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Angiotensin receptor blocker-neprilysin inhibitor for heart failure with reduced ejection fraction

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ABSTRACT

Heart failure with reduced ejection fraction (HFrEF) is a clinical syndrome characterized by volume overload, impaired exercise capacity, and recurrent hospital admissions. A major contributor to the pathophysiology and clinical presentation of heart failure is the activation of the renin-angiotensin-aldosterone system (RAAS). Normally, RAAS is responsible for the homeostatic regulation of blood pressure, extracellular fluid volume, and serum sodium concentration. In HFrEF, RAAS gets chronically activated in response to decreased cardiac output, further aggravating the congestion and cardiotoxic effects. Hence, inhibition of RAAS is a major approach in the pharmacologic treatment of those patients. The most recently introduced RAAS antagonizing medication class is angiotensin receptor blocker/ neprilysin inhibitor (ARNI). In this paper, we discuss ARNIs' superiority over traditional RAAS antagonizing agents in reducing heart failure hospitalization and mortality. We also tease out the evidence that shows ARNIs' renoprotective functions in heart failure patients including those with chronic or end stage kidney disease. We also discuss the evidence showing the added benefit resulting from combining ARNIs with a sodium-glucose cotransporter-2 (SGLT-2) inhibitor. Moreover, how ARNIs decrease the risk of arrhythmias and reverse cardiac remodeling, ultimately lowering the risk of cardiovascular death, is also discussed. We then present the positive outcome of ARNIs' use in patients with diabetes mellitus and those recovering from acute decompensated heart failure. ARNIs' side effects are also appreciated and discussed. Taken together, the provided insight and critical appraisal of the evidence justifies and supports the implementation of ARNIs in the guidelines for the treatment of HFrEF.

1. Introduction

Cardiovascular disease (CVD) comprises a range of conditions affecting the heart and vasculature, including but not limited to coronary heart disease, peripheral arterial disease, and heart failure [1]. CVD remains the leading cause of global death and a major cause of health loss worldwide [2,3]. Heart failure (HF) is a complex clinical syndrome characterized by hypoperfusion secondary to insufficient

Abbreviations: HFrEF, heart failure with reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system; ARNI, angiotensin receptor blocker/ neprilysin inhibitor; SGLT-2, sodium-glucose cotransporter-2; CVD, cardiovascular disease; HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, Heart failure with reduced ejection fraction; HFimEF, heart failure with improved ejection fraction; HFmrEF, heart failure mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association; SNS, sympathetic nervous system; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; AT_1, angiotensin II receptor type 1; AT_2, angiotensin II receptor type 2; ENaC, epithelial sodium channels; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; CGMP, cyclic guanosine monophosphate; SBP, systolic blood pressure; CKD, Chronic kidney disease; EGFR, estimated glomerular filtration rates; ATN, acute tubular necrosis; SCD, sudden cardiovascular death; OR, odds ratio; NT-proBNP, N-terminal prohormone of BNP; EF, ejection fraction; CRR, cardiac reverse remodeling; BMI, body mass index; ADHF, acute decompensated heart failure; ACCF/AHA, American College of Cardiology Foundation/American Heart Association; AHA/ACC/HFSA, American Heart Association/ American College of Cardiology/ Heart Failure Society of America; QALY, quality-adjusted life-year; ESC, European Society of Cardiology.

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cardiac output. The inadequate cardiac output is caused by either systolic or diastolic dysfunction or both together [4–6]. The burden of HF on healthcare systems is continuously increasing, driven by a rising prevalence that is expected to further escalate in the future [4,6]. In 2020, among individuals aged 20 and above, the prevalence was approximately 6.7 million in the United States, and it is expected to further increase to 8.5 million by 2030 [7]. This rise in HF prevalence can be attributed to several factors including increased life expectancy, enhanced cardiovascular disease survival rates, and greater populations at risk. The common risk factors for HF are primarily obesity, diabetes mellitus, and hypertension [8]. In addition, a typical coexistence of additional risk factors is reported. These include atherosclerosis, smoking, metabolic syndrome, hypercholesteremia, arrhythmias, congenital heart defects, connective tissue disorders, viral infections, cardiotoxic drug usage, and family history [8,9].

HF is primarily classified based on the left ventricular ejection fraction (LVEF). Heart failure with reduced ejection fraction (HFrEF), or systolic HF, is characterized by LVEF of $\leq$40%, caused by decreased left ventricular contractility. This reduced LVEF results in volume overload which induces eccentric remodeling and subsequent chamber dilatation. HFrEF patients who improve clinically with an increase in ejection fraction above 40% are classified as heart failure with improved ejection fraction (HFimEF) [4,9]. HF cases with an initial LVEF between 40% and 50% are said to have mid-range or mildly reduced ejection fraction (HFmrEF) [10]. Heart failure with preserved ejection fraction (HFpEF), sometimes referred to as diastolic HF, is associated with reduced left ventricular compliance and filling, leading to pressure overload and concentric hypertrophy, while maintaining a LVEF of $\geq$50% [11,12].

The New York Heart Association (NYHA) functionally classifies symptomatic and advanced HF into four stages, each encompassing patients with a confirmed HF diagnosis [4]. In Class I, individuals experience no limitations in physical activity and exhibit no symptoms such as fatigue, shortness of breath, or palpitations during mild physical activity. Class II patients experience these symptoms with ordinary physical activity, resulting in mild limitations though they remain comfortable at rest. Class III individuals, while comfortable at rest, encounter significant physical limitations due to symptoms arising with less than ordinary physical activity. The last class, Class IV, involves severe limitations in physical activity and discomfort at rest. These patients are usually said to be bedbound [13].

During the course of HFrEF, multiple compensatory mechanisms are activated in response to the hemodynamic changes. The neurohormonal model explains a fundamental compensatory mechanism in HF wherein two systems, the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), become activated [14]. However, these compensatory homeostatic responses in the initial phase of HF will later lead to deleterious effects on hemodynamic stability and cardiac function. This is because such responses will increase both preload, the degree of end-diastolic cardiomyocyte stretch, and afterload, the resistance against ventricular blood ejection. Consequently, this combined increase in preload and afterload amplifies the cardiac workload, further exacerbating the left ventricular dysfunction [5,15].

