FEATURE ARTICLE

Medication Optimization for New Initiators of Empagliflozin for Diabetic Kidney Disease

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors are recommended agents for the treatment of diabetic kidney disease (DKD). Additionally, SGLT2 inhibitors lower blood glucose, decrease blood pressure, and can be useful for volume management. For these reasons, we hypothesized that initiating SGLT2 inhibitor therapy may be associated with deprescribing of other medications in patients with DKD. We compared medication lists at SGLT2 inhibitor initiation and 6 months post-initiation in 21 patients with DKD who were followed in our interprofessional outpatient nephrology clinic to evaluate deprescribing patterns in diabetes, hypertension, and diuretic medications. Six months of SGLT2 inhibitor therapy in patients with DKD was associated with deprescribing of high-risk diabetes agents, antihypertensives, and loop diuretics with minimal changes in A1C and fewer adverse events.

KEY POINTS

- SGLT2 inhibitors can replace medications with high hypoglycemic risk.
- SGLT2 inhibitor therapy may lead to deprescribing of antihypertensives and diuretics.
- Following a deprescribing algorithm can decrease polypharmacy and adverse events.
- SGLT2 inhibitors reduce urinary albumin excretion in patients with diabetic kidney disease.

Type 2 diabetes is a highly prevalent condition affecting ~10% of adults in the United States (1). Roughly 30% of patients with type 2 diabetes have cardiovascular disease (CVD) (2), and 25% have diabetic kidney disease (DKD) (3). Each of these comorbidities increases the risk of cardiovascular death, which is the leading cause of death among people with type 2 diabetes, DKD, or both (4,5).

As individuals with DKD age, they have an increased risk of experiencing polypharmacy (6,7). Polypharmacy refers to the use of five or more medications, taking more medications than clinically indicated, or use of medications where harm outweighs benefit (8). Polypharmacy has been associated with inappropriately dosed medications, drug-drug and drug-disease interactions, and morbidity and mortality in people with DKD (6,7). Thus, it is crucial to consider approaches that may improve morbidity and mortality associated with type 2 diabetes, CVD, and DKD, while minimizing medication burden (7–10). When appropriate, clinicians may consider deprescribing, which is the process of systematically reducing or removing medications that may pose a greater risk than benefit to an individual (9). Deprescribing may reduce pill burden and improve individual quality of life (7,10).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are newer blood glucose-lowering agents that decrease the risk of cardiovascular events (11–13), lower the rate of heart failure exacerbations (14), slow the progression of kidney disease (15), and reduce cardiovascular death (15,16) in adults with type 2 diabetes. SGLT2 inhibitors improve morbidity and mortality in type 2 diabetes, CVD, and DKD and may allow clinicians to deprescribe other, less beneficial diabetes agents. The American Diabetes Association (ADA) recommends an SGLT2 inhibitor as the first medication to be added to metformin for individuals with DKD because SGLT2 inhibitors

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reduce morbidity in type 2 diabetes, CVD, and DKD with a single, once-daily pill (17). The ADA also recommends that, when possible, agents with no CVD or kidney benefits be deprescribed in favor of those with such benefits such as SGLT2 inhibitors (17). However, the ADA does not provide guidance on which agents to deprescribe once an SGLT2 inhibitor has been started or by how much. The objective of this quality improvement initiative was to evaluate deprescribing patterns that occurred after 6 months of SGLT2 inhibitor therapy among people with DKD who were followed in a real-world nephrology clinic.

