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The effects of Sacubitril/Valsartan on Vascular Properties in Heart Failure Patients with Reduced Ejection Fraction

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Abstract :

Background:

Increased aortic stiffness is known to be an independent predictor of mortality in patients with heart failure with reduced ejection fraction (HFrEF). The effects of sacubitril–valsartan on vascular structure and function have not been systematically studied in this patient population.

Aim: The aim of this study was evaluate the effect of sacubitril-valsartan on central aortic stiffness in patients suffering from heart failure.

Conclusion:

We concluded that among patients with heart failure with reduced ejection fraction (HFrEF), sacubitril-valsartan improve the aortic stiffness.

Keywords: HFrEF, Sacubitril–Valsartan, Aortic Stiffness.

Introduction:

The most recent breakthrough in the pharmacological management of HF was the demonstration that adding a neprilysin inhibitor (sacubitril) to a renin-angiotensin system blocker (and other standard therapy) reduced morbidity and mortality in patients with chronic, symptomatic, ambulatory HF with reduced ejection fraction (HFrEF) **(1).**

In the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in HF trial (PARADIGM-HF), valsartan combined with sacubitril (ARNI) was superior to the current gold standard of an ACEI, specifically enalapril, reducing the risk of the primary composite outcome of CV death or first HF hospitalization **(1).**

The results of PARADIGM-HF led to the approval of sacubitril/valsartan by American and European regulatory authorities, among others, for the treatment of HFrEF and its recommendation in international guidelines **(2).**

Natriuretic peptides and Neprilysin:

Myocardial damage, most commonly as a result of poorly controlled hypertension, myocardial ischaemia or infarction, results in activation of the renin-angiotensin-aldosterone system (RAAS) **(3).**

Whilst initially compensatory to help maintain cardiac output, prolonged and sustained RAAS activation can have detrimental effects including increasing cardiac afterload due to vasoconstriction, promoting myocardial fibrosis and fluid retention secondary to an anti-natriuretic action. Ultimately these processes become deleterious and result in the development of the syndrome of HF and its progressive worsening over time **(3).**

The natriuretic peptides (NPs) are a family of vasoactive peptides which are released by the heart, in response to increased myocardial wall stress, and from blood vessels and the kidneys. The NPs help to nullify the harmful effects of an overactive RAAS. The first NP to be described was atrial NP (ANP), when Bold demonstrated the increased urinary sodium and water excretory effect of atrial extracts **(4).**

Subsequently, B-type NP (BNP), C-type NP (CNP) and urodilatin were identified, sharing the beneficial vasodilatory, natriuretic, anti-fibrotic and anti-hypertrophic properties of ANP. The potential benefits of the NPs, including amelioration of the effects of RAAS overactivity, led to several lines of research into how these peptides might be used therapeutically **(5).**

One obvious approach was short-term intravenous administration of supra-physiological does of exogenous NP in patients hospitalized with decompensated HF. However, in 2 trials neither nesiritide (a recombinant form of BNP) nor ularitide (a recombinant form of urodilatin) reduced mortality or re-hospitalization **(6).**

The alternative, and ultimately successful, approach was to augment level of endogenous NPs by reducing their elimination which occurs through 2 major pathways. One is through a NP clearance receptor (NPRC or NPRC3) and the other is through degradation by the enzyme neprilysin (also known as membrane metallo-endopeptidase or neutral endopeptidase [NEP]), a membrane bound endopeptidase found in many tissues, most prominently in the kidney **(7).**

It is important to note that neprilysin also plays a role in the degradation several other peptides including bradykinin, adrenomedullin, substance P and calcitonin, apelin, glucagon-like peptide-1, vasoactive intestinal peptide, and enkephalins and these other substrates may contribute to the benefits of neprilysin inhibition **(8).**

Neprilysin inhibition:

Roques and colleagues reported the first neprilysin inhibitor, thiorphan in animal models with demonstration of favorable hemodynamic and hormonal responses. Early reports showed that acute inhibition of neprilysin with oral racecadotril (formerly acetorphan) and intravenous candoxatrilat demonstrated stimulation of natriuresis and diuresis along with increases in circulating ANP levels in humans without any associated deleterious activation of RAAS or sympathetic activity as observed with loop diuretics **(3).**

Furthermore, it was also seen that candoxatrilat and ecadotril reduced pulmonary capillary wedge pressure in patients with HF. However, it was subsequently demonstrated that chronic dosing with candoxatril did not lead to a sustained reduction in blood pressure and development of the drug was consequently halted. The amelioration of the hypotensive action of this agent likely resulted from accumulation of angiotensin II, the breakdown of which was inhibited by candoxatril, and which offset the vasodilatory effects of NP accumulation. In retrospect, this finding demonstrated the need to combine neprilysin inhibition with blockade of the renin-angiotensin system **(9).**

Angiotensin converting enzyme-neutral endopeptidase inhibition:

