Evaluating the safety and tolerability of inpatient sacubitril/valsartan initiation in a community hospital

Katie L. Peppin, Katie B. Tellor, Anastasia L. Armbruster and Martin W. Schwarze

Department of Pharmacy, Missouri Baptist Medical Center, St. Louis, MO, USA; Department of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, MO, USA; BJC Medical Group Cardiology, St. Louis, MO, USA

ABSTRACT

Background: Sacubitril/valsartan has been incorporated into guidelines based on the results of the PARADIGM-HF trial, which demonstrated reduced mortality in stable patients with heart failure with reduced ejection fraction (HFrEF). Sacubitril/valsartan is recommended in addition to other HF therapies in place of an angiotensin-converting-enzyme inhibitor or angiotensin-receptor-blocker. 

Objectives: To evaluate the safety and tolerability of sacubitril/valsartan initiation in a community hospital.

Design/methods: This single-center, retrospective review evaluated patients that received ≥24 hours of sacubitril/valsartan therapy August 2015-March 2018. The primary outcome included the incidence of hypotensive events during hospitalization. Secondary outcomes included: incidence of inpatient acute kidney injury (AKI) and hyperkalemia, rates of inpatient discontinuation, and change in ejection fraction (EF) ≥30 days after initiation.

Results: Of the 59 patients included, 21 (35.6%) experienced a hypotensive event. A total of 6 patients (10.2%) discontinued therapy while inpatient, which was more likely in patients that developed AKI (n = 3; p = 0.005) or those who experienced a hypotensive event (n = 5; p = 0.018). There was a significant difference in mean EF from baseline to ≥30 days post-initiation (24.8% vs. 33.2%; p = 0.018).

Conclusion: Careful patient selection and monitoring for hypotension, AKI, and hyperkalemia can help increase successful outcomes and improve patient safety.

1. Background

Heart failure (HF) is a debilitating disease that is estimated to affect around 6.5 million people. This number is expected to increase by 46% by the year 2030, leading to the need for new therapy that can reduce morbidity and mortality and improve outcomes for patients [1,2].

Prior to the 2016 and 2017 updates, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines focused on the use of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) in addition to other pharmacologic therapies such as beta-blockers and mineralocorticoid-receptor antagonists (MRAs) for the treatment of heart failure with reduced ejection fraction (HFrEF) [2]. After the 2016 and 2017 updates, the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) recommended sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), as initial therapy in patients with symptomatic HFrEF or as a substitution for an ACE inhibitor or ARB [3,4]. Sacubitril/valsartan is currently FDA-indicated to reduce the risk of cardiovascular death and hospitalization for HF in patients with New York Heart Association (NYHA) class II-IV and a reduced ejection fraction with a target dose of 97/103 mg twice daily [5,6].

Sacubitril/valsartan was approved by the FDA based on the results of the PARADIGM-HF study which included 8,442 stable HF patients age 18 and older with NYHA class II-IV and a LVEF ≤35%. Patients were randomized to sacubitril/valsartan or enalapril in addition to other guideline-directed medical therapy (GDMT).The primary outcome, a composite of death from cardiovascular causes or hospitalization for HF, occurred in 914 (21.8%) patients in the sacubitril/valsartan group and 1,117 (26.5%) patients in the enalapril group (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.73–0.87; P < 0.001). However, sacubitril/valsartan was associated with a significant risk of symptomatic hypotension, renal insufficiency, and elevations in serum potassium when compared to enalapril [6].

Following the publication of PARADIGM-HF trial, the PIONEER-HF trial evaluated the safety and efficacy of sacubitril/valsartan in patients hospitalized for acute decompensated HF. Eight hundred and...
eighty-one patients were randomly assigned to sacubitril/valsartan or enalapril in addition to other recommended therapies. Safety outcomes included rates of worsening renal function (13.6% vs. 14.7%), hyperkalemia (11.6% vs 9.3%), symptomatic hypotension (15% vs. 12.7%), and angioedema (0.2% vs. 1.4%); none of which were statistically significant in patients receiving sacubitril/valsartan compared to enalapril [7].

