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SACUBITRILE/VALSARTAN FOR HEART FAILURE

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Heart failure is a condition in which the heart is unable to pump blood to meet tissue needs for metabolism. It is necessary to increase the heart's abnormal pressure to meet tissue metabolic needs. In congestive heart failure there is an increase in pulmonary vascular pressure due to left heart failure causing pressure overload and right heart failure (Gupta, Malhotra, & Sharma, 2016).

The current maintherapy for Heart Failure Reduction Ejection Fraction (HFrEF) is enalapril, while the use of ARB is not recommended unless the patient is intolerant of ACEinhibitors. The combination of angiotensin-neprilysin inhibitors from valsartan-sacubitrile has shown effectiveness in the PARADIGM-HF trial in reducing cardiovascular disease mortality compared to enalapril. Although sacubitrile-valsartan has shown good results, enalapril is still the preferred first-line treatment in patients with HFrEF because further research is still needed on this combination of drugs (Irhuma & VAlley, 2016).

The US Food and Drug Administration has given approval for sacubitrile/valsartan tablet products as a therapy for heart failure since July 7,2015 under the trade name Entresto®, indicated for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. It has been aimed at reducing the incidence of deaths from heart failure in hospitals compared to enalapril, and also to reduce the incidence of causes of death compared to enalapril (FDA, 2015) (Fala & Writer, 2016).

Pathophysiology of HF

Decreasing fraction ejection begins with events resulting in myocardial dysfunction and decreased cardiac output. As a result, preload and afterload experience an increase and

decrease in the perfusion system, thus activating various compensation mechanisms to increase cardiac output and end-organ perfusion. These compensation mechanisms include activation of the renin-angiotensin-aldosterone system, the adrenergic nervous system, cytokines, and the release of natriuretic peptides. In the short term, through systemic vasoconstriction, the kidneys experience sodium and water retention, and increased chronotropic and inotropic support. This mechanism restores cardiac output, peripheral perfusion, and reduces symptoms. However, in the long run, activation of this system causes secondary damage to the myocardium, myocardial growth and remodeling, cardiac fibrosis, ischemia, and energy depletion (King, Bress, Reese, & Munger, 2015).

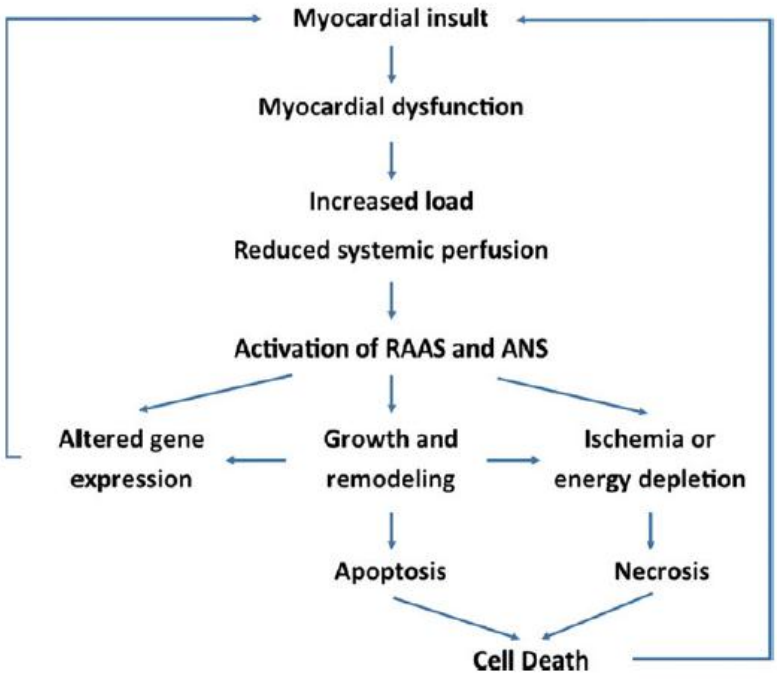

Figure 2.1: Pathophysiology of Heart Failure (King, Bress, Reese, & Munger, 2015).

