Original Work

Impact on Loop Diuretic Doses When Combining with Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure

by Marcus Pribyl, PharmD, Jared Verber, PharmD

Abstract

Objective: The primary objective of this evaluation was to determine loop diuretic doses when establishing patients on sodium-glucose cotransporter-2 inhibitors (SGLT2i) in patients with heart failure with reduced ejection fraction (HFrEF). A secondary objective was to evaluate the correlation between the risk of developing acute kidney injury (AKI) or dehydration leading to emergency department (ED) visits when combing SGLT2i with loop diuretics compared to loop monotherapy.

Methods: This quality improvement project used retrospective observational design. Through chart review, patients were included if they were being followed by the SSM Health Monroe Clinic cardiology clinic with a diagnosis of HFrEF and were using a loop diuretic. Patients were separated into the combination group, which included those who were using both an SGLT2i and a loop diuretic, or the control group if they were utilizing a loop diuretic as monotherapy. Data was collected upon initiation of SGLT2i, at 3 months, at 6 months, at 1 year, and at the end of the evaluation. The dose of loop diuretic normalized to furosemide equivalents was recorded along with the patients' renal labs.

Results: The patients in the combination group had an ~ 8 mg/day reduction in their average loop diuretic usage compared to an increase of about 6 mg/day in the loop monotherapy group. There was no indication of a difference in rates of acute kidney injury between the two groups.

Conclusions: Providers should monitor for the opportunity to reduce loop diuretic doses when initiating an SGLT2i. There were no major changes in renal function when adding an SGLT2i to loop diuretics in patients with HFrEF.

In 2020, heart failure impacted around 6.2 million Americans and in 2018 accounted for 13.4% deaths in the country.[1] Heart failure cost the United States $30.7 billion in 2012, and that number has been expected to rise even more with the increased cost of healthcare and medications.[2] Currently, the American Heart Association and American College of Cardiology recommend a multifaceted approach to treating heart failure with reduced ejection fraction.[3] This includes but is not limited to angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNI), beta blockers, aldosterone antagonists, diuretics, and other individualized therapies. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce major cardiac events (MACE) and were added as one of the pillars of guideline-directed medical therapy for heart failure, regardless of type II diabetes status, due to removal of more fluid and sodium to reduce strain on the heart.[3] The American Diabetes Association (ADA) also recommends using SGLT2i in diabetes patients if they have heart failure or have a history of cardiovascular disease or chronic kidney disease.[4]

The combination of a loop diuretic and SGLT2i can result in increased diuresis.[3] This is due to the loop diuretic's ability to block sodium and chloride reabsorption in the loop of Henle, causing water to follow the higher salt content into the concentrated urine. Since SGLT2is work in the proximal tubule before the loop of Henle, this results in additional diuresis before the loop diuretic takes effect downstream. This additive effect could be beneficial in managing heart failure patients' fluid levels. However, in theory this can also lead to dehydration, acute kidney injury (AKI) and long-term kidney damage if not managed properly. This could put heart failure patients with fragile renal function at risk for further damage if these medications are not properly managed.

Currently, there is limited information available regarding the use of loop diuretics with SGLT2i. Heise and colleagues conducted a crossover study that compared the effects on serum creatinine (Scr) among 22 patients using empagliflozin and torsemide, compared to using one of the agents individually.[5] Patients were given one agent (either empagliflozin or torsemide) for a period of 5 days. Patients then went through a washout period and were given the other agent individually or both agents for 5 days, followed by a 5-day washout period, and then received the final 5-day treatment of the group they had not received yet. Scr levels were evaluated after each period. Over this time, patients undergoing therapy with both empagliflozin and torsemide had a Scr increase of 0.7 mg/dL ($p<0.05$) compared to either agent individually. This indicates that upon initiation of these agents there is potential

for renal damage and AKI.

Charaya and colleagues looked at patients admitted to the hospital for acute heart failure exacerbation and compared 50 patients receiving dapagliflozin 10 mg to 52 patients receiving placebo.[6] All patients received standard of care medications during their hospital stay, which included loop diuretics. Patients who were already initiated on a loop diuretic were also included in this trial. The primary outcome of renal function decline (defined as a Scr increase of 0.3 mg/dL or greater in less than 48 hours) found a prevalence rate of 34.4% of patients in the dapagliflozin group compared to 15.2% in the placebo group but was not statistically significant (p=0.07). It was also found that loop diuretic doses were an average of 78 mg/day in the treatment group compared to 102 mg/day in the placebo group (p=0.001).