There was over a 4 year gap in the medical literature from the time PARADIGM-HF was published until the data from PIONEER-HF was available. During this time period, data from PARADIGM-HF was extrapolated to hospitalized patients. The objective of this study was to evaluate real world data regarding the safety and efficacy of initiating sacubitril/valsartan in hospitalized patients prior to publication of PIONEER-HF. In light of the safety data observed in PIONEER-HF, additional secondary objectives were to identify a patient population more likely to tolerate inpatient initiation of sacubitril/valsartan.

2. Methods

A retrospective chart review was conducted evaluating all patients receiving at least 24 hours of sacubitril/valsartan from August 2015 to March 2018 at a 489-bed tertiary care community hospital in suburban Missouri, United States. Patients were excluded if they were women of childbearing age, pregnant or nursing, or had heart failure with a preserved ejection fraction (HFrEF). This study was approved by the Institutional Review Board and informed consent was not required based on the retrospective nature of the study.

Any patient at least 18 years of age with a diagnosis of HF as evidenced by NYHA class I-IV, a history of HFrEF (ejection fraction ≥ 40%), and was initiated on sacubitril/valsartan for at least 24 hours during hospital admission from 1 August 2015 through 31 March 2018 was screened for enrollment. Only patients who had not previously been treated with sacubitril/valsartan were considered for inclusion. The starting date of this time period was chosen because sacubitril/valsartan was approved by the FDA in July 2015, and adequate time was allowed for hospital acquisition of the medication and for prescriber familiarity. The primary outcome was the incidence of hypotensive events during hospitalization, defined as a systolic blood pressure < 90 mmHg. This definition differs slightly from the PIONEER-HF AND PARADIGM-HF study that includes symptomatic hypotension as it is difficult to measure this outcome retrospectively from chart review. Additionally, PIONEER-HF was not published until 2019 which was after completion of the present study. Secondary safety outcomes included the incidence of inpatient acute kidney injury (AKI), rate of inpatient discontinuation and rationale, HF readmission at 30 days, and incidence of hyperkalemia, defined as a serum potassium > 5 mEq/L. AKI was assessed using the KGIGO 2012 definition of a decline in renal function as an increase in serum creatinine ≥ 0.3 mg/dL within 48 hours of sacubitril/valsartan initiation [8]. Secondary efficacy outcomes included the change in diuretic dose upon admission and discharge, ejection fraction within 30 days before and ≥ 30 days after initiation, and sacubitril/valsartan continuation and dose at 6 month follow-up. The secondary efficacy outcomes were collected as data became available. Oral furosemide equivalent dosing was based on those used in the DOSE trial, where 40 mg furosemide was considered to be equivalent to 20 mg torsemide or 1 mg bumetanide [9].

The following parameters were evaluated based on data collected from the patients’ electronic medical records: demographics, systolic blood pressure, serum potassium, serum creatinine, eGFR, BNP or NT-proBNP, ejection fraction within 30 days of admission and after ≥ 30 days of discharge, and NYHA class. Medication information collected included the dose and frequency of sacubitril/valsartan upon initiation, discharge, and at 6 months. Other medication information included the name and dose of other antihypertensive medications prior to admission and continued or initiated during hospital stay and at discharge including any beta-blocker, diuretic, aldosterone antagonist, ACE inhibitor,ARB, or digoxin. The name of any other concomitant antihypertensive agent not listed above or potassium supplement was collected. An indication of whether target doses of a beta-blocker or aldosterone antagonist were achieved at discharge was noted.

Descriptive statistics were utilized to characterize baseline demographics, rate of inpatient discontinuation and reason, and sacubitril/valsartan continuation and dose at 6 months. Chi-Square or Fischer’s exact was utilized for the primary outcome as well as secondary safety outcomes of inpatient AKI and hyperkalemia. Heart failure readmission at 30 days was compared to the 2017 Centers for Medicare and Medicaid Services (CMS) national average. Secondary efficacy outcomes of change in diuretic dose on admission and discharge and EF before and after initiation were analyzed using a paired T-test. P values less than 0.05 were considered to indicate statistical significance. All analyses were performed with IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp, 2013).

