REVIEW ARTICLE

Sacubitril/valsartan Use for the Hospitalist

Mitchell Padkins[1], James Hart[1], Rachel Littrell[2]

[1]University of Missouri School of Medicine, Columbia, MO
[2]Division of Cardiovascular Medicine, Department of Medicine, University of Missouri Health Care, Columbia, MO

Correspondence: Rachel Littrell. One Hospital Dr. Columbia, MO 65212 (littrellrl@health.missouri.edu)

Received: August 15, 2017 Accepted: October 10, 2017 Published: November 9, 2017

Am J Hosp Med 2017 Oct;1(4):2017.029 https://doi.org/10.24150/ajhm/2017.029

INTRODUCTION

The mainstays of therapy for heart failure with reduced ejection fraction (HFrEF) have traditionally been angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), beta-blockers, aldosterone receptor antagonists, and diuretics for symptomatic relief (1). With few advances made over the past few decades, the principles of treating HFrEF have been revolutionized following the results of the PARADIGM-HF trial (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) in 2014. The trial compared the novel agent sacubitril/valsartan (Entresto®) to Enalapril (1). Sacubitril/valsartan is a combination angiotensin II receptor blocker-neprilysin inhibitor (ARNI) that replaces traditional ACEI and ARB therapy in the treatment of HFrEF. The PARADIGM-HF trial was stopped early due to overwhelming evidence of decreased mortality and decreased HFrEF related hospitalizations with sacubitril/valsartan when compared to Enalapril (2). Since the study was released, the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA) released updated guidelines in May 2016. Sacubitril/valsartan now holds a Class I Recommendation for the treatment of HFrEF in patients with New York Heart Association (NYHA) class II or III heart failure (3). These recommendations were further upheld in the recently released 2017 ACC/AHA/HFSA Focused Update for the Management of Heart Failure (4).

ACC/AHA/HFSA 2017 Guidelines:

Class I Recommendation to reduce mortality and morbidity in patients with chronic HFrEF	Inhibition of RAAS system with ACEI, ARB, or ARNI in conjunction with beta-blockers, aldosterone antagonists.
Class I Recommendation for patients with HFrEF NYHA II or III who previously tolerated an ACEI or ARB.	Recommended to replace ACEI or ARB with ARNI therapy to further reduce morbidity and mortality.

Since the release of this trial, sacubitril/valsartan use has been growing rapidly among heart failure patients, and hospitalists will encounter this medication on a more regular basis. Thus, it is imperative for hospitalists to understand the clinical data and side effect profile to manage patients on sacubitril/valsartan in the hospital setting.

Role of Neprilysin

Neprilysin is a multiple substrate, membrane-bound neutral endopeptidase enzyme present in many tissues throughout the body with the highest concentrations in the renal tissue (1, 5). Neprilysin is often referred to as a

"promiscuous" enzyme for its ability to degrade multiple neurohormonal substrates, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), angiotensin II, bradykinin, adrenomedullin, glucagon, vasoactive intestinal peptide (VIP), and substance P (1). Through the inhibition of neprilysin, vasodilatory substances (specifically: ANP, BNP, and CNP) remain in an active form and promote vasodilation, diuresis, and prevent negative tissue remodeling of the heart (5, 6).

Evidence of Efficacy

The PARADIGM-HF trial was a groundbreaking study demonstrating the superiority of ARNI therapy over Enalapril in the treatment of HFrEF. Investigators for the trial included patients with NYHA class II, III, and IV heart failure who had an ejection fraction of less than 40%. These patients were also already receiving the standard of care medical therapy including ACEI, ARB, beta-blockers, and aldosterone antagonists (7). Primary end-points included death from cardiovascular causes and first hospitalizations for heart failure. The trial ended early, after only 27 months, because the primary outcomes were met before the scheduled conclusion of the study. Difference in death from cardiovascular causes or first hospitalizations for worsening heart failure was significant between the two groups with 21.8% in the sacubitril/valsartan group and 26.5% in the Enalapril group (1). Furthermore, 27 months after study initiation, sacubitril/valsartan showed a 20% relative risk reduction in hospitalizations and heart-failure mortality compared to Enalapril (6).

Clinical Use of Sacubitril/valsartan

How can hospitalists use this information to initiate and manage sacubitril/valsartan use in patients with heart failure?