Research, Design and Methods

Study Design and Setting

In 2018, we established an interprofessional model of care in which nephrologists and clinical pharmacists partnered to initiate and monitor SGLT2 inhibitor therapy in patients with DKD (18). This model occurred in a Veterans Affairs (VA) outpatient nephrology clinic in the Northeastern United States. In brief, the nephrologist prescribed an SGLT2 inhibitor, and the pharmacist and nephrologist adjusted the patient's diabetes medications, antihypertensives, and diuretics at SGLT2 inhibitor initiation. Then, the pharmacist contacted patients regularly for 6 months, adjusting medications as needed based on patients' self-monitoring of blood glucose (SMBG) results, blood pressure, weight, and adverse effects (18). We previously noted that SGLT2 inhibitor prescription led to several medication changes for each patient, including modifications to diabetes, blood pressure, and diuretic medications. In many cases, our team was able to optimize blood glucose, blood pressure, and volume control by starting an SGLT2 inhibitor and deprescribing other, less beneficial medications (10,18).

Also in 2018, we developed a deprescribing algorithm for the initiation of SGLT2 inhibitor therapy (10,18). The algorithm was based on previous studies and the most current ADA guidelines at that time (19,20). The goal of the algorithm was to minimize the risk of hypoglycemia or hypotension, while aligning prescribing with current ADA guidelines. We piloted the algorithm for 6 months and, through an iterative process of audit and feedback, developed a final algorithm based on the most recent ADA guidelines at that time (Figure 1) (21–23). In this study, we retrospectively reviewed electronic health record (EHR) data for patients seen in our clinic from April 2018 through November 2019. All patients started empagliflozin, the SGLT2 inhibitor in our formulary. Our objectives were to *1*) evaluate the efficacy and safety of using this deprescribing algorithm and *2*) characterize patterns of deprescribing that might occur in the first 6 months of SGLT2 inhibitor therapy. At that time, we had been using the deprescribing algorithm (Figure 1) for 6 months. This project was deemed a quality improvement initiative by our internal Research and Development Committee and was exempt from further Institutional Review Board oversight.

Study Definitions

Patients were determined to have polypharmacy if they had five or more active prescriptions in the EHR at the time of SGLT2 inhibitor initiation. We categorized DKD medications as medications for the treatment of diabetes, hypertension, or fluid balance (i.e., loop diuretics). Patients were categorized as having heart failure (HF) if they had a prior diagnosis of HF or a TIMI Risk Score for Heart Failure in Diabetes Mellitus score ≥3 (24). Patients were categorized as having clinical atherosclerotic cardiovascular disease (ASCVD) if they had a history of myocardial infarction, coronary artery disease, transient ischemic attack, or peripheral artery disease. Hypoglycemia was defined as patient-reported symptoms or documented SMBG result <70 mg/dL. Hypotension was defined as a patient-reported or documented blood pressure reading <90/60 mmHg. Acute kidney injury (AKI) was defined as an increase of serum creatinine ≥0.5 mg/dL and an increase in blood urea nitrogen of 10 mg/dL from baseline.

Outcomes

The primary outcome was the number and type of changes to DKD medications after 6 months of SGLT2 inhibitor therapy. We compared each patient's medication list, per the VA integrated electronic health and prescription records, at SGLT2 inhibitor initiation and 6 months post-initiation. We determined medication doses, dose changes, and medication adherence through patient self-reporting and provider documentation in the EHR. We classified medication changes as dose decreases, dose increases, medication stops, and medication starts.

Secondary outcomes included changes in clinical markers and patient-reported adverse events after 6 months of SGLT2 inhibitor therapy. Diabetes-related clinical markers included the mean change in A1C and the number of patients at their individualized A1C goal. We determined individualized A1C goals based on ADA guidelines (21,23). Although these goals were based on