3. Results and discussion

Of the 198 patients identified with an order for sacubitril/valsartan from August 2015 to March 2018, 59
were evaluated (Figure 1). Exclusion reasons included: sacubitril/valsartan therapy prior to admission (n = 136), death during hospitalization (n = 1), history of HFpEF (n = 1), and inaccurate active therapy order (n = 1). Baseline demographics for evaluated patients were recorded (Table 1). The mean age was 69.4 years and 64.4% of patients were male. Of note, 30.5% of the patient population was classified as NYHA class IV on admission, which was a higher percentage than 0.2% included in the PARADIGM-HF study and 8.9% in PIONEER-HF [6,7]. This may be due to patients admitted for acute decompensated HF identifying as NYHA class IV compared to the more stable outpatient population in PARADIGM-HF. The PIONEER-HF study also had stricter exclusion criteria including patients classified as hemodynamically unstable, those requiring increased diuretic dose, IV vasodilators, and no inotropes in the previous 24 hours. This was also the index HF admission for 30.5% of the total patient population. There were no known hemodialysis patients. When looking at GDMT, 64.4% of patients were either on an ACE inhibitor or ARB on admission and overall, a higher percentage of patients were discharged on a beta-blocker, diuretic, and spironolactone therapy than at baseline (Figure 2). The number of patients previously on an ACE inhibitor or ARB was slightly higher than the patient population evaluated in PIONEER-HF (47.3%) [7]. However, when compared to the PARADIGM-HF study, where only 20 patients (< 1% of overall study population) were not receiving the protocol-required treatment with an ACE inhibitor or ARB at the screening visit, the current study included a higher percentage of de novo sacubitril/valsartan initiations [6].

Sacubitril/valsartan regimens based on initial dose and frequency are reported in Table 2. Six patients (10.2%) were initiated on doses lower than the traditional starting dose of 24–26 mg twice daily. One patient (1.7%) was initiated on 12–13 mg once daily due to baseline hypotensive events requiring midodrine. Three patients (5.1%) were initiated on 12–13 mg twice daily also related to hypotension. Two patients (3.4%) were started on 24–26 mg once daily, one due to baseline hypotension and the other due to concerns with tolerability and AKI. Taking

**Table 1. Baseline demographics.**

| Baseline Demographics | N = 59 |
|-----------------------|-------|
| Age (years), mean     | 69.4  |
| Male sex, n (%)       | 38 (64.4) |
| Race, n (%)           |       |
| Caucasian             | 53 (89.8) |
| Black                 | 6 (10.2) |
| Length of stay (days), mean ± SD | 8.7 ± 7.2 |
| NYHA Class, n (%)     |       |
| 2 to 3                | 41 (69.5) |
| 4                     | 18 (30.5) |
| Diabetes, n (%)       | 30 (50.8) |
| Hypertension, n (%)   | 41 (69.5) |
| Ischemic HF, n (%)    | 26 (44.1) |
| Chronic kidney disease, n (%) | 11 (18.6) |
| Implantable cardioverter device (ICD), n (%) | 14 (23.7) |
| Index heart failure admission, n (%) | 18 (30.5) |
| sCr (day of initiation), mean | 1.13 mg/dL |
| sCr (peak), mean      | 1.17 mg/dL |
| Serum potassium peak, mean | 4.3 mEq/L |
| BNP (admission), mean | 1204 pg/mL |
| BNP (discharge), mean | 708 pg/mL |
| NT-Pro BNP (admission), mean | 8573 pg/mL |
| NT-Pro BNP (discharge), mean | 4169 pg/mL |
| Hospital day initiated, mean | 5.1 |
these patients into consideration, there were 38 (64.4%) initiated on the standard 24–26 mg twice daily dose. All patients previously on ACE therapy were appropriately initiated after a 36-hour washout period. Four of the 15 patients initiated on the 49–51 mg twice daily dose had not been on ACE or ARB therapy prior to admission, indicating an inappropriate starting dose according to traditional initiation of the medication.

