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Sacubitril with valsartan, a modern pharmacotherapy in heart failure - a literature review

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Abstract

Introduction and purpose: Heart failure is one of the most common cardiovascular diseases worldwide. It is an important factor leading to a reduced, health-related quality of life (HRQoL) not only because of its various symptoms but also due to loss of jobs or increase in medical expenses impairing the socioeconomic status of the sick. Nowadays scientists face this problem and are trying to invent specific pharmacotherapy that allows it to extend life and improve its quality. One of the elements of modern pharmacotherapy is the combination of sacubitril with valsartan. This work aims to evaluate the effect of this drug on the length and quality of life of patients with heart failure.

Materials and methods: This article is a literature review based on publications from PubMed, Cochrane Library, ClinicalKey released since 2014, keywords included: sacubitril/valsartan; angiotensin receptor–neprilysin inhibitor; ARNI; heart failure.

The state of knowledge: The use of sacubitril/valsartan drugs is an established agent used to reduce the risk of death from any cause in all patients with heart failure with reduced ejection fraction, death from cardiovascular causes and the rate of hospitalization due to exacerbation of symptoms. Some study analyses also indicate the utility of using sacubitril/valsartan in HFmrEF and HFpEF to reduce the rate of cardiovascular events and hospitalization because of heart failure.

Conclusions: The use of sacubitril/valsartan is recognized to improve prognosis in patients with HFrEF. Evidence supporting its efficacy in the subgroup of patients with mid-range and preserved ejection fraction is still insufficient and requires further investigation.

Keywords: sacubitril/valsartan; angiotensin receptor–neprilysin inhibitor; ARNI; heart failure

Introduction

Heart failure (HF) is a condition in which the heart, as a pump, is unable to provide sufficient output relative to the body's demand. Main symptoms are dyspnoe, orthopnoe, weakness, fatigue, oedema, fainting and occur due to low cardiac output and retrograde stasis of blood in the venous system [1]. There are several different classifications of HF, the most important of which seems to be the classification proposed by the ESC in 2016 based on ejection fraction, in which we distinguish [2]:

a. Heart failure with reduced ejection fraction (HFrEF) – LVEF ≤40%
b. Heart failure with mid-range ejection fraction (HFmrEF) – LVEF 41-49%
c. Heart failure with preserved ejection fraction (HFpEF) – LVEF ≥50%

It is important to determine the type of disease due to different aetiology, treatment and prognosis.

Epidemiology

HF is a condition that is widespread around the world and it is estimated that in 2017 the number of patients exceeded 64 million [3]. The overall prevalence is increasing [3] while the age-adjusted incidence seems to be declining since the last decade, especially for HFrEF diagnosis [4]. This is due, in part, to medical advances in the treatment of ischemic heart disease, which is one of the main causes of HFrEF. However, we observe higher incidence for HFpEF [4] which right now stands for approximately 50% of total HF cases [5]. No similar decline has been observed in terms of mortality which remains almost constant [6]. Heart failure is a disease associated with a poor prognosis. Statistics data related to mortality vary depending on the source. In 2019 Jones et al. [7] conducted a meta-analysis of 60 studies including 1,5 million people with heart failure in total, estimating the following survival rate for all-type HF: 1 year – 87%, 2 years – 73%, 5 years – 57%, 10 years – 35%. Heart failure is a disease that affects people differently depending on their gender. Women with HF survive longer than men and have a lower risk of sudden death [8]. Data obtained from the United States from 2018-2020 show that the mortality rate per 100 000 is higher for male than female in the 35+ group (Figure 1). National rate for men is 220 while women's rate is 157. For this reason, especially men, should be given surveillance to actively seek and eliminate risk factors of heart failure.