Based on the aforementioned pathophysiological mechanisms, the cornerstone of the pharmacological management of HFrEF involves the inhibition of these neurohormonal systems. This is of particular significance because chronic activation of RAAS/SNS contributes to the deterioration in HF along with the manifestation of the associated clinical signs and symptoms [16]. First-line therapy for HFrEF includes angiotensin-converting enzyme inhibitors (ACEi), angiotensin (II) receptor blockers (ARB), and angiotensin receptor-neprilysin inhibitors (ARNI) [4]. ARNI, being the most recently implemented drug class in clinical practice, has introduced a significant shift in the pharmacological mechanism in managing HF [17]. This review explores the physiology of RAAS, with emphasis on the pathophysiology of HF, and further delves into the role of ARNIs in the management of HF, particularly HFrEF.

2. RAAS under physiological conditions

The homeostatic regulation of blood pressure, extracellular fluid volume, and serum sodium concentration is a complex constellation of events that are orchestrated by the renal and cardiovascular systems [18]. A pivotal system responsible for this regulation is the RAAS [19]. Under physiological conditions, RAAS is activated in response to poor renal perfusion secondary to decreased cardiac output [9,15,20]. This decline in renal perfusion is sensed by baroreceptors in the renal afferent arterioles, which in turn stimulate the secretion of renin from juxtaglomerular cells. Renin release is further stimulated by the macula densa of the distal tubule in response to decreased tubular sodium concentration [20–22].

Renin, a protease, converts angiotensinogen to angiotensin I, which is the first and rate-limiting step in the RAAS cascade [19,23]. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE), primarily located in the pulmonary capillary endothelium. However, ACE is also expressed in the kidneys and vasculature throughout the body, allowing for a local production of angiotensin II [18,19,22]. Angiotensin II serves as the primary active metabolite and mediates diverse effects on various organs and tissues [18]. It exerts its effect by binding to its receptors, angiotensin type 1 (AT_1) and angiotensin type 2 (AT_2), which produce opposing effects [24]. AT_1 is responsible for the traditional effects of RAAS including systemic arterial and renal arteriolar vasoconstriction, renal tubular sodium and water, pro-inflammatory processes, and cellular proliferation [15,19,22]. The AT_1-mediated increase in intravascular volume and systemic resistance plays a key role in maintaining hemodynamic homeostasis [18]. On the other hand, the function of AT_2 is not clearly understood, but it has been suggested to have a role in anti-fibrosis and vasodilation [25,26]. The normal ratio of AT_2 to AT_1 in cardiomyocytes is 2:1; yet it is interesting to note that there is a maladaptive increase in AT_1 expression within the setting of HF [24,27].

Another important function of angiotensin II signaling through AT_1 is the production of aldosterone from the adrenal cortex. Aldosterone is a mineralocorticoid that further regulates sodium balance by signaling through mineralocorticoid receptors to upregulate epithelial sodium channels (ENaC) in the late renal distal tubule and collecting ducts [19,24,28,29]. Mineralocorticoid receptors are also expressed on other sites including cardiomyocytes, vascular smooth muscle cells, endothelial cells, and neuronal cells. The effects of aldosterone in these sites become more significant when there is excess aldosterone production in pathological conditions [30].

The renal and vascular effects of RAAS are opposed by natriuretic peptides which include atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [27]. ANP is a counterregulatory peptide released from the atria in response to atrial stretch resulting from elevated atrial intramural pressure or increased intravascular volume [20,31]. As the name indicates, ANP inhibits sodium reabsorption, thereby promoting natriuresis and diuresis in the renal medullary collecting tubules [1,31]. This effect is enhanced by ANP's ability to suppress renin release, thereby inhibiting RAAS-mediated sodium reabsorption [31,32]. ANP also causes systemic vasodilation and increases vascular permeability which aids in reducing blood pressure [31,33]. BNP exhibits effects similar to ANP but is released in response to ventricular stretch rather than atrial stretch [34]. It is also suggested that BNP exerts an additional cardioprotective effect by virtue of its ability to abrogate myocardial apoptosis and fibrosis [35]. Both ANP and BNP serve as biomarkers for cardiac function with ANP reflecting atrial pressure and BNP representing ventricular overload [34]. This can be utilized for various diagnostic purposes, such as classifying HF, assessing its severity, and determining the prognosis of HF patients [34,36].

Natriuretic peptides function through three different natriuretic peptide receptors, NPR-A, NPR-B, and NPR-C [1]. While NPR-A and NPR-B elicit for the aforementioned effects through the cyclic guanosine

monophosphate (cGMP) secondary messenger system, NPR-C is a "clearance receptor" that clears natriuretic peptides from the systemic circulation by internalization and lysosomal degradation [1,20,24,27]. Natriuretic peptides can also be broken down by neprilysin, a zinc-dependent type II integral membrane metalloprotease, which also metabolizes other substances like bradykinin, angiotensin II, and amyloid-β. Neprilysin is a highly abundant enzyme primarily expressed in the proximal renal tubules, as well as other sites like cardiomyocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, and neuronal cells [31].

3. Pharmacological targets

In the early stages of HF, neurohormonal activation attempts to maintain the perfusion to vital organs. However, chronic activation of these compensatory mechanisms leads to vascular and cardiac remodeling, inappropriate increases in preload and afterload, cardiomyocyte apoptosis, and oxidative stress [37,38] (Fig. 1). The fastest adaptive mechanism in HF is SNS activation, initiated in response to decreased baroreceptors activation in the carotid sinus and aortic arch [9]. Chronic elevation of catecholamines results in downregulation of myocardial β-adrenergic receptors, further contributing to the deterioration of ventricular contractility. Prolonged activation of SNS could also cause tachycardia and arrhythmias, potentially increasing the risk of sudden cardiac death [8]. Additionally, the persistent activation of RAAS contributes to the cardiotoxic effects seen in HF through several mechanisms. This includes the upregulation of mineralocorticoid receptors and elevation aldosterone levels [39]. Indeed, the subsequent increase in aldosterone signaling results in myocardial inflammation, vascular remodeling, and interstitial fibrosis, thereby exacerbating the deterioration in cardiac function [40,41]. Another mechanism implicated in these cardiotoxic effects is the upregulation of AT_1 receptors which further aggravates myocardial fibrosis by inducing fibroblast hypertrophy and collagen deposition [42]. Importantly, these cardiotoxic effects of RAAS predominate as the cardiac and renal protective effects of ANP gradually diminish [10,43]. Taken together, these events result in ventricular remodeling that is characteristic of HFrEF [44].