Management of Heart Failure

1. Stage A

Hypertension and lipid disorders must be controlled according to guidelines to reduce the risk of heart failure. Other risk factors must be avoided such as obesity, diabetes mellitus, smoking, and cardiotoxic agents.

1) Therapy for the increase of blood pressure

The selection of anti-hypertensive agents must be adjusted to the guidelines and diseases such as diabetes mellitus or coronary artery disease. Anti-hypertensive diuretics can prevent heart

failure in most patients, meanwhile ACE inhibitors, ARBs, and beta blockers are also effective.

2) Dyslipidemic therapy and vascular risk

Hyperlipidemic therapy with statins reduces the chances of heart failure in patients at risk.

3) Obesity and diabetes mellitus

Disglycemia is a risk factor for heart failure. DM patients with HbA1c >10.5% have a risk of heart failure 4 times higher compared with those who have HbA1c <6.5%. Additional therapy in DM patients such as ACE inhibitors or ARBs can prevent the development of risk factors for heart failure.

2. Stage B

Stage B therapy is intended to minimize additional injuries and prevent or slow down the remodeling process. In addition to treatments clarified at stage A, ACE inhibitors and beta blockers are important components of therapy. Patients with previous myocardial infarction and decreased LVEF (left ventricular ejection fraction) must receive both of these therapies. ARBs are effective alternatives in patients intolerant of ACE inhibitors (Yancy & al, 2013).

3. Stage C

In addition to therapy given at stage A and B, the majority of patients at stage C must get diuretics, ACE inhibitors and beta blockers. Such therapy slows the progression of heart failure, decreases morbidity and mortality, and improves symptoms. ARBs, digoxin and hydralazine-isosorbid dinitrate are also effective for some patients. Monitoring in these patients is sodium retention, daily weight measurement, physical activity, and prevention of treatment that aggravates heart failure (Yancy et al, 2013).

4. Stage D

Individuals with the most advanced stage of heart failure receive therapy including positive inotropic continuous intravenous, mechanical circulation, heart transplantation, and hospital care (Yancy et al, 2013).

