Prevalence of Sodium Glucose Cotransporter 2 (SGLT-2) Inhibitor Prescribing in Patients with Type 2 Diabetes Mellitus and Reduced Estimated Glomerular Filtration Rate

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Abstract

Sodium glucose cotransporter 2 (SGLT-2) inhibitors have demonstrated benefit in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD), including slowing the progression of CKD and lowering the risk of kidney failure and death. Despite this evidence, literature suggests SGLT-2 inhibitors are underutilized in this population. To assess prescribing practices and identify potential variables predictive of SGLT-2 inhibitor prescribing, a non-interventional, retrospective, cross-sectional study was conducted in patients with T2DM and reduced estimated glomerular filtration rate (eGFR). The primary outcome compared prevalence of SGLT-2 inhibitor prescribing in patients with T2DM and eGFR of 30-44 mL/min/1.73m^2 to patients with T2DM and eGFR 45-59 mL/min/1.73m^2. The secondary outcome described possible predictors of prescribing SGLT-2 inhibitors in this population. Of the 9,387 patients identified with T2DM and reduced eGFR, an SGLT-2 inhibitor was prescribed to 324 (12.2%) patients with eGFR of 30-44 mL/min/1.73m^2 versus 799 (11.9%) patients with eGFR of 45-59 mL/min/1.73m^2. Patients more likely to be prescribed SGLT-2 inhibitors were younger, male, had a higher body mass index (BMI), a higher hemoglobin A1c (HbA1c), were on other antihyperglycemic medications, had concomitant cardiovascular disease, or had concomitant heart failure. This study found no significant difference in prevalence of SGLT-2 inhibitor prescribing between patients with T2DM and eGFR 30-44 mL/min/1.73m^2 versus eGFR 45-59 mL/min/1.73m^2 (p=0.70). Further exploration into the causes of low SGLT-2 inhibitor prescribing prevalence is warranted given the growing evidence supporting the use of these agents in patients with T2DM and reduced renal function.

Keywords: Type 2 diabetes; sodium-glucose cotransporter-2 (SGLT-2) inhibitors; chronic kidney disease (CKD); prescribing prevalence

Background

People diagnosed with type 2 diabetes mellitus (T2DM) are at an increased risk for multiple comorbidities, including chronic kidney disease (CKD), cardiovascular events, and heart failure.[1, 2] Additionally, diabetes is one of the leading causes of kidney failure, and it is estimated that 1 out of 3 adults with diabetes has kidney disease.[3] Chronic kidney disease is typically diagnosed by the presence of albuminuria or low estimated glomerular filtration rate (eGFR). Screening for albuminuria is recommended to be performed at least annually through a urinary albumin to-creatinine ratio (UACR). Moderately increased albuminuria ranges from 30-299 mg/g creatinine (Cr) while severely increased albuminuria is considered a UACR ≥300 mg/g Cr. There are different stages of chronic kidney disease based on level of albuminuria and eGFR. Stages 1 and 2 include an eGFR>60 mL/min/1.73m^2 and stages 3-5 CKD include lower ranges of eGFR.[4] Current guidelines recommend the addition of an antihyperglycemic agent with demonstrated renal benefit in people with T2DM and established CKD in addition to maximally tolerated angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).[5-9]

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Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are antihyperglycemic agents with proven benefits in people with T2DM. These agents inhibit renal glucose reabsorption in the early proximal tubule which provides enhanced urinary glucose excretion and thus, lower blood glucose levels. The glucose-lowering effect of SGLT-2 inhibitors depends on the rate at which a person's kidney is able to filter the glucose; therefore, people with impaired kidney function were largely excluded from initial clinical trials since glycemic benefits were not expected in this population. SGLT-2 inhibitors were not initially indicated for people with T2DM and advanced CKD.[10]

Despite reduced glucose lowering with decreased eGFR, it was hypothesized that SGLT-2 inhibitors may provide benefits to the kidney by reducing intraglomerular pressure through increased distal sodium delivery and inhibition of tubuloglomerular feedback.[11] Multiple SGLT-2 inhibitors were studied in people with reduced renal function with or without T2DM. These studies showed overwhelming renal benefits in these populations. In the EMPA-REG OUTCOME trial, treatment with empagliflozin was associated with a significantly decreased incidence of worsening nephropathy in people with T2DM and an eGFR of at least 30 mL/min/1.73m^2 compared to placebo.[12] Similarly, in the CREDENCE trial, canagliflozin added to renin-angiotensin system blockade in people with an eGFR of 30 to <90 mL/min/1.73m^2 and a UACR >300 mg/g was associated with a lower risk of kidney failure and cardiovascular events compared to placebo.[13] Finally, in the DAPA-CKD trial,