Given these deleterious effects of chronic RAAS activation, pharmacologic therapy has been extensively studied to block this axis in an attempt to improve cardiovascular morbidity and mortality [4]. These therapies include renin inhibitors, ACEi, ARB, ARNI, and mineralocorticoid receptor antagonists [19] (Fig. 1). The first class introduced into clinical practice was ACE inhibitors, which blunt ACE-mediated production of angiotensin II [45]. ARBs, on the other hand, block the actions of angiotensin II by competitively binding to its AT_1 receptors [24]. Additionally, given natriuretic peptides' cardioprotective effects, the effectiveness of neprilysin inhibitors was tested for the management of HF and hypertension [38]. However, neprilysin inhibitor monotherapy was found to be ineffective [46]. Therefore, neprilysin inhibitors were combined with other classes of drugs to investigate whether they had an

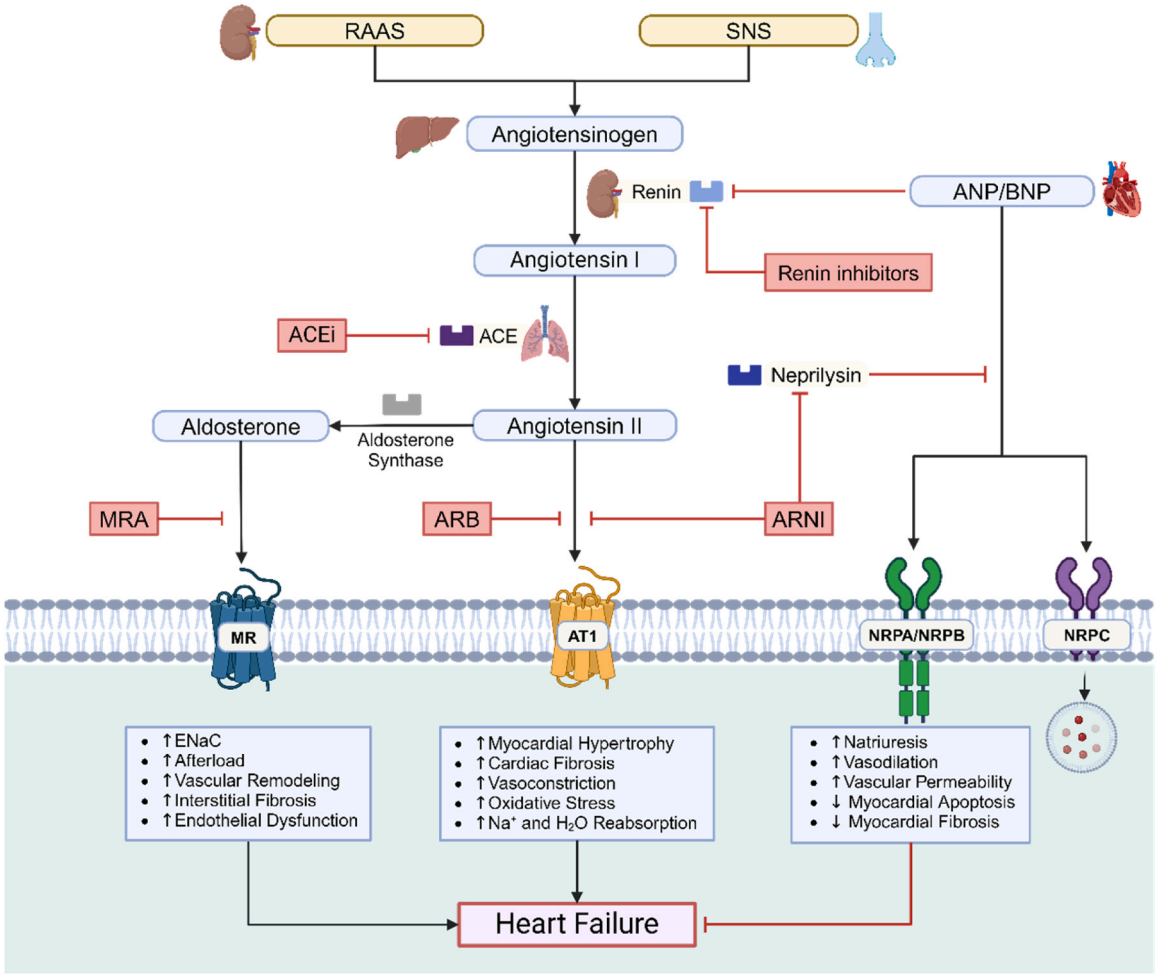

Fig. 1. Neurohormonal activation in HF: Chronic RAAS and SNS activation contributes to detrimental effects on cardiac and renal functions by increased signaling through AT_1 and MR. This is counteracted, to a certain extent, by the effect of cardiac NP, signaling through NPRA/ NPRB. Inhibition of RAAS presents a viable therapeutic strategy, achievable by targeting various key components along the cascade of RAAS. Elevating levels of NP through neprilysin inhibition is another therapeutic target of HF. (Created with Biorender.com).

added therapeutic effect. Notably, omapatrilat, a dual neprilysin and ACE inhibitor, was evaluated in multiple clinical trials for the treatment of hypertension and HF [47–49]. However, omapatrilat was never employed in clinical practice as it was found to be associated with an increased risk of angioedema. This was explained by omapatrilat's dual inhibition of ACE and neprilysin, both of which catabolize bradykinin, a potent vasodilator. Hence, omapatrilat prompted bradykinin accumulation, increasing the incidence of angioedema [38,47,49].

