Original Work

Retrospective Assessment of Sacubitril/Valsartan Prescribing Practices and Utilization in Patients With Heart Failure in a Rural Health System

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Abstract

Objective: The number of individuals diagnosed with heart failure is projected to increase in the coming years, and newer medications, such as angiotensin receptor-neprilysin inhibitors (e.g., sacubitril/valsartan) and sodium-glucose transport (SGLT-2) inhibitors (e.g., empagliflozin and dapagliflozin) have shown promising results in heart failure. The real-world prescribing practices of these newer medications warrant further investigation.

Methods: This retrospective descriptive study included reviewing electronic health records for 200 patients prescribed sacubitril/valsartan from January 1, 2015, to March 1, 2022. All patient records found to be eligible (n=163) underwent data abstraction through manual and electronic means. The primary outcome evaluated the prescribing patterns and use of sacubitril/valsartan in patients with heart failure. Secondary outcomes included whether the target dose of sacubitril/valsartan was achieved.

Results: At initiation of sacubitril/valsartan, approximately 2.5% (n=4) of study patients had a serum potassium of 5.2 mmol/L or greater, 2.5% (n=4) had an eGFR of less than 30 mL/min, and 11.9% (n=19) had a systolic blood pressure of less than 100 mmHg. Following initiation of sacubitril/valsartan, hypotension was reported in 51.5% of patients, which was the highest adverse drug reaction (ADR) identified. Dizziness, hyperkalemia, acute renal failure/acute kidney injury (AKI), cough, and angioedema were identified in 19.6%, 14.7%, 11.7%, 6.1%, and 1.8% of patients taking sacubitril/valsartan, respectively. No ADRs were identified in 30.7% of patients. The sacubitril/valsartan target dose was found to be achieved in 23.1% of all patients.

Conclusions: This study aligned with various findings from the PARADIGM HF trial and demonstrated that providers largely comply with recommended prescribing standards for sacubitril/valsartan. Adverse drug reactions seen after starting sacubitril/valsartan (e.g., decreased eGFR and systolic blood pressure, or increased serum potassium) may have influenced the titration of sacubitril/valsartan to target dose.

In the United States (US), more than 6 million adults have heart failure (HF), and that number is projected to dramatically increase in the coming years as the population ages.[1] Heart failure is one of the leading causes of hospital admission in the US, resulting in approximately 6.5 million hospital days annually.[2] Patients hospitalized for HF are at high risk of readmission.[2] Within 30 days of hospital discharge, nearly one in four patients with HF are readmitted, and almost half of those patients are readmitted within 6 months.[3] These cumulative events strongly predict mortality, and data from 2018 showed HF was mentioned on 13.4% of total death certificates in the US.[4] The high morbidity and mortality associated with HF is compounded by its significant cost burden.

Total costs associated with HF are estimated to be between $24 billion and $47 billion per year, with this number predicted to climb as HF prevalence grows.[2] Over the years, advances in HF treatment options, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta blockers (BB), and mineralocorticoid receptor antagonists (MRAs), have decreased mortality, decreased hospitalizations, lowered health care-associated expenditures, and improved quality of life.[2] Recent additions to the compendium of HF treatment options include the angiotensin receptor-neprilysin inhibitor (ARNi) sacubitril/valsartan, and sodium-glucose co-transporter 2 (SGLT-2) inhibitors (e.g., empagliflozin and dapagliflozin).

Sacubitril/valsartan is a combination of an angiotensin (II) receptor blocker (ARB) and a neprilysin inhibitor. Neprilysin is an

enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides.[5] In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, sacubitril/valsartan was shown to reduce cardiovascular death and HF hospitalization compared with enalapril in patients with chronic HF and a reduced ejection fraction.[6] Despite sacubitril/valsartan demonstrating significant mortality benefit in clinical trials and placement as first-line treatment for patients with HF with reduced ejection fraction (HFrEF) in the 2021 Guideline Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment, previous cornerstone, low-cost, effective pharmacotherapy options, such as ACEi, have largely continued to be used. However, cost analyses have consistently found sacubitril/valsartan to be a cost-effective treatment, with results being sensitive to the estimated reduction in mortality and the effectiveness associated with sacubitril/valsartan treatment.[5] This project was conducted prior to the most recent publication of the 2022 American Heart Association, American College of Cardiology, and Heart Failure Society of America (AHA/ACC/HFSA) Guidelines for the Management of Heart Failure.[7] A separate assessment of SGLT-2 inhibitor prescribing was conducted outside of this project.

