Review Article

ARNI: A New Approach to the Treatment of Heart Failure

Anjali A. Nair*, Aarsha Joby, Adhin John Varghese, Anamika Chalise, Ashutosh Shrestha Bana, Bidhan Kafle, Prannoy Shanker P.V., Vrinda Sreekumar

Department of Pharmacy Practice, Krupanidhi College of Pharmacy, affiliated with Rajiv Gandhi University of Health and Sciences, Bangalore, India.

***Corresponding author's E-mail:** anjalinair94@gmail.com

Received: 05-06-2018; **Revised:** 27-06-2018; **Accepted:** 11-07-2018.

ABSTRACT

Heart failure affects approximately 5.7 million people in the United States, and the number is projected to grow to more than 8 million by the year 2030.Heart failure is a complex clinical syndrome that results when diastolic ventricular filling or systolic ejection of blood is impaired or result from any structural or functional cardiac disorders which impair the ability of ventricles to fill with or eject blood. In July 2015, the FDA approved the first of a new class of drugs for the treatment of heart failure; valsartan/sacubitril (formerly known as LCZ696 and currently marketed by Novartis as Entresto). Sacubitril/valsartan is unique in simultaneously blocking the renin angiotensin system while augmenting the body's intrinsic natriuretic peptide system through neprilysin inhibition which may represent an attractive and serendipitous therapeutic approach for a range of CV diseases, including hypertension and HF, in which vasoconstriction, volume overload and neuro-hormonal activation play a part in pathophysiology. Sacubitril/valsartan should not be given in conjunction with another ARB or renin inhibitor (because of the risk of renal impairment and hyperkalemia) or an ACE inhibitor (risk of renal impairment, hyperkalemia and angio-edema). The starting dose of sacubitril/valsartan is 49 mg/51 mg twice daily. The dose should be doubled every 2–4 weeks as tolerated by the patient to the maximum dose of 97 mg/103 mg twice daily. Undoubtedly, sacubitril/valsartan opens a wide horizon for research and development in the direction of angiotensin receptors-neprilysin inhibitors, an altogether different approach in combating hypertension, cardiovascular disorders and heart failure.

Keywords: FDA, Heart Failure, Sacubitril, Treatment, Valsartan.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that results when diastolic ventricular filling or systolic ejection of blood is impaired or result from any structural or functional cardiac disorders which impair the ability of ventricles to fill with or eject blood. [1-3]

Classification

HF is classified based on left ventricular ejection fraction (LVEF) into HF with reduced EF (HFrEF) with an LVEF 40% and HF with preserved EF (HFpEF) with an LVEF ≥50%. [4] An EF between 40% and 49% is considered an intermediate zone and is termed as HF with borderline EF or HF with mid-range EF. Epidemiologic data indicate that HFpEF and HFrEF contribute equally to the total HF population.[4]

New York Heart Association Functional Classification [5]

Functional class

I. Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnoea, or palpitation.

II. Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina.

III. Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less-than-ordinary activity will lead to symptoms.

IV. Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

Clinical presentation of Heart Failure [5]

- General

  Patient presentation may range from asymptomatic to cardiogenic shock

- Symptoms

- Dyspnea, particularly on exertion
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Exercise intolerance
- Tachypnoea
- Cough
- Fatigue

- Nocturia
- Hemoptysis
- Abdominal pain
- Anorexia
- Nausea
- Bloating
- Poor appetite, early satiety
- Ascites
- Mental status changes
  - Signs
- Pulmonary rales
- Pulmonary edema
- S3 gallop
- Cool extremities
- Pleural effusion
- Cheyne-Strokes respiration
- Tachycardia
- Narrow pulse pressure
- Cardiomegaly
- Peripheral edema
- Jugular venous distension
- Hepatojugular reflux
- Hepatomegaly

Causes of Heart Failure[5]

Systolic dysfunction (decreased contractility)

- Reduction in muscle mass (e.g., myocardial infarction)
- Dilated cardiomyopathies
- Ventricular hypertrophy
  - Pressure overload (e.g., systemic or pulmonary hypertension, aortic or pulmonic valve stenosis)
  - Volume overload (e.g., valvular regurgitation, shunts, high-output states)