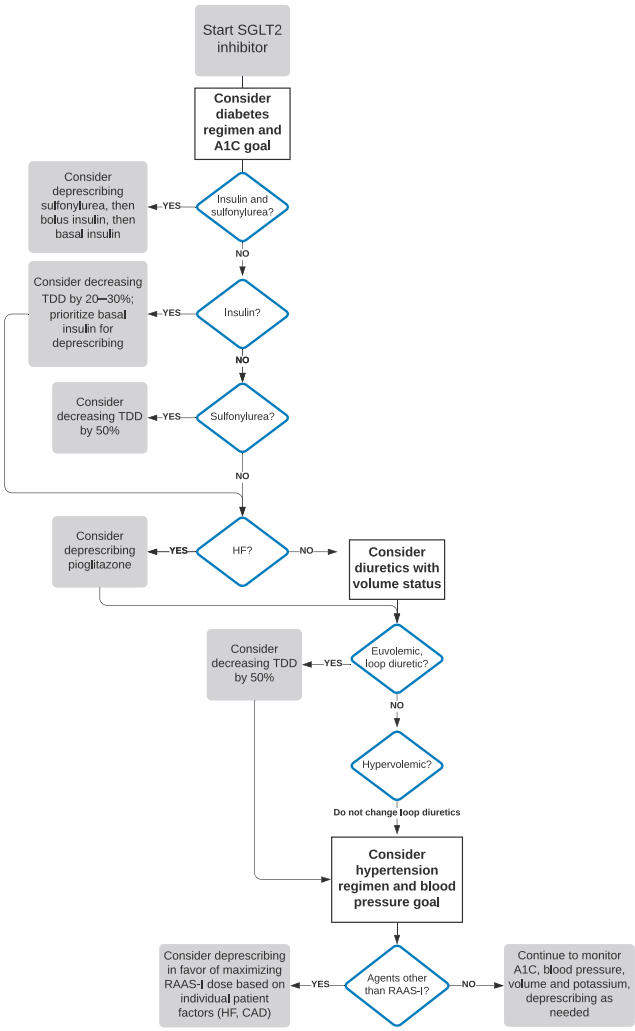

FIGURE 1 Deprescribing algorithm for SGLT2 inhibitor initiation in patients with DKD. The primary goal of the algorithm is to minimize the risk of hypoglycemia or hypotension, while aligning prescribing with current ADA guidelines. SGLT2 inhibitor therapy may affect blood glucose, volume status, blood pressure, proteinuria, and electrolytes. Although some of these effects may be desirable, others may cause harm. At each step of the algorithm, there are patient-specific considerations and associated steps for deprescribing or decreasing doses. Following this algorithm may reduce the risk of harm associated with SGLT2 inhibitors in the first 6 months of therapy. CAD, coronary artery disease; RAAS-I, renin-angiotensin-aldosterone system inhibitor.

the ADA guidelines available at the time, they were in line with subsequent ADA guidelines issued in 2020 and 2021 (25,26). Kidney-related clinical markers included the mean change in urine albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR) (27), and serum potassium. Volume-related clinical markers included mean change in systolic blood pressure and body weight. We tested for significant differences in the rates of adverse events, including hypoglycemia, polyuria, hypotension, AKI, genital infections, amputations, and a composite of all adverse events before and after 6 months of SGLT2 inhibitor therapy using Fisher exact tests.

Results

Population

From April 2018 through November 2019, 29 patients started an SGLT2 inhibitor. Four patients were started on an SGLT2 inhibitor by another provider and were not followed by our team for diabetes management. Two patients started and stopped an SGLT2 inhibitor within 3 months, (One patient died of unrelated causes, and one patient stopped because of increased urination.) Two patients started an SGLT2 inhibitor later in the study period, so they could not be included in this analysis, which required at least 6 months of follow-up. The remaining 21 patients completed at least 6 months

TABLE 1 Characteristics and Medication Profile of Patients With DKD (N = 21)