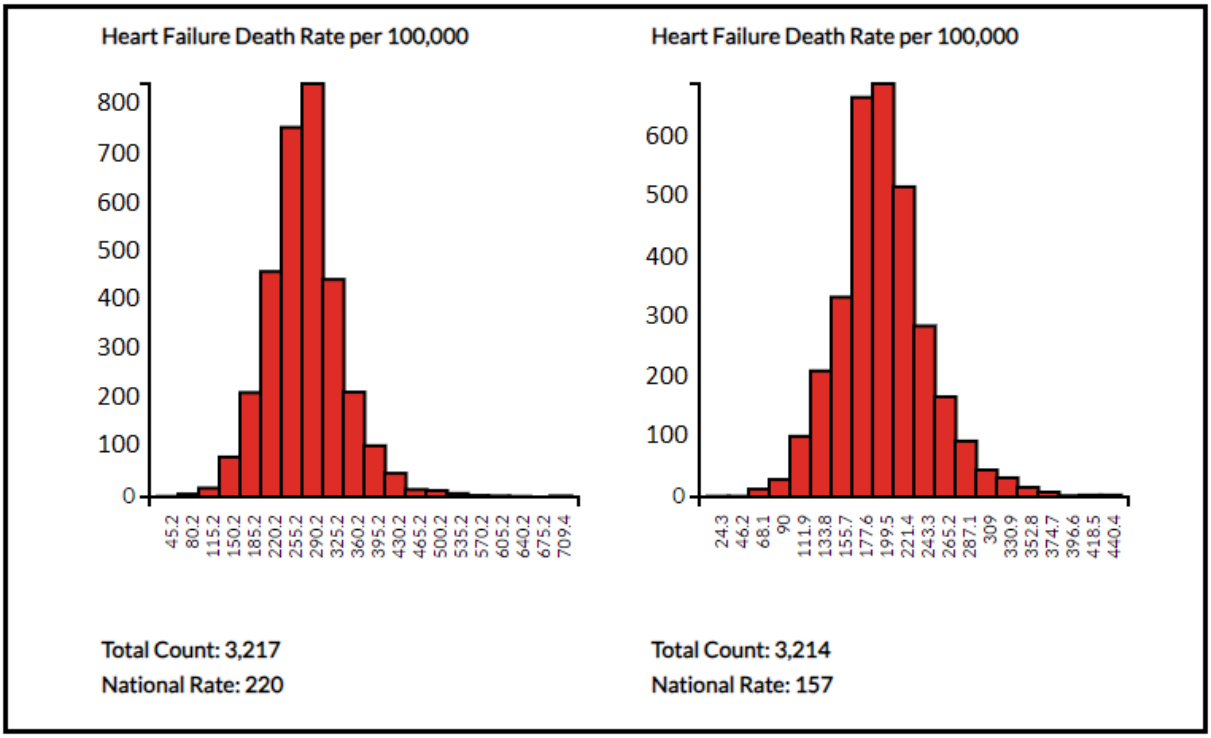

Figure 1. Age-adjusted average annual death rate per 100 000 citizens in United States from 2018-2020 for 35+ males (left) and females (right). Obtained from Interactive Atlas of Heart Disease and Stroke by Centers for Disease Control and Prevention.

Pathophysiology

Heart failure with reduced ejection fraction (HFrEF) typically arises following a primary incident that diminishes the heart's ability to pump blood effectively. This incident might manifest as an acute injury to the heart, such as a myocardial infarction, or it could gradually develop due to prolonged hemodynamic stress. Additionally, it might emerge in response to genetic mutations that impair the heart's contractile function. This causes a decrease in cardiac output, which leads to decompression of baroreceptors located peripherally in arteries and number of

compensatory mechanisms are activated. The compensatory mechanisms identified include the activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system. These systems work to uphold cardiac output by its positive chronotropic effect, enhancing salt and water retention or inducing hypertension [9]. Initially, these compensatory mechanisms effectively offset the decline in myocardial function. However, if chronically activated, they can result in pathological cardiac remodeling leading to its dysfunction, exacerbation of heart failure symptoms and contributing to the progressive decline in a patient's health. Upregulated neurohumoral systems initially induce favorable short-term adjustments, especially in the kidneys and heart to sustain cardiovascular homeostasis [10].

Angiotensin II is an intermediate product of the renin-angiotensin-aldosterone system (RAAS) activation. It induces various effects, such as smooth muscle contraction (especially in blood vessels, causing hypertension), local inflammation, fibrosis, and endothelial dysfunction. These changes are unfavorable in the long term and lead to transformations in the structure of cardiac muscle and vessels (remodeling), impairing their function [11].

