common 17-amino acid ring structure. 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, Ang II/aldosterone-dependent sodium and water re-absorption. In addition, NPs are known to oppose RAS and have anti-proliferative and anti-hypertrophic effects [25,26]. As the clinical stage of HF progresses, the responsiveness to natriuretic peptides, in particular ANP and BNP, decreases. This can be due to down-regulation of natriuretic peptide receptors, increased clearance of BNP by NEP or the NPR-C receptor, or decreased downstream signaling. Expression of phosphodiesterase 5, which degrades Cyclic guanosine monophosphate (cGMP), is also increased in experimental HF [27] Decreased degradation of natriuretic peptides with valsartan/sacubitril could overcome natriuretic resistance resulting from any one of these mechanisms.

A question is raised here: can LCZ696 be applied in CHF patients with progressive WRF, with no improvement in ACEI treatment? According to the drug pharmacokinetics, after oral administration, 52-68% of sacubitril is excreted in the urine and 37-48% is excreted in the faeces, in both cases primarily as LBQ657. Eighty-six percent of valsartan and its metabolites are excreted in faeces. The Cmax and AUC of LBQ657 are increased in patients with renal insufficiency, and a lower starting dose of valsartan/sacubitril 50 mg (24/26 mg) is recommended in patients with severe renal impairment (i.e. eGFR <30 mL/min/1.73 m^2) [25]. In the PARADIGM-HF study lower incidences of renal impairment-related adverse effects leading to study drug discontinuation were reported for LCZ696-treated patients compared with enalapril-treated patients despite a greater blood pressure lowering effect associated with LCZ696 therapy. Additionally, categorical changes in eGFR and serum creatinine showed lower rates in the LCZ696 group *vs* the enalapril group. A lower incidence of renal impairment-related AEs was also observed for LCZ696-treated patients with moderate and severe renal impairment compared with enalapril-treated patients with moderate and severe renal impairment [27,28].

The results of PARADIGM-HF showed a lower incidence of hyperkalaemia for patients treated with LCZ696 than for patients treated with enalapril as well as less frequent hyperkalaemia-related adverse effects leading to discontinuation compared with enalapril. This may be explained by the natriuretic and diuretic effect of LCZ696 through naprilysin inhibition that releases natruretic peptides [7].

Diabetes mellitus, cardiovascular and chronic kidney diseases

Among all diabetic complications, CVD and chronic kidney diseases (CKD) are the main culprits for morbidity and mortality [12,13]. The pathogenesis of diabetes associated CVD and CKD is complex and inter-linked with multiple transmembrane signalling cascades. Initial metabolic insults promoted by underlying genetic predisposition, hyperglycaemia, and hyperinsulinaemia activate neurohumoral stressor systems like the sympathetic nervous system, endothelin (ET) system and, the pressor arm [Ang II (angiotensin II)/ACE (angiotensin-converting enzyme)/AT1R (Ang II type 1 receptors)] of the renin-angiotensin system (RAS) [29]. The activation of neuro-hormonal systems is one of the consistent features in array of diseases like hypertension, HF, stroke, CVD and CKD, and hence their blockade denotes a key therapeutic strategy in treatment of these diseases. A meta-analysis from various clinical trials for the effects of RAS blockage on diabetes reported that in delaying end-stage renal disease in patients with type 2 diabetes, early RAS interventions are more beneficial than late interventions [30]. However, other clinical studies and meta-analysis have reported that for diabetic patient, treatment with ARB or ACEi do not offer any advantages over other antihypertensive medications [31,32]. In addition, "aldosterone escape" and "Ang II reactivation" have been observed during either ARB or ACEi pharmacotherapy which clinically manifested as copious water and salt retention and reduction in GFR [31,32].

The role of sacubitril/valsartan on glucose metabolism has not been thoroughly investigated although there are limited references in the literature. In addition, obesity paradox has been described in HF patients that may be associated with the impact of natriuretic peptides on adipose distribution and enhancement of adiponectin production [33,34]. In a recent study following 8 weeks of treatment of obese hypertensive patients, sacubitril/valsartan 400 mg QD, but not amlodipine 10 mg QD, was associated with a significant increase from baseline in insulin sensitivity index and tended to be higher in patients treated with sacubitril/valsartan compared with amlodipine. Abdominal adipose tissue interstitial glycerol concentrations increased with sacubitril/valsartan, but decreased with amlodipine. It seems that sacubitril/valsartan treatment leads to a metabolic benefit in the study population and supports the relevance of neprilysin inhibition along with AT1-receptor blockade in the regulation of human glucose and lipid metabolism [35,36]. However, the underlying pathophysiologic mechanisms are not yet clear and may be attributed to changes in the production and concentrations of various metabolically active peptides by neprilysin inhibition (i.e. atrial natriuretic peptide, BNP, bradykinin, glucagon like peptide) necessitated further investigation [37-42]. In the whole PARADIGH-HF trial the risk ratio for the primary outcome, in participants with diabetes, was 0.84 (95% CI 0.74-0.95), very similar to the overall treatment effect for the entire cohort (HR 0.80, 95% CI 0.73-0.87).