Diastolic dysfunction (restriction in ventricular filling)

- Increased ventricular stiffness
  - Ventricular hypertrophy (e.g., hypertrophic cardiomyopathy, other examples above)
  - Infiltrative myocardial diseases (e.g., amyloidosis, sarcoidosis, endomyocardial fibrosis)
  - Myocardial ischemia and infarction
- Mitral or tricuspid valve stenosis
- Pericardial disease (e.g., pericarditis, pericardial tamponade)

Mortality

In the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, valsartan/sacubitril significantly reduced mortality and hospitalization for heart failure, as well as blood pressure, compared to enalapril in patients with heart failure, reduced ejection fraction, and an elevated circulating level of brain natriuretic peptide or N-terminal pro-brain natriuretic peptide. [6]

Cardiovascular disease (CVD) is the major cause of mortality in developed and many developing countries, accounting for about 30% of the overall mortality [7]. Heart failure affects approximately 5.7 million people in the United States, and the number is projected to grow to more than 8 million by the year 2030. [8]

Early mortality rates associated with CVD, including those related to acute coronary syndromes, valvular and congenital heart disease, stroke, and hypertension, have decreased substantially.[9-10]

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists have improved mortality in patients with heart failure and reduced ejection fraction, but mortality remains high.[9]

FDA Approval

In July 2015, the FDA approved the first of a new class of drugs for the treatment of heart failure; valsartan/sacubitril (formerly known as LCZ696 and currently marketed by Novartis as Entresto) [10]. Neprilysin is an enzyme that participates in the breakdown of biologically active natriuretic peptides and several other vasoactive compounds. The inhibition of neprilysin has been a therapeutic target for several drugs tested in cardiovascular disease, mainly for heart failure and/or hypertension.

LCZ696 is a first-in-class neprilysin- and angiotensin-receptor inhibitor that has been developed for use in heart failure [11]. This drug is composed of two molecular moieties in a single crystalline complex: a neprilysin-inhibitor prodrug (sacubitril) and the angiotensin-receptor blocker (valsartan). This compound is able to exert a dual action while valsartan blocks the angiotensin receptor, sacubitril inhibits neprilysin, an endopeptidase which cleaves natriuretic peptides [12]. Given its mechanism of action, there is a strong mechanistic rationale for the use of sacubitril/valsartan in the treatment of heart failure (HF).[13]

Pharmacokinetics [14, 15]

Absorption

Following oral administration, sacubitril/valsartan dissociates into individual components with plasma concentrations of sacubitril, sacubitrilat, and valsartan achieving peaks in 0.5 h, 2 h, and 1.5 h, respectively.

Distribution

Sacubitril, sacubitrilat and valsartan are highly bound to plasma proteins (94%–97%) with average apparent volumes of distribution of valsartan and sacubitril around 75 L and 103 L respectively.

Metabolism

Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite can be identified in plasma at low concentrations (<10%).

Excretion

Following oral administration, 52% to 68% of sacubitril (primarily as sacubitrilat) and 13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as sacubitrilat), and 86% of valsartan and its metabolites are excreted in faeces.

Pharmacodynamics

In a 21-day study in patients with HFrEF, sacubitril/valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. It also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations[15,16]. Administration of sacubitril/valsartan for 2 weeks to healthy subjects was associated with an increase in CSF Ab1-38 with no changes in concentrations of CSF Ab1-40 or CSF Ab1-42. Notably, though sacubitrilat crosses blood–brain barrier (BBB), no corresponding increase in amyloid-b levels or amyloid-b accumulation were noted in the brain tissues of cynomolgus monkeys. [17, 18]

Dosage and administration[15,19,30]

Sacubitril/valsartan should not be given in conjunction with another ARB or renin inhibitor (because of the risk of renal impairment and hyperkalemia) or an ACE inhibitor (risk of renal impairment, hyperkalemia and angio-edema). Due to the potential risk of angio-edema when used concurrently with an ACE inhibitor, sacubitril/valsartan must not be started for at least 36 half an hour after discontinuing an ACE inhibitor. Patients and carers should discard any remaining doses to reduce the risk of accidental dosing. The starting dose of sacubitril/valsartan is 49 mg/51 mg twice daily. This should be reduced in certain groups. The dose should be doubled every 2–4 weeks as tolerated by the patient to the maximum dose of 97 mg/103 mg twice daily. Patients should also be prescribed other evidence-based drugs(β-blocker, mineralocorticoid receptor antagonist, ivabradine and digoxin) and devices (Cardiac Resynchronisation Therapy (CRT),implantable cardioverter defibrillator (ICD), as appropriate (Table-1).

