Title

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Journal

Clinical Diabetes, 38(3)

ISSN

0891-8929

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Publication Date

2020-07-01

DOI

10.2337/cd19-0087

Peer reviewed

FEATURE ARTICLE

Patient and Provider Characteristics Associated With Sodium–Glucose Cotransporter 2 Inhibitor Prescription in Patients With Diabetes and Proteinuric Chronic Kidney Disease

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Despite accumulating evidence of cardiorenal benefits from sodium–glucose cotransporter 2 (SGLT2) inhibitors, prescription of agents in this drug class may be limited by concerns regarding adverse effects and interdisciplinary care coordination. To investigate these potential barriers, we performed a cross-sectional study of SGLT2 inhibitor prescriptions in 2017 in 3,779 adults with type 2 diabetes and proteinuric chronic kidney disease from a nationwide database. Only 173 (5%) of these patients received an SGLT2 inhibitor in 2017. Younger age, renin-angiotensin-aldosterone system inhibitor prescription, and higher estimated glomerular filtration rate were associated with SGLT2 inhibitor prescription. Primary care providers were responsible for the majority of the prescriptions. Continued efforts should be made to track and improve SGLT2 inhibitor use in indicated populations.

Patients with type 2 diabetes and chronic kidney disease (CKD) have been waiting for innovation for decades. Despite hope for novel agents including aliskiren (1), bardoxolone (2), and other treatments (3–5), no new medications were found to slow the progression of CKD in patients with type 2 diabetes since the angiotensin receptor blockers (ARBs) in 2001 (6,7). However, sodium–glucose cotransporter 2 (SGLT2) inhibitors, originally developed as medications to enhance glycemic control in type 2 diabetes, have been shown to decrease major adverse cardiovascular events and the incidence and progression of CKD in multiple randomized controlled trials (8–11). In fact, the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial showed a 32% lower risk of end-stage kidney disease (ESKD) in patients with proteinuric CKD randomized to canagliflozin versus placebo (hazard ratio 0.68, 95% CI 0.54–0.86, $P = 0.002$) (10). The American Diabetes Association (ADA) has released new recommendations that all patients with type 2 diabetes and diabetic kidney disease whose estimated glomerular filtration rate (eGFR) is ≥30 mL/min/1.73 m^2, and particularly those with albuminuria >300 mg/day, should be considered for treatment with an SGLT2 inhibitor (based on A-level evidence) (12).

Despite the impressive effects of these medications, clinicians may be reluctant to prescribe them for several reasons. In addition to being relatively new and unfamiliar, SGLT2 inhibitors face another barrier: uncertainty regarding which medical specialty "owns" them. Because these medications have effects on glycemic control, blood pressure, cardiovascular events, and progression of CKD, prescribers may wonder whether endocrinologists, nephrologists, cardiologists, or primary care providers (PCPs) should be the practitioners responsible for prescribing them. Other barriers to SGLT2 inhibitor initiation may include reported adverse effects (i.e., increased risk of amputations, urinary tract infections [UTIs] and genital mycotic infections, diabetic ketoacidosis [DKA], and fractures) and the costs of these medications, which are not yet available in generic formulations. These barriers may aggregate and prevent eligible patients from enjoying important health benefits, including lower risks of needing dialysis or having a cardiovascular event.

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This article contains supplementary material online at Figshare: https://doi.org/10.2337/figshare.12020976.

https://doi.org/10.2337/cd19-0087

In this study, we sought to estimate the proportion of eligible patients with type 2 diabetes and proteinuric CKD who were treated with SGLT2 inhibitors in 2017. We further aimed to investigate patient characteristics associated with SGLT2 inhibitor prescription such as eGFR or history of peripheral arterial disease (PAD), UTIs, fractures, or DKA. We also examined which medical specialties typically prescribed SGLT2 inhibitors, with the hypothesis that most prescriptions were written by endocrinologists. We hypothesized that the majority of eligible patients did not receive SGLT2 inhibitors and that SGLT2 inhibitor prescription was less common among older patients with lower eGFRs and a history of the comorbidities selected.

