Review Article

A Review on the Wonder Drug: Sacubitril-Valsartan

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ABSTRACT

There are an estimated 17.9 million people worldwide who have heart failure, despite the widespread use of guideline-directed medical therapies such as angiotensin-converting enzyme inhibitors (ACEI), beta-adrenergic blockers, angiotensin receptor blockers, and mineralocorticoid receptor antagonists (MCRAs) for chronic systolic HF for nearly two decades. In patients with heart failure, reduced ejection fraction, and an elevated circulating level of N-terminal pro-brain natriuretic peptide or BNP, valsartan/sacubitril significantly reduced mortality and hospitalisation for heart failure, as well as blood pressure. Numerous studies have shown that this new treatment is economical. Heart failure patients with reduced ejection fraction receive valsartan/sacubitril in the form of a lower dosage and are closely monitored to ensure tolerance. We summarise the evidence for this treatment and highlight the potential for its use in heart failure with preserved ejection fraction as well as hypertension.

Keywords: Sacubitril / Valsartan, Heart Failure, Ejection Fraction, LBQ567, Neprilysin inhibitor.

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INTRODUCTION

An estimated 37 million people throughout the globe suffer from heart failure. Heart failure has a 50% chance of occurring in a person's lifetime. There has been an increase in life expectancy, increased risk factors for heart failure, and better management of acute cardiovascular events. [1,2] Several compensatory processes, such as ventricular remodeling and neurohormonal activation, take place in patients with heart failure. The problem is that with time, these compensatory mechanisms may become dysfunctional, culminating in heart failure that is worse than it was before. Nearly 1 million individuals are admitted to hospitals each year with heart failure, which is linked with a 50% death rate after five years. Over the next three decades, the total cost of treating heart failure will rise to $70 billion, up from $30 billion in 2012. [9] Patients with heart failure have a variety of compensatory strategies, such as ventricular remodeling and neurohormonal activation. Heart failure may deteriorate as a result of these compensatory mechanisms becoming maladaptive over time. ACE inhibitors, ARBs, -blockers, and aldosterone antagonists, all of which target these compensatory alterations, have been shown to lower mortality in patients with heart failure with a reduced ejection fraction. These drugs are all available over-the-counter[4]. Death and hospitalisation for heart failure are decreased with the use of sacubitril/valsartan (ARNI) over angiotensin converting enzyme (ACE) inhibition in a symptomatic patient group with reduced EF less than 35%.[1] Succinylcholinesterase inhibitor prodrug sacubitril is a sodium supramolecular mixture of valsartan and neprilysin inhibitor valsartan. Natriuretic peptides and many other vasoactive peptides are degraded by neprilysin, which is inhibited by esterases that change sacubitril into LBQ657. These two drugs work together to target two of the underlying causes of heart failure: stimulation of the renin/angiotensin/aldosterone system and decreased responsiveness to natriuretic peptide. They are both antagonists of angiotensin receptors.[16]

Neprilysin Inhibition

An enzyme known as Neprilysin, which is zinc-dependent, metallopeptidase, is one of the two principal means of NP clearance from the body (NEP). Natriuretic peptides (NPs) mitigate the pathophysiology of HF-rEF by counteracting the RAAS and SNS upregulation. 4 SNS aldosterone stimulation causes salt and water retention whereas RAAS stimulation causes higher heart rate and myocardial contractility. The SNS and RAAS, respectively, offer further measures of cardiac hypertrophy and fibrosis, as well as endothelial dysfunction and vascular remodeling. Thus, blocking NEP would elevate blood levels of NPs, which in turn stimulate the production of cGMP, which in turn promotes diuresis, vasodilation (good in HF)[5]. Angiotensin II (Ang II) overactivation causes vasoconstriction and salt retention in the bloodstream[6]. (hazardous to high-frequency hearing)[1]. Because of this, the RAAS must be inhibited concurrently in order to enjoy the benefits of

elevated NP levels. Drugs that target both NEP and Ang-II have a solid pharmacological basis. There would be an increase in Natriuretic Peptide (NP) synthesis and diuresis as a consequence of NEP suppression, but an increase in Angiotensin II (Ang-II), which contributes to vasoconstriction and salt retention, would occur as a result[1]. Because of this, the RAAS must be inhibited concurrently in order to enjoy the benefits of elevated NP levels. This means that medications that block both NEP and Ang-II have a strong medical foundation. In this case, many NEP inhibitors were clinically examined. Inhibiting neprilysin reduces the degradation of the natriuretic peptides, which are less susceptible to degradation. Natriuretic peptides activate particulate guanylate-cyclase, which causes blood vessels to dilate, in order to produce cGMP. The elevation in brain natriuretic peptide (BNP) in heart failure patients treated with valsartan/sacubitril is indirect indication that the medicine reduced BNP degradation[12].