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).[15,19,30]

Population with HF-REF	Starting dose of Sacubitril/Valsartan	Uptitration and target dose
No patient characterstics 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 97mg/103 mg twice daily is reached.
Currenty only taking a low target dose of ACE inhibitor or ARB+	24mg/26mg twice daily	
No ACE inhibitor or ARB in the past	24mg/26mg twice daily	
eGFR <30ml/min^2	24mg/26mg twice daily	
Moderatehepatic impairment(Child-Pugh class B)	24mg/26mg twice daily	

- Target doses of ACEI and ARBs are as follows:-captopril 50mg three times a day,enalapril 10mg twice daily,lisinopril 20mg once a day,ramipril 5 mg twice daily,trandolopril 4mg once a day ARBs-candesartan 32mg 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 24mg/26mg can be considered if eGFR is 30-6-ml/min/m^2.ARB, Angiotensin Receptor Blocker,eGFR,estimated glomeruar filtration rate

Benefits of ARNI

Hypertension

The study concluded that sacubitril/valsartan + amlodipine combination could be an effective treatment for patients with systolic hypertension uncontrolled with Amlodipine. [20, 21]

Post Myocardial Infarction

The sacubitril/valsartan group also had a lower left ventricular end-diastolic diameter, a higher left ventricular ejection fraction, and higher circular and diastolic wall strain, confirming improved left ventricular function 4 weeks after treatment. [21, 22]

Renal Impairment

Better eGFR progression, a greater decrease in BP and serum creatinine levels in patients on sacubitril-valsartan when compared to valsartan. [23, 24]

Diabetes

Those on sacubitril/valsartan were also less likely to start taking insulin or other meds for glycemic control and showed better improvements in HDL cholesterol. The significant improvement in HbA1c levels (P = 0.0055) over 3 years in the sacubitril/valsartan group vs enalapril implies that heart-failure patients with diabetes who take the drug might benefit from and even require lower doses of any antidiabetic agents they may be taking. [25, 26]

Contraindications

Sacubitril/valsartan is contraindicated:

- in pregnancy & lactation
- in patients with hypersensitivity to any component
- in patients with severe renal (eGFR <30 mL/min/1.73 m2) or hepatic impairment (Child-Pugh classification Class B and C, >7 points score)
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy
- with concomitant use of ACE inhibitors. Do not administer within 36 h of switching from or to an ACE inhibitor
- with concomitant use of Aliskiren in patients with diabetes. [27-30]

Drug interactions and Adverse reactions

Use with an ACE inhibitor is contraindicated due to increased risk of angioedema. Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increase in serum potassium concentrations. In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible though periodic monitoring of renal function should be performed. Concomitant administration with lithium may result in an increase in serum lithium concentration and lithium toxicity. Clinically significant ADR include hypotension (18%), hyperkalemia (12%), cough (9%), dizziness (6%), orthostasis (2.1%), angioedema (<1%), impaired renal function (reversible), dementia risk (theoretical). [27-30]

Mechanism of action [31]

Heart failure stimulates both the renin–angiotensin system and the natriuretic peptide system. LCZ696 is composed of two molecular moieties, the angiotensin receptor blocker valsartan and the neprilysin inhibitor prodrug sacubitril. Valsartan blocks the AT1 receptor. Sacubitril is converted enzymatically to the active neprilysin inhibitor LBQ657, which inhibits neprilysin, an enzyme that breaks down ANP, BNP, and CNP, as well as other vasoactive substances. NT-proBNP is not a substrate for neprilysin (Figure1).

