The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 3684-3687

Role of Echocardiography in Evaluation of the Effects of Sacubitril–Valsartan on Vascular Stiffness in Patients with Heart Failure: Review Article

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ABSTRACT

Background: Heart failure with reduced ejection fraction (HFrEF) people are exposed to increased risk of death that can be predicted by several factors, one of which is increased vascular stiffness. Sacubitril-valsartan has not been thoroughly investigated in this population to determine its effects on vascular function and structure. Based on the vasodilatory features of sacubitril–valsartan, we expected that fractional area change (AFAC) as well as aortic distensibility (AD), when measured through 2D transthoracic echocardiography (TTE), should enhance with treatment course in HFrEF patients.

Objective: This review article aimed to determine whether aortic stiffness can be measured by echocardiography in heart failure patients receiving sacubitril-valsartan medication or not.

Methods: Search terms for the study included echocardiography, HFrEF, sacubitril-valsartan, aorta, and entresto in PubMed and Google Scholar. After the writers carefully analysed references from the relevant literature, including all the acknowledged research and reviews, only the most recent or complete studies between February 1995 and July 2021 were included. Since no sources for interpretation could be found, non-English language documents have been ignored. Dissertations, discussions, abstract papers from conferences, and everything else that wasn't a fundamental scientific research had been excluded.

Conclusion: The positive benefits of sacubitril–valsartan on AD and AFAC as evaluated by TTE are increasing gradually from baseline to six months.

Keywords: Echocardiography, HFrEF, Sacubitril–Valsartan, Aorta, Entresto.

INTRODUCTION:

Hypertensive heart failure patients who have reduced ejection fraction, were recently investigated for well toleration of sacubitril/valsartan (LCZ696) which is angiotensin receptor neprilysin inhibitor (ARNI) composed of angiotensin II receptor blocker (ARB) (valsartan) as well as the neutral endopeptidase inhibitor 377 (neprilysin) showing good benefits. Mortality rate declined markedly as well as hospital admission for patients using sacubitril/valsartan in comparison to other group using angiotensin-converting enzyme (ACE) inhibitor, in patient population with class II, III, or IV heart failure having ejection fraction (EF) lower than 40%. The trial was blinded on two levels. Analysis of the Global Impact of ARNI and ACEI on death and illness courses from heart failure (PRARDIGM-HF). Sacubitril/valsartan was according to this information, the Food and Drug Administration has given its permission, as has the Committee for Medicinal Products for Human Use. Evidence is also mounting for its possible application in treating post-myocardial infarction, chronic renal disease, stroke, as well as preserved ejection fraction heart failure [(1)].

In individuals with hypertension of grades I to III, sacubitril/valsartan has been demonstrated to efficiently lower both systolic and diastolic blood pressure without substantial adverse effects such as angioedema (blood pressure equal or higher than 180/110 mmHg) with or without chronic kidney disease, and its blood pressure-lowering effects are long-lasting for twenty-four hours among both the night and the morning. Multiple trials in both Western and Asian hypertension patients have shown that once-daily administration of dosages ranging from 100 mg to 400 mg of sacubitril/valsartan reduces 24-hrs ambulatory BP, including nocturnal to morning blood pressure [(2,3)].

Along with calcium channel blockers, this medication effectively lowers both office and 24-hours BP and pulse pressure [(4)], in addition to having a theoretical benefit for resistant hypertension patients [(5)]. Studies of angiotensin receptor blockers and angiotensin receptor neprilysin inhibitors for management of arterial stiffness in the elderly have recently been conducted as systolic hypertension with a broad pulse pressure is more effectively treated with sacubitril/valsartan than with angiotensin receptor blockers in the elderly. The older population has a high prevalence of systolic hypertension, which is a major threat for preserved ejection fraction heart failure. Thus, sacubitril/valsartan could have the capability of reduction the progression of cardiovascular disease (age-related), which includes anything like heart failure as well as high blood pressure [(3)].