Angiotensin Receptor Blocker Neprilysin Inhibitors

Sacubitril and valsartan (formerly LCZ696), two NEP inhibitors, are combined in a 1:1 molar ratio to generate a single NEP inhibitor molecule. The maximum-strength combination tablet, sacubitril/valsartan 97 mg/103 mg, gives the same amount of valsartan as the single-drug formulation of valsartan 160 mg, as it includes a distinct salt for[10]. ARNI is a first-of-its-kind medicine that precisely suppresses NEP in addition to mitigating the deleterious effects of RAAS and bradykinin (raising NPs concentration). 11 In order to deliver LBQ657 and valsartan twice a day, the half-lives are 12 and 14 hours, respectively. When administered to patients with renal impairment, sacubitril and valsartan exhibited longer half-lives, greater peak concentrations, and larger areas under the plasma concentration-time curve than in healthy controls. Hepatic impairment raises the plasma concentration-time curves of both sacubitril and valsartan in persons.

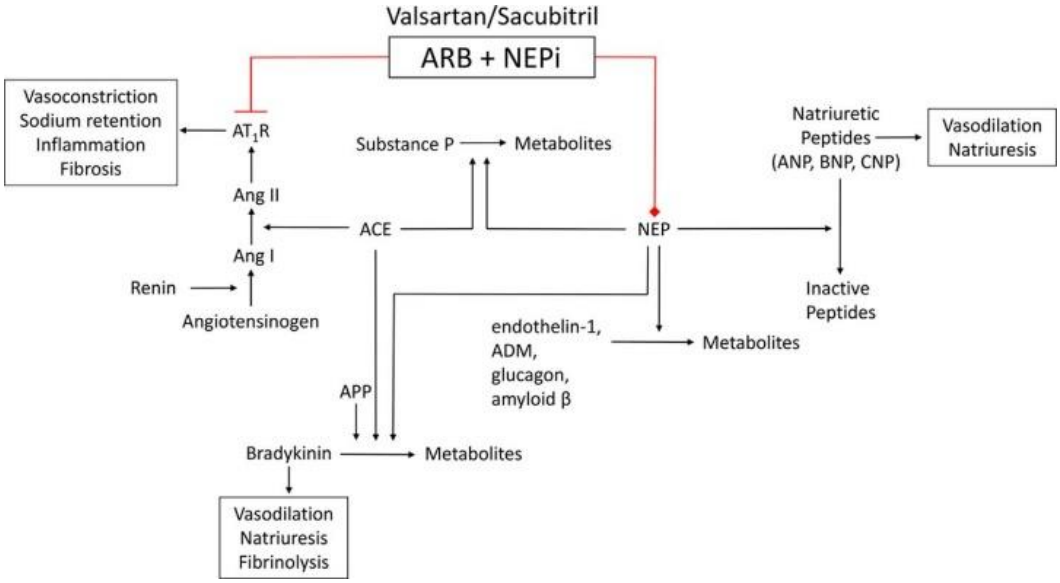


Figure 1: Effects of valsartan/sacubitril through inhibition of neprilysin (NEP) and blockade of the renin-angiotensin-aldosterone system

Red represents antagonism/inhibition. ACE indicates angiotensin-converting enzyme; ADM, adrenomedullin; Ang I, angiotensin I; Ang II, angiotensin II; ANP, atrial natriuretic peptide; APP, aminopeptidase P; ARB, angiotensin receptor blocker; AT1R, angiotensin type 1 receptor; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; and NEPi, neprilysin inhibitor.

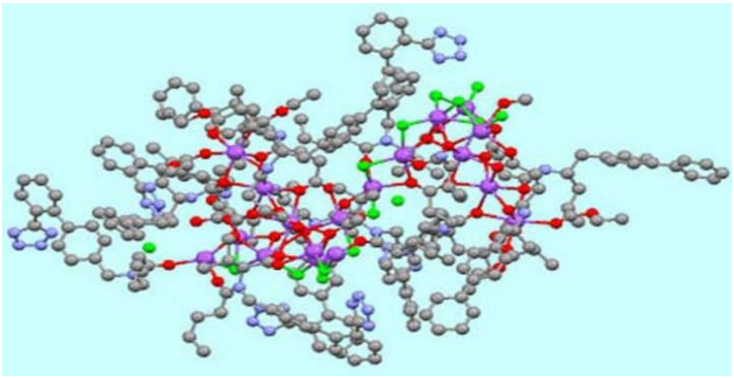


Figure 2: Structure of valsartan/sacubitril using a ball-and-stick model. Carbon atoms are represented in gray; sodium, purple; carboxylate and carbonyl oxygen, red; and water oxygen, green. Hydrogen atoms are not shown[4].