Wilcox and colleagues evaluated the effects on Scr when using bumetanide and dapagliflozin in 42 patients.[7] Patients were randomized to receive one week of either dapagliflozin 10 mg, bumetanide 1 mg, or both. Then after one week, they received the combination of dapagliflozin 10 mg and bumetanide 1 mg for one week. In all groups they found a 0.1 mg/dL increase in Scr after 8 days of therapy (p<0.005). This study indicates the two medication classes might not have a clinically significant medication interaction.

Recently, the EMPEROR-Preserved Trial completed a post hoc analysis in 5,815 patients who were using loop diuretics with empagliflozin who had heart failure with preserved ejection fraction.[8] Patients were taking either empagliflozin or placebo and receiving loop diuretics dosed to their fluid status. It was found that patients who were taking empagliflozin were found to have a decreased chance of loop diuretic dose escalation compared to placebo (HR, 0.74; 95% CI, 0.65-0.84). It was also found that patients who were taking empagliflozin were more likely to require a loop diuretic dose reduction (HR, 1.15; 95% CI, 1.02-1.30). The empagliflozin group was also associated with an increased risk of volume depletion compared to placebo (HR, 1.34; 95% CI, 1.13-1.59). This study highlights the possible risk when combining these two medication classes in HFpEF but does not address patients diagnosed with HFrEF..

These studies are limited by short duration or small patient populations, or did not discuss patients with HFrEF. Even with these limitations, the studies do illustrate the potential for renal damage with the combination therapy, which warrants further investigation. The objective of this evaluation was to determine loop diuretic doses when patients with HFrEF were initiated on an SGLT2i.

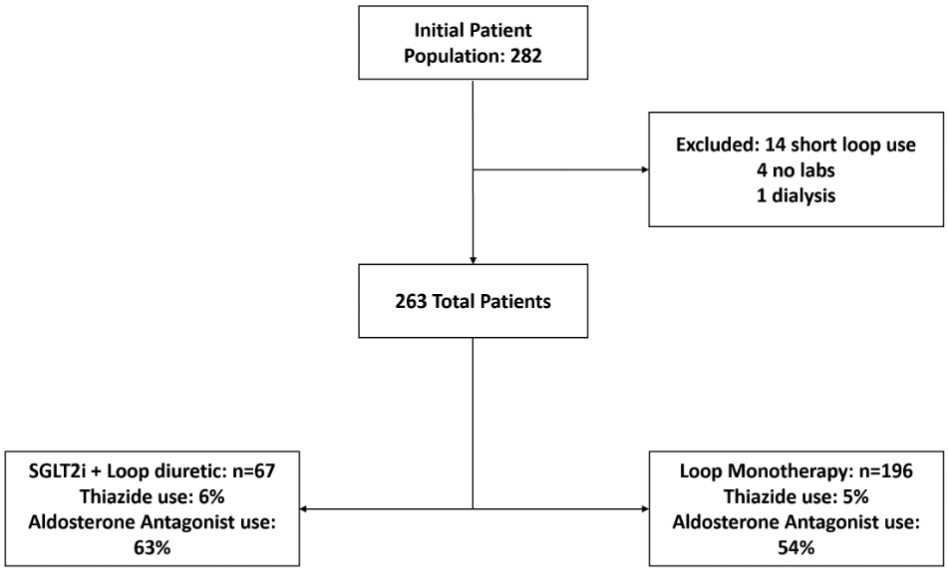
Methods

The SSM Health Monroe Clinic's cardiology clinic sees a variety of patients for cardiology related disease states including, but not limited to, heart failure, hypertension, coronary artery disease, and various arrythmias. Patients can self-refer or be referred by another provider to be seen in the clinic. The cardiology clinic employs an ambulatory care pharmacist who sees patients with a cardiologist for one half-day day per week for patients with a diagnosis of heart failure, regardless of classification. These cardiology clinic visits focus mostly on the respective disease state for which the patient was referred. Patients are typically seen in 3-month intervals initially with follow-ups lengthening as greater control of the disease state is achieved.