Subjects

The Clinformatics Data Mart, OptumInsight Life Sciences dataset (OptumInsight, Eden Prairie, MN), is a single-payer, closed data system that consists of patient-level administrative and demographic information, including but not limited to type of insurance plan, age, sex, eligibility, income, medical and prescription claims, laboratory values, and unique identifiers for linking patients. We used fully de-identified data from this large claims and integrated database that included employed and commercially insured patients in the United States. This study was approved by the institutional review board of Stanford University and was conducted in accordance with the Declaration of Helsinki guidelines.

We first identified patients with at least one serum creatinine value and one urine albumin-to-creatinine ratio (UACR) in 2016. We then selected the patients with diabetes defined by at least one A1C value ≥6.5% between 1 January 2016 and 1 January 2017. We next required proteinuric CKD, defined using laboratory data from 2016 as the combination of a UACR ≥300 mg/g creatinine (Cr) and the latest eGFR ≥30 and <90 mL/min/1.73 m^2 determined by the four-variable Chronic Kidney Disease Epidemiology Collaboration formula (13). Patients without race or ethnicity identified were excluded because this variable is required for the eGFR calculation. We chose this definition of CKD because it mirrors the inclusion criteria for the CREDENCE trial (10) and defines the group for whom ADA recommends consideration of SGLT2 inhibitors (12). We excluded patients with an *International Classification of Diseases*, 10th edition (ICD-10), code for type 1 diabetes (E10). Our final cohort included only adults (age ≥18 years on 1 January 2017) with type 2 diabetes and proteinuric CKD who had continuous enrollment from 1 January 2016 or earlier until at least 1 January 2017 (Figure 1).

Research Design and Methods

SGLT2 Inhibitor Use

We defined SGLT2 inhibitor use for 2017 as the presence of at least one prescription for an SGLT2 inhibitor with either the prescription date or the prescription date + the number of days prescribed falling between 1 January 2017 and 1 January 2018. The prescribing provider's specialty was determined by taxonomy code. Prescribing providers without a taxonomy code or with a nonspecific taxonomy code were classified as specialty unknown. Patients with SGLT2 inhibitor prescriptions from both specialty providers and PCPs were classified as specialty-prescribed.

Covariate Definitions

We defined the following comorbidities by ICD-9/ICD-10 codes (Supplementary Appendix A) recorded before 1 January 2017: hypertension, ischemic heart disease, heart failure, cerebrovascular disease, PAD, amputation, UTI, genital mycotic infection, fracture, osteoporosis, and DKA. Inpatient and outpatient codes were included. We obtained the other sociodemographic variables from the Optum SES Member file (SES data file, v. 7.0). Coprescription of an ACE inhibitor or ARB in 2017 was measured in the same method described for SGLT2 inhibitors above.

Statistical Analysis

We report binary variables as proportions and continuous variables as median (25th–75th percentiles). We used univariate logistic regression to evaluate the association of patient characteristics (all Table 1 variables included) with receipt of an SGLT2 inhibitor. Data were missing only for the income variable (14% missing). Analysis of the other variables by income category suggested that these data were not missing completely at random; patients with missing income information were younger with higher UACRs (Supplementary Table 1). However, it is reasonable to assume that missingness is related to the measured characteristics and not to itself or to unmeasured factors (missing at random assumption). Therefore, we performed multiple imputation, generating 15 datasets with imputed income category values, with pooling of the results of logistic regression from each dataset. We performed multivariable logistic regression including only Table 1 variables for which univariate