DOI: https://doi.org/10.24926/iip.v14i2.5456

dapagliflozin led to a statistically significant decrease in the primary composite outcome of sustained decline in the eGFR of at least 50%, end-stage renal disease (ESRD), or death from renal or cardiovascular causes in people with an estimated eGFR of 25 to 75 mL/min/1.73m^2 and a UACR of 200 to 5000 mg/g.[14]

In response to these trials, the American College of Cardiology (ACC), American Diabetes Association (ADA), American Association of Clinical Endocrinology (AACE), and Kidney Disease: Improving Global Outcomes (KDIGO) have all published guidance recommending the use of SGLT-2 inhibitors in people with T2DM. The 2020 update of the ACC Expert Consensus Decision Pathway recommends initiating SGLT-2 inhibitors in people with kidney disease caused by diabetes or those with established or at very high risk of atherosclerotic cardiovascular disease (ASCVD) or heart failure.[6] According to the 2023 ADA Standards of Care, for people with T2DM and established ASCVD or indicators of high cardiovascular risk, established kidney disease (eGFR <60 mL/min/1.73 m^2 and UACR ≥300 mg/g Cr), or heart failure, SGLT-2 inhibitors are recommended to be initiated independent of baseline hemoglobin A1c (HbA1c), individualized HbA1c target, or metformin use.[7] The 2022 AACE Comprehensive Treatment Algorithm makes a similar recommendation to both the ACC and the ADA guidelines, stating these agents should be initiated in people with T2DM with established or at high risk of ASCVD, heart failure, or CKD.[8] Finally, the updated 2022 KDIGO guidelines recommend starting an SGLT-2 inhibitor in people with T2DM, CKD, and an eGFR ≥20 mL/min/1.73m^2.[5]

Despite the data supporting the use of SGLT-2 inhibitors in people with T2DM and CKD, recent evidence suggests that utilization may be low. According to a 2021 multicenter, retrospective study conducted in South Korea by Jeong et al., the prevalence of prescribing SGLT-2 inhibitors was only 12.8% in patients with T2DM and eGFR 45-59 mL/min/1.73m^2. The prevalence of SGLT-2 prescribing was further reduced in patients with eGFR 30-44 mL/min/1.73m^2 to approximately 4.5%.[15] Since this data was collected in a population outside the United States (US), it was unclear what the prevalence would be in a US population.

The purpose of this study is to evaluate the current prevalence of prescribing SGLT-2 inhibitors in a US population with T2DM and reduced renal function. Additionally, the aim was to identify potential variables predictive of SGLT-2 inhibitor prescribing. Recognizing the characteristics which make patients more likely to be prescribed SGLT-2 inhibitors could provide insight into potential barriers that may be preventing others from receiving these guideline-recommended medications.

Methods

This was a non-interventional, retrospective, cross-sectional study evaluating patients with T2DM and reduced kidney function in the primary care population of a large, nonprofit, multicenter, academic health system. Eligible patients were included if they were age 18 years or older, had a diagnosis of T2DM based on ICD-10 codes, and had at least two values of eGFR <60 mL/min/1.73m^2 documented within 18 months prior to September 23, 2021 (index date). These two values were required to be at least 3 months apart, with the most recent eGFR occurring within the previous 12 months of the index date. These criteria for reduced kidney function are in alignment with the KDIGO definition of CKD (persistently reduced eGFR <60 mL/min/1.73m^2 for greater than 3 months).[5] This approach allowed for the identification of patients with reduced kidney function in the absence of a formal CKD diagnosis. Patients were excluded if they had a diagnosis of type 1 diabetes mellitus, were pregnant on the index date, had an eGFR value of <30 mL/min/1.73m^2, or had any documented allergy or intolerance to SGLT-2 inhibitors.

The primary outcome was a comparison of the prevalence of SGLT-2 inhibitor prescribing among patients with T2DM and eGFR 30-44 mL/min/1.73m^2 to patients with T2DM and eGFR 45-59 mL/min/1.73m^2. The secondary outcome of this study was to identify predictors of SGLT-2 inhibitor prescribing in this patient population.