To identify patients for this retrospective evaluation, the electronic medical record's search function was used to perform a patient search to identify patients who received care at the Monroe Clinic Cardiology Clinic with a diagnosis code for HFrEF and who had been taking a loop diuretic since 2018. The patient list ran through June 2022 when the search was completed. Patients were included in the evaluation if they had a diagnosis of HFrEF and were taking a loop diuretic and/or an SGLT2i. The combination group was considered to be patients who were taking both an SGLT2i and a loop diuretic and the control group was defined as the patients who were only taking a loop diuretic. All SGLT2i medications at any dose were included in this evaluation, independent of target HFrEF dose and prescribed indication. Patients were excluded from this evaluation if they had only used a loop diuretic for less than 1 month, no lab data was available, or they were receiving dialysis. Data were collected via chart review at the following time points: baseline initiation of SGLT2i, 3 months, 6 months, 1 year, and end of evaluation (June 2022). At each time interval, the patient's daily loop diuretic dose was recorded and converted to furosemide equivalents. Renal labs (Scr, blood urea nitrogen [BUN]) and any emergency department (ED) visits with a primary diagnosis of AKI or dehydration were also collected at each time interval. Use of a thiazide diuretic or an aldosterone antagonist were recorded as possible confounding variables.

The primary outcome for this evaluation was the reduction of loop diuretic doses after initiation of an SGLT2i. Secondary outcomes included number of ED visits due to AKI or dehydration along with

FIGURE 1. Patient Inclusion Into Evaluation



changes in renal labs (Scr and BUN). Once all patient data was collected, the mean daily loop diuretic dose (in furosemide equivalents) in each group was calculated along with mean Scr and BUN at each time interval. A two-sample t-test was used to determine statistical significance between the two groups for mean daily loop diuretic use. Some patients were taking a loop diuretic on an as-needed basis at various points during the review. This data was important to capture because it still represents a dose change. To try to capture the true value of a patient's loop diuretic usage, the mean loop diuretic dose was calculated under the assumption that the as-needed dose was 0 mg per day initially. Then a sensitivity analysis was completed assuming the loop diuretic usage was 20 mg of furosemide per day because this is what the as-needed patients were prescribed.

Results

When the initial data pull was completed, 282 patients were identified as candidates for this evaluation. After completing chart reviews of patients, 19 were excluded due to at least one of the following reasons: short term course of a loop diuretic (defined as less than 1 month of therapy), no labs were available for the patient, or patient was on dialysis. Of the remaining 263 patients, 67 were taking an SGLT2i. The loop diuretic monotherapy group was comprised of 196 patients (Figure 1). Regarding concurrent diuretic use, similar proportions of patients used thiazides in the combination group compared to the loop diuretic monotherapy group (6% vs. 5%, respectively). A higher proportion of patients took aldosterone antagonists in the combination group compared to the loop diuretic monotherapy group (63% vs. 54% respectively).

Some patients used a loop diuretic only as needed in both groups. This value varied throughout the evaluation timeline as some patients transitioned on and off an as-needed dose (Table 1). Table 2 indicates the mean loop diuretic dose (in furosemide equivalents) if the patients were taking 0 mg per day of their furosemide, and Table 3 indicates the mean dose if they were taking 20 mg per day of furosemide. For patients who were taking SGLT2is, the mean loop diuretic dose at baseline was 53.1 ± 0.4 mg of furosemide per day compared to 45.0 ± 0.2 mg per day in the monotherapy group. Following combination therapy, the average loop diuretic dose decreased to 46.9 ± 0.6 mg and 45.2 ± 0.8 mg after 6 months and 1 year, respectively. The mean loop diuretic dose in the monotherapy group increased to 47.1 ± 0.2 mg at 6 months and 48.4 ± 0.3 mg at 1 year (Tables 2 and 3). See Table 4 for mean changes in daily loop diuretic dose.

For patients who were taking both an SGLT2i and a loop diuretic, the average baseline Scr was 1.19 mg/dL and the average BUN at baseline was 24.76 mg/dL. Patients who were taking only a loop diuretic had an average baseline Scr of 1.17 mg/dL and BUN of 25.17 mg/dL. After 6 months of therapy the loop monotherapy group increased to 110% of the original Scr baseline level, compared to the combination group staying at 106% of the original Scr baseline level (Table 5).