The increased risk of angioedema in the combined regimen of ACEi with neprilysin inhibitor triggered the development of a new class of drugs namely ARNIs, a combination of an ARB and neprilysin inhibitor [38]. Sacubitril/valsartan is a first-in-class drug that was compared to enalapril (ACEi) in the PARADIGM-HF double-blind randomized clinical trial [50]. Sacubitril/valsartan was found to be superior to enalapril resulting in a 20% reduction in HF hospitalization or cardiovascular death in patients with HFrEF, which was the primary outcome of the trial [51]. Results also showed that sacubitril/valsartan was well tolerated and was associated with a lower incidence of cough, elevated creatinine ($\geq$2.5 mg/dL), and elevated potassium (>6 mmol/L) as compared to enalapril. Unlike ACEi/neprilysin inhibitor, no cases of angioedema with compromised airway were documented with ARNIs [51]. Sacubitril/valsartan was associated with a higher incidence of symptomatic hypotension as compared to enalapril, but rarely resulted in treatment withdrawal [51]. The results of PARADIGM-HF granted sacubitril/valsartan the approval to be prescribed for patients who met the inclusion criteria of the trial and was implemented in clinical practice thereafter [38].

The occurrence of ARNI-induced symptomatic hypotension in the PARADIGM-HF trial triggered an investigation into the efficacy of ARNIs in lowering blood pressure among patients with hypertension. Sacubitril/valsartan significantly reduced systolic blood pressure (SBP) compared to valsartan in HFpEF patients with apparent resistant hypertension [52]. When compared to olmesartan, sacubitril/valsartan resulted in significant decrease in mean ambulatory systolic and diastolic blood pressures in patients with essential hypertension [53]. These results suggest that ARNIs can be potentially used in the management of hypertension [54]. This antihypertensive effect is postulated to result from sacubitril's inhibition of the breakdown of ANP by neprilysin, thereby allowing ANP to accumulate and exert its beneficial effects, namely, natriuresis and vasodilation [54–56]. Moreover, ANP, through the activation of phosphokinase G cGMP-dependent, stimulates the production of nitric oxide, a gasotransmitter known for its vasodilatory effect [57]. Another suggested explanation is that ARNIs cause the accumulation of angiotensin II by inhibiting neprilysin while simultaneously blocking AT_1. This promotes the binding of angiotensin II to AT_2, which exerts vasodilatory effects [58]. These effects collectively manifest as anti-inflammatory, antifibrotic, and antihypertrophic over time [57].

4. ARNIs and cardio-renal function

Chronic kidney disease (CKD) and HF often coexist, with each condition capable of being both a cause and a consequence of the other. Patients with HF can develop CKD due to hemodynamic and neurohormonal processes. This can be ascribed to renal congestion resulting from increased water and sodium retention, secondary to the decreased cardiac output [59,60]. Conversely, CKD can contribute to HF by inducing low-grade systemic inflammation that could trigger cardiac remodeling [61]. Regardless of the direction of causality, studies have demonstrated that the use of ARNIs in such populations improves cardiac and renal function, including patients with concurrent HFrEF and end stage kidney disease [62–68]. A meta-analysis of RCTs comparing sacubitril/valsartan to irbesartan (ARB), valsartan (ARB), and enalapril (ACEi) in patients with HF and CKD concluded that, besides the significant cardiac benefits of sacubitril/valsartan, it was also associated with significantly higher estimated glomerular filtration rates (eGFR) compared to ACEi/ARBs. However, sacubitril/valsartan did not cause a significant reduction in urinary albumin/creatinine ratio when compared to ACEi/ARB [66]. Contextually, sacubitril/valsartan can cause slower decrease in eGFR than ACEi/ARB in patients with HFpEF and CKD [69]. Hence, all of the above suggests that ARNIs elicit renoprotective effects in patients with concurrent HF and CKD [70].

The cardiorenal protective effects of ARNIs transcend the population of HF patient with CKD, encompassing the entire spectrum of HF patients. These beneficial effects of ARNIs were initially reported in the PARADIGM-HF trial and were subsequently corroborated by other studies [71–74]. Indeed, it was recently shown that ARNIs are associated with a significantly decreased risk of renal dysfunction and significantly higher eGFRs as compared to ACEi/ARB [73]. These observations can be attributed to the integrated improvement of cardiac and renal functions caused by ARNIs (Fig. 2). The enhancement in cardiac function leads to an increase in renal perfusion, collectively reducing the activation of RAAS, thereby alleviating the symptoms of HF [75].

Interestingly, enhanced renal function was observed when combining ARNIs with SGLT-2 inhibitors, which are primarily hypoglycemic agents with antihypertensive, renoprotective, and cardioprotective functions [76,77]. A meta-analysis showed a 32% reduction in deterioration of renal function when using a combination of ARNI with SGLT-2 inhibitor compared to either ARNI or SGLT-2 inhibitor monotherapy [77]. This combination was also found to significantly reduce the rates of hospitalization and cardiovascular death in multiple other studies [77–79]. However, it was noted that volume depletion was an adverse effect of this combination, warranting further investigations [77]. In another study, only early initiation ($\leq$ 14 days) of the ARNI/SGLT-2 inhibitor combination resulted in improved left ventricular remodeling and systolic function, characterized by a significantly lower left ventricular end systolic volume compared to the late combination (> 14 days) [80]. It is hypothesized that the cardiorenal protective effects of SGLT-2 inhibitors stems from their ability to cause glycosuria and natriuresis, inducing diuresis, alongside with ARNIs (Fig. 3)[81].

It is worth mentioning that a case reported on a patient who developed acute tubular necrosis (ATN) after initiating treatment with sacubitril/valsartan [82]. This acute kidney injury might have been due to the medication-induced hypotension. It is possible that this was further aggravated by the patient's anemia, which could have worsened the oxygen demand-supply mismatch [82]. Therefore, such complication underscores the necessity to monitor for hypotension, given the mounting evidence from observational studies and clinical trials associating ARNIs with an increased risk of hypotension compared to ACEi/ARBs [74,82–87].