Overall, 21 (35.6%) patients experienced a hypotensive event, which was more likely to occur in patients without a past medical history (PMH) of hypertension ($P = 0.007$) (Table 3). All patients who experienced a hypotensive event were Caucasian. This could potentially be attributed to decreased blood pressure responses to ARBs observed in Black patients compared to Caucasian patients [10].

---

**Table 2.** Sacubitril/valsartan starting dose and frequency.

| Starting Dose and Frequency, n (%) | N = 59 |
|----------------------------------|-------|
| 12–13 mg once daily              | 1 (1.7) |
| 12–13 mg twice daily             | 3 (5.1) |
| 24–26 mg once daily              | 2 (3.4) |
| 24–26 mg twice daily             | 38 (64.4) |
| 49–51 mg twice daily             | 15 (25.4) |

**Table 3.** Characteristics of adverse drug events.

| Characteristic, n (%) | Hypotension | AKI | Hyperkalemia |
|-----------------------|-------------|-----|--------------|
| Age, mean             | 67.1        | 70.6 | 0.316        |
| Weight (kg), mean     | 84.8        | 96.8 | 0.081        |
| Caucasian             | 21 (100.0)  | 32 (84.2) | 0.080 |
| PMH of hypertension   | 10 (47.6)   | 31 (81.6) | 0.007 |
| PMH of CKD            | 5 (23.8)    | 6 (15.8) | 0.498 |

---

**Figure 2.** Guideline-directed medical therapy.

**Figure 3.** Sacubitril/valsartan dose.
were 4 cases of AKI and 5 cases of hyperkalemia that occurred while inpatient. However, 1 patient that experienced hyperkalemia also was receiving concomitant potassium supplementation. On average, patients who experienced an AKI were older (73.2 vs. 68.9 years; p = 0.527) with a higher average weight (102.5 vs. 88.3 kg; p = 0.280) than those who did not. Two of the 4 patients who experienced AKI also experienced a hypotensive event. A total of 6 patients (10.2%) discontinued therapy while inpatient, which was more likely in patients that developed AKI (n = 3; p = 0.005) or those who experienced a hypotensive event (n = 5; p = 0.018). Of the 3 patients who developed an AKI, only 1 appeared to have discontinued solely for this reason. Other causes of discontinuation included cost-related issues (n = 3) (Table 4). There were 7 (11.9%) HF readmissions at 30 days compared to the CMS 2017 national average of 21.6%, representing a lower overall readmission rate [11]. The CMS rate appears to be similar to that of the current study intuition. There was a statically significant difference in mean EF before initiation and ≥ 30 days post-initiation. (24.8% vs. 33.2%; p = 0.018) (Table 5). There was a non-significant increase in mean total daily diuretic dose between admission and discharge, expressed as oral furosemide equivalents (62.1 mg vs. 70.6 mg; p = 0.124). It has been theorized that sacubitril’s effectiveness in promoting diuresis may lead to a reduction in the dose of a concomitant loop diuretic.

A total of 51 patients were discharged on sacubitril/valsartan. Of these patients, 28 (54.9%) were discharged on the 24–26 mg twice daily regimen, while 17 (33.3%) were sent home on 49–51 mg twice daily (Figure 3). A small subset of 4 (7.8%) patients who remained hypotensive throughout hospitalization were discharged on a lower than recommended dose of 12–13 mg twice daily. Finally, there were 2 (3.9%) patients discharged on the target dose of 97–103 mg twice daily, however, both had been initiated on the median dose of 49–51 mg twice daily. This varies from the recommended titration pattern of doubling the dose every 2 to 4 weeks, as tolerated by the patient. There were 25 patients with 6-month follow-up dose data available. There were 9 (36%) patients who achieved the target dose, while 7 (28%) of patients continued on 49–51 mg twice daily. Of those that met the target dose, four were initiated on 49–51 mg twice daily and 5 on 24–26 mg twice daily while inpatient. The remaining 9 patients (36%) remained on 24–26 mg twice daily. Six of the 9 patients on the lowest dose at 6-months were also initiated on that same dose, while 2 were originally initiated on 12–13 mg twice daily and one was initiated on 24–26 mg once daily due hypotensive events. There were 14 patients who did not have any follow-up data available to analyze.