Mechanism of Action

LCZ696 is broken down into AHU337 and valsartan when taken orally. It doesn't take long for either of them to be digested. Once absorbed, AHU337 undergoes enzymatic cleavage of an ethyl ester group in the liver to generate the active NEPi, LBQ657 (AHU337 t1/2: 1.1 -3.6 (h r); 0.89 -1.35 h r). A rapid and practically simultaneous rise in the plasma concentrations of the two main active molecules valsartan and LBQ657 can be seen here. When excreted in the urine or bile, valsartan is undisturbed. In the proximal tubule, organic anion transporter 1 and 2 are responsible for LBQ657's active excretion into the urine. LBQ657 was shown to have a linear dose-exposure relationship at the doses studied (50 -400 mg). LCZ696 may be administered once or twice a day because of the lengthy half-life of valsartan and LBQ657. LCZ696's suggested daily dosage is between 100 and 400 mg. ARBs like Valsartan are on the market. The increased affinity of Valsartan for AT1R does not influence the antihypertensive and cardioprotective actions of AT2R, which prevent the BP-raising and profibrotic effects induced by AT1R-mediated overproduction of reactive oxygen species, which cause hypertrophic cell growth and cell senescence, as well as endothelial dysfunction and cardiovascular and renal remodelling. By inhibiting the neutral endopeptidase enzyme, LBQ657 prevents the degradation of NP. NPs' ability to lower blood pressure and protect the heart may be enhanced by preventing this process [3.]

A dose of 400 mg of valsartan/sacubitril is effective for both men and women. AUC and Cmax of valsartan in the combination valsartan/sacubitril are 24 percent and 30 percent greater in those 65 and older than in people 18 to 45 years old. However, Valsartan and sacubitril have no significant impact on pharmacokinetics when taken with CYP450 blockers since they are not metabolised by CYP450. Sacubitril inhibits the organic anion transporting polypeptides (OATPs) in vitro, according to a research on cellular uptake transporters (OATPs). There are two transporters on the hepatocytes' basolateral membrane, which may remove a range of medicines from the liver, including furosemide and statins. There are conflicting reports on whether or not atorvastatin will enhance or decrease a patient's Cmax or AUC of furosemide. Hydrochlorothiazide or metformin's Cmax and AUC are reduced as a consequence of taking valsartan or sacubitril. Valsartan and sacubitril are often prescribed to patients with cardiovascular disease, and more study is required to determine the potential for drug-drug interactions. Due to the lack of an effect of the combination of valsartan and sacubitril on OATP1 inhibition, it seems unlikely that sacubitril is responsible for its enhanced bioavailability when taken alone[4]. Because of this, Sacubitril/Valsartan is available in tablet doses of 24 mg sacubitril and 26 mg valsartan, 49 mg sacubitril and 51 mg valsartan, and 97 mg sacubitril and 103 mg valsartan. As valsartan tablets are more bioavailable than sacubitril/valsartan tablets, taking a dosage of 26mg, 51mg or 103mg is equivalent to taking 40mg, 80mg or 160mg in an average tablet. In contrast to sacubitril, which is largely eliminated in the urine (52–68 %), the majority of valsartan is excreted in the faeces (86 %).