Mechanisms of sacubitril and valsartan in heart failure with preserved ejection fraction:

Sacubitril-valsartan, an angiotensin receptor–neprilysin inhibitor, was more beneficial than enalapril for patients with heart failure and a poor ejection fraction in the PARADIGM-HF trial, although the mechanisms by which the medicine exerts its effects were not evident. Mechanisms of sacubitril–favorable valsartan's effects on reverse cardiac remodeling without impacting central aortic stiffness were explored

Received: 21/3/2022
Accepted: 18/5/2022

in two studies presented at the European Society of Cardiology Congress. [6].

Patients treated with sacubitril plus valsartan had reduced levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), which was associated with an increase in survival in the PARADIGM-HF investigation. Because of the link between NT-proBNP levels and cardiac architecture and function, **Januzzi *et al.*** [6] established the prospective PROVE-HF study with 794 patients with HFrEF to test whether or not a decrease in NT-proBNP levels with sacubitril–valsartan therapy indicated improved cardiac performance. An improvement in cardiac volume and function was associated with a 37% decrease in NT-proBNP levels from baseline at 1 year. Early diastolic filling as a percentage of early diastolic annular velocity (E/e′) increased by 9.4 percentage points from baseline, as did the sizes of the left ventricle (LV) and the left atrium. Many other heart failure medicines have not shown such dramatic improvements in cardiac remodeling. Consistent with what **Januzzi *et al.*** [6] stated. Prespecified subgroups of patients who were underrepresented in PARADIGM-HF, including those who were not being treated by ARBs or ACEI or who had just developed HFrEF, also showed improvement. Researchers are now evaluating the effects of sacubitril and valsartan on patients' quality of life, symptoms, and they plan to look at other molecular biomarkers in the near future [7, 8].

To determine the effects of sacubitril–valsartan and enalapril on central aortic stiffness and cardiac remodeling, 464 individuals with HFrEF were included in the EVALUATE-HF trial. By the end of the 12-week study period, there were no significant differences in central aortic stiffness between the treatments. Secondary outcomes, such as left ventricular (LV) ejection fraction, were not significantly different between sacubitril-valsartan and placebo participants. In the PARADIGM-HF research, sacubitril-valsartan was associated with improvements in heart structure and function, as reported by **Januzzi *et al.*** [6].

Role of Echocardiography in evaluation of treatment:

Karagodin *et al.* [9] results revealed that treatments with sacubitril-valsartan were associated with incremental enhancements in AD and AFAC. These two aortic compliance indices were shown to be significantly greater in healthy controls than in patients with heart failure with reduced ejection fraction, and they are gradually normalised in patients treated with sacubitril–valsartan beginning as early as 3 months after therapy started. For establishing a baseline, they compared their measurements of aortic distensibility in healthy controls to those that had been reported before. [10].

The aorta not only carries blood to the rest of the body, but also stores it. The Windkessel effect describes how, during diastole, the aorta takes in and retains half of the blood that has been ejected and pumps the other half out into the peripheral circulation. Damage to the elastic fibers of the aorta wall brings on an increase in aortic stiffness, which increases with age, stress, and the presence of cardiovascular risk factors [11].

Chirinos *et al.* [12] validated the pulsatile load hypothesis, which postulates that, during the middle to late phases of systole, the afterload on the left ventricle is increased by wave reflections from the periphery travelling back to the proximal aorta. An increased risk of cardiovascular events and the onset of heart failure symptoms has been linked to higher arterial wave reflections, as demonstrated by these authors. For this reason, it has been suggested that treating heart failure by reducing aortic stiffness may be an important therapeutic goal [13]. The ACC/AHA presently recommends ACE inhibitors (or angiotensin receptor blockers in ACE inhibitor-resistant persons) and beta blockers for patients with HFrEF due to their efficacy in reducing mortality [14]. In patients with long-lasting symptoms, treatment with mineralocorticoid receptor antagonists reduced death [15].