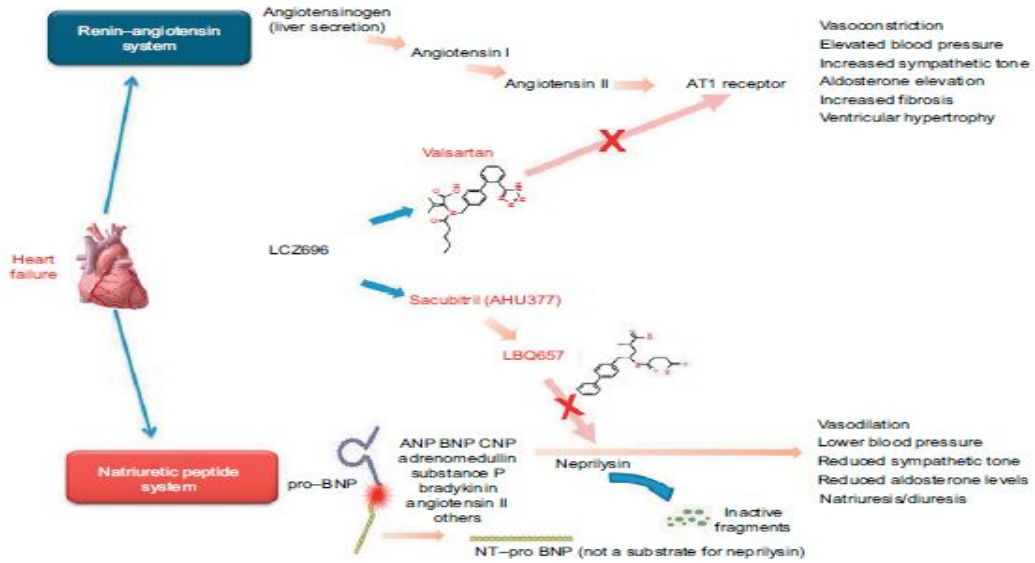

Figure 1: Mechanism of action of sacubitril/valsartan in heart failure [31].

Abbreviations

ANP, atrial natriuretic peptide; AT1, angiotensin type I; BNP, brain (or B-type) natriuretic peptide; CNP, C-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP.

Treatment [5]

Patients in stage A do not have structural heart disease or heart failure symptoms but are at high risk for developing heart failure because of the presence of risk factors.

Although treatment must be individualized, ACE inhibitors or ARBs should be strongly considered for antihypertensive therapy in patients with multiple vascular risk factors. Diuretics and β-blockers may also useful in this setting. [5]

Patients in stage B have structural heart disease, but do not have heart failure symptoms. This group includes patients with left ventricular hypertrophy, recent or remote MI, valvular disease, or reduced LVEF (less than 40%). Patients with a previous MI should receive both ACE inhibitors and β-blockers, regardless of the LVEF. Similarly, patients with a reduced LVEF should also receive both these agents, whether or not they have had aMI.1 ARBs are an effective alternative in patients intolerant to ACE inhibitors (Figure-2). [5]