Sacubitril Development

Patients with heart failure and a reduced ejection fraction in the randomised, double-blind PARADIGM-HF (Prospective Comparison of ARNI with ACEI ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; NCT01035255) study experienced significant reductions in overall and cardiovascular mortality when RAAS and neprilysin inhibition (sacubitril/valsartan) and ACE inhibitors (enalapril) (HFrEF) 8. One of the largest HF clinical trials ever conducted, PARADIGM-HF was a critical phase 3 study when the FDA authorised sacubitril/valsartan (N = 8442). To reduce cardiovascular mortality or hospitalisation for HF, sacubitril/valsartan was shown to be superior to enalapril (hazard ratio (HR) 0.80; 95% confidence interval (CI) 0.73–0.87; P 0.001)[8]. The PARADIGM-HF programme was abruptly shut down (median follow-up 27 months). There was also a decreased risk of death (HR 0.80; 95 percent confidence range 0.71–0.89; P=0.001) for heart attack and the first hospitalisation for worsening heart failure[8]. It was shown that sacubitril/valsartan/enalapril was 16 percent less likely than enalapril to cause mortality (95 percent CI 0.76–0.93; P 0.001) p. 21 This was shown by the PARADIGM-HF research, which tracked the outcomes of more than 27,000 patients who were given sacubitril/valsartan instead of enalapril for 27 months. With the American Heart Association/Heart Failure Society of America recommendation for HF treatment, individuals with HFrEF should be treated with anti-angiogenic drugs (ARNIs), as well as anti-inflammatory drugs (ACEIs). It is recommended by the guideline (class I recommendation, moderate-quality evidence) that patients with long-term chronic, symptomatic, or New York Heart Association (NYHA) class II or III HFrEF move to an ARNI. However, fewer than 10% of the 2.29 million patients who are eligible for sacubitril/valsartan are really taking it.

Treating Chronic Heart Failure with Reduced Ejection Fraction

Myocardial relaxation and remodelling are reduced, as are apoptotic cell death, hypertrophy, and fibrosis in response to RAAS inhibition[19]. Endothelial cells are the primary source of C-type Natriuretic Peptide (CNP), an endothelial vasodilator that is not found in considerable concentrations in the bloodstream[19]. Neprilysin enzymatic degradation and Natriuretic Peptide Receptor Clearance eliminate these peptides. A neprilysin inhibitor has little effect on HF because of this combination of activity, which weakens the regulator of opposing pathways of blood vessel dilation and dilation, thereby neutralising each other. Additionally, angiotensin II elevation induced by neprilysin inhibitors may worsen HF and increase angioedema risk by activating the RAAS.

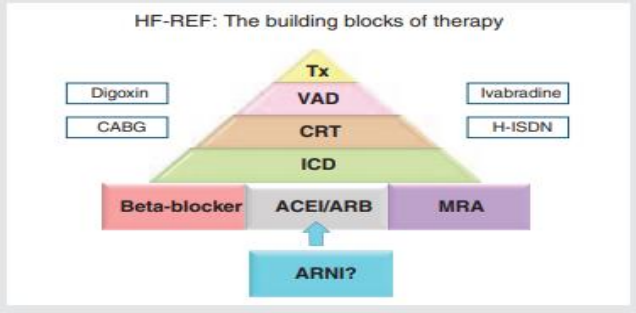


Figure 3: Treatment options for heart failure with a decreased ejection fraction based on current and future research (HF-REF)[21].

Heart transplantation; ventricular assist device; angiotensin receptor neprilysin inhibitor (ARNI) CABG coronary artery bypass grafting; implanted cardioverter-defibrillator (ICD) Tx The HF-REF therapy pyramid shows the most important pharmacological, device, and surgical options. There are a few popular treatments for HF-REF at the bottom of the pyramid, with devices and surgery being utilized on top of them (with the less common treatments at the top of the pyramid). To the left and right of the pyramid, there are pharmacological therapy for certain patients (as is CABG).

Sacubitril/Valsartan Use in Clinical Practice:

Patients with HF are often managed by professionals who are well-informed about the disease. This transition necessitates those practitioners not only know whether patients are suitable for treatment with ARNIs, but also know how to properly administer these drugs when necessary. There is a maximum recommended dosage of 97/103 mg of sacubitril and valsartan twice day. Patients currently taking an ACEI or ARB at C 50% of the target dosage should begin treatment with a beginning dose of sacubitril/valsartan 49/51 mg twice day. It is recommended that the goal dosage of 97/103 mg of sacubitril/valsartan be increased after 2–4 weeks Sacubitril/valsartan 49/51 mg twice day should be used as a starting dose for patients presently receiving an ACEI or ARB at C 50% of the target dosage. A target dose of 97/103mg of sacubitril/valsartan should be reached after two to four weeks of treatment[21]. The US prescription instructions for sacubitril/valsartan suggests beginning at a lower dosage of 24/26 mg twice day in patients who are not already on an ACEI or ARB or who were previously receiving modest doses of these medicines. This medication is not recommended for people on angiotensin II receptor blockers (ACEIs) or for those who have a history of angioedema[21]. ACEIs and sacubitril both have a risk of angioedema, therefore combining the two presents a safety issue. As a result, a 36-hour washout time is necessary for individuals who have previously been on ACEIs 23. Because the risk of angioedema is minimal with ARBs, there is no need for a washout period and the usual dosage start and uptitration plan may be followed. While ACEIs and ARBs have similar warnings and contraindications, ARNIs may raise the risk of symptomatic hypotension because they reduce intravascular volume. At C 65 mmHg of mean arterial pressure, uptitration of sacubitril/valsartan should be discontinued in order to maintain appropriate total body perfusion. To guarantee that the clinical reactions to such changes are not deleterious, close monitoring is required. As a side effect of inhibiting protein breakdown, therapy with sacubitril/valsartan raises BNP[21]. As a result, ARNI treatment should be approached with care when interpreting a rise in BNP concentration. because neprilysin is not a substrate for NT-proBNP, it is a more accurate indicator of a patient's clinical state.