In a post-hoc analysis of the PARADIGM-HF trial, which included 3778 patients with known diabetes or an HbA_{1c} ≥6·5% at screening out of 8399 patients with HF with reduced ejection fraction (HFrEF) who were randomly assigned to treatment with sacubitril/valsartan or enalapril. Of these patients, most (98%) had type 2 diabetes. There were no significant differences in HbA_{1c} concentrations between randomized groups at screening. During the first year of follow-up, HbA_{1c} concentrations decreased by 0.16% (SD 1.40) in the enalapril group and by 0.26% (SD 1.25) in the sacubitril/valsartan group (between-group reduction 0.13%, 95% CI 0.05-0.22). HbA_{1c} concentrations were persistently lower in the sacubitril/valsartan group than in the enalapril group over the 3-year follow-up (between-group reduction 0.14%, 95% CI 0.06-0.23). Additionally, new onset insulin use was 29% lower in patients receiving sacubitril/valsartan (114 [7%] patients) compared with patients receiving enalapril (153 [10%]; hazard ratio

0.71, 95% CI 0.56-0.90). Similarly, fewer patients were started on oral antihyperglycaemic therapy (0.77, 0.58-1.02) in the sacubitril/valsartan group. Those data suggest that sacubitril/valsartan might enhance glycaemic control in patients with diabetes and HFrEF [43,44].

There are several potential mechanisms by which inhibition of neprilysin might lead to improvement in glycaemic control. Natriuretic peptides, which are increased by neprilysin inhibition, might play a crucial role in insulin sensitivity and metabolism. Neprilysin is known to promote lipid mobilization from adipose tissue, increase postprandial lipid oxidation, promote adiponectin release, and enhance muscular oxidative capacity. Furthermore, blood glucose concentrations have been shown to decrease after infusion of B-type natriuretic peptide [37,45,46]. In the Atherosclerosis Risk in Communities study in a population of 7822 individuals, with a median follow-up of 12 years, higher concentrations of N-terminal proBNP were associated with a significantly decreased risk of diabetes, even after adjustment for traditional risk factors and fasting glucose. Augmentation of other neprilysin substrates by neprilysin inhibition might also play a part in glycaemic control. Bradykinin, a neprilysin substrate, can also improve insulin sensitivity and attenuate lipolysis. Cyclic guanosine monophosphate, increased by neprilysin inhibition, has known vasodilatory effects in skeletal muscle and facilitates lipolysis [34,47-49]. Moreover, GLP-1, a neuropeptide of the incretin family and potent antihyperglycaemic hormone with a very short circulating half-life, is partially degraded by neprilysin. In high-fat-fed neprilysin deficient mice, the improvement in glycaemic status was associated with elevated active GLP-1 concentrations, reduced plasma dipeptidyl peptidase 4 (DPP-4) activity and improved beta cell function, suggesting beneficial metabolic effects of neprilysin inhibition. Inhibition of the renin-angiotensin system also benefit glycaemic control, as angiotensin II promotes insulin resistance [45]. Nevertheless, the improvement of glucose metabolism by renin-angiotensin system inhibition alone is most likely to be modest.

Dual ACE-neprilysin inhibitors improve insulin sensitivity in preclinical studies. Inhibition of neprilysin with the dual ACE-neprilysin inhibitor omapatrilat improved whole-body insulin-mediated glucose disposal, induced profound insulin sensitisation, and increased myocardial glucose uptake in obese insulin-resistant Zucker rats [46]. In a study comparing the effects of sacubitril/valsartan and amlodipine on insulin resistance in obese hypertensive patients treated for 8 weeks, those treated with sacubitril/valsartan showed a significant increase in insulin sensitivity using the hyperinsulinaemic-euglycaemic clamp technique [39]. Additionally, LCZ696 attenuated cardiac remodeling and dysfunction after MI [50]. This may be contributed to the superior inhibition of cardiac fibrosis and cardiac hypertrophy by LCZ696 than either stand-alone neprilysin inhibitor or angiotensin receptor blocker.

Neurological safety concerns

Neurological safety concerns have also risen with usage of NEPi in diabetes. The NEP also takes part in degradation of amyloid-b peptides in the brain. Hence, NEPi may lead to accumulation of amyloid-b peptides which in turn increases the risk of Alzheimer's disease [51]. Since, diabetic patients are more susceptible to the development of Alzheimer's disease [52]; an exposure to NEPi may lead to a further upsurge in disease. In a short-term study in cynomolgus monkeys, active metabolites of sacubitril, LBQ657 crossed the blood brain barrier and increased the cerebrospinal fluid amyloid-b peptides. However, there was no significant increase in amyloid-beta peptide levels in the brain [52,53]. Interestingly, in the PARADIGM-HF trial, cognitive impairment like adverse effects were not increased by LCZ696, which were thought to be because of the beneficial cardiovascular actions of ANRi [7]. Nevertheless, several other enzymes are involved in the clearance of amyloid-b peptides in the brain and, hence NEPi may not have a significant effect on accumulation of these peptides, but while dealing with diabetic patients, who are already at a higher risk of Alzheimer's disease, it is worthy to give attention to cognition related side effects in pre-clinical and clinical studies.

Concluding remarks

Systolic HF is a syndrome of mechanical, structural or electrical abnormality of the heart that can lead to disability. Ischemic, metabolic, endocrine, immune, inflammatory, infective, endocrine, genetic and neoplastic processes can be implicated in the pathogenesis of HF [54,55]. In daily clinical practice an emerging number of patients treated for HF show diabetes mellitus and kidney dysfunction. The recently introduced combined molecule, sacubitril/valsartan, has been recognized as a Class I indication, for treatment of chronic symptomatic HF. Additionally, experimental and clinical evidence suggest that this molecule offers nephroprotective effects offering an increase in urinary atrial natriuretic peptide, in natriuresis and GFR. More recently, improvement in glucose tolerance was also illustrated, attributed to the combined effects of angiotensin blockade and augmentation of other neprilysin substrates by neprilysin inhibition.

Conflict of interest

CC and DT have received educational grants from Novartis.

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