TABLE 1. Number of patients on a PRN Loop Diuretic

Number of Patients	*Baseline*	*3 Months*	*6 Months*	*1 Year*	*End of Evaluation*
Loop Monotherapy	5	4	4	4	2
SGLT2i + Loop Diuretic	3	7	5	3	2
PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors					

TABLE 2. Mean Daily Loop Diuretic Usage (prn = 0 mg/day)

(Doses Adjusted to Furosemide Equivalents)	*Baseline (mg/day)*	*3 Months (mg/day)*	*6 Months (mg/day)*	*1 Year (mg/day)*	*End of Evaluation (mg/day)*	*P-value (baseline to end of Evaluation)*
Loop Monotherapy	44.8	47.5	46.9	48.2	51.2	0.104
SGLT2i + Loop Diuretic	52.7	50.6	46.3	44.4	44.0	0.302
PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors						

TABLE 3. Daily Loop Diuretic Usage (prn = 20 mg/day)

(Doses Adjusted to Furosemide Equivalents)	*Baseline (mg/day)*	*3 Months (mg/day)*	*6 Months (mg/day)*	*1 Year (mg/day)*	*End of Evaluation (mg/day)*	*P-value (baseline to end of Evaluation)*
Loop Monotherapy	45.2	47.9	47.3	48.7	51.6	0.103
SGLT2i + Loop Diuretic	53.4	52.3	47.5	46.0	45.6	0.346
PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors						

TABLE 4. Average Change in Loop Diuretic Usage

	PRN = 0 mg/day	*PRN = 20 mg/day*
Loop Monotherapy	6.3 mg/day	6.4 mg/day
Loop + SGLT2i	-8.8 mg/day	-7.8 mg/day
P values	p=0.049	p=0.06
PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors		

The breakdown of the number of patients who were taking each SGLT2i is listed in Table 6. The two patients who were prescribed canagliflozin were initially prescribed empagliflozin but were changed due to insurance coverage. The most common SGLT2i used was empagliflozin (75%).

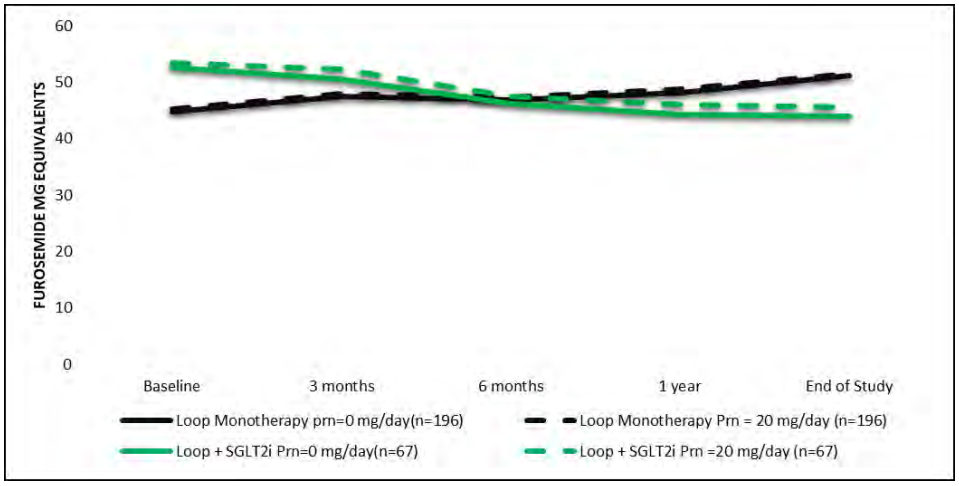
The proportion of patients who presented to the ED with a primary diagnosis of dehydration or AKI was 3% for patients in the combination group and 2.6% for the loop monotherapy group. The 2 patients who presented to the ED in the combination group were both on empagliflozin 10 mg daily.

Discussion

We found that loop diuretic doses were reduced by about 8 mg/day in the combination group compared to a dose increase of about 6 mg/day in the monotherapy group over time. There was no clinically significant change in Scr when comparing the two groups, and based on Table 5, the combination group may have demonstrated a slower rate of renal decline. The slight increase in BUN for the combination group was likely due to a higher amount of fluid loss if patients were possibly less hydrated compared to the monotherapy group. However, this risk was not shown in the proportion of ED visits due to dehydration or AKI, with clinically insignificant differences between the two groups.