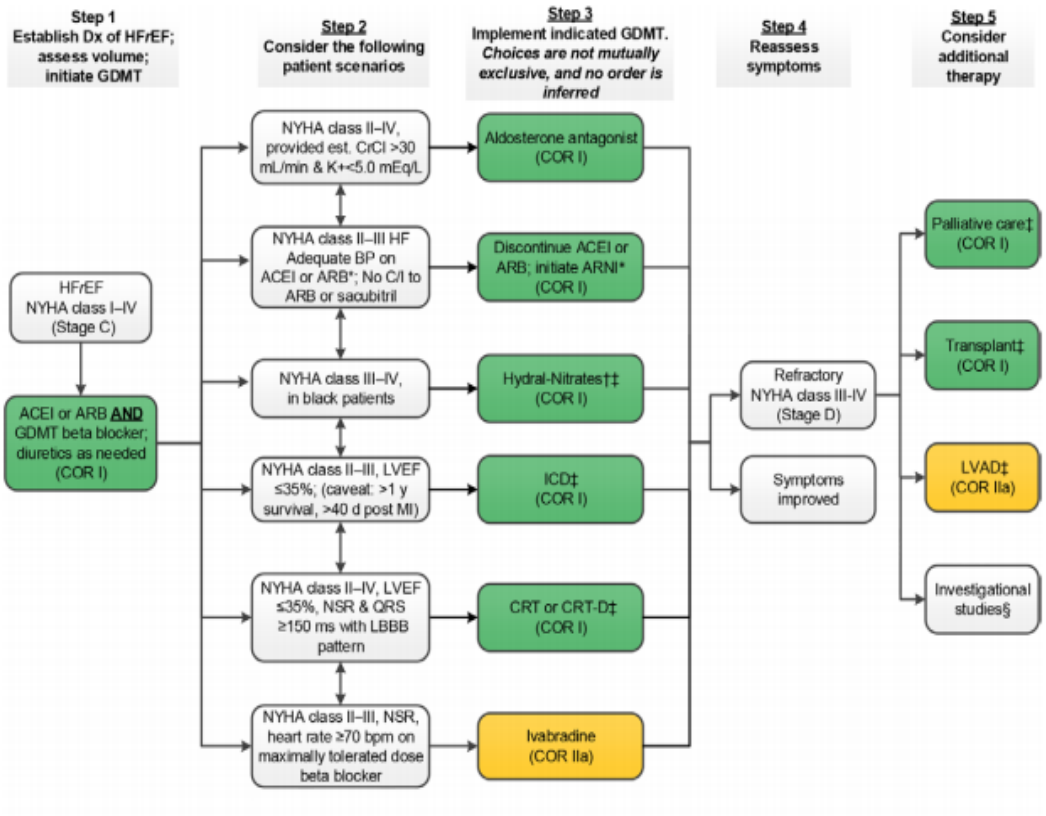

Figure 2. 2: Stage C and D HFrEF therapy algorithms (Yancy, et al., 2017).

Natriuretic Peptide (NP) System

The first neurohormon compensation mechanism to be studied and also the most influential, is RAAS. The heart has another mechanism to fight this active compensation system in the form of the Natriuretic Peptide (NP) system (Singh & Lang, 2015).

The Natriuretic Peptide (NP) system plays an important role in maintaining cardiorenal homeostasis using similar structural peptides but genetically and physiologically different. Of the four known NPs, atrial natriuretic peptide (ANP) is released by atrial response to myocardial stretch, indicating an increase in intravascular volume, whereas brain natriuretic peptide (BNP) is released by the ventricles in response to increased ventricular volume and pressure. ANP and BNP have similar physiological effects, they both induce diuresis, natriuresis and vasodilation, and inhibit the sympathetic nervous system (with reduced catecholamine secretion) and RAAS system (with decreased renin).

There are three types of natriuretic peptide receptors (NPR), namely NPR-A, NPR-B, and NPR-C. NPR-A and NPR-B have the same effect and bind all three NPs, but NPR-A has a stronger affinity for ANP and BNP than CNP. Conversely, NPR-B is more selective towards

CNP. When these two receptors are activated by NP, these receptors catalyze the formation of intracellular cyclic guanosine monophosphate from guanosine triphosphate. Cyclic Guanosine monophosphate then acts as the second messenger to mediate the effect of NP. NPR-C, on the other hand, has a very different effect, because its function is to remove NP from circulation (Singh & Lang, 2015).

NP is catabolized through enzymatic division by a membrane-bound enzyme called neprilysin, also known as a neutral endopeptidase or metallo-endopeptidase membrane. Nephrilysin is an enzyme encoded by the MME gene Neprilysin, which is widely expressed but most abundant in the kidneys, bypasses the NP ring structure, making them biologically inactive (Oparil & Schmieder, 2015; Singh & Lang, 2015).

Chemical Properties

Sacubitrile/valsartan is a supramolecular sodium salt complex inhibiting neprilysin prodrug sacepitrile and ARB valsartan in a 1: 1 molecular ratio (Figure 2.1). It has a stable crystal structure, is very soluble in water and contains six sacubitriles and six valsartan anionic molecules complexed with sodium and water cations. After oral administration, the complex dissociates into sacubitrile and valsartan (McCormack, 2016).

Sacubitrile/valsartan is a cocrystallized structure (molar ratio 1: 1) with a molecular mass of 5748.03 g/mol, which is stable in solid and liquid form (pH 5-7) (Richardson, David, Grace, & Guirguis, 2016).