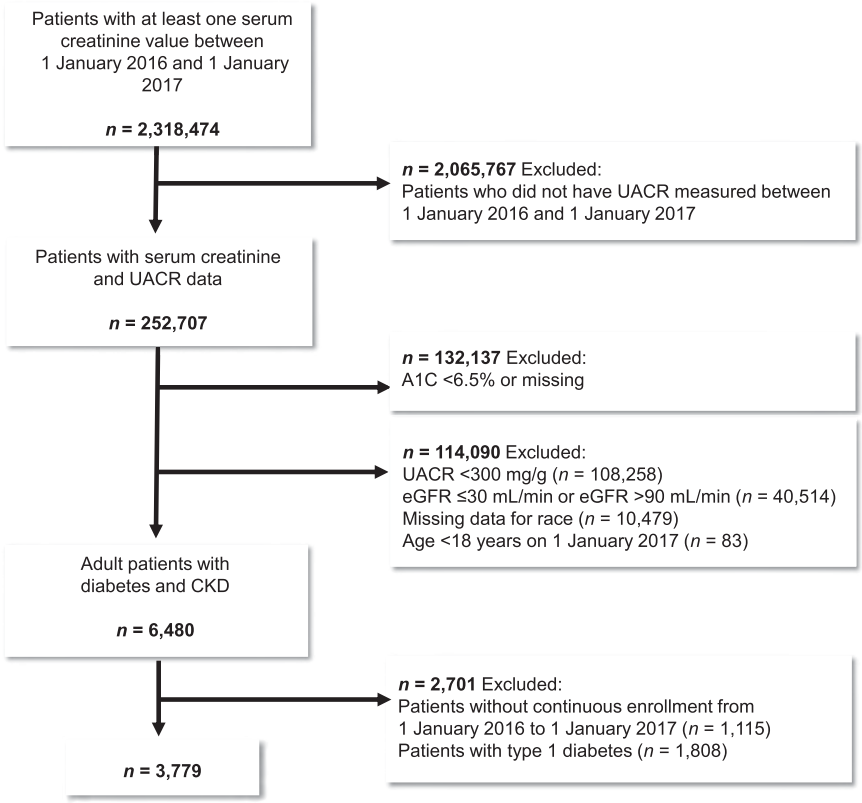

FIGURE 1 Cohort assembly of adult patients with type 2 diabetes and CKD in the Clinformatics Data Mart, OptumInsight Life Sciences dataset, in 2017.

P values were <0.2. We considered two-sided *P* values <0.05 as significant. In a sensitivity analysis to check for dropout from the database during 2017, we evaluated the percentage receiving SGLT2 inhibitors in the subset of patients with continuous enrollment for all of 2017. We performed all statistical analyses using SAS, v. 9.4, software (SAS Institute, Cary, NC).

Results

We identified 3,779 adult patients with type 2 diabetes and proteinuric CKD. They were elderly (median age 72 years) with a median eGFR of 57 mL/min/1.73 m^2, median UACR of 753 mg/g Cr, and median A1C of 8.0% (Table 1). Almost all of the patients (97%) had hypertension, and 77% had a prescription for an ACE inhibitor or ARB. At least one SGLT2 inhibitor was prescribed for 5% of the patients in the cohort (173 of 3,779). This percentage was unchanged in our sensitivity analysis assessing for dropout during the 2017 measurement period (5%; 156 of 3,402). Among patients with an eGFR of 30–44 mL/min/1.73 m^2, only 2% were prescribed an SGLT2 inhibitor.

Younger age, ACE inhibitor or ARB prescription, higher A1C, higher eGFR, and lower UACR were associated with SGLT2 inhibitor prescription in multivariable logistic regression (all *P* <0.05) (Table 2). The odds of SGLT2 inhibitor prescription were 76% higher in patients with than in those without an ACE inhibitor or ARB prescription. Patients with a history of UTI were less likely to be prescribed an SGLT2 inhibitor, but the results were not significant in multivariable analysis (adjusted odds ratio [OR] 0.69, 95% CI 0.47–1.03, $P = 0.07$).

Cardiologists did not prescribe any SGLT2 inhibitors in this study, and only two patients received SGLT2 inhibitor prescriptions from nephrologists (not shown). Only four patients received SGLT2 inhibitor prescriptions from multiple providers (i.e., from both an endocrinologist and a PCP). The majority of the SGLT2 inhibitor prescriptions identified were written by PCPs (59% of patients) (Table 3). Endocrinologists prescribed most of the remainder (25% of patients). Compared with patients prescribed SGLT2 inhibitors by endocrinologists, patients prescribed SGLT2 inhibitors by other providers had a higher prevalence of male sex, heart failure, fracture, osteoporosis, DKA, and UTI.