Demographic characteristics were derived from the electronic medical record (EMR) and included age, sex, race/ethnicity, eGFR, HbA1c, UACR, and body mass index (BMI). Data was collected up to 18 months prior to the index date. If more than one value was available in the previous 18 months, the value closest to the index date was used for analysis. Comorbid conditions were identified using ICD-10 codes from the active problem list. Comorbid conditions collected included diabetes complications, which encompassed ICD-10 diagnosis codes for retinopathy (E11.3) and neuropathy (E11.4); heart disease, which encompassed ICD-10 diagnosis codes for cardiomyopathy (I42), myocardial infarction (I21), ischemic heart disease (I25), and peripheral arterial/vascular disease (I73.9); heart failure, which encompassed ICD-10 diagnosis codes for heart failure (I50) and ischemic cardiomyopathy (I25.5); ischemic stroke (I63); hypertension (I10); urinary tract infection (Z87.440); proteinuria (R80.9); and osteoporosis (M80).

Use of concomitant antihyperglycemic medications was also collected. Specific medication classes included biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, insulins, sulfonylureas, thiazolidinediones, and "other medications" which included meglitinides, alpha-glucosidase inhibitors, and amylinomimetics. Patients were categorized as having commercial/private insurance, Medicare, Medicaid, or other,

DOI: https://doi.org/10.24926/iip.v14i2.5456

which included military, unknown, or no insurance on file at the index date.

Descriptive statistics were used to analyze baseline characteristics (Table 1). The data is presented as mean ± standard deviation (SD) or median [25th, 75th percentiles] for continuous variables and N (%) for categorical variables. Comparisons among groups defined by the use of SGLT-2 inhibitors and eGFR category were performed by analysis of variance (ANOVA) or Kruskal Wallis tests for continuous variables based on distribution. Chi-square test or Fisher exact test were used for categorical variables.

Predictors for SGLT-2 inhibitor prescribing were identified by model selection of logistic regression. Step-down backward variable selection was used based on Akaike's Information Criterion (AIC) and Bayesian Information Criteria (BIC) to identify the final model (Table 2). A full model including all predictors was initially chosen by clinical significance and univariable analysis. One variable was excluded by each step based on statistical principle. The final model was decided as a parsimonious model using a minimum number of variables to make the best predictive accuracy. The discriminatory power and absolute predictive ability of the final model was evaluated by the concordance index (c-index), which was internally validated by bootstrapping. Multiple imputation was performed before model selection in order to fill in missing values of BMI, UACR, and HbA1c before modeling. All analyses were performed based on an overall significance level of 0.05, using R 4.0 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

After applying exclusion criteria, 9,387 patients were included in the final analysis (Figure 1). The study population was a mean age of 73.0 years, 54.2% female, and 71.2% white. The patients had a mean HbA1c of 6.7%, a mean BMI of 32.2 kg/m^2, and a mean eGFR 50.0 mL/min/1.73m^2, with 2,663 (28.4%) having an eGFR 30-44 mL/min/1.73m^2 vs 6,724 (71.6%) having an eGFR 45-59 mL/min/1.73m^2. The most common insurance type was Medicare (81.5%). Table 1 further describes the patient population.

For the primary outcome, there was no significant difference in prevalence of SGLT-2 inhibitor prescribing between patients with T2DM and eGFR 30-44 mL/min/1.73m^2 versus eGFR 45-59 mL/min/1.73m^2 (p=0.70). An SGLT-2 inhibitor was prescribed to 324 (12.2%) patients with eGFR of 30-44 mL/min/1.73m^2 versus 799 (11.9%) patients with eGFR of 45-59 mL/min/1.73m^2.

