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ARNI: Newer Strategy in Chronic Heart Failure with Reduced Heart Function: A Review

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ABSTRACT:

Heart failure has emerged as a global pandemin in recent times with at least 26 plus million people affected globally with an ever-increasing prevalnace worldwide. Traditionally, “beta blockers, ACE inhibitors, ARB’s and aldosterone antagonists” have improved both morbidity and mortality, in heart failures with reduced EF, but the high morbidity and mortatlity and socio-economic burden remains a global public health issue. The FDA in 2015 July, approved a new class of drug: Valsartan/Sacubitril (earlier also known as LCZ696) combination of “ARB(VALSARTAN) and Neprilysin Inhibitor (SACUBITRIL) in a 1:1 ratio in a SODIUM SUPRAMOLECULAR COMPLEX”, to reduce both morbidity and mortality in Heart failure with reduced ejection fraction. The combination acts by targeting two major patho physiological mechanisms of heart failure. “The first being the activation of the Renin-Angiotensin-Aldosterone system and second decreasing the sensitivity to natriuretic peptides. A major clinical trial- The Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, resulted in reducing significant mortality and hospitalization for HF with Valsartan/Sacubitril combination with additional benefits of lowering blood pressure as well compared to enalapril in patients with reduced EF, and elevated circulating levels of N-terminal Pro BNP or BNP”. Many ongoing trials are also asserting the role of the Valsartan/Sacubitril combination in HF with preserved EF and hypertension. In this review we study the machanism of action of valsartan/sacubitril combination, its pharmacokinetics and pharmacodynamics and safety and efficacy in treatment of both hypertension and heart failure.

Keywords: ARNI, PARADIGM-HF, Valsartan/Sacubitril ARB(VALSARTAN), Neprilysin Inhibitor

INTRODUCTION:

Heart failure has emerged as a global pandemin in recent times with at least 26 plus million people affected globally with an ever-increasing prevalnace worldwide. Traditionally, “beta blockers, ACE inhibitors, ARB’s and aldosterone antagonists” have improved both morbidity and mortality, in heart failures with reduced EF, but the high morbidity and mortatlity and

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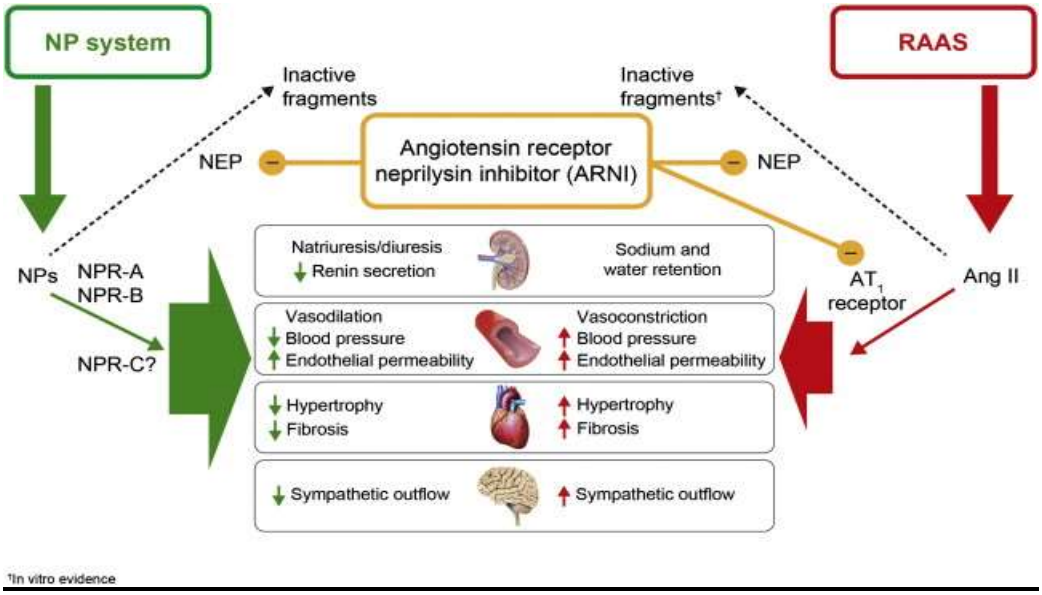
PHARMACODYNAMICS:



Valsartan/Sacubitril combination **(ARB+NEPi)** is a newer combination that is being studied extensively in HFrEF/HFmrEF and hypertension. The RAAS system is blocked by the angiotensin receptor blocker (ARB) valsartan. Neprilysin, however, degrades angiotensin II, hence blocking it will create an accumulation of angiotensin II. The blood pressure-lowering peptides atrial and brain natriuretic peptide, which both decrease blood pressure primarily by reducing blood volume, are degraded by the enzyme neprilysin, which is inhibited by sacubitril. Neprilysin inhibitor enhances the availability of natriuretic peptides, bradykinin aids in vasodilation and natriuresis (excretion of sodium), and decreases blood pressure, all of which are positive effects of the combo. "Valsartan selectively prevents angiotensin II from binding to the AT1 receptor in numerous tissues, including vascular smooth muscle and the adrenal gland, in order to inhibit the vasoconstrictor and aldosterone-secreting effects of angiotensin II".