Current guidelines, put forth by the ACC, AHA, and HFSA, recommend that patients with HFrEF NYHA II or III, who have previously tolerated an ACEI or an ARB, be switched to sacubitril/valsartan to further reduce morbidity and mortality (3). This switch from ACEI/ARB therapy to ARNI therapy usually occurs in the outpatient setting, but may be carefully considered in clinically stable inpatients with normal vital signs and volume status. A starting dose of 49 mg sacubitril/ 51 mg valsartan twice daily is recommended after a 36 hour ACEI washout period (2). At a follow-up appointment in two to four weeks from initiation, the dose can be increased to the target dose of 97 mg of sacubitril/ 103 mg valsartan twice daily barring any side effects (8). If patients were not on optimal ACEI/ARB therapy prior to starting ARNI therapy, or were on a low ACEI/ARB dose, then it is recommended to start at 24 mg sacubitril/ 26 mg valsartan twice daily (2). This lower initial dose is also recommended in patients with severe renal impairment and moderate hepatic impairment (2).

FDA Approved Indications:

Indications: Approved for HFrEF NYHA II-IV	To be used with other currently approved heart failure therapies.

FDA Dosing Guidelines:

Recommended Starting Dose:	49 mg sacubitril/ 51 mg valsartan. Titrate up every 2-4 weeks to reach target dose of 97 mg sacubitril/ 103 mg valsartan.
Dosing Adjustments for Patients Not Currently taking ACEI or ARB therapy, Severe Renal Impairment (GFR <30mL/min/1.73 m^2), or Hepatic Impairment (Child-Pugh B classification):	Starting dose is 24 mg sacubitril/ 26 mg valsartan. Titrate the Dose up every 2-4 weeks to target dose of 97 mg sacubitril/ 103 mg valsartan.

Upon initiation of sacubitril/valsartan there are few statistically significant side effects that clinicians should be aware of. Sacubitril/valsartan has superior vasodilator effects compared to Enalapril and thus has higher rates of symptomatic hypotension (1). However, there was no increase in the rate of discontinuation of ARNI in PARADIGM-HF due to this symptomatic hypotension (6). Furthermore, the concomitant use of diuretics in the treatment of heart failure may exacerbate this hypotension. Many clinicians decide to decrease diuretic doses when initiating sacubitril/valsartan to combat this potential hypotension and then titrate the diuretic up or down depending on the patient's clinical response.

Hyperkalemia is also a serious concern when using sacubitril/valsartan, thus patients receiving this drug should have their potassium levels closely monitored. Furthermore, patients at a higher risk for hyperkalemia (such as patients with renal failure, diabetes, or hypoaldosteronism) should not concomitantly be prescribed potassium-sparing diuretics, potassium supplements, or any medication that may significantly increase potassium (2).

The most serious side effect of sacubitril/valsartan treatment is the development of angioedema which occurred at a similar rate with Enalapril in PARADIGM-HF (6). Sacubitril/valsartan use should be avoided in patients with a history of angioedema (3). Moreover, for patients on ACEI therapy that are switching to ARNI therapy it is recommended to have a 36-hour washout period to prevent this life-threatening angioedema (3, 8).

A common occurrence among hospitalists now is to admit patients who are already established on sacubitril/valsartan. There is limited data on how physicians should handle this medication in terms of continuing or withholding its use while inpatient. Most clinicians continue sacubitril/valsartan if the patient is clinically stable and normotensive. On the other hand, if the patient presents in an acute renal failure, decompensated heart failure, or is hypotensive, sacubitril/valsartan is usually withheld until the patient stabilizes. Since there is limited data, clinicians should use their clinical judgment on whether to continue or withhold sacubitril/valsartan in newly admitted patients depending on the patient's presentation and the physician's experience and comfort level.

Patients admitted to the hospital for heart failure exacerbations provide physicians with a unique opportunity to intervene and start those patients on sacubitril/valsartan. Unfortunately, there is limited data on starting patients on sacubitril/valsartan in the hospital setting. Nevertheless, hospitalists can be an important resource in identifying patients who could benefit from this medication. If sacubitril/valsartan is to be started inpatient, it is recommended to wait until the patient stabilizes from their acute heart failure exacerbation. For instance, it is wise to wait until the patient is normotensive, has normal volume status, and laboratory measurements have returned to baseline. Furthermore, if sacubitril/valsartan is initiated in the hospital, it is necessary to ensure close follow-up with the patient's primary care provider or cardiologist to monitor symptoms, electrolytes and titrate the medication.