	At Initiation	After 6 Months
Age, years	69 ± 7	–
Male	21 (100)	–
Hypertension	21 (100)	–
Dyslipidemia	21 (100)	–
Clinical ASCVD	11 (52)	–
Obese (BMI >30 kg/m^2)	14 (67)	–
Atrial fibrillation	6 (29)	–
HF	17 (81)	–
UACR >300 mg/g	13 (62)	12 (57)
eGFR <60 mL/min/1.73 m^2	17 (81)	18 (86)
Number of medications	15 ± 7	16 ± 6
On diabetes medication	20 (95)	21 (100)
Insulin, basal only	5 (24)	7 (33)
Insulin, basal-bolus regimen	8 (38)	4 (19)
Metformin	10 (48)	10 (48)
Sulfonylurea	7 (33)	4 (19)
DPP-4 inhibitor	1 (5)	2 (10)
GLP-1 receptor agonist	2 (10)	6 (29)
Thiazolidinedione	1 (5)	0 (0)
On antihypertensive medication	20 (71)	21 (100)
Beta blocker	16 (76)	16 (76)
ACE inhibitor/ARB	15 (71)	12 (57)
Calcium channel blocker	12 (57)	11 (52)
Direct vasodilator (hydralazine)	1 (7)	1 (7)
α blocker	1 (7)	1 (7)
On diuretic medication	8 (38)	7 (33)
Loop diuretic	6 (23)	6 (23)
Potassium-sparing diuretic (spironolactone)	0 (0)	1 (5)
Thiazide diuretic	2 (10)	1 (5)

Data are n (%) except for age and number of medications, which are mean ± SD. DPP-4, dipeptidyl peptidase 4.

of SGLT2 inhibitor therapy and were included in the study.

All patients (100%) were men, and the majority (91%) were White and non-Hispanic, with ages ranging from 50 to 84 years (mean age 70 years). In addition to DKD, patients had a high number of comorbidities, including hypertension (100%), dyslipidemia (100%), ASCVD (52%), and HF (81%). Patients had a mean UACR of 1,397 mg/dL (range <1 to 7,840). Thirteen of 21 patients (62%) had macroalbuminuria (UACR >300 mg/dL, range 342–7,840), seven (33%) had microalbuminuria (UACR 30–300 mg/dL, range 36–262), and one (5%) had no albuminuria. All patients met the definition of polypharmacy, with an average of 15 prescriptions per patient (Table 1).

Primary Outcome: DKD Medication Changes

Between initiation and 6 months, there were many medication changes (Table 2). At initiation, 20 out of 21 patients (95%) were taking at least one medication for type 2 diabetes. Eighteen patients (86%) were taking diabetes medications with a high risk of hypoglycemia, including insulin (basal only n = 5 [24%], basal-bolus n = 8 [38%], and sulfonylureas n = 7 [33%]).

TABLE 2 Medication Changes Over 6 months of Empagliflozin Therapy ($N = 21$)

	Before SGLT2 Inhibitor											After SGLT2 Inhibitor									
Patient	Basal Insulin	Bolus Insulin	SFU	TZD	DPP-4i	GLP-1 RA	Loop	MET	SPIR	ACEi/ARB	Basal Insulin	Bolus Insulin	SFU	TZD	DPP-4i	GLP-1 RA	Loop	MET	SPIR	ACEi/ARB
1	✓							✓			(-)							↔		
2			✓				✓			✓			(-)				↓			↓
3	✓	✓						✓			↓	(-)				(+)	(+)	↑		
4								✓									(+)	↓		
5	✓	✓	✓				✓			✓	↓	(-)	(-)			(+)	↓			(-)
6			✓					✓					↔			(+)		↔		
7					✓					✓					↔					↑
8	✓	✓								✓	↓	↔								↔
9	✓						✓			✓	↓						(-)			↓
10			✓					✓		✓			↔					↔		↔
11	✓	✓				✓	✓	✓		✓	↑	↑				↔	(-)	(-)		↓
12																		(+)		(+)
13			✓							✓			(-)			(+)				↓
14			✓	✓			✓	✓		✓			↓	(-)			↔	↔		(-)
15	✓	✓						✓		✓	↓	(-)						↔		↓
16	✓	✓					✓			✓	↔	(-)					↓		(+)	↓
17	✓	✓				✓				✓	↓	↓				↔				(-)
18	✓							✓			(-)							↓		
19	✓		✓					✓		✓	↑		↔					↔		(-)
20	✓									✓	↓									↓
21	✓	✓								✓	↓	↓			(+)					↔
Total	**13**	**8**	**7**	**1**	**1**	**2**	**6**	**10**	**0**	**15**	**11**	**4**	**4**	**0**	**2**	**6**	**6**	**10**	**1**	**12**