For the secondary outcomes, the initial full model included all variables from Table 1 except for osteoporosis and urinary tract infection (UTI), which were excluded due to low incidence of occurrence. Step-down backward variable selection identified twelve predictors of SGLT-2 inhibitor prescribing in the final model with a good performance in discriminatory capability (c-index: 0.778, 95% CI 0.766-0.791) using the smallest number of predictors. These included age (OR=0.96; 95% CI, 0.95-0.97), male sex (OR=1.35, 95% CI 1.18-1.55), BMI (OR=0.98; 95% CI, 0.97-0.99), HbA1C (OR=1.27; 95% CI,1.21-1.34), use of insulins (OR=1.38, 95% CI, 1.18-1.61), GLP-1 agonists (OR=2.45; 95% CI, 2.09-2.86), DPP-4 inhibitors (OR=1.82; 95% CI, 1.54-2.15), biguanides (OR=1.67; 95% CI, 1.45-1.93), sulfonylureas (OR=1.83; 95% CI, 1.59-2.11), thiazolidinediones (OR=1.40; 95% CI, 1.07-1.82), heart disease (OR=1.33; 95% CI, 1.15-1.54), and heart failure (OR=1.76; 95% CI, 1.49-2.07). Diabetic complications (retinopathy and neuropathy) were not determined to be predictors. Patients prescribed an SGLT-2 inhibitor were more likely to be younger, male, and have a higher BMI and HbA1c than those not prescribed SGLT-2 inhibitors. Patients prescribed SGLT-2 inhibitors were more likely to be on other diabetes medications, including insulins, GLP-1 agonists, DPP-4 inhibitors, biguanides, sulfonylureas, and thiazolidinediones; and have concomitant heart disease or heart failure. See Table 2 for results of the final model.

Discussion

Multiple randomized controlled trials have demonstrated that SGLT-2 inhibitors reduce the incidence of cardiovascular events, slow the progression of kidney disease, and decrease complications related to CKD.[12-14] As a result of these clinical trials, several recent guidelines have indicated SGLT-2 inhibitors for people with T2DM and established or at high risk of ASCVD, heart failure, or CKD.[5-7] However, despite the growing evidence supporting the use of these medications in this patient population, SGLT-2 inhibitors are still not frequently being used.[15] Given the known benefits of SGLT-2 inhibitors, it is important to understand the prescribing pattern for these medications in patients with T2DM and reduced kidney function. This information can assist the health care team in determining approaches to overcome the possible challenges to prescribing these agents in this population that would seemingly benefit from SGLT-2 inhibitor initiation.

Similar to previous studies, this study found SGLT-2 inhibitor prescribing prevalence to be low in patients with T2DM and reduced eGFR. The 2021 study conducted by Jeong et al. identified the prevalence of SGLT-2 inhibitor prescribing to be approximately 12.8% in patients in South Korea with T2DM and eGFR 45-59 mL/min/1.73m^2. The prevalence of SGLT-2 inhibitor use was further reduced in patients with eGFR 30-44 mL/min/1.73m^2 to approximately 4.5%.[15] Although the 2020 ADA guidelines at the time of the Jeong et al. study conducted from September 2019 to May 2020 recommended the use of SGLT-2 inhibitors for patients with eGFR ≥30 mL/min/1.73m^2, drug labeling for SGLT-2 inhibitors was only extended to eGFR ≥45 mL/min/1.73m^2 following the results of the CREDENCE trial months earlier in 2019.[13, 16] The 2022 KDIGO guidelines now recommend SGLT-2 inhibitor use for people with T2DM and eGFR ≥20 mL/min/1.73m^2.[5] This may help to explain the

DOI: https://doi.org/10.24926/iip.v14i2.5456

increased prevalence of SGLT-2 inhibitor prescribing in the current study population with eGFR 30-44 mL/min/1.73m^2 (12.2%) which was not significantly different from patients with eGFR 45-59 mL/min/1.73m^2 (11.9%). Though the prevalence of SGLT-2 utilization has increased among patients with eGFR 30-44 mL/min/1.73m^2, the overall prescribing prevalence has not increased significantly in the years since the Jeong et al. study in the US study population, despite growing evidence of benefits and safety of SGLT-2 inhibitors in patients with CKD.