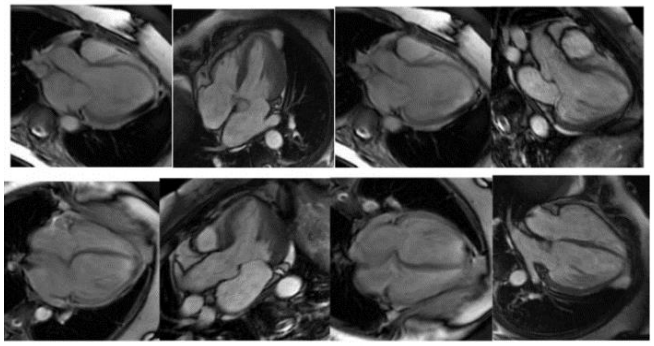


Figure 4: Image: Cardiac magnetic resonance image of non-compaction left ventricle with functional improve after a 6-month treatment with sacubitril/ valsartan[14] .

Sacubitril Usage

An ACE inhibitor should not be taken in conjunction with sacubitril/valsartan because of the risk of renal impairment and hyperkalemia associated with this combination (risk of renal impairment, hyperkalemia and angio-oedema). There should be at least 36 hours between stopping an ACE inhibitor and starting sacubitril/valsartan to avoid angio-oedema. To minimise the chance of an accidental overdose, patients and caregivers should throw away any unused medication. Initially, the recommended dosage of sacubitril/valsartan is 49mg/51mg taken twice daily. In certain cases, this should be trimmed from the table. Each 2–4 weeks, the dosage should be raised to 97 mg/103 mg twice day, as tolerated by the patient[22].

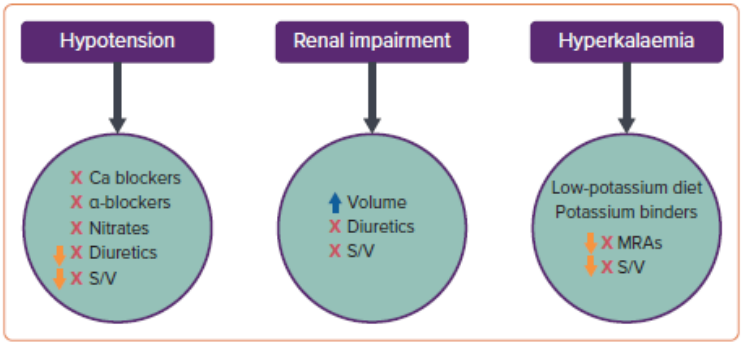
Adverse Effects

Sacubitril/valsartan should be discontinued immediately if angioedema develops, and it is critical to emphasise the absolute requirement of discontinuing any previous ACEi therapy for 36 hours before to commencing Sacubitril/valsartan[11]. Sacubitril/valsartan is contraindicated during pregnancy and breastfeeding since it may cause foetal harm (like any medicine operating on the RAAS system). Use of a potassium-sparing diuretic in conjunction with this medication may raise blood potassium levels, thus this should be monitored closely if this is the case. Risk of renal failure and lithium toxicity may rise if Sacubitril/valsartan is used with nonsteroidal antiinflammatory medications and lithium. BNP is not an adequate biomarker of HF severity in patients on Sacubitril/valsartan since it is a substrate for NEP; NT-proBNP is more helpful because its levels reflect a true reflex of wall stress reduction [11] .