The first approach to combining neprilysin inhibition with renin-angiotensin system blockade was using molecules that inhibited both ACE and NEP, the most studied of which was omapatrilat. In the Inhibition of Metalloprotease by Omapatrilat in a randomized exercise and symptoms study (IMPRESS) in HF trial, omapatrilat was compared to lisinopril to assess for improvement in functional capacity and clinical outcomes in 573 patients with HFrEF. While there was no significant difference seen in the primary outcome of exercise tolerance, a positive trend was seen in favour of omapatrilat in reducing the composite of death, admission, or discontinuation of study treatment for worsening HF **(4).**

Two years later, the results of the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial, a randomized controlled trial of omapatrilat 40 mg once daily compared to enalapril 10 mg twice daily, were published. There was no benefit of omapatrilat over enalapril in reduction of the primary endpoint of all-cause death or HF hospitalization **(6).**

However, a nominally statistically significant 9% reduction in the secondary endpoint of all-cause death and CV hospitalization was seen in patients randomized to receive omapatrilat. Moreover, in a post hoc analysis of the primary end point using the definition used in the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial there was an 11% lower risk in patients treated with omapatrilat (nominal, p=0.012). It also appeared that the single large daily dose of omapatrilat used in OVERTURE led to excessive hypotension and study drug discontinuation, while at the same time failed to provide sustained 24-hour inhibition of either neprilysin or the renin-angiotensin system. Together, these considerations suggested that, used in the right way, combined neprilysin and renin-angiotensin system inhibition might still be useful in HF **(4).**

However, further development of omapatrilat was halted because of an excessively high rate of serious angioedema, particularly in the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril trial (OCTAVE) in hypertension where 2.2% of patients randomized to omapatrilat had angioedema compared to 0.7% of those randomized to enalapril **(3).**

The higher rate of angioedema observed with omapatrilat was felt to be secondary to the accumulation of bradykinin, resulting from combined ACE and neprilysin inhibition (because both enzymes breakdown bradykinin). Omapatrilat was later found to also inhibit aminopeptidase P, another key enzyme involved in degradation of bradykinin **(10).**

Angiotensin receptor-Neprilysin inhibitors:

The solution to the problem of safely combining neprilysin and renin-angiotensin system inhibition was solved by using an angiotensin receptor blocker (ARB), instead of an ACE inhibitor, and the development of sacubitril/valsartan **(4).**

Sacubitril/valsartan (originally named LCZ696) is the first in class ARNI. Upon oral administration, sacubitril/valsartan dissociates and sacubitril is converted to its active metabolite sacubitrilat. Sacubitrilat and valsartan have half-lives of approximately 12 and 9.9 hours respectively and given twice daily ensure sustained neprilysin and RAAS inhibition over the 24-hour period **(11).**

The valsartan formulation in sacubitril/valsartan is more bioavailable than conventional valsartan, with a 40% higher systemic exposure per mg of drug **(4).**

Consequently, the target dose of sacubitril/valsartan (97/103 mg twice daily) gives plasma concentrations of valsartan equivalent to 160 mg twice daily of the conventional compound (the dose as studied in the Valsartan Heart Failure Trial [Val-HeFT]). This dose also gives a sustained increase in cyclic guanosine monophosphate, reflecting the second-messenger response to the increase in natriuretic (and possibly other) peptides resulting from neprilysin inhibition by sacubitrilat **(12).**

Prospective comparison of Angiotensin receptor-Neprilysin inhibitor with Angiotensin converting enzyme inhibitor to determine impact on global mortality and morbidity in heart failure (PARADIGM-HF) trial:

PARADIGM-HF was designed to test the efficacy and safety of adding a neprilysin inhibitor (sacubitril) to a renin-angiotensin system blocker (and other standard therapy), compared with a renin-angiotensin system blocker (and other standard therapy) alone. Specifically, sacubitril/valsartan 97/103 mg twice daily was compared to enalapril 10 mg twice daily **(13).**

The choice of comparator, enalapril 10 mg twice daily, was based on the evidence from the SOLVD-Treatment trial, the only large-scale, long-term, trial in a broad ambulatory HFrEF population, demonstrating superiority of and ACE inhibitor compared to placebo in reducing morbidity and mortality in HFrEF. For this reason, enalapril 10 mg twice daily has been the "gold-standard" comparator in other trials and is the most studied ACE inhibitor in HFrEF trials **(4).**

Patients were recruited between 2009 and 2012. All patients underwent a sequential run-in period first with enalapril 10 mg twice daily followed by sacubitril/valsartan 97/103 mg twice daily for a total of 6–8 weeks. If no unacceptable side-effects were seen, patients were randomized 1:1 in a double-blind fashion to either sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily and followed up for occurrence of prespecified outcomes (or adverse events) **(3).**

PARADIGM-HF was terminated early in March 2014 on the recommendation of the Data Monitoring Committee due to overwhelming benefit observed with sacubitril/ valsartan therapy. The median duration of follow-up in PARADIGM-HF was 27 months. **(Cada, 2015)**

Clinical efficacy of SACUBITRIL/VALSARTAN in PARADIGM-HF:

Sacubitril/valsartan significantly reduced the risk of the primary composite outcome and each of its components i.e., CV death and HF hospitalization. Equal and significant reductions in the risk of the 2 major modes of CV death, sudden death, and death from worsening HF, were also observed, and there was a 16% reduction in the risk of all-cause mortality**.** Hence, for every 1,000 patients switched from enalapril to sacubitril/valsartan, there would be 46 fewer primary composite endpoint events, 27 fewer first HF hospitalizations, 31 fewer CV deaths and 28 fewer deaths from any cause over a follow-up of 27 months **(14).**

In addition, subsequent post-hoc analyses of PARADIGM-HF have shown no difference in the benefit of therapy with sacubitril/valsartan compared to enalapril according to age or to geographical region of enrolment. No other significant treatment effect interactions were seen in any of the other prespecified sub-groups or in relation to background drug or device therapy **(15).**

Safety and tolerability of SACUBITRIL/VALSARTAN in PARADIGM-HF:

Patients randomized to sacubitril/valsartan had significantly more hypotension than patients randomized to enalapril even though study-drug discontinuation as a result of hypotension was very

rare and not significantly different between the treatment groups. No significant difference in the rate of angioedema was reported**.** Renal dysfunction, hyperkalaemia and cough were less commonly reported with sacubitril/valsartan compared to enalapril. Dementia and cognition related adverse events were not increased by sacubitril/valsartan in PARADIGM-HF **(16).**

Regulatory approval and statistical robustness of results:

The results of PARADIGM-HF were swiftly followed by regulatory approval of sacubitril/ valsartan for use in patients with HFrEF and conforming to the main inclusion criteria used in the trial. Regulatory approval of a new drug requires that its effectiveness and safety be demonstrated in either 2 trials with a 2-sided p value<0.05, or a single, large, internally consistent multicenter study with a p value<0.00125. PARADIGM-HF was a large (8,399 patients), highly statistically significant (p value=0.0000004), internally consistent (lack of subgroup interaction), multicenter (sites in 47 countries) study with large treatment effects on morbidity and mortality **(3).**

As a result of the robustness of the results of PARADIGM-HF it has been considered unethical to conduct a second large clinical trial with sacubitril/valsartan in patients HFrEF. With a p value of 0.0000004 for the primary composite outcome, the chance that sacubitril/valsartan is not superior to enalapril is less than one in a million. On the basis of a single trial providing evidence of benefit, the American College of Cardiology (ACC) and the European Society of Cardiology guidelines have afforded sacubitril/valsartan a class I, level of evidence B treatment recommendation for use in HFrEF to reduce HF hospitalization and mortality in patients who remain symptomatic despite pharmacotherapy with ACE/ARB, a beta blocker, and a mineralocorticoid antagonist **(17).**

A meta-analysis of the 3 trials (PARADIGM-HF, IMPRESS, and OVERTURE) comparing combined neprilysin/ RAAS inhibition to RAAS inhibition alone in HFrEF, reported a significant pooled HR in reducing the risk of a composite endpoint of all-cause mortality or HF hospitalization **(18).**

Based on the results of this meta-analysis, as well as the degree of statistical certainty of benefit reported in PARADIGM-HF, it is believed that it can be reasonably argued that the body of evidence in favour of neprilysin inhibition supports a level of evidence A recommendation for treatment with sacubitril/valsartan in patients with symptomatic HFrEF, with now additional support for comparison of sacubitril/valsartan versus Enalapril in patients stabilized from an acute Heart Failure episode (PIONEER-HF) **(3).**

PARADIGM-HF required patients to be tolerant of a dose of an ACE-inhibitor or ARB equivalent to enalapril 10 mg/day prior to enrolment. Several trials now support the use of sacubitril/ valsartan in ACE-inhibitor or ARB naïve patients including those stabilized from presentations of acutely decompensated HF (a proportion of which we first or “de novo” presentations). The ACC guidance permits prescription of sacubitril/valsartan to ACEI/ARB naïve patients, a strategy which is supported by the results of the TITRATION and TRANSITION studies. Sacubitril/ valsartan was also found to result in a greater reduction in the N-terminal prohormone of BNP levels, compared to enalapril, among patients hospitalized for acute decompensated HF in the PIONEER-HF trial **(19).**

A significant reduction in risk of rehospitalization for HF was also seen, although the trial was not powered for clinical outcomes. There are a number of ongoing studies to assess the efficacy and safety of sacubitril/valsartan in other populations. PARAGON-HF will evaluate the efficacy of sacubitril/valsartan compared to valsartan in reducing morbidity and mortality in patients with HF with preserved ejection fraction (HFpEF). It is the largest and the most globally representative HFpEF clinical trial to date and the results are expected this year. PARADISE-MI will assess the effect of sacubitril/valsartan compared to ramipril in reducing the occurrence of the composite endpoint of CV death, HF hospitalization and outpatient HF in post-acute MI patients with left ventricular systolic dysfunction and/or pulmonary congestion with no prior history of chronic HF **(18).**

Conclusion:

We concluded that among patients with heart failure with reduced ejection fraction (HFrEF), sacubitril-valsartan improve the aortic stiffness.

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Conflict of interest: Nil.

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