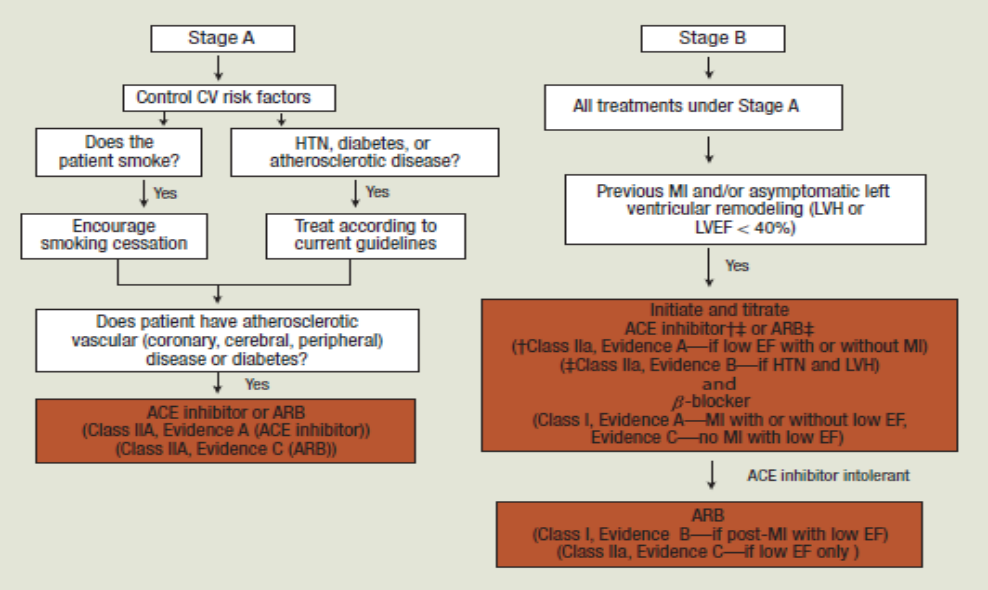

Figure 2: Treatment algorithm for patients with ACC/AHA stages A and B heart failure [5]

Patients with structural heart disease and previous or current heart failure symptoms are classified in stage C. In addition to treatments in stages A and B, most patients in stage C should be routinely treated with three medications: a diuretic, an ACE inhibitor, and a β-blocker. Aldosterone receptor antagonists, ARBs, digoxin, and hydralazine-isosorbide dinitrate are also useful in selected patients (Figure-3). [5]

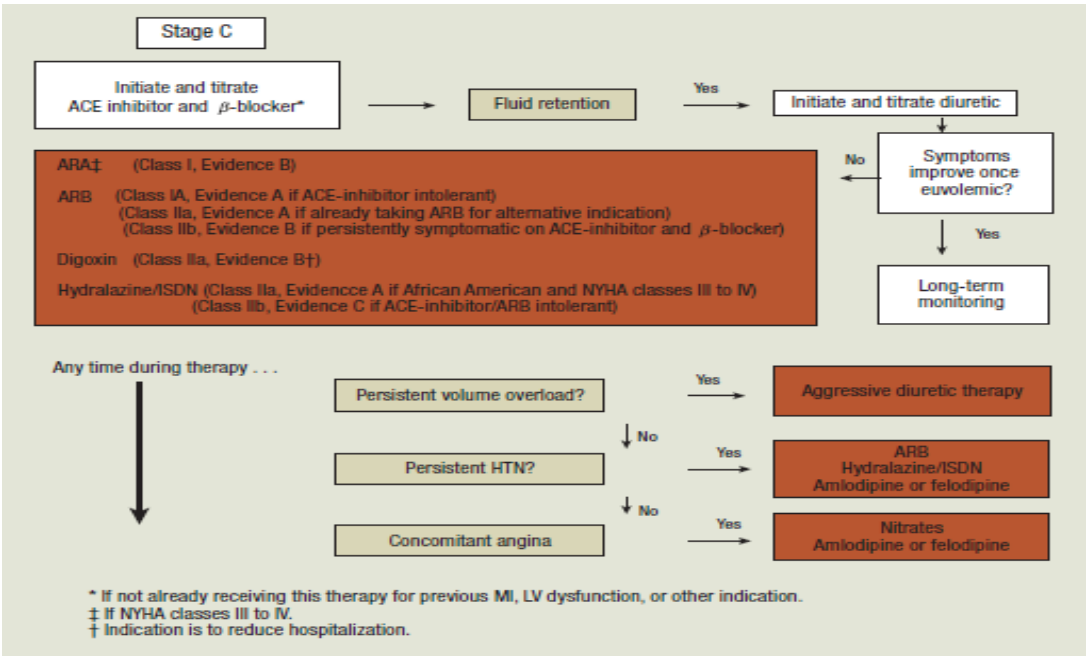

Figure 3: Treatment algorithm for patients with ACC/AHA stage C heart failure. [5]

In the double-blind period, safety was evaluated in 4,203 patients treated with ENTRESTO and 4,229 treated with enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the ENTRESTO run-in period, an additional 10.4% of patients permanently discontinued

treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice. [32]