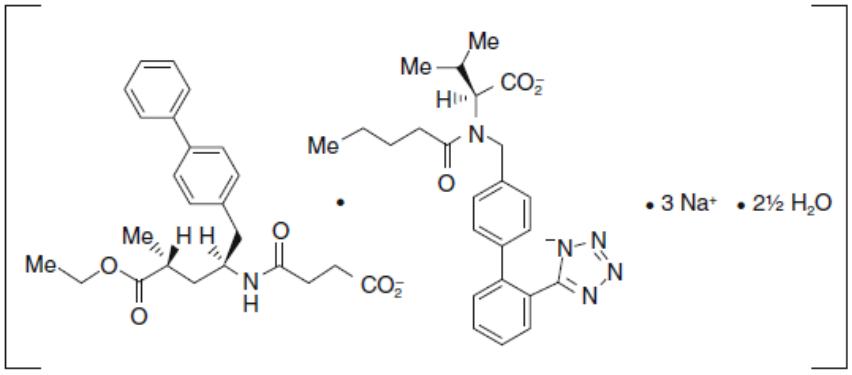

Figure 2.3 Chemical structure of sacubitrile/valsartan (McCormack, 2016).

Doses and Administration

There are three doses available, namely 24 mg sacubitrile/26 mg valsartan, 49 mg sacubitrile/51 mg valsartan, and 97 mg sacubitrile/103 mg valsartan. If the patient previously

used an ACE inhibitor, leave 36 hours of washout time before starting sacubitrile/valsartan therapy. For patients with heart failure class II to IV (not using ACEi or ARB, or using a low dose) it is recommended to use the initial dose, namely sacubitrile 24 mg/valsartan 26 mg orally twice a day. (Micromedex, 2018).

The initial recommended dose for HF treatment is 49/51 mg sacubitrile/valsartan twice a day (with or without food). This dose should be doubled after a period of 2-4 weeks in the use of 97/103 mg sacubitrile/valsartan twice a day (target maintenance dose). The initial dose should be reduced to 24/26 mg sacubitrile/valsartan twice daily for patients not receiving ACEi or ARB, receiving ACEi or low-dose ARB, patients with severe renal impairment (GFR <30 mL/min per 1.73m^2) and for patients with moderate hepatic insufficiency. Dosage adjustments are needed and tolerance by patients must be achieved within 2-4 weeks (table 2.1) (Kaplinsky, 2016).

Table 2.1: Initial doses and titration of sacubitrile/valsartan doses in heart failure patients and fraction ejection measurements (EF) (Jhund & McMurray, 2016).

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.

Dosage Adjustments

In patients with severe kidney damage (eGFR less than 30 mL/minute/1.73m the initial dose is 24 mg sacubitrile/26 mg valsartan twice daily, double doses every 2 to 4 weeks to target a 97 mg sacubitrile/103 mg valsartan dose twice a day. For mild and moderate kidney damage (eGFR 30 mL/min/1.73m or greater), dosage adjustments do not need to be done (Micromedex, 2018).

This drug combination is not recommended for patients with severe liver damage (Child-Pugh class C). For moderate liver damage (Child-Pugh class B), the initial dose is 24 mg sacubitrile/26 mg valsartan twice daily, double doses every 2 to 4 weeks to target 103 mg

sacubitrile/103 mg valsartan dose twice daily. Meanwhile for patients who experience mild liver damage (Child-Pugh class A) no dose adjustment is needed (Micromedex, 2018).

Mechanism of Action Sacubitrile

Neprilysin is a neutral endopeptidase mainly found in the kidneys but can be present in many tissues including smooth muscle in blood vessels, lungs, and cardiac myocytes. It is responsible for stopping and killing many peptides that have vasodilation and other beneficial cardiovascular effects such as NP (especially ANP and BNP), bradykinin, and adrenomedullin. Neprilysin also inactivates systemic vasoconstrictors such as endothelin I and angiotensin II. In addition, it can convert angiotensin I to angiotensin, a peptide that can compensate for the many effects of angiotensin II which causes the effect to direct vasodilatory, natriuretic, and anti-proliferative. Thus, inhibition of neprilysin alone will have a mixed effect based on its ability to increase both peptides that have vasodilation and other beneficial effects and peptides such as angiotensin II which have undesirable cardiovascular effects (Hsiao & Greenberg, 2016).