Discussion

In this study of patients with type 2 diabetes and CKD from a nationwide cohort, we found that only 5% of patients for

TABLE 1 Demographic and Clinical Characteristics of Patients

	All patients (n = 3,779)	eGFR 30–44 mL/min/1.73 m^2 (n = 1,000)	eGFR 45–59 mL/min/1.73 m^2 (n = 1,111)	eGFR 60–89 mL/min/1.73 m^2 (n = 1,668)
Age, years	72 (67–78)	74 (69–81)	74 (67–79)	70 (64–76)
Female sex	43	48	39	42
Race/ethnicity				
White	43	44	45	41
Hispanic	37	36	36	37
Black	14	15	13	14
Asian	6	5	6	7
Income				
<$40,000	33	35	32	31
$40,000–49,999	8	8	8	9
$50,000–59,999	9	9	8	9
$60,000–74,999	11	10	11	10
$75,000–99,999	11	10	13	11
≥$100,000	15	12	14	16
Unknown	14	15	13	13
Comorbidities				
Hypertension	97	98	97	96
Ischemic heart disease	44	50	47	38
Heart failure	30	38	32	23
Cerebrovascular disease	30	34	31	27
PAD	35	39	38	31
Amputation	4	4	5	4
Fracture	13	14	13	12
Osteoporosis	11	13	9	10
DKA	2	2	2	2
UTI	33	36	32	32
Genital mycotic infection	2	2	3	2
ACE inhibitor/ARB use	77	73	79	79
Laboratory data				
eGFR, mL/min/1.73 m^2	57 (44–72)	38 (34–42)	52 (49–56)	74 (66–82)
UACR, mg/g Cr	753 (449–1,437)	916 (494–1,924)	754 (448–1,407)	671 (430–1,256)
A1C, %	8.0 (7.1–9.5)	7.9 (7.0–9.2)	8.0 (7.1–9.4)	8.1 (7.2–9.7)

Data on categorical variables are proportions; data on continuous variables are median (25th–75th percentiles).

whom the ADA particularly recommends SGLT2 inhibitors received them in 2017. However, this finding was expected given the results of a 2017 study of patients in the National Cardiovascular Disease Registry, in which only 5% of patients who met the eligibility criteria for the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial were receiving SGLT2 inhibitor therapy (14).

The low prescription rate we observed may be in part because of a lack of recognition of the benefits of SGLT2 inhibitors, so it is important to consider the dates of our study in the context of the evidence available to prescribers at the time. We evaluated SGLT2 inhibitor prescriptions during 2017. Canagliflozin was approved by the U.S. Food and Drug Administration (FDA) in 2013, followed by dapagliflozin and empagliflozin in 2014. The results of the EMPA-REG OUTCOME trial (8) were published in 2015; those from the CANVAS (Canagliflozin Cardiovascular Assessment Study) research program (9) were published during our measurement period in 2017, and the CREDENCE trial (10) had been enrolling since 2014, but its results were not published until 2019. Analyses of EMPA-REG OUTCOME in 2016 (15) and the CANVAS program in 2017 (9) had both shown improvement in secondary kidney outcomes with SGLT2 inhibitors. In 2016, the FDA granted empagliflozin a second indication, apart from glycemic control, for the reduction of risk of cardiovascular death.

Thus, during our data collection period, SGLT2 inhibitors had been available in the United States for more than

TABLE 2 Factors Associated With SGLT2 Inhibitor Prescription

	Unadjusted OR	95% CI	Adjusted OR	95% CI	*P*
Age (per 5 years)	**0.74**	**0.69–0.79**	**0.77**	**0.72–0.84**	**<0.001**
Female sex	0.60	0.43–0.83	0.78	0.55–1.10	0.16
Heart failure	0.73	0.51–1.04	1.01	0.69–1.47	0.97
Cerebrovascular disease	0.73	0.51–1.04	1.08	0.74–1.57	0.70
Fracture	0.64	0.38–1.10	0.83	0.48–1.43	0.50
UTI	0.52	0.36–0.75	0.69	0.47–1.03	0.07
ACE inhibitor/ARB	**1.95**	**1.25–3.04**	**1.76**	**1.12–2.77**	**0.01**
eGFR (per 10 mL/min/1.73 m^2)	**1.32**	**1.21–1.45**	**1.21**	**1.09–1.33**	**<0.001**
UACR (per 100 mg/g Cr)	**0.99**	**0.97–1.00**	**0.98**	**0.97–1.00**	**0.02**
A1C	**1.16**	**1.09–1.24**	**1.09**	**1.01–1.17**	**0.03**