Medications in the leftmost columns within each time point are potentially harmful medications for older adults with CKD, whereas those in the rightmost columns are potentially beneficial. Key: ✓ denotes that a patient was taking that medication at SGLT2 inhibitor initiation. ↑ indicates that a dose was increased. ↓ indicates that a dose was decreased. ↔ indicates that the dose stayed the same. (+) indicates that a medication was newly started. (–) indicates that a medication was discontinued. ACEi, ACE inhibitor; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; Loop, loop diuretic; MET, metformin; SFU, sulfonylurea; SPIR, spironolactone; TZD, thiazolidinedione.

After 6 months of SGLT2 inhibitor therapy, our team reduced the doses of diabetes medications with a high risk of hypoglycemia for 14 of these 18 patients (78%) and stopped them for four patients (22%). Among insulin users ($n = 13$), we observed an average reduction in insulin total daily dose (TDD) of 26% (mean 28 units/day (range −54 to +37 units). Bolus insulin was discontinued altogether for four patients, representing half of those taking bolus insulin at SGLT2 inhibitor initiation.

The team increased insulin doses when deemed medically appropriate based on blood glucose data and individual hypoglycemia risk. Among those using basal insulin only ($n = 5$), the mean TDD reduction was 26%. Among those using both basal and bolus insulin ($n = 8$), the mean TDD reduction was 18%. Pioglitazone was discontinued in one patient with a history of HF because of that drug's increased risk of HF exacerbation (28). At initiation, two patients (10%) were taking a glucagon-like peptide 1 (GLP-1) receptor agonist. At 6 months, six patients were taking a GLP-1 receptor agonist, including four who were new initiators and two who stayed on the same dose throughout the 6 months. At 6 months, 12 patients were taking empagliflozin 10 mg daily, and nine were taking 25 mg daily.

At SGLT2 inhibitor initiation, 20 out of 21 (95%) patients were taking at least one medication for hypertension, 15 of whom were taking an ACE inhibitor or angiotensin receptor blocker (ARB). At 6 months, all patients were taking at least one antihypertensive medication, and 12 were taking an ACE inhibitor or ARB. The team decreased antihypertensive doses for seven of 20 patients (35%) and increased doses for two patients (10%). At initiation, six of 21 patients (29%) were taking a loop diuretic; this remained unchanged at 6 months. The team reduced the doses of loop diuretics for five of six patients (83%), stopped loop diuretics in two patients (33%), and started loop diuretics in two patients (33%) over 6 months. Among patients who took loop diuretics at any point during the follow-up period ($n = 8$), the mean TDD of furosemide or furosemide equivalents was decreased by 26 mg (range −80 to +20 mg/day) at 6 months (Table 2).

Secondary Outcomes: DKD Clinical Markers

From SGLT2 inhibitor initiation to 6 months post-initiation, the mean change in A1C was +0.4% (+5 mmol/mol). Individualized A1C goals ranged from <7 to <8% based on age, comorbidities, duration of disease, and microvascular complications (21,23). Fewer patients were at their A1C goal at 6 months compared with baseline ($n = 9$ vs. $n = 12$). Of those 12 patients who were not at goal, three had a goal of <7%, five had a goal of <7.5%, and four had a goal of <8% (21,23). The mean UACR decreased by 338 mg/dL. Three patients (14%) had a reduction in UACR of 30–49%, and five patients (24%) had a reduction of >50%. Five patients (24%) had a serum potassium >5.1 mEq/L at SGLT2 inhibitor initiation; none had a potassium value above this level at 6 months. The mean change in serum potassium was −0.2 mEq/L. The mean change in systolic blood pressure was +0.5 mmHg, and the mean change in eGFR was −1.1 mL/min/1.73 m^2. Eighteen (86%) patients lost weight over the 6-month period, with a mean weight loss of 3 kg (SD 6.4 kg). The difference in weight loss among those who had a dose decrease or stopped insulin or a sulfonylurea ($n = 13$) versus those who did not reduce or stop insulin ($n = 4$) was 0.29 kg (3.02 vs. 2.73 kg) (Table 3).