The retrospective study from Jeong et al. also identified several predictors related to SGLT-2 inhibitor prescribing. People who were younger, with a higher HbA1c, higher BMI, and/or had presence of diabetic retinopathy or previous heart failure events were associated with a positive incidence of SGLT-2 inhibitor initiation.[15] Similarly, this present study determined that younger age, higher HbA1c, higher BMI, and concomitant heart failure were predictors of SGLT-2 inhibitor prescribing. However, this study did not identify presence diabetes complications (including diabetic retinopathy and diabetic neuropathy) as a predictor of SGLT-2 inhibitor prescribing. Additional predictors identified through the current study included male sex, use of other antihyperglycemic medications (with the exception of those that fell into the "other medications" category) as well as concomitant heart disease. A diagnosis of heart disease and/or heart failure is expected to have an increased prevalence as canagliflozin is indicated for use in patients with T2DM and established cardiovascular disease and/or heart failure, while dapagliflozin and empagliflozin are also recommended for use in patients diagnosed with heart failure, with or without T2DM.[17-23]

The current study results suggest a disparity in SGLT-2 inhibitor prescribing prevalence between male and female patients. The overall population in this study was mostly female (54.2%), however, male sex was found to be a predictor of SGLT-2 inhibitor prescribing. Because SGLT-2 inhibitors increase the availability of glucose in the genitourinary tract, they provide a substrate for bacteria to proliferate. Due to anatomical differences between the sexes, UTIs typically occur more often in females.[24-26] Though the prevalence of UTI ICD-10 codes in the study population was very low, prescribers may still associate female sex as a significant risk factor for UTI, thus decreasing SGLT-2 inhibitor prescribing in this population.

SGLT-2 inhibitor prescribing may also be less prevalent among female patients due to their effect on bone health. SGLT-2 inhibitors indirectly target the FGF23/1,25- dihydroxyvitamin D/parathyroid hormone axis, which can cause increased bone fractures or accelerated loss of total bone density in large bones such as hips and femurs.[27] Increased incidence of bone fractures was observed in the clinical trials of canagliflozin, which may deter prescribers from initiating SGLT-2 inhibitors, as osteoporosis is more prevalent among females.[17, 28] However, bone fractures were not observed in large trials with empagliflozin or dapagliflozin, so it is unclear if this is a class effect.[6, 27] Of note, patients prescribed SGLT-2 inhibitors often have concomitant T2DM, CKD, and post-menopausal osteopenia or osteoporosis, all of which can negatively impact bone health as well.[27, 28] As elderly female patients are more likely to have post-menopausal osteopenia, this may offer an explanation as to why older patients are less likely to be prescribed SGLT-2 inhibitors in this study. However, the prevalence of osteoporosis diagnoses was also very low for all patients in the study, regardless of whether an SGLT-2 inhibitor was prescribed.

Patients in this study were more likely to be prescribed an SGLT-2 inhibitor if they had a higher HbA1c compared to patients with a lower HbA1c. Previous ADA guidelines from 2018 had only indicated SGLT-2 inhibitors for the treatment of uncontrolled T2DM, with only canagliflozin and empagliflozin indicated for people with cardiovascular risk factors. None of the medications were indicated for people with CKD.[29] However, according to the 2023 ADA and 2022 KDIGO guidelines, SGLT-2 inhibitors have exhibited benefit to people with T2DM and CKD, regardless of HbA1c, and should be initiated in patients with reduced kidney function, even if their HbA1c is at goal.[5, 7] Therefore, prescribers may benefit from targeted education to extend SGLT-2 inhibitor prescribing to T2DM patients with reduced eGFR, regardless of their HbA1c level. This is with the understanding that as a person's eGFR decreases to <60 mL/min/1.73m^2, HbA1c reduction by SGLT-2 inhibitors will also decline.[30]

A majority of the patients in this study had Medicare as their primary payer. Medicare's total expenditure for a 30-day supply of an SGLT-2 inhibitor is typically $450.15 (95% CI; $424.18 to $476.11).[31] The Medicare patient's out-of-pocket cost is typically $49.42 (95%CI; $25.41 to $73.43) for a 30 day supply, which may be prohibitive for some, especially patients on multiple expensive medications.[31] The current study did not assess procurement rate of the prescriptions, so it is unclear whether the cost affected the patient's ability to fill the SGLT-2 inhibitor prescription. Future studies are needed to understand the impact of SGLT-2 inhibitor cost and payer type on prescription fill rates.

Due to the retrospective nature of this study, investigators relied on accurate documentation in the medical record. Patients with a history of SGLT-2 inhibitor intolerance could only be identified if the intolerance was documented in the medical record, potentially overestimating the number of patients eligible for inclusion. Reliance on ICD-10 codes introduces further opportunities for inaccuracies. In addition, this study did not investigate the procurement of the prescribed SGLT-2 inhibitors, adherence to the medication, or rates of discontinuation as the study was a cross-sectional design. Therefore, it is possible that an SGLT-2 inhibitor was prescribed, but that the patient never started the medication due to

DOI: https://doi.org/10.24926/iip.v14i2.5456

medication procurement issues, or stopped the medication for any reason after it was prescribed, thereby overestimating the prevalence SGLT-2 inhibitor utilization.