Unadjusted ORs are shown for Table 1 variables with univariate *P* values <0.2. Those variables were included in the multivariable model, and those with adjusted ORs with *P* values <0.05 are shown in bold.

4 years. Benefits with regard to cardiovascular mortality and CKD incidence and progression had been observed in two large, randomized controlled trials (8,9), and a trial evaluating canagliflozin in more advanced CKD (10) had been enrolling for more than 3 years without being discontinued for safety concerns. However, the evidence on the benefits of SGLT2 inhibitors had not yet been incorporated into clinical practice guidelines, so many health care providers may have been unaware of them. Despite the FDA granting empagliflozin an indication for cardiovascular risk reduction regardless of glycemic control in 2016, we found no association between cardiovascular morbidities and SGLT2 inhibitor prescription.

Finally, SGLT2 inhibitor prescription was limited for patients with an eGFR of 30–44 mL/min/1.73 m^2, likely because of drug labeling requirements and consequent issues with insurance approval. Although the FDA-approved prescribing information at the time recommended against using these drugs in patients with an eGFR <45 mL/min/1.73 m^2, the CREDENCE trial initiated canagliflozin in patients with an eGFR as low as 30 mL/min/1.73 m^2 and did not stop the drug for eGFR until patients reached ESKD (16). Updated FDA-approved prescribing information (17) lowering the threshold to 30 mL/min/1.73 m^2 will likely increase SGLT2 inhibitor prescription to patients with an eGFR of 30–44 mL/min/1.73 m^2.

In addition to the costs of and limited experience with newer medications, as well as the need for prior insurance authorization that involves additional resources, fear of adverse side effects may also have contributed to the low rate of SGLT2 inhibitor prescription in eligible patients. Concerns regarding specific adverse events have been raised, most notably amputation (18), but also genital mycotic infections, UTIs, euglycemic DKA, and osteoporotic fractures (19). However, we did not detect an association between SGLT2 inhibitor prescription and patient history of these conditions, although UTI history was associated with 31% lower odds of SGLT2 inhibitor prescription, which did not reach statistical significance with multivariable adjustment, perhaps because of the low number of patients. We did find that older age was associated with decreased odds of SGLT2 inhibitor prescription, possibly indicating increased provider concerns about adverse effects in the more vulnerable elderly population.

Prescription of an ACE inhibitor or ARB was associated with SGLT2 inhibitor prescription, perhaps reflecting provider recognition of proteinuric CKD and intensity of care. Although ACE inhibitor or ARB therapy is indicated in proteinuric CKD and 97% of our cohort had hypertension, 23% of patients in our cohort were not on an ACE inhibitor or ARB concurrently. Patients with higher A1C were also more likely to receive SGLT2 inhibitors, which is expected for a class of drugs initially developed and marketed to lower A1C.

The task of bringing these powerful medications to patients with CKD who need them may be complicated by inter-specialty culture and already complex medical regimens. Contrary to our a priori hypothesis that most

TABLE 3 Characteristics of Patients Prescribed SGLT2 Inhibitors, Stratified by Prescribing Specialty