4. Conclusion

The results of the PIONEER-HF trial established that sacubitril/valsartan can safely be initiated in patients hospitalized with acute decompensated HF in a controlled-clinical trial environment [7]. The results of this retrospective study highlight the challenges that clinicians may encounter when initiating sacubitril/valsartan in hospitalized patients. Overall, the rate of inpatient discontinuation of sacubitril/valsartan was low at 10.2%, however, the risk was significantly associated with patients that developed AKI or those that experienced a hypotensive event. Medication cost also played a role in continuing therapy post-discharge. Initiating sacubitril/valsartan during hospitalization, including newly-diagnosed or unstable HF patients, as compared to the stable HF patients in the PARADIGM-HF trial may pose some challenges highlighted in this study. In general, patients with stable renal function, serum potassium levels, and blood pressure appear to be more likely to be successful when initiated in this setting. The overall 30-day readmission rate was lower than the CMS national average which may prove to be clinically significant [11]. Patients discharged on sacubitril/valsartan were found to have significant improvement in mean EF. However, the addition of other GDMT such as a beta-blocker or aldosterone antagonist must be considered as a potential confounder of improved EF, especially since 30.5% of the patient population were newly-diagnosed HF patients. There are also many other acute situations during hospitalization that can increase a patient’s risk of hypotension, acute kidney injury, and hyperkalemia, which may also have an influence on initiating therapy. Although sacubitril/valsartan initiation has been primarily studied in an outpatient setting,

| Table 4. Inpatient discontinuation. |
|-------------------------------------|
| Outcome, n (%) | N = 59 | P-value |
|----------------|--------|---------|
| Inpatient discontinuation | 6 (10.2) | – |
| Developed AKI | 3 (75) | 0.005 |
| Hypotensive Event | 5 (21.8) | 0.018 |
| Cost | 3 (5) | – |

| Table 5. Secondary efficacy outcomes. |
|--------------------------------------|
| Outcome | Admission n = 32 | Discharge n = 32 | P-value |
|------------------|----------------|----------------|---------|
| Total daily diuretic dose, mean | 62.1 mg | 70.6 mg | 0.124 |
| Before initiation | Post-Initiation n = 21 | n = 21 |
| Ejection fraction, mean | 24.8% | 33.2% | 0.018 |
careful attention to the previous factors can help ensure successful inpatient initiation.

In the PARADIGM-HF trial, hypotension was defined as a symptomatic patient with SBP < 90 mmHg and occurred in 112 (2.7%) of the patient population compared to 21 (35.6%) in the current study. The study investigators in the PIONEER-HF trial used a slightly more stringent definition of SBP < 100 mmHg with 15% of the patients randomized to sacubitril/valsartan experiencing an event. The increased findings in the present study could be related to the acuity of the current patient population and potential for other contributors to hypotension in hospitalized patients. In PARADIGM-HF decline in renal function, defined as end-stage renal disease, a decrease of ≥50% in eGFR or a decrease of > 30 ml/min/1.73m² to <60 ml/min/1.73m², occurred in 94 (2.2%) of patients as compared to a lower threshold of worsening renal function defined in PIONEER-HF, increased serum creatinine concentration > 0.5 mg/dL and >25% decreased in eGFR that captured an incidence of 66 patients (15%) [6,7]. The differences in definition between the two studies, and the present study (event rate of 8.9%), could potentially explain the various incidence rates. Lastly, the PARADIGM-HF and PIONEER-HF study defined hyperkalemia as a serum K > 5.5 mEq/L, occurred in 674 (16.1%) and 51 (11.6%) of the respective studies compared with 5 (11.1%) in this study. The variability in this outcome can be contributed to the definitions used in each study. The differences in the safety outcomes can also be explain based on the study population. In PARADIGM-HF patients had to complete a 4 to 6 week run-in period prior to receiving sacubitril/valsartan [6]. The PIONEER-HF study aimed to evaluate patients with acute decompensated HF; however, patients needed to hemodynamically stable prior to receiving the study medication [7]. Due to it to the retrospective nature of the study, the patients’ hemodynamic status could not always be accurately captured and treatment choices were at the discretion of the treating clinician.