5. ARNIs and cardiovascular death

Consistent with the PARADIGM-HF findings, several meta-analyses have reported significant reductions in the rates of cardiovascular death as well as all-cause mortality when using ARNIs compared to ACEi/ARBs [86,87]. One of the major causes of sudden cardiovascular death (SCD) in HF patients is arrhythmias, including ventricular tachycardia, ventricular fibrillation, and bradyarrhythmia [88]. This can be secondary to cardiac remodeling that occurs in the setting of HFrEF [89]. Cardiac remodeling is defined as a set of molecular, cellular, and interstitial alterations that take place in response to cardiac injury. Subsequently, these changes manifest as gross changes in heart's size, shape, and function [90]. This remodeling alters the distribution of ion channels in cardiomyocytes, resulting in heterogeneous prolongation in the durations of action potentials, thereby precipitating arrhythmias [89,91]. Therefore, reversing cardiac remodeling can prevent arrhythmias and decrease the incidence of SCD [89]. ARNIs appear to be superior to ACEi/ARBs in ameliorating both of these events. This may then explain the resultant reduction in cardiovascular death associated with ARNIs. Likewise, it was recently reported that compared with

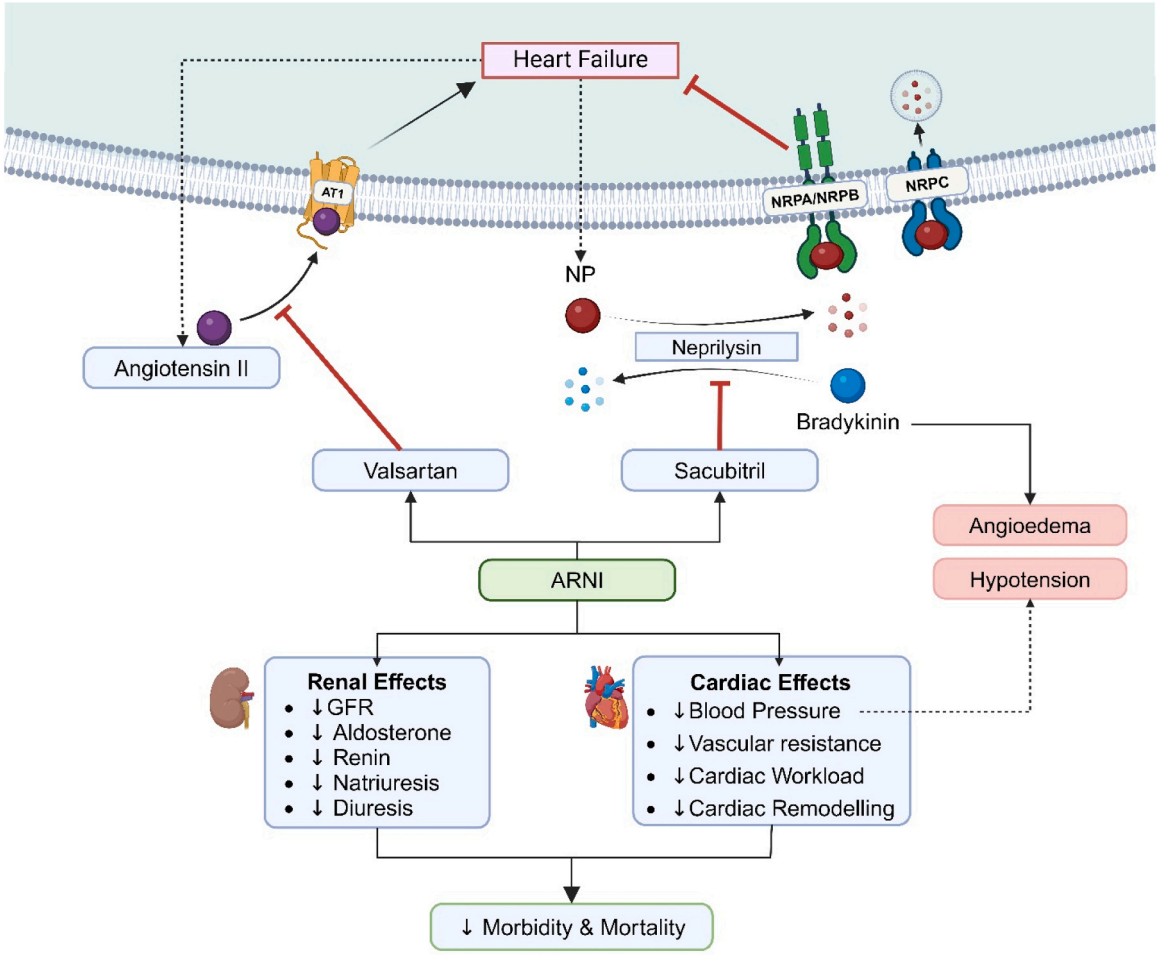

Fig. 2. Pharmacological effects of ARNIs: Neprilysin normally breaks down natriuretic peptides (NP), rendering them inactive. ARNIs' dual inhibition of AT_1 and neprilysin exerts beneficial effects on both the heart and the kidneys, collectively reducing the rates of HF-related morbidity and mortality. Angioedema, resulting from bradykinin accumulation, and hypotension are potential side effects of ARNIs that might limit their use in high-risk populations. (Created with Biorender.com).

ACEi/ARBs, ARNIs exert a significant decrease in SCD and ventricular arrhythmias with an odds ratio (OR) of 0.71 (p=0.01) [92]. This is supported by another meta-analysis which showed that ARNIs resulted in a 22% reduction in ventricular arrhythmias [93].

The effect of ARNIs on cardiac remodeling has been a subject of much interest and intensive research. Compared to valsartan, sacubitril/valsartan elicited a 26% greater reduction in the levels of N-terminal prohormone of BNP (NT-proBNP), a marker of HF. It was also observed that there was an 8.2% increase in ejection fraction (EF) in the treatment group compared to a modest 3.8% increase in patients receiving Valsartan [94]. Notably, the sacubitril/valsartan group had significant improvements in exercise tolerance evidenced by a 20% increase in the distance covered during a 6-minute walk test, as compared to an 11% increase in the valsartan group [94]. All these findings point towards the role of ARNIs in significantly reversing cardiac remodeling. This is consistent with results of a meta-analysis which proved that ARNIs outperformed ACEi/ARBs by measuring several cardiac reverse remodeling (CRR) indices, such as LVEF, diameter, and volume [95].