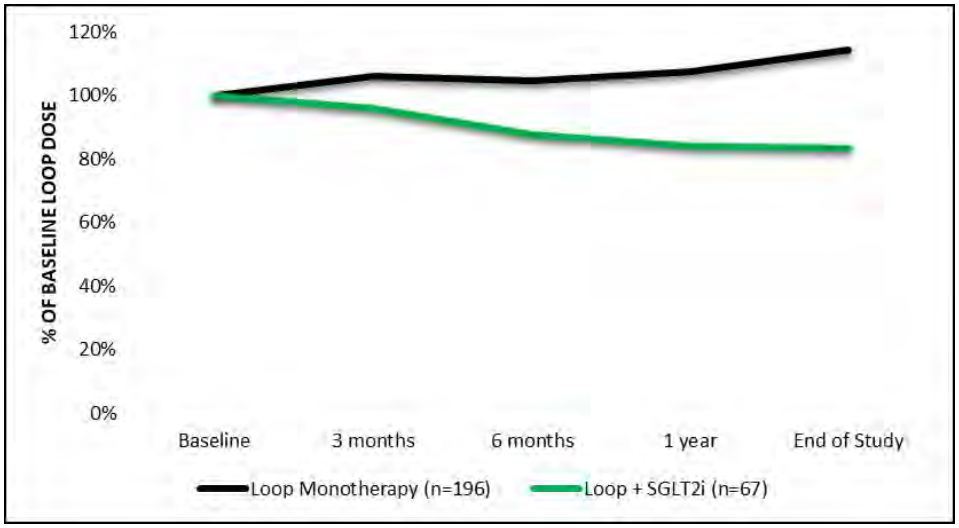
It was noted that patients in the combination group had a higher loop diuretic dose prescribed at baseline compared to the loop monotherapy group. One potential explanation for this is the cost of SGLT2is compared to loop diuretics. With SGLT2is being a more expensive medication, patients may be less willing to initiate an SGLT2i early on with a less advanced disease. However, patients may be more willing to try a more expensive agent for increased fluid output if their heart failure progresses and continues to worsen. The SGLT2i class is considered first-line agents for management of heart failure and are recommended to be initiated when a patient is diagnosed, which is not always seen in practice.[3] These agents are also recommended for patients with type 2 diabetes if patients also have a diagnosis of heart failure, cardiovascular disease, or chronic kidney disease.[4]

FIGURE 2. Loop Diuretic Dose Over Time



PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors

FIGURE 3. Percent of Loop Dose From Baseline



PRN = as needed; SGLT2i = sodium-glucose cotransporter-2 inhibitors

This evaluation does indicate that there is likely a pharmacodynamic interaction of increased diuresis that should be monitored when using an SGLT2i with loop diuretics. The rates of thiazide diuretics and aldosterone antagonists were relatively similar between the two groups, indicating these are unlikely to have a major impact on the results. Compared to the current literature, this evaluation closely examined the long-term concomitant use of SGLT2i and loop diuretics in patients with HFrEF.[5-7] Current literature is limited to studies with short duration or patients with HFpEF.[8] Furthermore, our findings mitigate the potential concern for renal damage in patients who have HFrEF on combination loop diuretic and SGLT2i who tend to be a more vulnerable population.

It may be reasonable in some circumstances to empirically reduce a patient's loop diuretic dose by 10 mg/day of furosemide. One circumstance where it would be reasonable to empirically reduce a patient's loop diuretic is if they have well controlled heart failure and are interested in starting an SGLT2i. In this situation the increased diuresis from the SGLT2i would likely require a dose reduction in the future due to being euvolemic. However, more data is needed to make a strong empiric dose reduction recommendation.

This evaluation is not without limitations and those should be noted. One limitation was the inability to quantify how often patients were taking their loop diuretic when they were using it as needed.

To try to mitigate this limitation, multiple calculations were performed with different dose assumptions. In addition, adherence rates to SGLT2is and loop diuretics were not tracked. Another limitation was the small number of patients in each group. Some patients could have been taking combination therapy for a longer period of time at the end of the evaluation which could also impact results. With this being a retrospective observational evaluation, there was no control over the prescribing patterns; this evaluation reflects real world practice.

Since there was a statistically significant dose reduction found, it is likely there is some pharmacodynamic interaction that takes place between these two classes of medications. However, further research needs to be completed to discover how strong the interaction is between these two medication classes. One future direction for this topic would be to expand this to other healthcare systems to evaluate if this is something that is observed everywhere or just in a subset of the population.