Chronic stimulation of the sympathetic nervous system leads to a significant hemodynamic burden on the heart, resulting in compensatory hypertrophy of cardiomyocytes. We can distinguish two primary types of cardiac muscle hypertrophy: eccentric and concentric. In the first type (systolic dysfunction), the cause is volume overload, leading to hypertrophy of cardiomyocytes in length and ventricular dilation, without an increase in the thickness of the muscular layer. Eccentric hypertrophy typically occurs in HFrEF. In the second type (diastolic dysfunction), the cause is pressure overload, resulting in hypertrophy of cardiomyocytes in thickness, with an increase in the thickness of the muscular layer and a reduction in the volume of the heart ventricle. Concentric hypertrophy usually occurs in HFpEF [12].

ARNI mechanism in heart failure

ARNI is a novel form of pharmacotherapy used in the treatment of heart failure. It includes a combination of sacubitril and valsartan, an inhibitor of neprilysin, and an angiotensin II receptor antagonist. Neprilysin is a hormone involved in the degradation of molecules such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), angiotensin II and bradykinin. Inhibiting the activity of this hormone by sacubitril results, among other things, in an increase of ANP and BNP serum levels, leading to increased diuresis and sodium excretion, as well as the inhibition of the RAA axis, indirectly inhibiting heart and vessel remodeling and fibrosis. Neprilysin also exhibits a dual effect on arterial blood pressure values, as it simultaneously degrades molecules responsible for vasodilation and vasoconstriction. Hence, the use of sacubitril in combination with valsartan, an angiotensin II receptor antagonist, allows us to counteract the undesirable effects of angiotensin II, whose levels may rise due to neprilysin inhibition. These side effects include increased blood pressure, remodeling, and fibrosis [13]. Additionally, due to the increase in the concentration of bradykinin in the blood, combining sacubitril with ACE inhibitors, which also raise its serum level, is contraindicated. This would significantly increase the risk of adverse effects, such as angio-oedema [14].

ARNI compared to the standard ACEi in heart failure with reduced ejection fraction

In 2014, the PARADIGM-HF study was published, comparing the effectiveness of sacubitril/valsartan to the standard angiotensin-converting enzyme inhibitor, specifically enalapril, in patients with heart failure with reduced ejection fraction. The medications were administered twice daily at a dose of 200mg sacubitril/valsartan and 10 mg enalapril [15]. Compared to enalapril, sacubitril/valsartan resulted in a 20% lower occurrence of cardiovascular death or hospitalization for heart failure and led to a 16% decrease in overall mortality [16]. The results of this study proved to be very promising and led to a better understanding of the fundamentals of heart failure treatment. Blocking chronically activated neurohormonal pathways like RAAS and SNS has become essential in treating chronic HFrEF. Furthermore, leveraging the positive impacts of natriuretic peptides on cardiovascular function in heart failure could offer added advantages to patients when used in conjunction with RAAS and SNS inhibition therapies. Sacubitril/valsartan introduces a new approach to pharmacotherapy by amplifying the natriuretic peptide system through neprilysin inhibition and by concurrently suppressing the RAAS through AT1 receptor antagonism. This dual mechanism enables more comprehensive neurohormonal modulation compared to the effects achievable through RAAS inhibition alone [17].

ARNI in heart failure with mildly reduced and preserved ejection fraction

In the PARAMOUNT trial, 301 patients diagnosed with HFpEF were randomly assigned to receive either valsartan alone or sacubitril/valsartan. During this study, the sacubitril/valsartan group experienced a decrease in the concentration of NT-proBNP, along with reductions in heart failure exacerbation based on the NYHA scale and decreases in LAV (left atrial volume) [18]. Another extensive trial PARAGON-HF sacubitril/valsartan to valsartan in HFpEF were compared. The outcomes indicated a slightly lower, but not statistically significant, frequency of overall hospitalizations due to heart failure (decline 13%; RR 0.85; 95% CI 0.72 to 1.00) and cardiovascular-