Table 2: Comparison of ARNI(Enestro)with ACE Inhibitor(Enalapril) [32]

	ENTRESTO (n = 4,203) %	Enalapril (n = 4,229) %
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

PARADIGM-HF demonstrated that ENTRESTO, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril), in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis (hazard ratio [HR]: 0.80, 95% confidence interval [CI], 0.73, 0.87, p <0.0001). The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization; ENTRESTO also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], p = 0.0009) (Table 3). This finding was driven entirely by a lower incidence of cardiovascular mortality on ENTRESTO. [32]

Table 3: Treatment Effect for the Primary Composite Endpoint, its Components, and All-cause Mortality [32]

	ENTRESTO N=4,187 n (%)	Enalapril N=4,212 n (%)	Hazard Ratio (95% CI)	p-value
Primary composite endpoint of cardiovascular death or heart failure hospitalization Cardiovascular death as first event	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	<0.0001
Heart failure hospitalization as first event	377 (9.0)	459 (10.9)		
	537 (12.8)	658 (15.6)		
Number of patients with events: *				
Cardiovascular death**	558 (13.3)	693 (16.5)	0.80(0.71,0.89)	
Heart failure hospitalizations	537 (12.8)	658 (15.6)	0.79(0.71,0.89)	
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76, 0.93)	0.0009

*Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity

**Includes subjects who had heart failure hospitalization prior to death

CONCLUSION

The FDA approval of sacubitril plus valsartan made available a novel, oral treatment option for patients with heart failure. Sacubitril/Valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor providing systemic exposure to sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker [32]. Sacubitril/valsartan is unique in simultaneously blocking the renin angiotensin system while augmenting the body's intrinsic. natriuretic peptide system through neprilysin inhibition which may represent an attractive and serendipitous therapeutic approach for a range of CV diseases, including hypertension and HF, in which vasoconstriction, volume overload and neuro- hormonal activation play a part in pathophysiology. The potential clinical benefits from neutral endopeptidase inhibition however can only be leveraged if the renin–angiotensin–aldosterone system (RAAS) is inhibited concomitantly. The recent evidence-based ESC and AHA/ACC guidelines have recommended ARNI as an important therapeutic for the management of heart failure and prevention of sudden cardiac deaths. Undoubtedly, sacubitril/valsartan opens a wide horizon for research and development in the direction of angiotensin receptors-neprilysin inhibitors, an altogether different approach in combating hypertension, cardiovascular disorders and heart failure.While clinical trial data in patients with HFpEF are ongoing, the FDA granted approval status for sacubitril–valsartan (Entresto) in July 2015 with the indication to reduce the risk of death and hospitalization in patients with NYHA Class II-IV HFrEF. The recommended starting dose is 49/51 mg (sacubitril/valsartan) twice daily with doses doubled after 2–4 weeks to a target maintenance dose of 97/103 mg twice daily, as tolerated. A lower starting dose of 24/26 mg twice daily is recommended for patients with severe renal impairment (GFR < 30 mL/min/173 m^2).

While treatment regimens must be individualized for all HF patients, sacubitril/valsartan now warrants consideration in all suitable patients given its impact on improved survival and reduced hospitalization. [17]

REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European Journal of Heart Failure* 14, 2012, 803-869.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013, 128, 240- 327.
3. Wang CC, Chen JH, YuWC, et al. Guidelines of the Taiwan Society of Cardiology (TSOC) for the Diagnosis and Treatment of Heart Failure. *Acta CardiologicaSinica* 2012, 28, 161-195.
4. Redfield MM. Heart Failure with preserved ejection fraction. The *New England Journal of Medicine* . 375(19), 2016, 1868–1877.
5. Joseph TD. "Pharmacotherapy-A Pathophysiologic Approach." 7th ed. The McGraw-Hill Companies, Inc; 2008. 173-216.
6. Hubers S, Brown N. Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition. Circulation. 133(11), 2016, 1115-1124.
7. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics – 2016 update: a report from the American Heart Association. Circulation. 133(4), 2016, 338–360.
8. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. Circulation. 131, 2015, 322–329.
9. Ford ES, Ajani UA, Croft JB, et al. explaining the decrease in U.S. deaths from coronary disease, 1980–2000. The *New England Journal of Medicine*. 356(23), 2007, 2388–2398.
10. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 380(9859), 2012, 2095–2128.
11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of American College of Cardiology. 62, 2013, 147–239.
12. Hubers S, Brown N. Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition. Circulation. 133(11), 2016, 1115-1124.
13. Voors AA, Dorhout B, van der Meer P. The potential role of valsartan+AHU377 (LCZ696) in the treatment of heart failure. *Expert Opinion on Investigational Drugs* 22, 2013, 1041–1047.
14. Langenickel TH, Dole WP: Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. Drug Discovery Today: Therapeutic Strategy 9, 2012, 131–139.
15. Vincenzi A, Cesana F, Cirò A, Garatti L, Achilli F. Sacubitril/Valsartan in "Field Practice" Patients with Advanced Heart Failure: A Monocentric Italian Experience. Cardiology. 138(1), 2017, 13-16.
16. Fala L. Entresto (sacubitril/valsartan): first-in-class angiotensin receptor neprilysin inhibitor FDA approved for patients with heart failure. American Health & Drug Benefits. 8(6), 2015, 330–334
17. U.S. Food and Drug Administration. ENTRESTO (sacubitril and valsartan). Highlights of prescribing information. (cited 01 April 2017) http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207620Orig1s000lbl.pdf.
18. Kobalava Z, Kotovskaya Y, Averkov O, Pavlikova E, Moiseev V, Albrecht D, et al. Pharmacodynamic and pharmacokinetic profiles of sacubitril/valsartan (LC) in patients with heart failure and reduced ejection fraction. Cardiovascular Therapeutics. 34(4), 2016, 191–198
19. McMurray JJV, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). European Journal of Heart Failure. 15, 2013, 1062–1073
20. McMurray J, Packer M, Desai A, Gong J, Lefkowitz M, Rizkala A, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. The New England Journal of Medicine. 371(11), 2014, 993–1004
21. Jhund P, McMurray J. The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan. Heart. 102(17), 2016, 1342-1347.
22. Singh JS, Lang CC. Angiotensin receptor-neprilysin inhibitors: clinical potential in heart failure and beyond. Vascular Health and Risk Manage.2015, 11, 283–295
23. Wang J, Yukisada K, Sibulo A, Hafeez K, Jia Y, Zhang J. Efficacy and safety of sacubitril/valsartan (LCZ696) add-on to amlodipine in Asian patients with systolic hypertension uncontrolled with amlodipine monotherapy. Journal of Hypertension. 35(4), 2017, 877–885
24. Von Lueder TG, Wang BH, Kompa AR, et al. Angiotensin receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy. Circulation: Heart Failure. 8(1), 2015, 71–78
25. Solomon S, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LC in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 380(9851), 2012, 1387–1395
26. Ito S, Satoh M, Tamaki Y, Gotou H, Charney A, Okino N, et al. Safety and efficacy of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Japanese patients with

hypertension and renal dysfunction. Hypertension Research. 38(4), 2015, 269–275

27. Kristensen S, Preiss D, Jhund P, Squire I, Cardoso J, Merkely B, et al. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction. Circulation: Heart Failure. 9(1), 2016.
28. Seferovic J, Claggett B, Seidelmann S, Seely E, Packer M, Zile M, et al. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. The Lancet Diabetes &Endocrinology. 5(5), 2017, 333–340.
29. Ponikowski P, Voors A, Anker S, Bueno H, Cleland J, Coats A, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 37(27), 2016, 2129–2200.
30. Yancy C, Jessup M, Bozkurt B, Butler J, Casey D, Colvin M, et al. ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Journal of Cardiac Failure. 136, 2017, 137-161.
31. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. Journal of American College of Cardiology: Heart Failure CME. 2(6), 2014, 663–670.
32. Yancy C, Jessup M, Bozkurt B, Butler J, Casey D, Colvin M, et al. ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. Circulation. 134(13), 2016, 282–293.

Source of Support: Nil, **Conflict of Interest:** None.