6. ARNIs in special populations

The effect of sacubitril/valsartan was investigated in multiple subsets of patients with HFrEF, such as diabetic patients, hospitalized individuals, and those undergoing long-term treatment.

6.1. Concomitant HFrEF and diabetes mellitus

In a post-hoc analysis of the PARADIGM-HF findings, diabetic patients with $HbA_{1c} \geq 6.5\%$ at baseline were selected and randomized to monitor changes in their levels of HbA_{1c} after taking either sacubitril/valsartan or enalapril [96]. A significantly higher reduction in HbA_{1c} levels was observed in patients taking sacubitril/valsartan compared to enalapril (p=0.0023) during the first year of follow-up. A similar trend was also observed over the three-year follow-up period (p=0.0055) [96]. These results imply that sacubitril/valsartan could potentially improve glycemic control in patients with concomitant HFrEF and diabetes [96]. It is worth noting that this was also observed in a case report describing a type 2 diabetes mellitus patient taking subcutaneous insulin injections who was started on sacubitril/valsartan. A year after treatment initiation, a progressive reduction in insulin requirements was noted as the patient had increased episodes of postprandial hypoglycemia [97]. The fact that there was no concurrent background therapy or clinical worsening of body mass index (BMI) and eGFR further supports the notion that the decrease in insulin requirement was due to sacubitril/valsartan [97].

The efficacy of sacubitril/valsartan in reversing cardiac remodeling in patients with diabetes mellitus is a subject of ongoing research. On one hand, it has been observed that sacubitril/valsartan has comparable LVEF improvement in HFrEF patients with and without diabetes mellitus [98]. On the other hand, sacubitril/valsartan has been shown to have some drawbacks in diabetic patients with concomitant HFrEF. A cohort

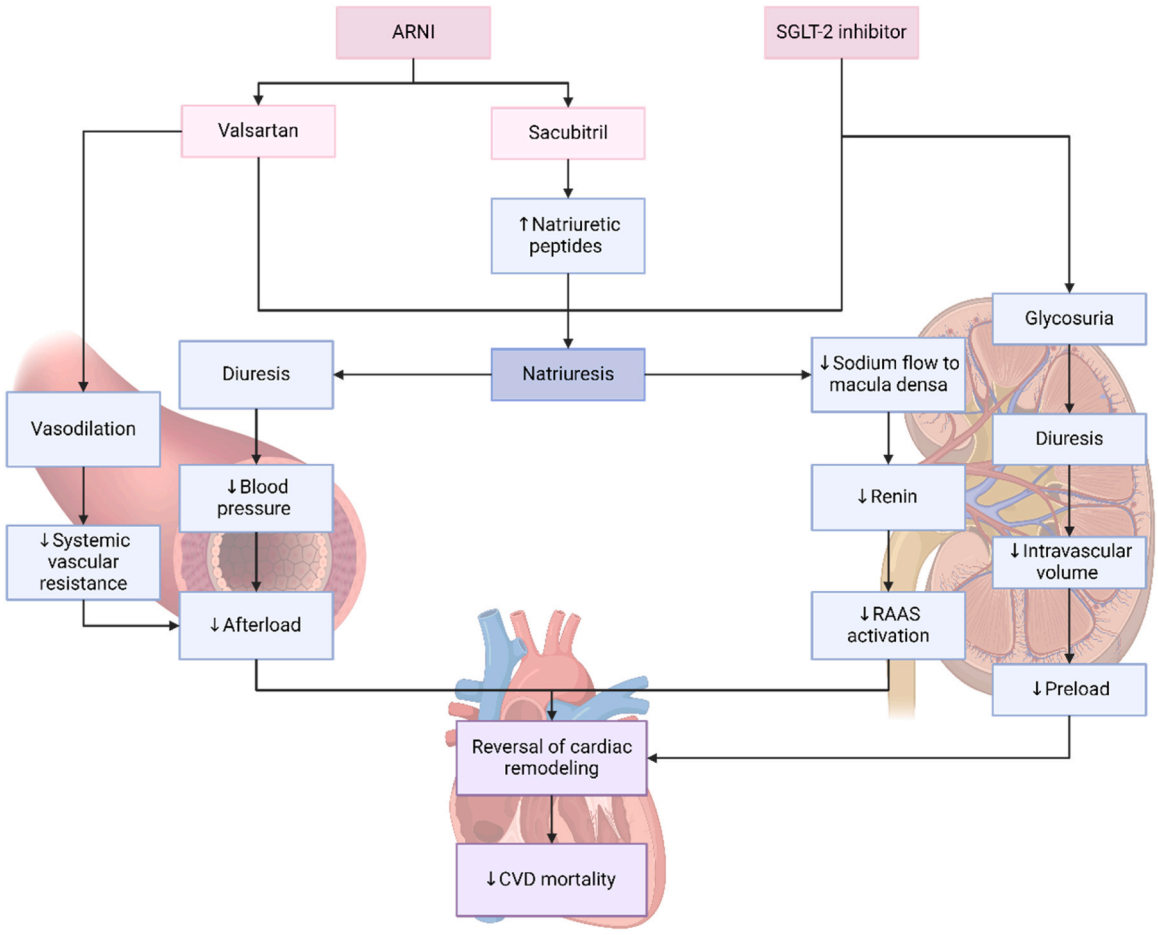

Fig. 3. Cardiorenal protection by ARNIs and SGLT-2 inhibitors: The combined effect of SGLT-2 inhibitors and ARNIs leads to reductions in preload, afterload, and RAAS activation. (Created with Biorender.com).

study highlighted the decreased efficacy of sacubitril/valsartan in reversing cardiac remodeling for HFrEF patients with diabetes mellitus compared to those without diabetes mellitus [99]. The all-cause mortality was also significantly higher in the diabetes mellitus group. However, reduction in congestion rates was similar in both groups [99].

Concurrent HF and diabetes mellitus can also have significant implications on vascular health given that patients with diabetes are at increased risk of microvascular damage and vascular diseases, secondary to the deposition of advanced glycation end products in the vasculature [100]. Interestingly, sacubitril/valsartan has been shown to have protective vascular effects in patients with HFrEF in general. In an echocardiographic evaluation for HFrEF patients receiving sacubitril/valsartan, the fractional area change, which is the precent change of the cross-sectional area of the vessels between the end-systole and end-diastole, was assessed. It was observed that the fractional area change progressively improved, indicating a vascular protective effect [101]. Additionally, it was reported that sacubitril/valsartan was superior to valsartan in improving vascular function in rats with induced heart failure, reflected by the improved vascular compliance and endothelium-dependent vasorelaxation [102].