related deaths (decline 4%; HR 0.95; 95% CI 0.79 to 1.16) among individuals with heart failure and an LVEF ≥ 45% [19]. In 2023, the results of another large study - PARAGLIDE-HF - were published. It is a study where patients with LVEF >40%, who experienced worsening heart failure (HFpEF decompensation) within 30 days, were enrolled and randomly assigned to receive either sacubitril/valsartan or valsartan alone in a double-blind, randomized controlled trial. The study involved 466 patients, half of whom received ARNI, and the other half received valsartan alone. The primary endpoints included the change in NT-proBNP levels from baseline to weeks 4 and 8. A statistically significant result was obtained, confirming a greater decrease in NT-proBNP serum levels in the sacubitril/valsartan-treated group (ROC 0.85; 95% CI 0.73 to 0.999; p = 0.049) [20]. Despite the PARAGLIDE-HF trial indicated a decrease in its primary measure and recognized potential advantages in a hierarchical clinical composite, it was not designed to study clinical outcomes. In 2023, Vaduganathan et al. conducted a combined analysis of data from both the PARAGLIDE-HF and PARAGON-HF studies to assess the efficacy and safety of sacubitril/valsartan in reducing cardiovascular and renal events in heart failure with mildly reduced or preserved ejection fraction. By identifying a subset of participants from the PARAGON-HF study who met the criteria of the PARAGLIDE-HF study, they were able to perform an integrated analysis. The findings revealed that sacubitril/valsartan led to a significant reduction in cardiovascular and renal events among patients with heart failure exhibiting mildly reduced or preserved ejection fraction, suggesting its potential benefits for individuals with HFmrEF/HFpEF [21].
Despite positive premises confirming the effectiveness of ARNI use in patients with mildly reduced and preserved ejection fraction, further high-quality studies are still needed to unequivocally determine the impact of this drug in that specific subgroup of patients.

Health-Related Quality of Life (HRQoL) among patients treated with ARNI

Patients experiencing heart failure face a notable decline in their health-related quality of life (HRQoL) compared to individuals with other chronic ailments, manifesting substantial limitations in physical and social activities [22]. In the PARADIGM-HF trial, patients filled out the Kansas City Cardiomyopathy Questionnaire (KCCQ) at the time of randomization, as well as during the 4-month and 8-month follow-up assessments. Of the 8399 patients enrolled, 7623 filled out KCCQ scores at randomization, with complete data available at the 8-month mark for 6881 patients (90% of the baseline). At the 8-month follow-up, the sacubitril/valsartan group showed improvements in both the KCCQ clinical summary score (+0.64 vs -0.29; p=0.008) and the KCCQ overall summary score (+1.13 vs -0.14; p<0.001) compared to those treated with enarapril. These results indicate that sacubitril/valsartan leads to enhanced HRQoL among patients with HF [23].

ARNI as an element of comprehensive therapy in HFrEF

In 2021, Yuling et al. conducted a meta-analysis of 6 different clinical trials comparing the efficacy of flozins and sacubitril/valsartan in patients with HFrEF. One aspect of their work was to compare the efficacy of sacubitril/valsartan used concurrently with SGLT2 inhibitors (flozins) and sacubitril/valsartan alone in monotherapy for patients with heart failure with reduced ejection fraction. The primary endpoint was cardiovascular death or hospitalization due to the heart failure. The results from the DAPA-HF study did not show a statistically significant advantage of combination therapy over monotherapy (HR 0.75; 95% CI 0.5 to 1.13) in terms of the primary endpoint. However, the second study, EMPEROR-HF, did demonstrate such a relationship, which was statistically significant (HR 0.64; 95% CI 0.46 to 0.90). The pooled analysis of both trials also showed a statistically significant advantage of combination therapy over monotherapy in reducing the risk of cardiovascular death or hospitalization due to the heart failure (HR 0.68; 95% CI 0.53 to 0.89) [24].
In 2020, Vaduganathan et al. also tackled a similar issue, aiming to determine whether „comprehensive disease-modifying pharmacological therapy", including additional SGLT2 inhibitors + ARNI + MRA, had an advantage over standard therapy consisting only of ACEI/ARB + BB (β1-blockers) in HFrEF. Three clinical trials were analyzed: EMPHASIS-HF, PARADIGM-HF, and DAPA-HF (total n=15,880). The primary endpoint was also cardiovascular death or hospitalization due to the heart failure. The results obtained unequivocally indicated the superiority of „comprehensive disease-modifying pharmacological therapy" over the standard one. The hazard ratio (HR) for the primary endpoint was 0.38 (95% CI 0.3 to 0.47), while for all-cause mortality, it was 0.53 (95% CI 0.4 to 0.7) [25]. These results support the combination of ARNI with SGLT2 inhibitors and MRA in HFrEF therapy.