Sacubitril–valsartan reduced mortality in patients with HFrEF with NYHA Class II–IV and symptoms in comparison to enalapril, as demonstrated by the PARADIGM-HF study. People who continue to experience symptoms, as well as certain subsets of the general patient population, may benefit from further treatments supported by evidence (i.e. isosorbide dinitrate, hydralazine, ivabradine) [14].

Important molecular targets in heart failure with decreased ejection fraction include ACEIs, ARBs, and mineralocorticoid antagonists because of their neurohormonal regulation of the renin-angiotensin-aldosterone system [15]. Reduced catecholamine stimulation and myocardial oxygen demand by beta blockers reduces the rate of adverse remodeling from cardiac myocyte hypertrophy as well as supply–demand difference [16].

By blocking neprilysin activity, which degrades natriuretic peptide, natriuretic peptide axis blockers increase vasodilation and diuresis while decreasing interstitial fibrosis and improving vascular stiffness. In the setting of hypertension, numerous studies have investigated whether or not sacubitril–valsartan reduces arterial stiffness. Twelve weeks of treatment with sacubitril–valsartan considerably lowered central aortic and brachial blood pressures, according to the results of the multicenter, randomised, double-blind PARAMETER research (blood pressure was taken with a non-invasive way of measurement), in comparison with olmesartan, among elder patients having stiff arteries (with pulse pressure higher than 60 mmHg) [17].

Schmieder *and colleagues* [18] also, central pulse pressure was reduced more in the sacubitril–valsartan group than in the olmesartan group by week 52 in a study of people with hypertension and excessive pulse pressure. In both groups, AD increased with time (as measured by cardiac MRI), although the rates of improvement were about the same. Their echo-based

analysis supports the findings of the other two trials that employed non-invasive approaches to evaluate AD and found improvement with sacubitril–valsartan over time. Heart failure has been linked to stiffer blood vessels, according to recent studies. **Tsao *and colleagues.*** [19] showed that increased carotid-femoral pulse wave velocities, a measure of aortic stiffness, are associated with the development of heart failure symptoms.

Patients with larger aortic roots also have a higher risk of heart failure, possibly as a result of concomitant remodeling of the ventricles and their blood vessels [20]. Higher aortic stiffness, as evaluated by pulse-wave velocity, is associated with an increased risk of cardiovascular disease and death overall, according to a new meta-analysis by **Vlachopoulous and colleagues** [21].

The studies have established a connection between clinical heart failure, aortic stiffness and death. As a result of these investigations, **Karagodin *et al.*** [9] set out to determine whether or not two imaging-based indices, aortic distensibility (AD) and aortic compliance (AFAC), might be used to monitor the impact of innovative medication therapy on aortic compliance. TTE-based measurement of vascular stiffness has the benefits of being more widely available, being less onerous for the patient and provider, and offering a great deal more diagnostic information, the most reliable non-invasive technique for this aim is the measurement of pulse-wave velocity. In light of these preliminary findings, further research is necessary. This proof-of-concept work opens the way for more research to be conducted to test this theory utilising additional non-invasive methods of assessing vascular compliance, such as velocity encoded magnetic resonance imaging and pulse-wave velocity.

Karagodin *et al.* [9] discovered only weak to moderate relationships between hypertension and AD and AFAC when using linear regression analyses. Most of these correlations can be considered to be statistically significant because their p-values are small. These results provide more evidence that changes in blood pressure, and more especially SBP, are not the primary predictor of aortic compliance. Vascular stiffness has a complex pathophysiology that is affected by a wide range of factors including, but not limited to, chronic renal disease, diabetes, microvascular illness, age, and environmental factors [11].

Therefore, the improvements in AD and AFAC seen in the research by **Karagodin *et al.*** [9] have contributed by the positive pleiotropic effects of sacubitril–valsartan on the vascular bed and overall hemodynamics.

CONCLUSION

The positive benefits of sacubitril–valsartan on AFAC and AD as evaluated by TTE are increasing gradually from baseline to six months. It is possible to calculate AD and AFAC from standard TTE measurements of ascending aortic diameters at end-systole and end-diastole, serving as physiologic indicators of medication influence on vascular function.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

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