Adverse Events

The most common patient-reported side effects at 6 months were hypoglycemia ($n = 4$) and polyuria ($n = 4$). Of note, all patients who reported hypoglycemia at 6 months were on concomitant insulin regimens and experienced level 1 hypoglycemia (blood glucose between 54 and 70 mg/dL). Two patients reported instances of hypotension. There was one case of AKI, in which a patient had an increase in SCr from 1.8 to 2.3 mg/dL and an increase in blood urea nitrogen from 26 to 36 mg/dL. The AKI resolved after the end of the 6-month follow-up period, and, while the SGLT2 inhibitor was temporarily discontinued, it was restarted at a later date. There were no cases of genital infection, amputations, or diabetic ketoacidosis. There was a statistically significant lower rate of composite adverse events after 6 months of SGLT2 inhibitor therapy (11 vs. 23, $P = 0.04$) (Table 4). There were no significant differences in rates of hypoglycemia, polyuria, hypotension, AKI, genital infections, or amputations.

Discussion

Our objectives were to *1*) evaluate the efficacy and safety of using this deprescribing algorithm, and *2*) characterize patterns of deprescribing that might occur in the first 6 months of SGLT2 inhibitor therapy. Our interprofessional model using a predetermined deprescribing algorithm demonstrated a reduction in proteinuria, blood pressure, weight, and patient-reported adverse events, with a 0.4% increase in blood glucose over 6 months. We identified two key deprescribing patterns: *1*) deprescribing diabetes medications with high

TABLE 3 Changes in Clinical Markers of DKD From Baseline to 6 Months of Empagliflozin Therapy (N = 21)

	Initiation	6 Months	Mean Difference ± SD
Diabetes-related clinical markers			
A1C, %	7.4 ± 1.1	7.8 ± 1.2	+0.4 ± 1.0
At A1C goal*	12 (57)	9 (43)	–
Kidney-related clinical markers			
UACR, mg/g†	1,397 ± 1,813	1,061 ± 947.9	−338 ± 1,251.7
Achieved UACR reduction of 30–49%	–	3 (14)	–
Achieved UACR reduction >50%	–	5 (24)	–
eGFR, mL/min/1.73 m^2	44.8 ± 9.2	45.9 ± 10.3	−1.1 ± 7.7
Serum potassium, mEq/L	4.6 ± 0.6	4.4 ± 0.5	−0.2 ± 0.5
Serum potassium >5.1 mEq/L	5 (24)	0 (0)	–
Volume-related clinical markers			
Weight, kg	97.3 ± 17.7	94.2 ± 19.0	−3.0 ± 6.4
Systolic blood pressure, mmHg	149 ± 20.7	140 ± 16.4	+0.5 ± 26.4

Data are mean ± SD or n (%). *Derived from the ADA's 2018 guidelines (19), which were in line with the ADA's 2020 and 2021 guidelines (25,26). †For inclusion, patients were required to have a UACR >300 mg/g in the past year; however, some patients may have subsequently updated laboratory tests and therefore had a UACR <300 mg/g at initiation as a result of taking other agents that lower UACR (e.g., an ACE inhibitor or ARB).

hypoglycemia risk and *2*) deprescribing hypertension medications to avoid hypotension and hypovolemia.