Currently, there are no studies that assess the use and prescribing patterns of sacubitril/valsartan in a rural health care system in the US. Marshfield Clinic Health System, located in Wisconsin, is one of the largest rural, integrated health systems in the country. More than 2,000 patients are enrolled in the Marshfield Clinic Health System Heart Failure Improvement Clinic (HFIC) at any given time. Referrals to the HFIC come from hospitalists, cardiologists, and primary care providers. Pharmacy is consulted to perform comprehensive medication reviews prior to each patient's first HFIC appointment. This study is a retrospective cohort aimed to assess the prescribing patterns and utilization of sacubitril/valsartan in a rural physician group practice setting.

TABLE 1. Sacubitril/Valsartan Adverse Drug Reactions Gathered Manually

Angioedema	Dizziness
Hypotension	Acute renal failure/acute kidney injury
Cough	No ADRs reported

Methods

Design and Setting

A retrospective descriptive study was conducted by reviewing the electronic health records of all patients prescribed sacubitril/valsartan from January 1, 2015, to March 1, 2022, at a large tertiary care center in rural Wisconsin. Patients were screened for eligibility through multiple coding systems, including the International Classification of Diseases Ninth and Tenth Revisions (ICD-9/10), laboratory components, observations, the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System, and the Current Procedural Terminology (CPT-4) numeric coding system managed by the American Medical Association (AMA). Patients at any age were included if they had been diagnosed with any type of HF, which includes HF with reduced ejection fraction (HFrEF), defined as an ejection fraction of ≤ 40%; HF with mildly reduced ejection fraction (HFmrEF), defined as an ejection fraction of between 41% and 49%; and HF with preserved ejection fraction (HFpEF), defined as an ejection fraction of ≥ 50%, during the pre-specified timeframe using the "rule-of-one," and had taken or were currently taking sacubitril/valsartan. The "rule-of-one" was defined as having at least one distinct date associated with diagnosis of HF. Patients were excluded if they were found to have never started sacubitril/valsartan for reasons such as prohibitive costs/lack of insurance, if no prescription record of sacubitril/valsartan was found in electronic medical record, and/or if insufficient evidence was available to support a discernible timeframe of sacubitril/valsartan use (e.g., no evidence patient ever took sacubitril/valsartan, patient was lost to follow-up after one visit). This study was approved by the Institutional Review Board.

All eligible patients underwent data abstraction through both manual and electronic means. Patients' baseline characteristics, such as patient demographics (age, gender, and ethnicity), comorbid conditions (stroke, atrial fibrillation [A-fib], diabetes, hypertension, and myocardial infarction [MI]), laboratory values (serum potassium levels, estimated glomerular filtration rate [eGFR], brain natriuretic peptide [BNP], and N-terminal BNP), HF ejection fraction classification (HFrEF, HFmrEF, and HFpEF) prior to and after starting sacubitril/valsartan, and history of ACEi and/or ARB use were collected via the electronic database. Gathering of manual data included sacubitril/valsartan medication status (never started, started but discontinued, started and taken, and no record of sacubitril/valsartan use/prescription), factors affecting medication adherence/discontinuation (insurance coverage, cost, other, none or not applicable), most recent HF hospital admission date within the last 12 months prior to starting sacubitril/valsartan, first HF hospital admission date after starting sacubitril/valsartan, use of other HF medications (beta blockers, diuretics, mineralocorticoid receptor antagonists, and digoxin) within 30 days prior to starting sacubitril/valsartan, adverse drug reactions (ADRs) from sacubitril/valsartan (Table 1), medication changes that occurred based on side effects (no change, dose decrease, medication discontinuation), factors that could have affected side effect evaluation (drug interactions, contraindications, other medications started concurrently, other medications changed/take concurrently, other, or none of the above), and if the target dose of sacubitril/valsartan was achieved. Based on criteria from the PARADIGM-HF trial, hyperkalemia was defined as a serum potassium level of 5.2 mmol/L or greater and hypotension was noted if a patient had a systolic blood pressure of < 100 mmHg after starting sacubitril/valsartan.