Sacubitrile/valsartan is a combination drug consisting of sacubitrile and valsartan. Valsartan works by inhibiting angiotensin II type 1 receptors, causing vasodilation, reducing vasopressin secretion, reducing aldosterone production and secretion, and increasing excretion of sodium and water by the kidneys, which causes a decrease in blood volume. The sacubitrile product can inhibit neprilysin. Neprilysin is an endopeptidase enzyme that converts active natriuretic peptides into inactive forms. It also inhibits increased levels of enzymes in natriuretic, bradykinin, and adrenomedullin peptides, which neutralize neurohormonal overstimulation in preventing vasoconstriction, sodium retention, and maladaptive remodeling (Richardson, David, Grace, & Guirguis, 2016) (Yandrapalli, Andries, Biswas, & Khera, 2017) (Menendez, 2016).

Sacubitrile is a pro-drug activated against LBQ657 through deetylation via esterase. LBQ657 inhibits the enzyme neprilysin, which is responsible for the destruction of ANP and BNP, a peptide that lowers blood pressure primarily through a decrease in blood volume. The increase in natriuretic peptides resulting from inhibition of neprilysin causes natriuresis, vasodilation, inhibition of the renin-angiotensin-aldosterone system, reduced sympathetic stimulation, antiproliferative, and antihypertensive effects on the heart and blood vessels (Oparil & Schmieder, 2015).

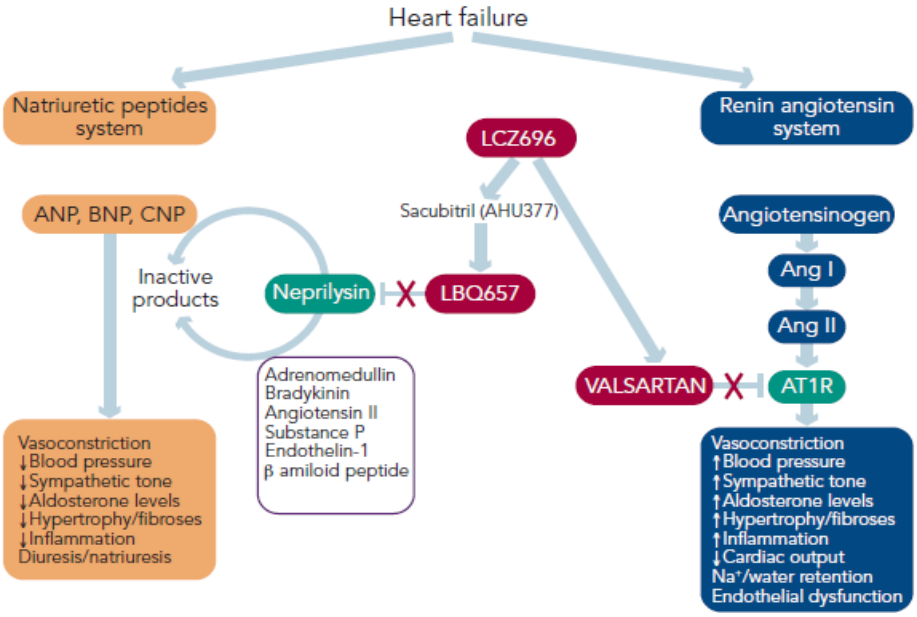

Figure 2.3 Natriuretic Peptide Mechanism in Heart Failure (Menendez, 2016).

Pharmacokinetics

After oral administration, the compound dissociates into sacubitrile and valsartan. Sacubitrile is a prodrug to be metabolized (by esterase) to LBQ657, which is its active form. Because these metabolites do not inhibit aminopeptidase P, the risk of angioedema can be minimized in comparison with omapatrilat. Peak plasma concentrations were reached at 1.5-2.2 hours for valsartan, 0.5-1.1 hours for sacubitrile and 1.9-3.5 hours in the case of LBQ657 (sacubitrile active metabolite). Steady state is achieved in three days and consumption with food does not change sacubitrile/valsartan pharmacokinetics (Kaplinsky, 2016).