Another limitation to this study design was that only electronically written, or e-prescribed prescriptions sent to pharmacies by providers within the health system were able to be captured. This limitation specifically impacts Medicare and uninsured patients who may financially qualify to receive brand-name medications at no cost via patient assistance programs (PAPs) through the drug manufacturers. If patients qualify and are enrolled in PAPs, the medications are distributed to the prescriber's office or patient's home directly from the manufacturer. If these SGLT-2 inhibitor prescriptions were e-prescribed by the provider to the PAP pharmacies, the prescriptions would have been accurately captured in this study design and these patients would be identified. However, if the provider faxed or mailed the prescription to the assistance program, these prescriptions would not have been captured in this study design, thereby potentially underestimating the prevalence of SGLT-2 inhibitor prescribing in this population. In addition, the current study design is such that SGLT-2 inhibitors prescribed by a provider outside of the health system would not be captured, possibly underestimating the prevalence of SGLT-2 inhibitor prescribing in this patient population.

A final consideration regarding the current study relates to the 2023 ADA and 2022 KDIGO guidelines. During the time of the study period, the 2021 ADA and 2020 KDIGO guidelines recommended SGLT-2 inhibitor therapy in patients with T2DM and eGFR ≥30 mL/min/1.73m^2.[32, 33] Due to the benefit shown in the EMPEROR-Reduced and EMPEROR-Preserved randomized controlled trials in patients with eGFR ≥20 mL/min/1.73m^2,[21, 22] the 2022 KDIGO and 2023 ADA recommendations have been expanded to now include this population with an eGFR ≥20 mL/min/1.73m^2. Therefore, prescribing prevalence of SGLT-2 inhibitors may have increased following these recent guideline updates.[5, 7] Further studies investigating whether prevalence in prescribing SGLT-2 inhibitors changes along with recent guideline recommendations may be helpful in predicting further trends.

Conclusion

Among patients with T2DM and reduced eGFR, there was no significant difference in the prevalence of prescribing SGLT-2 inhibitors between patients with an eGFR 30-44 mL/min/1.73m^2 and eGFR 45-59 mL/min/1.73m^2. However, the overall prevalence was low as only 12.2% of patients with eGFR of 30-44 mL/min/1.73m^2 were prescribed an SGLT-2 inhibitor versus 11.9% of patients with eGFR of 45-59 mL/min/1.73m^2. Patients more likely to be prescribed SGLT-2 inhibitors were younger, male, had a higher BMI, a higher HbA1c, were on other antihyperglycemic medications, had concomitant cardiovascular disease, or had concomitant heart failure. Population health interventions, prescriber education, and clinical support technologies should be explored as options to improve SGLT-2 inhibitor prescribing among patients with T2DM and CKD. Further exploration into the causes of low SGLT-2 inhibitor prescribing prevalence is warranted given the growing evidence supporting the use of these agents in patients with diabetes and reduced renal function. Follow up studies are needed to assess prescribing prevalence following recent expanded guideline recommendations and to further investigate the causes of the identified SGLT-2 inhibitor prescribing predictors to help ensure that all eligible patients are offered the opportunity to receive these medications.