Effect of ARNI on cardiac reverse remodeling

In 2019, Wang and colleagues from Xuzhou Medical University carried out a meta-analysis involving 20 studies published between 2010 and 2019 (with a total of 10,175 participants) to explore cardiac reverse remodeling (CRR) indices subsequent to ARNI administration. Their results indicated that ARNI surpassed ACEI/ARB in terms of cardiac reverse remodeling (CRR) indices, showing notable changes in left ventricular ejection fraction (LVEF), diameter and volume in patients with heart failure with reduced ejection fraction (HFrEF). However, except for left ventricular mass index (MD -3.25 g/m2, 95% CI -3.78 to -2.72) and left atrial volume (MD -7.20 mL, 95% CI

-14.11 to -0.29) in HFpEF, there were no notable improvements in indices. The alterations observed in the echocardiogram were mirrored in the clinical presentation. ARNI enhanced the functional ability of individuals with HFrEF, as evidenced by improvements in NYHA functional class (MD -0.79, 95% CI -0.86 to -0.71) and the distance covered in the 6-minute walk test (MD 27.62 m, 95% CI 15.76 to 39.48) [26].
Two years later, Bao et al., from the same university, conducted a subsequent meta-analysis. This analysis involved examining 55 different randomized clinical trials spanning from 1989 to 2019 (total n=12,727). It focused on combination pharmacotherapies for cardiac reverse remodeling in HFrEF. The findings were consistent with those of the previous meta-analysis but provided additional insights into specific drug combinations used in heart failure with reduced ejection fraction. The combination of ARNI+BB+MRA exhibited superior efficacy compared to ACEI+BB+MRA or ARB+BB+MRA. It was proven to be the most effective in enhancing cardiac reverse remodeling, improving serum biomarkers, echocardiographic parameters, and clinical status as evaluated by the NYHA scale and 6-minute walking distance (6MWD) [27].
In another study, 336 elderly individuals diagnosed with HFrEF (with an average age of 69.8 years), underwent an evaluation of echocardiographic parameters both prior to initiating ARNI treatment and after a span of 6 months. Substantial enhancement was observed, particularly in LVEF (48.49% to 39.07%, $p<0.01$) [28].
This is not an isolated example, in another study involving 93 patients from Taiwan, the mean LVEF improved from 35 ± 6.1% to 50 ± 8.8% after 6 months of sacubitril/valsartan treatment ($p<0.001$) [29]. ARNI not only improves echocardiographic parameters but also reduces blood biomarkers, particularly NT-proBNP. Yamamoto et al. demonstrated that the median concentration decreased from 250 pg/mL to 146 pg/mL after 6 months of therapy ($p < 0.001$) [30].

Summary

Heart failure is a serious life-threatening condition that poses a significant problem in our society and requires special attention. Patients not only experience severe symptoms that diminish their quality of life but also become socially isolated and often require long-term rehabilitation and assistance from caregivers, especially in advanced stages. In this article, by gathering and analyzing a series of high-quality articles and studies, we have presented the medical response to this problem. We have demonstrated that ARNI, as a modern therapy for heart failure, can prolong the lives of patients and improve their quality of life by reducing symptom severity. We have also shown the superiority of ARNI over conventional therapy in heart failure with reduced ejection fraction. There is also evidence indicating significant improvement among patients with mid-range and preserved ejection fraction; however, this is still insufficient to conclusively determine their impact in this subgroup of patients. This is an area that future research should particularly focus on, because despite the current equal distribution between reduced and preserved ejection fraction, we are likely to see a further significant increase in the prevalence of HFpEF in the near future.

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