This drug's oral bioavailability is 60% or more. The bioavailability of sacubitrile/valsartan is higher than the bioavailability of valsartan (figure 2.4). The protein bond is 94 to 97%. Volume distribution of sacubitrile is 82.7 to 103 liters, while valsartan's is 75 to 101 liters. From the excretion process view, sacubitrile is excreted in the kidneys by 52 to 68%, whereas in the cerebral the excretion is 37 to 48%. The total sacubitrile clearance is 49.4 liters per hour. For valsartan, renal excretion is 13%, whereas in fecal is 86%. Total valsartan clearance is 4.22 liters per hour. Sacubitrile's half-life is 1.31 hours, whereas in the form of active metabolites (LBQ657) the half-life is 11.5 to 12 hours. Valsartan's half-life is 9.9 to 20.8 hours (Micromedex, 2018) (Gibler, 2015).

Tabel 2.2: Basic Pharmacology and pharmacokinetics (Gibler, 2015).

Parameter	
Mechanism of Action	Inhibition of neprilysin (neutral endopeptidase) via LBQ657, the active metabolite of the prodrug sacubitril, and blockade of the angiotensin II type-1 receptor and inhibition of angiotensin II-dependent aldosterone release via valsartan.
Oral Bioavailability	Sacubitril: ≥60%. Note: the valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.
Distribution and Protein Binding	The average apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively. Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94% to 97%).
Elimination	52% to 68% of sacubitril (primarily as LBQ657) and ~13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as LBQ657), and 86% of valsartan and its metabolites are excreted in feces.
Half-Life	Sacubitril, LBQ657, and valsartan are eliminated from plasma with a mean elimination half-life of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively. Following twice-daily dosing of ENTRESTO, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days.
Metabolism	Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites.

Pharmacodynamics

Sacubitril/valsartan has been shown to increase plasma ANP and cyclic guanosine monophosphate (cGMP) concentration and increase renin, plasma renin activity, and angiotensin II. This effect peaked at 4 hours after the drug was used and still increased significantly compared to placebo 24 hours after dosing. The fact that all biomarkers increase at the same time indicates that the pharmacodynamic effects of sacubitrile and valsartan occur in parallel which contribute to the effectiveness of the drug. This is unlike neprilysin inhibition that is delayed and occurs in connection with ACEi with omapatrilat. In patients with hypertension, sacubitrile/valsartan and sacubitrile alone can increase the concentration of ANP and cGMP, while valsartan alone can reduce its concentration. An increase in ANP and cGMP is numerically greater with sacubitrile alone compared to sacubitrile/valsartan but is not dose dependent. Renin plasma also increases the amount comparable to sacubitrile/valsartan compared to valsartan alone (Sible, Nawarskas, Alajajian, & Anderson, 2016).

This study further shows that administration of LCZ696 results in increased plasma levels and urinary cGMP and increased urine ANP, thus providing evidence of inhibition of neprilysin in patients with HFrEF. In addition, treatment with LCZ696 reduced plasma aldosterone and endothelin-1 levels. Overall, these findings support the benefits of LCZ696 with respect to decreased CV mortality, HF hospitalization, and all causes of death compared to enalapril as shown in the PARADIGM-HF trial (Kobalava, Kotovskaya, Averkov, Pavlikova, Moiseev, & Albrecht, 2016).

Sacubitrile Effectiveness

There is not much comparative comparison between sacubitrile and other drugs in the treatment of Heart Failure. Comparative comparison of ARNI with ACE inhibitors in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) were performed to test whether 97 mg/103 mg sacubitrile/valsartan twice daily was superior to enalapril 10 mg twice a day in reducing cardiovascular death or hospitalization of HF patients. There was a 20% reduction in relative risk, and a 16% decrease in all-cause mortality. Cardiovascular death, sudden death, and death due to HF are significantly reduced. There was no statistically significant difference in the level of angio-edema with sacubitrile/valsartan compared to the enalapril group. However, the incidence of kidney dysfunction, hyperkalemia and cough occurs in the sacubitrile/valsartan is lower compared to enalapril. Low risk of renal dysfunction and hyperkalemia in sacubitrile/valsartan use can allow more patients to achieve optimal RAAS inhibition (Jhund & McMurray, 2016).