Manually abstracted fields were collected using Computerized Medical Records (CMRs) and a REDCap database. REDCap is a secure web platform for building and

managing online databases and surveys. For this project, an internal database was used; access was given only to those with a valid REDCap account and who had been approved by the Institutional Review Board to review data as part of this study. Data downloaded from REDCap and electronically abstracted fields data was stored in a secure project management directory. The contents and access to this location are maintained by the Office of Research Computing and Analytics (ORCA) staff and complies with Marshfield Clinic Health System's archival procedures. Laboratory samples in this study were collected onsite and at other locations where the health system processes laboratory specimens.

The primary study objective was to evaluate the prescribing patterns and utilization of sacubitril/valsartan in patients with HF. Secondary objectives included whether the target dose of sacubitril/valsartan was achieved.

Statistical Analysis

Descriptive summaries were created to characterize the study cohort using standard descriptive statistics. Analyses were completed using SAS® version 9.4 (SAS Institute Inc.) statistical software.

Results

Of the 200 patients screened, 163 patients underwent analysis, and 37 were excluded. Among these eligible patients (n=163), 74.2% were male and 92% were Caucasian. Patients with HFrEF predominated the cohort, comprising 90.8% of patients, while HFmrEF was 8%, and HFpEF had the lowest percentage of patients at 0.6%. Of the total patients, 44.2% were enrolled in the HFIC. Patient characteristics at baseline preceding sacubitril/valsartan initiation are listed in Table 2 and Table 3. Comorbidities in addition to HF were assessed prior to the patient's initiation of sacubitril/valsartan. The most common comorbid condition was hypertension, which was observed in 86.5% of patients. Atrial fibrillation was the second most common comorbid condition, followed by history of myocardial infarction, observed in 55.2% and 45.4% of patients, respectively. Some characteristics that deviated from typical sacubitril/valsartan prescribing considerations included the

TABLE 2. Baseline Characteristics

Characteristic	*n*	*Mean*	*SD*	*Minimum*	*Maximum*
Age (years)	163	68	12.5	20	96
BMI (kg/m2)	93	30.5	6.9	15.5	50.4
Systolic Pressure (mmHg)	160	119.4	18.4	90	186
Diastolic Pressure (mmHg)	160	71.2	11.5	50	133
Heart Rate (bpm)	160	75.5	15.9	48	182
eGFR (mL/min)	161	61.6	17.7	12	90
Serum Potassium (mmol/L)	161	4.2	0.5	3.2	7.1
BNP (pg/ml)	137	1085.9	2224.4	5	16386
NT BNP (pg/ml)	12	3552.1	4326.2	175	11492

Abbreviations: BMI, Body Mass Index : eGFR, Estimated Glomerular filtration Rate; BNP, brain natriuretic peptide , NT BNP, N-terminal brain natriuretic peptide

TABLE 3. Additional Baseline Characteristics

Characteristic	*n*	*Percent (%)*
Male	121	74.2
Female	42	25.8
Ethnicity		
Caucasian	150	92
Other	13	8
History of ACE/ARB Use	146	89.6
Other Heart Failure Medications		
Beta Blockers	150	92
Diuretic	129	79.1
Mineralocorticoid receptor antagonist	71	43.6
Digoxin	23	14.1
Comorbid Conditions		
Stroke	14	8.6
Atrial Fibrillation	90	55.2
Diabetes	62	38
Hypertension	141	86.5
Myocardial Infarction	74	45.4
Heart Failure Ejection Fraction Classification		
HFrEF (LVEF ≤ 40%)	148	90.8
HFpEF (LVEF ≥50%)	13	8
HFmrEF (LVEF 41% - 49%)	1	0.6

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; LVEF, Left ventricular ejection fraction

following: approximately 2.5% (n=4) of patients had a serum potassium greater than 5.1 mmol/L, 2.5% (n=4) had an eGFR less than 30 mL/min, and 11.9% (n=19) had a systolic blood pressure less than 100 mmHg at drug initiation.