Population with HF-REF	Starting dose of sacubitril/ valsartan	Uptitration and target dose
No patient characteristics requiring caution or dose reduction	49 mg/51 mg twice daily	Uptitration by doubling of dose every 2–4 weeks until a target dose of 97 mg/103 mg twice daily is reached.
Currently only taking a low or just low target dose of ACE inhibitor or ARB†	24 mg/26 mg twice daily	
No ACE inhibitor or ARB in the past	24 mg/26 mg twice daily	
eGFR <30 mL/min/m^2‡	24 mg/26 mg twice daily	
Moderate hepatic impairment (Child–Pugh class B)	24 mg/26 mg twice daily	
Elderly	24 mg/26 mg twice daily	

†Target doses of ACE inhibitors and ARBs are as follows: ACE inhibitors—captopril 50 mg three times a day, enalapril 10 mg twice daily, lisinopril 20 mg once a day, ramipril 5 mg twice daily, trandolopril 4 mg once a day ARBs—candesartan 32 mg once a day, losartan 150 mg once a day, valsartan 160 mg once a day.
‡The European Medicines Agency also suggests that a dose of 24 mg/26 mg can be considered if eGFR is 30–60 mL/min/m^2.[33]
ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.

Table 1: Starting dose and dose titration for sacubitril/valsartan in a variety of patient populations with heart failure and reduced ejection fraction (HF-REF)[22].



HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; S/V = sacubitril/valsartan.

Figure 5: Study of Sacubitril/Valsartan Usage in Patients with Reduced EF Heart Failure[23]

	Cautions and Contraindications
Chronic HFrEF	S/V should not be given in conjunction with ACEi/ARB because of the risk of renal impairment and hyperkalaemia
	In patients receiving ACEi, it should be discontinued for at least 36 h prior to S/V to reduce the risk of angioedema
	Renal function, potassium, blood pressure and possibly natriuretic peptides should be monitored during introduction and titration
	Starting dose of S/V is one 24 mg/26 mg tablet twice daily unless the patient is frankly hypertensive and/or is taking a large dose of ACEi/ ARB prior to ARNi
	The drug is not started in those with SBP <100 mmHg
	In the absence of obvious congestion, in the case of high dose of loop diuretic, empirically lower the loop diuretic dose to mitigate risk for symptomatic hypotension
	The dose of S/V should be doubled every 2—4 weeks until the optimal dose of one 97 mg/103 mg tablet twice daily is reached, based on the patient's tolerability
Acute HFrEF	In a patient already taking an ACEi, suspending the ACEi and initiating an ARB early on will facilitate the switch to ARNi
	Best time to initiate sacubitril/valsartan in acute HFrEF may be when the patient is not yet 'dry', in order to avoid hypotension
	Start at 24 mg/26 mg twice daily, with intention to ultimately titrate the dose to 97 mg/103 mg twice daily after discharge
	If patients experience tolerability problems, a dose adjustment of concomitantly administered drugs or temporary dose reduction or interruption of S/V is recommended
	When initiating therapy, pay more attention to patients with a tendency to hypotension, with chronic renal failure, with previous episodes of hyperkalaemia, and those who are elderly, due to the higher occurrence of side-effects

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNi = angiotensin receptor neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; SBP = systolic blood pressure; S/V = sacubitril/valsartan.

Table 2: Outcomes of Sacubitril/Valsartan Therapy are as follows [23] .

CONCLUSION

Patients with heart failure with a lower ejection fraction may benefit more from sacubitril/valsartan than from either ACE-I or ARB. in compared to enalapril with the biggest reaction in sexual interactions[3.] Patients with HFrEF may benefit more from sacubitril/valsartan than an ACEi or an ARB as a first-line treatment[11]. The American College of Cardiology and the European Society of Cardiology have agreed in consensus papers that commencement of sacubitril/valsartan is favoured independent of pretreatment with ACEi/ARB in view of current evidence from trials following PARADIGM-HF[24]. This ARNI seems to have a considerable cardiovascular benefit regardless of the type or cause of HF, according to the available data. This shows that sacubitril/valsartan may have a beneficial effect on individuals with HFrEF. Extensive clinical studies are underway that will broaden the existing use of this game changer medicine in the treatment of heart failure [16] . Men and women had equivalent (or larger, in the case of KCCQ-CSS) overall advantages from sacubitril-valsartan; the only difference was the decrease in heart failure hospitalisation, which was more pronounced for females than male. According to our findings in this study, sacubitril-valsartan treatment reduced hospitalisation for heart failure in women more than in men when compared to valsartan therapy [8] . At the 2-year follow-up in real-world HFrEF patients, sacubitril/valsartan treatment improved LV function and NYHA class. This shows that sacubitril/valsartan should be used with a "the sooner the better" approach in this patient group, perhaps avoiding or delaying the need for an ICD.

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