Conclusion

There was a significant decrease in the loop diuretic dose with combination therapy with no clinically significant impact on renal function when adding SGLT2is to loop diuretics in patients with HFrEF. Based on this evaluation, providers should monitor for the opportunity to reduce loop diuretic doses when initiating an SGLT2i in patients with HFrEF.

TABLE 5. Renal Labs Over Time

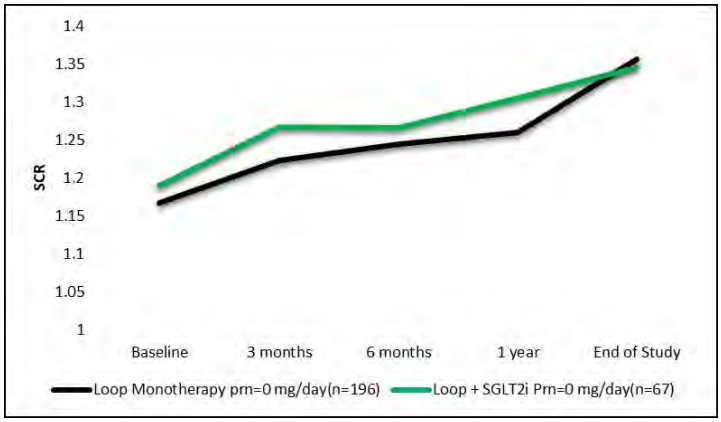
Number of Patients	*Baseline*	*3 Months*	*6 Months*	*1 Year*	*End of Evaluation*
Scr (mg/dL)					
Loop Monotherapy	1.17	1.22	1.24	1.26	1.54
SGLT2i + Loop Diuretic	1.19	1.27	1.27	1.30	1.35
Percent of Baseline Scr					
Loop Monotherapy	-	106%	110%	112%	127%
SGLT2i + Loop Diuretic	-	106%	106%	108%	113%
BUN (mg/dL)					
Loop Monotherapy	25.17	26.15	26.06	27.16	27.06
SGLT2i + Loop Diuretic	24.73	27.59	25.96	27.5	28.83

BUN = blood urea nitrogen; Scr = serum creatinine; SGLT2i = sodium-glucose cotransporter-2 inhibitors

TABLE 6. Prescribing Pattern of Sodium Glucose Cotransporter 2 Inhibitors

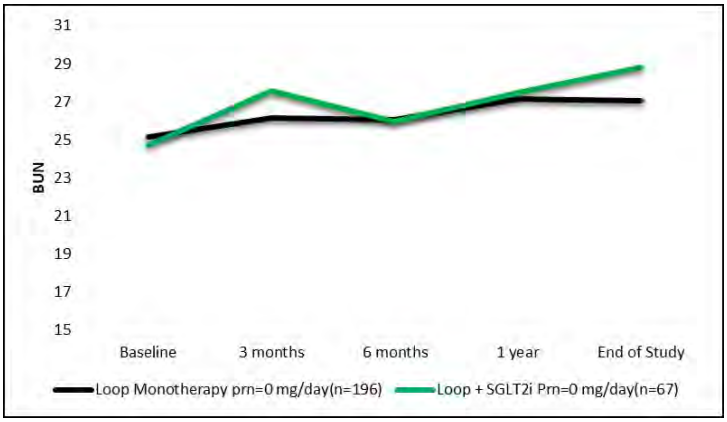
Unique Medications and doses	*Usage rate N (%)*
Dapagliflozin 5 mg	3 (4.5%)
Dapagliflozin 10 mg	11 (16.4%)
Canagliflozin 100 mg	1 (1.5%)
Canagliflozin 300 mg	1 (1.5%)
Empagliflozin 5 mg	1 (1.5%)
Empagliflozin 10 mg	41 (61.2%)
Empagliflozin 25 mg	9 (13.4%)

FIGURE 4. Serum Creatinine Over Time



SGLT2i = sodium-glucose cotransporter-2 inhibitors

FIGURE 5. BUN Over Time



BUN = blood urea nitrogen; SGLT2i = sodium-glucose cotransporter-2 inhibitors

Marcus Pribyl is a PGY-1 Pharmacy Resident at SSM Health Monroe Clinic Medical Group in Madison, WI. Jared Verber is a Pharmacotherapist at SSM Health Monroe Clinic Medical Group in Madison, WI.

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