The main concern among clinicians and patients alike is the cost associated with sacubitril/valsartan. The cost of sacubitril/valsartan has been estimated around $12.50 per day which adds up to $4560 per year (9). This figure is many times the cost of an ACEI or ARB therapy which averages to less than ten cents per day (9). On the other hand, heart failure admission rates are expected to decline with sacubitril/valsartan use. A recent study, which performed a cost-effective analysis

comparing sacubitril/valsartan and Enalapril, estimated there would be 220 fewer hospital admissions per 1000 patients over 30 years when using sacubitril/valsartan (10). Thus, medical savings from reduced hospital admissions could be significant. An individual patient's coverage and prior authorization requirements can be quickly assessed using an online calculator (https://www.sacubitril/valsartan-coverage.com).

ARNI Therapy: Current Recommendations and Future Research

Given all the data, sacubitril/valsartan represents a revolution in the treatment of HFrEF. The 2017 ACC/AHA/HFSA Focused Update of the Guidelines for Management of Heart Failure gives sacubitril/valsartan a Class I recommendation (4). This endorsement has solidified the use of sacubitril/valsartan for the management of HFrEF. Consequently, hospitalists will be seeing this medication more and more in the inpatient setting. In addition, hospitalization may represent an ideal opportunity to initiate stable patients on sacubitril/valsartan, which provides a 20% relative risk reduction in cardiovascular death and a significant decrease in heart failure hospitalizations as compared to Enalapril. Future studies are currently underway to compare the effects of ARNI with other standard treatments, evaluate the use of ARNI therapy in patients with Heart Failure with Preserved Ejection Fraction (HFpEF), and evaluate the use of ARNI therapy after an acute myocardial infarction. Of particular interest, the upcoming TRANSITION trial will compare in-hospital initiation of sacubitril/valsartan to initiation after hospital discharge in HFrEF patients recently hospitalized for an acute decompensation. The study is expected to be completed in 2018.

The PARADIGM-HF trial paved the way for these trials and set the management of HFrEF patients on a new path to decreased patient mortality, decreased hospitalizations, and improved quality of life while living with this devastating disease.

Notes

Author contributions: All authors have seen and approved the manuscript, and contributed significantly to the work.

Financial support: Authors declare that no financial assistance was taken from any source.

Potential conflicts of interest: Authors declare no conflicts of interest. Authors declare that they have no commercial or proprietary interest in any drug, device, or equipment mentioned in the submitted article.

References

1. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. JACC Heart Fail. 2014;2(6):663-70.

2. Fala L. Entresto (Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure. Am Health Drug Benefits. 2015;8(6):330-4.

3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey JDE, Colvin MM, et al. 2016 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 FailureA 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 the American College of Cardiology. 2016;68(13):1476-88.

4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2017 ACC/AHA/HFSA Focused 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. Journal of cardiac failure. 2017.

5. McMurray JJ. Neprilysin inhibition to treat heart failure: a tale of science, serendipity, and second chances. Eur J Heart Fail. 2015;17(3):242-7.

6. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.

7. Jessup M. Neprilysin Inhibition — A Novel Therapy for Heart Failure. New England Journal of

Medicine. 2014;371(11):1062-4.
8. Okwuosa IS, Princewill O, Nwabueze C, Mathews L, Hsu S, Gilotra NA, et al. The ABCs of managing systolic heart failure: Past, present, and future. Cleve Clin J Med. 2016;83(10):753-65.
9. Sandhu AT, Ollendorf DA, Chapman RH, Pearson SD, Heidenreich PA. Cost-Effectiveness of Sacubitril-Valsartan in Patients With Heart Failure With Reduced Ejection Fraction. Ann Intern Med. 2016;165(10):681-9.
10. Gaziano TA, Fonarow GC, Claggett B, Chan WW, Deschaseaux-Voinet C, Turner SJ, et al. Cost-effectiveness Analysis of Sacubitril/Valsartan vs Enalapril in Patients With Heart Failure and Reduced Ejection Fraction. JAMA Cardiol. 2016;1(6):666-72.