Initial empiric dose reductions as noted in Figure 1 may be appropriate starting points for deprescribing. The goal of the algorithm was to minimize the risk of hypoglycemia or hypotension, while aligning prescribing with current ADA guidelines. The ADA recommends reducing insulin by 2–4 units or 10–20% when a patient is experiencing hypoglycemia, but the ADA does not make recommendations about insulin or other medication reductions when initiating an SGLT2 inhibitor (17).

The algorithm led to no change in hypo- or hyperglycemia and an overall decrease in adverse events. Although there was an overall increase in A1C of 0.4%, this was not a clinically significant increase, per the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (29). This was similar to findings in the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial, in which rates of hypoglycemia in the treatment and control groups were similar. Although the EMPA-REG OUTCOME trial protocol offered no guidance regarding diabetes medication management, insulin (11.5 vs. 5.8%) and sulfonylureas (7.0 vs. 3.8%) were less likely to be used in patients receiving empagliflozin (16). In contrast, our study was small and brief and included older adults with DKD.

Maintaining glycemic control and avoiding severe hypoglycemia is challenging, especially in patients with diabetes and chronic kidney disease (CKD), for whom the choices of glucose-lowering agents are often limited (7) and the risk of severe hypoglycemia is exponentially increased (2). A key strength of our approach was the pharmacists' ability to use the algorithm at initiation and to provide individualized follow-up over 6 months to reduce the risk of adverse events and maintain glycemia control. We expect that, over a longer period, the pharmacist-patient dyad may have achieved better glycemic control.

In our study, patients with intensive insulin regimens often added an SGLT2 inhibitor, but remained on insulin. Table 2 shows the nuances of managing basal insulin and basal-bolus insulin regimens when initiating an SGLT2 inhibitor. Regimens at 6 months were patient-specific and did not follow one single pattern.

Pharmacists consistently deprescribed or decreased the dose of agents with a high risk of hypoglycemia.

TABLE 4 Adverse Events From Initiation to 6 Months of Empagliflozin Therapy ($N = 21$)

	Initiation	6 Months	*P**
Hypoglycemia†	6 (29)	4 (19)	0.72
Polyuria	5 (24)	4 (19)	1
Hypotension‡	6 (29)	2 (10)	0.24
AKI§	5 (24)	1 (5)	0.18
Genital infections	0 (0)	0 (0)	1
Amputations	1 (5)‖	0 (0)	1
Total adverse events	23	11	0.04

Data are *n* (%) or *n*. *Counts were compared at initiation and 6 months using Fisher exact tests. †Hypoglycemia was defined as a documented or patient-reported blood glucose <70 mg/dL in the past year (initiation) or since starting empagliflozin (6 months). All reports of hypoglycemia were level 1 (blood glucose between 54 and 70 mg/dL). ‡Hypotension was defined as a documented or patient-reported blood pressure <90/60 mmHg in the past month (initiation) or since starting SGLT2 inhibitor therapy (6 months). §AKI was defined as a documented increase in SCr ≥0.5 mg/dL, and an increase in blood urea nitrogen ≥10 mg/dL in the past year (initiation) or since starting SGLT2 inhibitor therapy (6 months). ‖One patient had an amputation of the left fifth metatarsal head in 2016 before initiation of an SGLT2 inhibitor.

Pharmacists deprescribed basal insulin for six patients and bolus insulin for four patients. For all patients on insulin, pharmacists adjusted doses based on SMBG results and adverse events. Pharmacists also deprescribed sulfonylureas for three patients and pioglitazone in a patient with HF.

Pharmacists also deprescribed medications for hypertension and volume. Of note, many patients ($n = 12$) required dose adjustments in ACE inhibitor or ARB therapy based on blood pressure, volume, and electrolytes. SGLT2 inhibitors can reduce systolic blood pressure by 3–6 mmHg and diastolic blood pressure by 1–2 mmHg, which may allow for deprescribing of other antihypertensive medications if a patient's blood pressure is at goal.