Sacubitrile/valsartan accepts I-BR recommendations with 'strong' recommendations and the evidence level of BR is 'moderate quality' (evidence based on only one study). Therefore, ARNI should be recommended to reduce morbidity and mortality in patients with HF, patients with EF reduction, NYHA class II or III, and in patients with ACE inhibitor or ARB intolerance (as a replacement). Sacubitrile/valsartan is recommended to be incorporated into standard therapy for HF with EF reduction as an alternative ACE inhibitor or ARB, and is given together with beta-blockers and mineralocorticoid receptor antagonists (Kaplinsky, 2016).

When viewed from the cost effectiveness for 1 year, the administration of sacubitrile/valsartan is relatively higher compared to the administration of enalapril. Sacubitrile/valsartan administration also further increases the life expectancy of patients with HF (Thomas A. Gaziano, Gregg C. Fonarow, Brian Claggett, & Wing W.Chan, 2016) (Jordan B, sha, Adam P, Richard, & bellows, 2016).

Findings from the cost-effectiveness analysis show that if the benefits of sacubitrile/valsartan are quite beneficial. Sacubitrile/valsartan therapy provides substantial clinical benefits compared to the current standard of care for HF, due to the reduction in cardiovascular mortality and hospitalizations related to HF (Daniel A. Ollendorf, Alexander T. Sandhu, & Steven D. Pearson, 2015).

Cost effectiveness of sacubitrile/valsartan compared with ACEi/ARB use in improving patient quality of life is more cost effective, seen from reduced hospitalization of patients with HF so that it can reduce the cost of care (McMurray, Trueman, Hancock, Cowie, & Brigg, 2018).

Sacubitrile/valsartan is considered as a alternative gold standard to ACE inhibitors enalapril in patients with chronic systolic heart failure (Murray, Packer, Desai, Gong, & Lewkofitz, 2013).

High-dose sacubitrile/valsartan effectively shows an increase in LVEF and reverse remodeling parameters. Besides that, it can also reduce LVESD (left ventricular endsystolic diameter), LVEDD (left ventricular end dyastolic diameter) and LV mass, so that it can reduce cardiovascular deaths (Almufleh, et al., 2017).

Another study comparing sacubitrile/valsartan with ACEi/ARB in increasing LVEF showed that sacubitrile/valsartan increased LVEF as much as 9% compared to ACEi/ARB (Nazzari, Yeung, Marceau, Luong, Clark, & Ahuja, 2017).

HF patients with type 2 diabetes who received sacubitrile/valsartan had a lower risk of kidney damage than patients who received enalapril. Inhibition of neprilysin in patients receiving high-dose sacubitrile/valsartan will block RAAS which will reduce the occurrence of diabetes nephropathy in patients (Packer, et al., 2018) (Tousoulis, 2017).

In addition, the use of sacubitrile/valsartan in diabetes patients shows that both of these drugs can control sugar levels by reducing HbA1c rather than using enalapril. Pharmacist must be able to provide information to clinicians using sacubitrile/valsartan for diabetic patients with HFrEF in order to be able to regulate the insulin dose used in relation to the ability of this drug to reduce the patient's sugar levels so they can prevent hypoglycemia (Jelena P Seferovic, Brian Claggett, Seidelmann 2017).

Elderly patients who received sacubitrile/valsartan showed better results compared to the ones using enalapril in terms of controlling blood pressure. Sacubitrile/valsartan is not recommended for elderly patients who have low blood pressure, and it is better to use enalapril instead (Bauersachs, 2017).

Young patients who do not have risk factors such as diabetes and hypertension, the use of sacubitrile/valsartan is relatively safe for HF and low EF patients with systolic <110mmHg (Bruno & Taddei, 2017).