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were prescribed in approximately 89.6% of patients prior to starting sacubitril/valsartan. Among the other HF medications received before initiating sacubitril/valsartan, beta blockers were used in 92% of patients, diuretics in 79.1%, mineralocorticoid receptor antagonists (i.e., spironolactone, eplerenone) in 43.6%, and digoxin in 14.1%. The target dose of sacubitril/valsartan was found to be achieved in approximately 23.1% of all patients included in the analysis.

Hypotension was reported in 51.5% of patients, which was the highest ADR associated with the prescribing of sacubitril/valsartan. Dizziness was identified in 19.6% of patients, hyperkalemia in 14.7%, acute renal failure/acute kidney injury (AKI) in 11.7%, cough in 6.1%, and angioedema in 1.8% of patients. No ADRs were identified in 30.7% of patients. Some of the most common factors potentially influencing the development of ADRs included other medications being started concurrently (e.g., patient was started on spironolactone after sacubitril/valsartan was recently initiated, and then patient developed hyperkalemia) and concurrent medication dose adjustments (e.g., metoprolol dose increased at same time patient was started on sacubitril/valsartan and hypotension was noted). Factors impacting sacubitril/valsartan adherence/discontinuation for the entire population included ADRs, sacubitril/valsartan cost concerns/affordability, and lack of insurance coverage (18.4%, 11%, and 0.6%, respectively). The reason for sacubitril/valsartan discontinuation was not clearly identifiable in 67.5% of patients. When looking solely at patients prescribed sacubitril/valsartan but never started sacubitril/valsartan (n=14), cost was the main reason, comprising 78.6% of patients. Both lack of insurance coverage and ADRs were equivalent, with each category totaling 14.3%. For patients who started but ended up discontinuing sacubitril/valsartan (n=52), ADRs were the largest factor impacting discontinuation, for approximately 55% of patients, and medication cost was the second largest factor at 26.9%.

Discussion

This study revealed relevant considerations in prescribing practices and utilization of sacubitril/valsartan. Several baseline characteristics preceding initiation of sacubitril/valsartan had values that closely aligned with the PARADIGM HF pre-treatment group. In our study versus the PARADIGM HF trial, mean age was 68 years vs. 63.8 years, female sex was 25.8% vs. 21%, systolic blood pressure was 119.4 mmHg vs. 122 mmHg, heart rate was 75.5 beats per minute (bpm) vs. 72 bpm, BMI was 30.5 kg/m2 vs. 28.1 kg/m2, and hypertension was the most common comorbid medical condition prior to patients' initiation of sacubitril/valsartan. However, a number of patients in the baseline characteristics analysis had laboratory values that deviated from certain prescribing considerations.

Sacubitril/valsartan prescribing information includes a warning/precaution about development of hyperkalemia. Four patients had serum potassium level greater than 5.1 mmol/L at time of drug initiation in our study. Current findings are limited on sacubitril/valsartan use in patients with severe renal impairment, but our study included four patients with an eGFR of < 30 mL/min. Patients were also started on sacubitril/valsartan with systolic blood pressures of < 100 mmHg, although sacubitril/valsartan has been found to cause significant hypotension. Surprisingly, systolic blood pressure of < 100 mmHg contained the highest number of patients (n=19) compared to serum potassium and eGFR. One exclusion criteria in the PARADIGM HF trial was patients with a systolic blood pressure of < 100 mmHg at screening, and both the TRANSITION as well as PIONEER HF required patients to have a systolic blood pressure of at least 100 mmHg to demonstrate hemodynamic stability.[6,8,9] These findings contribute an overall view of what patient demographics, laboratory values, and comorbidities were prior to initiation of sacubitril/valsartan.