Intriguingly, when this potential vascular protective effect of sacubitril/ valsartan was tested on rat models of diabetes type 2, it was found that it not only slowed the progression of vascular and neural complications, but also stimulated restoration of vascular integrity [103]. These findings raised questions about whether sacubitril/valsartan is beneficial for patients with concurrent HFrEF and diabetes. Accordingly, it has been recently reported that the use of sacubitril/valsartan alone or with SGLT-2 inhibitors is associated with lower risk of atherosclerotic cardiovascular disease [104]. However, a closer look at the data presented in the paper argues otherwise. Surprisingly, the numbers therein show that sacubitril/valsartan (Entresto) is associated with a markedly higher risk of atherosclerotic cardiovascular disease (adjusted HR= 5.89), contradictory to what has been concluded [104]. This indicates that further research is needed to confirm whether sacubitril/valsartan is beneficial or detrimental for this cohort in regard to vascular function.

Hospitalized patients after acute decompensated heart failure (ADHF):

Acute decompensation of HF can be described as the gradual or abrupt onset of a set of signs and symptoms that indicate deterioration of chronic HF. ADHF therefore necessitates unscheduled visits to the emergency department, clinics, or even hospitalization [105]. PIONEER-HF was a multicenter, double-blind RCT that assessed the efficacy and safety of sacubitril/valsartan, compared to enalapril, in hospitalized ADHF patients after hemodynamic stabilization (SBP $\geq$ 100 mmHg for the preceding 6 hours) [106]. Efficacy was reflected by the reduction in NT-proBNP and safety was indicated by measurements of hyperkalemia, symptomatic hypotension, angioedema, and worsening renal function reflected by serum creatine level and eGFR. Sacubitril/valsartan was found to be superior to enalapril in reducing NT-proBNP, exhibiting a 46.7% reduction compared to 25.3% ($p<0.001$), a difference that was evident from the first week of the trial. There were no significant differences in any of the safety outcomes between both groups, suggesting a similar safety profile [107]. By week 8 of the trial, approximately 20% of the patients in either group had withdrawn the medication, mainly because of adverse events. Hence, this indicates that RAAS-antagonizing drugs should be used with extra caution in patients with ADHF [107].

7. Long term treatment with ARNIs for HFrEF

Although a large body of research is available regarding the impact of ARNI, data on its long-term effects is still minimal, for both patients who showed improvement and those who did not respond to treatment with sacubitril/valsartan [108]. A recent cohort study examined the effect of sacubitril/valsartan one year after the initiation of treatment in patients with HFrEF. It was concluded that regardless of the initial response to treatment, prolonged use of sacubitril/valsartan resulted in an improved prognosis with less adverse drug events compared to ACEi/ARBs [108]. Additionally, an extension of the PARALLEL-HF trial explored the efficacy and safety of sacubitril/valsartan one year after treatment initiation in Japanese patients with HFrEF [109]. Their findings also indicated the tolerability and safety of sacubitril/valsartan 12 months after treatment with a positive risk-benefit profile. In most patients, neither the NYHA class nor the essential cardiac functional and structural parameters changed [109].

8. Theoretical side effects of ARNIs

Although the major side effect of ARNIs is hypotension, several other side effects have been investigated, including dementia. Given that neprilysin inhibitors (sacubitril) decrease the breakdown of amyloid-β, it was postulated that ARNIs may result in the formation of amyloid-β plaques in the brain, thereby precipitating dementia-related disorders such as Alzheimer's [110]. Hence, a pharmacovigilance analysis was conducted to evaluate whether dementia is considered an adverse drug event of sacubitril/valsartan [111]. However, the results suggested that sacubitril/valsartan does not currently pose a safety concern in HF patients [111]. This is supported by the very recent findings that associated sacubitril/valsartan with a lower risk of new onset dementia compared to ACEi/ARBs (adjusted hazard ratio= 0.83, 95% CI 0.72,0.95) [112].

The association between ARNIs and hepatotoxicity has also been studied. A prospective comparison of the PARADIGM-HF participants with abnormal liver function test at baseline showed superiority of sacubitril/valsartan compared to enalapril in normalizing it [113]. Nevertheless, a documented case report described a patient that developed severe liver injury after using sacubitril/valsartan, evidenced by elevated levels of hepatic transaminases [114]. Other causes of liver injury were ruled out and sacubitril/valsartan was discontinued. Subsequently, the levels of hepatic transaminases gradually normalized, confirming that sacubitril/valsartan was indeed the cause of liver injury [114].

9. Guidelines for HFrEF treatment

Given the accumulating clinical evidence supporting the efficacy and safety of ARNIs, recent guidelines have incorporated them alongside the traditional RAAS inhibitors, ACEi/ARBs, as a first-line management for patients with HFrEF [4] (Fig. 4). Originally, the 2013 the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the management of HF recommended the use of ACEi/ARBs only as first-line therapies in patients with chronic HFrEF [115]. However, this guideline was updated in 2017, introducing ARNIs to the recommended first-line RAAS inhibitors for HFrEF [116]. This recommendation was primarily driven by the PARADIGM-HF trial, which demonstrated the superiority of sacubitril/valsartan (ARNI) over traditional ACEis in reducing morbidity and mortality in patients with symptomatic HFrEF [50]. To date, the most recent 2022 American Heart Association/ American College of Cardiology/ Heart Failure Society of America (AHA/ACC/HFSA) guidelines strongly recommend the use of ARNIs as first-line therapy for the management of HFrEF. In fact, the 2022 AHA/ACC/HFSA guidelines suggest that patients with chronic symptomatic HFrEF in NYHA class II or III should be switched from ACEi/ARB to ARNIs for improved outcomes and favorable prognoses [4]. Additionally, given their significant benefits in terms of reduced NT-proBNP levels and improved LV remodeling parameters compared to ACEi/ARBs, ARNIs are recommended as *de novo* treatment in hospitalized patients with acute HF [4]. Furthermore, treatment with ARNIs has been found to be cost-effective according to the established clinical practice guideline benchmarks. This has been evidenced by multiple analyses illustrating that ARNI treatment costs less than $60,000 per quality-adjusted life-year (QALY) added, thereby providing a high economic value compared to ACEis [117–119].