Side effects

According to Gupta, the most commonly reported adverse reactions caused by the use of sacubitrile/valsartan combinations are hypotension, hyperkalemia, coughing, dizziness, and kidney failure. Sacubitrile/valsartan should not be given together with ACEi (eg: enalapril), renin inhibitors (eg: aliskiren), or with other angiotensin receptor inhibitors (ARBs). If sacubitrile/valsartan is given together with an ACE inhibitor it can increase the risk of angioedema.

The use of sacubitrile/valsartan along with potassium-sparing diuretics, potassium supplements, or with salt substitutes can cause an increase in potassium. A sacubitrile/valsartan combination with NSAIDs can increase the risk of kidney damage. The joint use of sacubitrile/valsartan combination with lithium causes an increased risk of lithium toxicity (Gupta, Malhotra, & Sharma, 2016) (Cada, Baker, & Leonard, 2015).

Patients treated with mineralocorticoids in symptomatic HFrEF, who experience side effects of severe hyperemia are more common in patients who get enalapril compared to patients who get sacubitrile/valsartan (Desai, Vardeny, & Claget, 2017).

A study comparing angiotensin-neprilysin inhibitors with enalapril in heart failure patients showed that their effectiveness was not followed by a good level of safety. Some patients discontinued treatment because of side effects in the LCZ696 group rather than the enalapril group. Because of the large vasodilator effect, treatment with LCZ696 causes symptomatic hypotension. Although the effects of severe hypotension can have an impact on renal perfusion, increasing serum creatinine levels clinically occur less in the LCZ696 group compared to the enalapril group (John, et al., 2014).

Contraindications

Sacubitrile/valsartan combinations are contraindicated in patients with severe liver disorders and all patients with a history of angioedema due to exposure to previous ACE inhibitors or ARBs. Patients using a sacubitrile/valsartan combination must be closely monitored for signs

and symptoms of angioedema and hypotension. Kidney function and potassium levels must be monitored regularly (Gupta, Malhotra, & Sharma, 2016).

Sacubitrile/valsartan is not recommended to be started in patients with systolic blood pressure <100 mmHg or serum potassium >5.4 mmol/L. The need to adjust the dosage of other agents (diuretics, antihypertensive drugs, etc.) must be considered in the development of conditions of hypotension, kidney disorders, or hyperkalemia (Kaplinsky, 2016).

In addition, sacubitrile/valsartan use is also contraindicated for diabetic patients with aliskiren. This therapy is not allowed to be used in 36 hours during the use of ACEi as well as contraindications for patients with hypersensitivity to sacubitrile, valsartan, or other compositions of this drug product (Micromedex, 2018).

Pregnancy and Breastfeeding

There is no information about sacubitrile/valsartan use in breastfeeding women, so this is not recommended for use. Sacubitrile/valsartan can cause fetal damage if given to pregnant women. The use of drugs acting on the renin-angiotensin system, such as sacubitrile/valsartan combinations during the second and third trimesters of pregnancy can reduce fetal kidney function and increase fetal and neonatal morbidity and mortality. If a pregnant patient uses sacubitrile/valsartan, the drug must be stopped immediately to prevent teratogenic effects (Gupta, Malhotra, & Sharma, 2016).

Monitoring

Patients using sacubitrile/valsartan therapy are advised to monitor the following points: improvement in signs or symptoms of chronic heart failure (an indication of drug effectiveness), serum creatinine, kidney function in patients with renal artery stenosis, serum potassium especially in patients with factors the risk of hyperkalemia (DM patients, chronic kidney failure, hypoaldosterone, or high potassium diet), as well as signs and symptoms of angioedema or hypertension (Micromedex, 2018).

CONCLUSION

Sacubtrile/valsartan is a promising drug combination in management of HF due to multiple inhibitions in RAAS and NP. The use of these two drugs showed a decrease in cardiovascular deaths when compared to enalapril (Pai, SunilL, Kamath, & Priyanka, 2016). In addition, if

viewed from cost effectiveness, sacubitrile/valsartan is more effective in terms of improving paients' quality of life.

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