Acknowledgements: None
Conflicts of Interest: None
Funding/Support: None

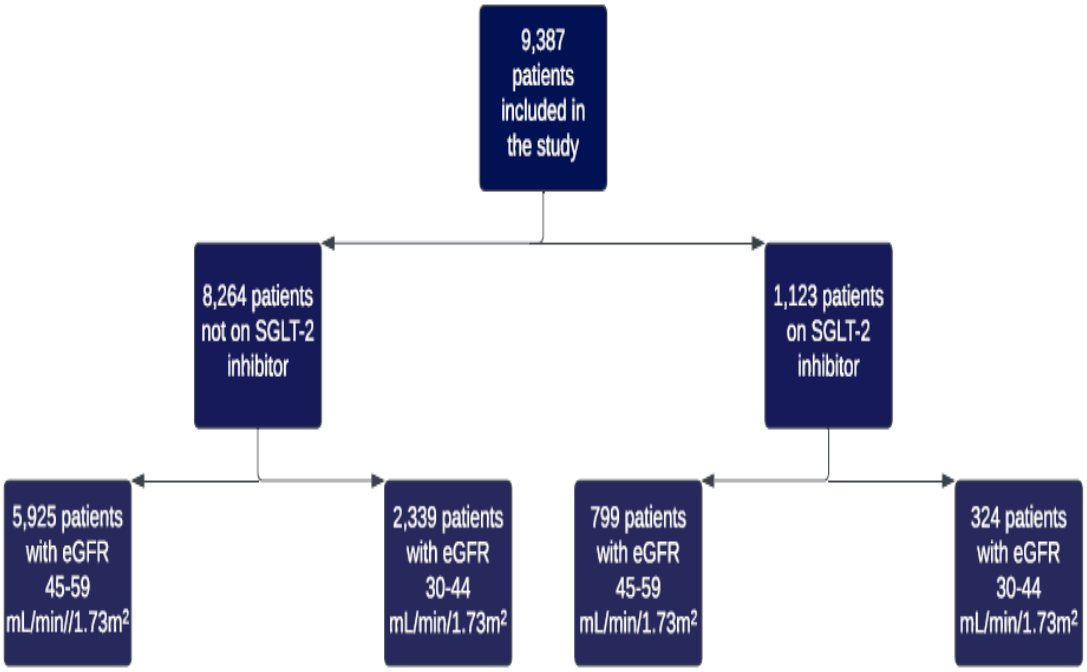
The statements and opinions expressed in this paper are those of the author(s).

References

1. Cavender MA, Steg PG, Smith SC Jr, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the reduction of atherothrombosis for continued health (REACH) registry. Circulation. 2015 Sep 8;132(10):923-31.
2. Centers for Disease Control and Prevention. Chronic kidney disease basics. Page reviewed February 28, 2022. Accessed December 23, 2022.
3. Centers for Disease Control and Prevention. *Chronic kidney disease in the United States, 2019*. Atlanta, GA: US Department of Health and Human Services. Centers for Disease Control and Prevention. 2019.
4. American Diabetes Association. 11. Chronic kidney disease and risk management: standards of medical care in diabetes – 2022. Diabetes Care 2022;45(Suppl 1):S175-S184.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2022 Nov;102(5S):S1-S127.
6. Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology solution set oversight committee. J Am Coll Cardiol. 2020 Sep 1;76(9):1117-1145.
7. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S140-S157.
8. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan – 2022 update. Endocr Pract. 2022 Oct;28(10):923-1049.

9. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive Type 2 diabetes management algorithm – 2023 update. Endocr Pract. 2023 May;29(5):305-340.
10. Nespoux J, Vallon V. Renal effects of SGLT2 inhibitors: an update. Curr Opin Nephrol Hypertens. 2020 Mar;29(2):190-198.
11. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 inhibitors in patients with CKD: expanding indications and practical considerations. Kidney Int Rep. 2022 May;7(7):1463-1476.
12. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Eng J Med. 2016 Jul 28;375:323-334.
13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306.
14. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446.
15. Jeong SJ, Lee SE, Shin DH, Park IB, Lee HS, Kim KA. Barriers to initiating SGLT2 inhibitors in diabetic kidney disease: a real-world study. BMC Nephrol. 2021 May 14;22(1):177.
16. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes-2020. Diabetes Care. 2020 Jan;43(Suppl 1):S135-S151.
17. Invokana [package insert]. Janssen Pharmaceuticals, Inc.;2013.
18. Farxiga [package insert]. AstraZeneca Pharmaceuticals; 2017.
19. Jardiance [package insert]. Boehringer Ingelheim;2016.
20. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. Circulation. 2022;145(18):e895-e1032.
21. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424.
22. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461.
23. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008.
24. Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol. 2019 May 2;11:1756287219832172.
25. Harringon RD, Hooton TM. Urinary tract infection risk factors and gender. J Gend Specif Med. 2000 Nov-Dec;3(8):27-34.
26. Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections: a population-based cohort study. Ann Intern Med. 2019 Aug 20;171(4):248-256.
27. Blau JE, Taylor SI. Adverse effects of SGLT2 inhibitors on bone health. Nat Rev Nephrol. 2018 Aug;14(8):473-474.
28. Sarafrazi N, Wambogo EA, Shepherd JA. Osteoporosis or low bone mass in older adults: United States, 2017–2018. NCHS Data Brief, no 405. Hyattsville, MD: National Center for Health Statistics. 2021.
29. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2018. Diabetes Care. 2018 Jan;41(Suppl 1):S73-S85.
30. Cherney DZI, Cooper ME, Tikkanen I, et al. Pooled analysis of phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. Kidney Int. 2018 Jan;93(1):231-244.
31. Aggarwal R, Vaduganathan M, Chiu N, Bhatt DL. Out-of-pocket costs for SGLT-2 (sodium-glucose transport protein-2) inhibitors in the United States. Circ Heart Fail. 2022 Mar;15(3):e009099.
32. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes – 2021. 2021 Jan;44 (Suppl 1):S111-S124.
33. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020 Oct;98(4S):S1-S115.