In this study, the majority of patients were found to have a history of ACEi or ARB use prior to sacubitril/valsartan initiation. The PARADIGM-HF trial required patients to receive an ACEi or ARB at stable doses equivalent to enalapril 10 mg daily with a duration of at least 4 weeks along with sequential run-in periods before randomization.[6] ACEi/ARB naïve patients have been included in previous landmark trials, such as the PIONEER HF and TRANSITION study, with results demonstrating comparable safety and efficacy in this sub-population.[8,9] Approximately 10% of patients in our study had no prior ACEi or ARB use prior to taking sacubitril/valsartan. Moreover, a large majority of the patients were on guideline-directed medication therapy (GDMT) for HFrEF, with beta blockers and diuretics having the top percentages (92% and 79.1%), and mineralocorticoid receptor antagonists being the third largest HF medication used (43.6%).

When analyzing safety outcomes, our study had high rates of hypotension and dizziness compared to other ADRs, which aligns with other clinical trial results. The PARADIGM HF trial showed a higher incidence of hypotension and symptomatic hypotension, but had a lower incidence of other ADRs, such as elevation in serum potassium, serum creatinine, or cough.[6] ADRs were noted to be the most common factor for non-adherence or discontinuation, while cost was the predominant factor deterring patients from starting sacubitril/valsartan. ADRs could be one of many factors that influenced sacubitril/valsartan dose titration.

We observed that both cost and ADRs still play a considerable role with adherence/discontinuation of sacubitril/valsartan. Although sacubitril/valsartan can be more cost prohibitive compared to ACEi, several studies have determined it is associated with high economic value. One study examined the cost-effectiveness of sacubitril/valsartan relative to ACEi for the treatment of HFrEF, with clinical probabilities based predominantly on the PARADIGM HF trial.[10] It found that sacubitril/valsartan was both more costly and effective over a lifetime, yielding $50,959 per quality-adjusted life-years (QALY) gained versus ACEi.[10] Treatment duration was a crucial contributing factor and at 3 years of follow-up, the QALY gained was approximately $250,000. Another study similarly reported that compared to an ACEi, sacubitril/valsartan use derives $45,017 per QALY

gained.[11] Additionally, it concluded that patients with HFrEF could derive cost benefits from additional life expectancy and lower rates of hospitalizations from sacubitril/valsartan use.[11] Overall, the decision must be made as to whether the extra benefit of sacubitril/valsartan seen in PARADIGM HF (e.g., cardiovascular mortality, HF hospitalization rates) outweighs the upfront drug costs.

This study has several limitations. First, it is retrospective in nature, making it more prone to confounding variables. Another limitation of this study is that patient adherence was unable to be confirmed or followed. Gaps in care can be difficult to determine, especially if patients are being seen at multiple health care facilities. Generalizability of this study is reduced due to the smaller sample size confined to one health system, the small number of ethnically diverse patients, and the population mainly consisting of males. Strengths for this study include having verified coding systems to evaluate data, analyzing relevant endpoints that were influenced by the PARADIGM HF trial design, and conducting a real-world study.

Conclusion

This study aligned with several PARADIGM HF trial findings, although there was not a comparison group. Similarities were shown with baseline patient characteristics prior to sacubitril/valsartan initiation. Our data demonstrated that providers prescribing sacubitril/valsartan mainly comply with recommended standards such as having a serum potassium of less than 5.2 mmol/L before starting sacubitril/valsartan. However, there were a few deviations noted in terms of eGFR, serum potassium, and systolic blood pressure prescribing patterns. These factors could be influencing the adverse drug reactions seen after starting sacubitril/valsartan and should be considered before patients are prescribed this medication, as a large proportion of patients attributed adherence/discontinuation to these unfavorable affects (e.g., hypotension, hyperkalemia, dizziness). The large majority of patients are also being prescribed sacubitril/valsartan with a reduced ejection fraction HF classification and are mostly on additional GDMTs. Overall, cost barriers were noted in a relatively small number of patients (11%), especially compared to ADRs, which could indicate that patients are having fewer difficulties with affordability and could lead to greater uptake in future prescribing practices of sacubitril/valsartan considering the health care-associated cost benefits.

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