One recognized potential side effect of SGLT2 inhibitor therapy is volume depletion (30,31). When an SGLT2 inhibitor is added to a maintenance dose of diuretics in euvolemic patients, proactive reduction of diuretics and monitoring for volume depletion can avoid an acute decline in eGFR, which is represented in our data. Of note, the two patients who were initiated on loop diuretics during their first 6 months of SGLT2 inhibitor therapy both had a confirmed diagnosis of HF. Our data suggest that empiric dose reductions (Figure 1) for hypertension and volume medications was safe and that pharmacists made frequent adjustments to medications to prevent adverse effects (18).

We observed a reduction in proteinuria with stable eGFR at 6 months, reduced blood pressure, and weight loss using our deprescribing algorithm, all factors which contribute to the prevention of CKD progression. Seven patients had a UACR reduction of >30%, which is associated with a reduced incidence of CKD and end-stage kidney disease (32). Our patients are at high risk for eGFR decline because of DKD (33); therefore, no decline in eGFR over 6 months is seen as a favorable outcome for this cohort. We also saw a reduction in hyperkalemia, in line with other clinical trials (11–13,15). Hyperkalemia is common in patients with DKD, which often leads to prescription of potassium-lowering agents (34) and worsens polypharmacy.

No major adverse events were observed during the first 6 months of empagliflozin therapy. This finding leads us to believe that our deprescribing algorithm improves the safety of our patients with DKD upon initiation of an SGLT2 inhibitor, but further research is needed on the short- and long-term safety profiles of this class of medications.

In our clinic, we continue to use this model, which includes a pharmacist on the team, and to follow and update the algorithm with two key points in mind: *1*) Initial deprescribing and dose decreases per the algorithm were not associated with a significant change in adverse events and *2*) patients taking insulin may require additional changes to their regimens after empiric dose reductions. For some patients, we saw an overall decrease in insulin at 6 months; for others, we saw an overall increase. Our model and algorithm may be adapted to fit the needs of other medical practices and patient populations.

Limitations of this study were both its small sample size and the short duration of follow-up. Our cohort included 21 male patients at one VA medical center, which may limit generalizability. The study population lacked robust diversity in sex and race, which may further reduce the generalizability of these data to a broader U.S. population. This was a retrospective study that relied heavily on patient-reported SMBG results and adverse events. Finally, this study did not assess the cost-effectiveness of our approach. All patients in this study started empagliflozin. We started a GLP-1

receptor agonist in four patients for whom it would be recommended based on ADA guidelines. Cost is a known barrier to SGLT2 inhibitor and GLP-1 receptor agonist use (17); thus, further research is needed to weigh the benefits associated with lowering blood glucose, preventing CVD and reducing DKD progression against drug costs.

In conclusion, we evaluated deprescribing patterns among patients with DKD after 6 months of SGLT2 inhibitor therapy in a real-world nephrology clinic. Six months of SGLT2 inhibitor therapy resulted in deprescribing of medications with a high risk of hypoglycemia and antihypertensives. By using a deprescribing algorithm, our team aligned DKD medication therapy with current guidelines without increasing adverse events.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

A.A.S. designed the study, reviewed the data, developed study materials, and wrote the manuscript. C.E.H. assisted in the study design, developed study materials, and conducted data analysis. K.L. collected the data, developed study materials, and assisted in the study design. L.K.T. assisted in the study design. J.L. assisted in the study design and assisted with data analysis. J.M.P. assisted in the study design and reviewed the data. All authors reviewed, edited, and approved the manuscript. A.A.S. and J.M.P. are the guarantors of this work and, as such had full access to the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

PRIOR PRESENTATION

The preliminary research methods and design described in this article were presented as a poster at the American Society of Health-System Pharmacists Midyear Clinical Meeting, Las Vegas, NV, 8–12 December 2019.

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