There are several limitations to this study. This is a single-institution, retrospective review at a community hospital that only focused on sacubitril/valsartan without a control group to rule out other potential factors that may have influenced the results of the experiment. The retrospective nature of the study allows for error in data abstraction from electronic medical records. The patients were not prospectively observed during their hospitalization; therefore, physician documentation was heavily relied upon. This leaves room for bias in the interpretation of medical records, and allows for error in documentation at the time of hospitalization. Several patients were initiated on sacubitril/valsartan the day prior to discharge, making the measurement of key outcomes such as hypotension, AKI, and hyperkalemia not possible to assess. In addition, the retrospective nature of the study makes it difficult to directly attribute the improvement in ejection fraction to sacubitril/valsartan alone, since other HF therapies may have been modified or initiated around the same time. Sampling bias of prescribers must also be noted as the majority of sacubitril/valsartan was initiated by cardiologists, who may have extensive knowledge of patients who are more likely to be successfully initiated. Additionally, the small sample size and low rates of ADEs and inpatient discontinuation rates could underestimate the true effects.

Based on the aforementioned limitations, further investigation is warranted. However, in the absence of additional real world data regarding the safety and tolerability of sacubitril/valsartan, these results can help prescribers be mindful of the common ADRs that may lead to drug discontinuation while inpatient and the benefits of continued therapy. Important parameters to consider when initiating therapy include frequent blood pressure monitoring and daily assessment of sCr and serum potassium. These parameters can help increase appropriateness of modifying HF therapy regimens in order to provide optimal patient outcomes and improve patient safety. As the treatment for HF continues to evolve, it is important for hospitals to ensure appropriate medication therapy is being implemented to guarantee the highest rates of patient success post-discharge to prevent future readmissions. By providing education to healthcare providers in order to increase appropriateness of therapy, sacubitril/valsartan can be safely initiated in an inpatient setting when careful monitoring of the above parameters occur. Opportunities for improvement in the prescribing of sacubitril/valsartan have been identified, particularly those that pertain to dosing the medication appropriately.

Disclosure statement
Dr. Peppin has no conflicts of interest; Dr. Tellor has no conflicts of interest; Dr. Armbruster has no conflicts of interest; Dr. Schwarze is on the speaker’s bureau for Novartis Pharmaceuticals.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID
Katie L. Peppin http://orcid.org/0000-0001-9710-6976
Katie B. Tellor http://orcid.org/0000-0003-0980-9888
Anastasia L. Armbruster http://orcid.org/0000-0002-1516-4118
References

[1] Yancy CW, Jessup M, Bozkurt B, et al. 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(16):e240–e327.

[2] Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. DOI:10.1161/CIR.0000000000000485.

[3] Yancy CW, Jessup M, Bozkurt B, et al. ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guidelines for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on clinical practice guidelines and the heart failure society of America. J Am Coll Cardiol. 2016;2017. DOI:10.1016/j.jacc.2017.04.025

[4] Yancy CW, Jessup M, Bozkurt B, et al. ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guidelines for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on clinical practice guidelines and the heart failure society of America. J Am Coll Cardiol. 2017;2017. DOI:10.1016/j.jacc.2017.04.025

[5] Entresto [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2015.

[6] McMurray JV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.

[7] Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2018 Nov 11. DOI:10.1056/NEJMoa1812851

[8] Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney inter., Suppl. 2012;2:337–341.

[9] Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797–805.

[10] Helmer A, Slater N, Smithgall S. A review of ACE inhibitors and ARBs in Black patients with hypertension. Ann Pharmacother. 2018 Nov;52 (11):1143–1151.

[11] Centers for Medicare & Medicaid Services. 2017. https://www.medicare.gov/hospitalcompare/