PHARMACOKINETICS

"After ingestion and absorption, the combination Valsartan/Sacubitril dissociates to Valsartan and Sacubitril, bsorption of and conversion of sacubitril (prodrug) to sacubitrilat (neprilysin

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inhibitor) with rapid maximum plasma concentrations of sacubitril, sacubitrilat, and valsartan (angiotensin receptor blocker) reaching within 0.5, 1.5-2.0, and 2.0-3.0 h, respectively. After conversion to esterases to active inhibitor of neprilysin LBQ657, neither sacubitril nor valsartan are not further metabolized. 52% to 68% of sacubitril is excreted in urine and 37-48% is excreted in feces, in both as LBQ657. Lower starting doses are advised in renal impairment and moderate hepatic impairment".

TRIALS

(PARADIGM-HF)- In a prospective, multi-center trial titled "The Prospective Comparison of ARNi with ACRi to Determine Impact on Global Mortality and Morbidity in Heart Failure," 8442 patients with a reduced ejection fraction and NYHA classes II–IV were randomly assigned to treatment groups receiving either valsartan/sacubitril 200mg twice daily or enalapril 10mg twice daily. Patients had to have an EF of at least 40% (later reduced to at least 35%), be on a stable dose of a beta-blocker and either an ACEi (6532 patients) or an ARB (1892 patients) for at least 4 weeks prior to screening, and have a stable EF. Patients had to have NT-proBNP levels of at least 600 pg/mL or a plasma BNP level of at least 150 pg/mL. BNP levels of at least 100 pg/mL or NT-proBNP levels of at least 400 pg/mL could be present in patients who had previously been hospitalised for heart failure. Each patient received enalapril for a minimum of two weeks (median 15 days) before receiving valsartan/sacubitril for four to six weeks (median 29 days) in order to gauge tolerability. The average patient age was 64, and 87% of the patients were men. "The majority of the patients were white (66%) or Asian (18%), while only a tiny percentage (5%) were black. At the time of randomization, 82% of patients used a diuretic, 94% were taking a beta-blocker, and 58% were using a mineralocorticoid receptor antagonist". Compared to the enalapril group, which had a relative risk reduction of 26.5%, the valsartan/sacubitril group had a primary composite outcome of either death from cardiovascular causes or hospitalisation for heart failure in 21.8% of patients after a median follow-up of 27 months (p 0.001).

(PARAMOUNT) – "In the Prospective Comparison of ARni with ARB on Management Of heart failure with Preserved Ejection Fraction Trial, Solomon et al. examined the effects of valsartan/sacubitril in patients with heart failure and preserved ejection fraction (HFpEF)". In this study, patients with NYHA classes II–IV heart failure, an ejection fraction of at least 45%, and an NT-proBNP level more than 400 pg/mL were randomised to receive either valsartan/sacubitril 200 mg bid or valsartan 160 mg bid. A two-week run-in with a placebo was conducted before randomization. The main outcome was the change in NT-proBNP, a biomarker of wall stress even in the presence of neprilysin inhibition because it is not a substrate of neprilysin. In individuals with persistent heart failure, elevated NT-proBNP levels are linked to negative outcomes.[48] The mean age of the randomly selected patients, who made up 57% of them, was 71. Prior to randomization, most patients (54%) or those receiving ARBs (39%), were taking ACE inhibitors. "After 12 weeks, the valsartan/sacubitril

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group's NT-proBNP level was considerably lower than the valsartan group's (ratio of change LCZ696/valsartan, 0.77 (95%CI 0.64-0.92), p=0.005)".

ADVERSE EFFECTS:

The most frequent adverse event reported in the PARADIGM-HF and PARAMOUNT studies, occurring 18% and 19% respectively, was symptomatic hypotension. When ACEi and neprilysin inhibitor omapatrilat were combined, the risk of angioedema was three times higher than when ACEi were used alone. In addition, they can worsen renal function, cough, and hyperkalemia. Women who are pregnant shouldn't take the combination.

COST BURDEN:

Valsartan/Sacubitril combination has a high-cost burden as compared to other treatment modalities of heart failure and hypertension.

CONCLUSION:

Patients with HFrEF/HEmrEF have a lower death rate when taking Valsartan/Sacubitril, the first angiotensin receptor antagonist/neprilysin inhibitor combination. The effectiveness in additional illnesses, such as hypertension and HFpEF, will be determined in the upcoming years by ongoing clinical trials. Importantly, the long-term renal effects of the combination of angiotensin receptor antagonism and neprilysin inhibition have not yet been established; however, they are likely to be examined in upcoming trials. These studies will undoubtedly advance our understanding of the pathophysiology of heart failure and the role of this combination in treating it.

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