The 2021 European Society of Cardiology (ESC) guidelines for the treatment of HF recommend the combination of an ACEi or ARNI, a beta-blocker, and a mineralocorticoid receptor antagonist as the first-line treatment for HFrEF, unless any of the medications is contraindicated or not tolerated [120]. It was also recommended to replace ACEi with sacubitril/valsartan in HFrEF patients to decrease the incidence of

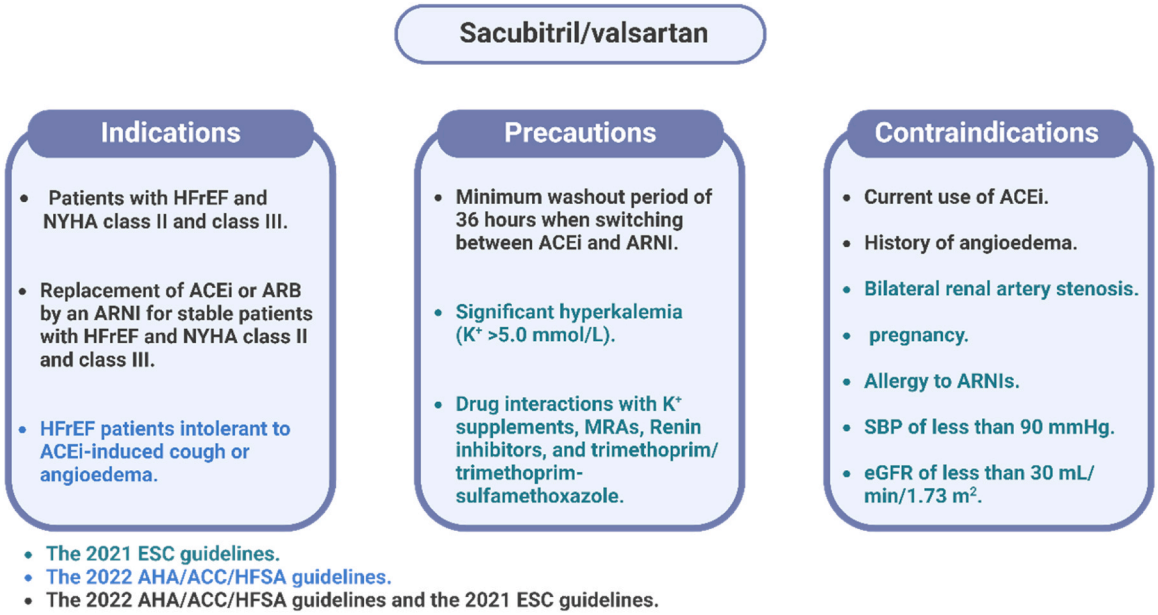

Fig. 4. Guidelines for sacubitril/ valsartan: An overview of the indications, precautions, and contraindications of sacubitril/ valsartan in the 2022 AHA/ACC/HFSA and in the 2021 ESC guidelines. Created with Biorender.com.

cardiovascular hospitalization and death [120]. The 2023 focused update on the 2021 ESC guidelines did not introduce any modifications on the recommendations for the treatment of HFrEF. Instead, it solely focused on updates related to other types of heart failure, namely HFmrEF, HFpEF, and acute HF [121].

Despite the overall safety and tolerability of ARNIs, the 2022 AHA/ACC/HFSA guidelines highlighted a few contraindications for their use. Based on the omapatrilat trial which underscored the increased risk of angioedema associated with dual ACE and neprilysin inhibition, guidelines have contraindicated the simultaneous administration of ARNIs and ACEis (1,8). Moreover, to decrease the risk of angioedema when switching from ACEis to ARNIs or vice versa, there should be a washout period of at least 36 hours [4]. ARNIs have also been contraindicated in patients with a history of angioedema to avoid its recurrence [4]. In accordance with the 2021 ESC guidelines, similar precautionary measures were advised [120]. The 2021 ESC guidelines listed additional contraindications for ARNIs including known renal bilateral arterial stenosis, pregnancy, allergy to the drug, eGFR <30 mL/min/1.73 m^2, and symptoms of hypotension or SBP <90 mmHg [120]. In HFrEF cases where the use of ARNIs is not feasible or contraindicated, 2022 AHA/ACC/HFSA guidelines recommend opting for ACE inhibitors initially, with a subsequent switch to ARBs in ACEi-intolerant patients that develop cough or angioedema [4]. Hence, careful consideration of contraindications should guide the initiation and switching between ARNIs, ACE inhibitors, and ARBs for optimal patient outcomes.

10. Conclusion

In conclusion, heart failure remains a significant contributor to the burden of cardiovascular disease. The persistent activation of the RAAS as the body's natural response to inadequate blood perfusion in heart failure patients further exacerbates the condition. Hence, targeting RAAS through various antagonistic drugs, including ARNIs, emerged as effective and promising therapeutic approaches. ARNIs have demonstrated favorable outcomes by not only reversing cardiac remodeling, but also improving cardiovascular morbidity and mortality. Notably, these drugs exhibit blood pressure reduction in hypertensive individuals, enhance renal function in CKD patients, and showcase positive effects in those suffering from diabetes mellitus, recovering from ADHF, and undergoing prolonged ARNI treatment for HFrEF. Therefore, while the fundamental mechanisms of ARNIs in improving HF have been extensively studied, it remains essential to cultivate a comprehensive understanding of their off-target effects. This approach is crucial not only to minimize potential adverse effects, but also to unlock the full potential and benefits ARNIs can offer in the management of HF.

CRediT authorship contribution statement

Yaman Al-Haneedi: Writing – original draft. **Habib Dakik:** Writing – review & editing. **Ali Eid:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Dima Nasrallah:** Writing – original draft. **Alaa Albdelhamid:** Writing – original draft. **Omar Tluli:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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