	Endocrinology (n = 43, 25%)	Primary Care (n = 102, 59%)	Unknown* (n = 26, 15%)
Age, years	64 (57–70)	67 (59–71)	64 (58–72)
Female sex	9	40	31
Race/ethnicity			
White	53	37	46
Hispanic	26	46	38
Black	12	12	15
Asian	9	5	0
Income			
<$40,000	26	33	42
$40,000–49,999	5	8	4
$50,000–59,999	12	8	8
$60,000–74,999	7	14	4
$75,000–99,999	12	12	12
≥$100,000	21	11	31
Unknown	19	15	0
Comorbidities			
Hypertension	100	97	96
Ischemic heart disease	40	39	42
Heart failure	14	24	42
Cerebrovascular disease	28	23	27
PAD	35	29	38
Amputation	2	5	4
Fracture	7	9	12
Osteoporosis	2	11	8
DKA	0	3	8
UTI	9	21	38
Genital mycotic infection	2	1	0
ACE inhibitor/ARB use	88	83%	96
eGFR, mL/min/1.73 m^2			
30–44	9	14	8
45–59	26	26	31
60–89	65	60	62
UACR, mg/g Cr	548 (399–1,203)	637 (429–1,148)	893 (532–1,431)
A1C, %	8.8 (7.9–10.1)	8.8 (7.8–9.8)	9.1 (8.0–11.0)

Data on categorical variables are proportions; data on continuous variables are medians (25th–75th percentiles). *The Unknown category includes prescribers missing taxonomy codes and prescribers with nonspecific taxonomy codes.

SGLT2 inhibitor prescriptions would come from endocrinologists, most patients received their SGLT2 inhibitors from a PCP. Despite an FDA-approved indication to lower cardiovascular risk regardless of glycemic control, few SGLT2 inhibitor prescriptions were written by cardiologists or nephrologists. Analysis of 2013–2017 data from a single health care system in Boston found that only 5% of SGLT2 inhibitor prescriptions were written by cardiologists, compared with endocrinologists (40%) and PCPs (23%) (20). The benefits of SGLT2 inhibitors on the risks of cardiovascular death and ESKD place these medications within the purviews of cardiology and nephrology, and we will likely see more SGLT2 inhibitor use in these specialties in the future.

Our study has several strengths, most notably the real-world data on usage of SGLT2 inhibitors in a contemporary nationwide cohort. The claims and integrated database allowed us to use both laboratory and diagnosis codes to construct our cohort and to capture both prescription and prescriber information. Limitations of our study include the single laboratory values (serum creatinine, urine albumin) rather than trends or averages for inclusion. UACR data were only available for a small proportion of patients, although this circumstance is consistent with other large clinical datasets (e.g., a finding that UACR values were available for <7% of patients in a dataset from five health care organizations [21]). Because new cohorts are added to the OptumInsight dataset each year, we were unable to perform trend analyses over time.

Finally, patients may have died or changed insurance providers in 2017, although our sensitivity analysis indicated that dropout did not affect the proportion of patients prescribed SGLT2 inhibitors.

Conclusion

Using data from a national cohort in 2017, we found very low utilization of SGLT2 inhibitors among patients with type 2 diabetes and proteinuric CKD, a group with high cardiovascular risk and high rates of progression to ESKD (22). These findings manifested despite ample evidence from randomized clinical trials demonstrating the cardiorenal benefits of SGLT2 inhibitors. The early termination of the CREDENCE trial for efficacy and publication of its results, which occurred after the time period of our study, should focus PCPs, endocrinologists, nephrologists, and cardiologists on using this class of agents in patients with type 2 diabetes and proteinuric CKD. Continued efforts should be made to track how the proportion of eligible patients receiving SGLT2 inhibitors changes as knowledge of their benefits is disseminated and long-term data on their safety and effectiveness in clinical practice accumulate.

FUNDING

This work was supported by the National Institutes of Health grant numbers 5T32DK007357 (I.E.M.), K24DK085446 (G.M.C. and M.E.M.-R.), and 5K01DK110221 (J.J.R.).

DUALITY OF INTEREST

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

AUTHOR CONTRIBUTIONS

I.E.M. participated in the study design and data analysis and wrote the manuscript. J.H. participated in data collection and analysis. M.E.M.-R. participated in the study design, data collection, and data analysis. G.M.C. participated in data analysis. J.J.R. participated in the study design and data analysis. All authors edited the manuscript and approved the final version for submission. I.E.M. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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