Figure 1. Breakdown of patients included in study



SGLT-2: sodium glucose cotransporter-2
eGFR: estimated glomerular filtration rate

Table 1. Baseline Characteristics

		Overall N= 9,387
Age (years)		73.0 (10.3)
Sex:		
Female		5,086 (54.2%)
Male		4,301 (45.8%)
Race:		
Black		2,215 (23.6%)
Other		489 (5.2%)
White		6,683 (71.2%)
Ethnicity:		
Not Hispanic		9,130 (97.3%)
Hispanic		257 (2.7%)
Insurance Type:		
Medicaid		426 (4.5%)
Medicare		7,651 (81.5%)
Other/Unknown		384 (4.1%)
Private		926 (9.9%)
BMI (kg/m^2)		32.2 (7.2)
UACR (mg/g)		30.0 [17.0;120.0]
HbA1c (%)		6.7 [6.2;7.5]
eGFR:		50.0 [44.0;55.0]
eGFR 30-44 mL/min/1.73m^2		2,663 (28.4%)
eGFR 45-59 mL/min/1.73m^2		6,724 (71.6%)
Insulins		2,495 (26.6%)
GLP-1 Agonists		1,437 (15.3%)
DPP-4 Inhibitors		1,375 (14.6%)
Biguanides		5,160 (55.0%)
Sulfonylureas		2,863 (30.5%)
Thiazolidinediones		437 (4.7%)
Other		109 (1.2%)
Diabetes Complications		2,983 (31.8%)
Heart Disease		3,589 (38.2%)
Heart Failure		1,849 (19.7%)
Ischemic Stroke		875 (9.3%)
Hypertension		8,820 (94.0%)
UTI		40 (0.4%)
Proteinuria		907 (9.7%)
Osteoporosis		33 (0.4%)

Mean ± standard deviation (SD) or median [25th, 75th percentiles] for continuous variables and N (%) for categorical variables

eGFR: estimated glomerular filtration rate
UACR: urinary albumin creatinine ratio
GLP-1: glucagon-like peptide-1
DPP-4: dipeptidyl peptidase-4
BMI: body mass index
HbA1c: hemoglobin A1c
UTI: urinary tract infection

DOI: https://doi.org/10.24926/iip.v14i2.5456

Table 2. Multivariable logistic regression of secondary outcome

Characteristic	OR[A]	95% CI[B]	p-value
Age	0.96	0.95,0.97	<0.001
Male Sex	1.35	1.18,1.55	<0.001
BMI	0.98	0.97,0.99	0.001
HbA1c	1.27	1.21,1.34	<0.001
Use of Insulins	1.38	1.18,1.61	<0.001
Use of GLP-1 Agonists	2.45	2.09,2.86	<0.001
Use of DPP-4 Inhibitors	1.82	1.54,2.15	<0.001
Use of Biguanides	1.67	1.45,1.93	<0.001
Use of Sulfonylureas	1.83	1.59,2.11	<0.001
Use of Thiazolidinediones	1.40	1.07,1.82	0.013
Concomitant Heart Disease	1.33	1.15,1.54	<0.001
Concomitant Heart Failure	1.76	1.49,2.07	<0.001

[A] OR = Odds Ratio, [B]CI = Confidence Interval
BMI: body mass index
HbA1c: hemoglobin A1c
GLP-1: glucagon-like peptide-1
DPP-4: dipeptidyl peptidase-4