Safety of sodium-glucose cotransporter-2 inhibitors in patients with CKD and type 2 diabetes: population-based US cohort study

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Safety of Sodium-Glucose Cotransporter-2 Inhibitors in Patients with CKD and Type 2 Diabetes: Population-Based US Cohort Study

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Abstract

Background Limited information exists regarding the safety of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in patients with CKD treated in routine care. We evaluated the safety of SGLT2i in patients with CKD and type 2 diabetes treated in US routine practice.

Methods Using claims data from Medicare and two large US commercial databases (April 2013–December 2021), we included 96,128 adults with CKD stages 3–4 and type 2 diabetes who newly filled prescriptions for SGLT2i versus glucagon-like peptide-1 receptor agonists (GLP-1RA). Safety outcomes included diabetic ketoacidosis (DKA), lower limb amputations, nonvertebral fractures, genital infections, hypovolemia, AKI, hypoglycemia, and severe urinary tract infections (UTIs). Hazard ratios (HRs) and incidence rate differences per 1000 person-years were estimated after 1:1 propensity score matching, adjusted for >120 baseline characteristics.

Results Compared with GLP-1RA, SGLT2i initiators had a higher risk of nonvertebral fractures (HR, 1.30 [95% confidence interval (CI), 1.03 to 1.65]; incidence rate difference, 2.13 [95% CI, 0.28 to 3.97]), lower limb amputations (HR, 1.65 [95% CI, 1.22 to 2.23]; incidence rate difference, 2.46 [95% CI, 1.00 to 3.92]), and genital infections (HR, 3.08 [95% CI, 2.73 to 3.48]; incidence rate difference, 41.26 [95% CI, 37.06 to 45.46]). Similar risks of DKA (HR, 1.07 [95% CI, 0.74 to 1.54]; incidence rate difference, 0.29 [95% CI, −0.89 to 1.46]), hypovolemia (HR, 0.99 [95% CI, 0.86 to 1.14]; incidence rate difference, 0.20 [95% CI, −2.85 to 3.25]), hypoglycemia (HR, 1.08 [95% CI, 0.92 to 1.26]; incidence rate difference, 1.46 [95% CI, −1.31 to 4.23]), and severe UTI (HR, 1.02 [95% CI, 0.87 to 1.19]; incidence rate difference, 0.35 [95% CI, −2.51 to 3.21]) were observed. SGLT2i had lower risk for AKI (HR, 0.93 [95% CI, 0.87 to 0.99]; incidence rate difference, −6.75 [95% CI, −13.69 to 0.20]).

Conclusions In US patients with CKD and type 2 diabetes receiving routine care, SGLT2i use was associated with higher risks of genital infections and potentially lower limb amputations and nonvertebral fractures.

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Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are recommended as first-line therapy in patients with type 2 diabetes and CKD who have an eGFR ≥20 ml/min per 1.73 m^2.[1,2] Although randomized controlled trials have shown the cardiovascular and renoprotective effects of SGLT2i in patients with diabetic kidney disease,[3,4] their uptake in routine clinical practice has been slow: Recent studies show that as few as 6% of patients with CKD and type 2 diabetes are currently prescribed SGLT2i in the United States.[5,6] This is especially concerning because these patients are at high risk for cardiovascular disease and kidney disease progression.[7,8]

The slow clinical adoption of SGLT2i may partly be due to concerns about potential adverse effects, including diabetic ketoacidosis (DKA), fractures, amputations, and urogenital infections.[9–11] These safety events are especially important as patients with CKD have a higher baseline risk of fractures and lower limb amputations than the non-CKD population, due to disorders in mineral and bone metabolism and high prevalence of risk factors for foot ulceration.[12–15]

Currently, there is a paucity of safety data on SGLT2i in patients with CKD and type 2 diabetes. Clinical trials are generally underpowered to assess rare but potentially severe side effects.[3,4] They also include highly selected patient populations with different characteristics from those who receive SGLT2i in routine care[16,17] and apply monitoring protocols to lower the risk of adverse effects which may not be adopted in routine practice. We therefore aimed to comprehensively investigate the safety profile of SGLT2i in routinely cared patients with CKD and type 2 diabetes using three nationwide US databases.

Methods

Data Source

We used data from three large US health insurance databases: Optum's deidentified Clinformatics Data Mart Database (CDM), IBM MarketScan, and

Medicare Fee-for-Service Parts A, B, and D. CDM and IBM MarketScan include a national commercially insured US population. Medicare is a federal health insurance program providing health care coverage for US residents 65 years or older or younger than 65 years with disabilities. The databases contain deidentified, longitudinal, individual-level data on health care use, inpatient and outpatient diagnoses, diagnostic tests and procedures, outpatient laboratory results (approximately 45% of patients in CDM and 5%–10% in IBM MarketScan), and pharmacy dispensing of drugs. This study was approved by the Mass General Brigham Institutional Review Board, and signed data license agreements were in place for all data sources.

Study Design and Study Population

We conducted an active comparator, new-user cohort study of patients 18 years or older (65 years or older for Medicare) who newly initiated an SGLT2i (*i.e.*, empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin) or a glucagon-like peptide-1 receptor agonist (GLP-1RA) (*i.e.*, liraglutide, dulaglutide, semaglutide, exenatide, albiglutide, and lixisenatide) between April 2013, when the first SGLT2i was released in the United States, and the end of available data (April 2021 in CDM, December 2019 in Medicare Fee-for-Service, and December 2020 in IBM MarketScan) (Supplemental Figure 1). New initiation was defined as a filled prescription for SGLT2i or GLP-1RA, with no previous filled prescriptions of either drug in the previous 365 days. We used GLP-1RA as the active comparator[18–20] because GLP-1RA has similarly been shown to reduce cardiovascular events in randomized trials.[21] Both drugs had similar clinical indications during the study period (*i.e.*, second-line or third-line glucose-lowering drugs for patients at high cardiovascular risk) and similar temporal trends in use.[5,22–24] To be eligible, patients were required to have at least 12 months of continuous health insurance enrollment preceding the cohort entry date as well as diagnoses for CKD and type 2 diabetes. CKD was defined as at least one inpatient or two outpatient diagnosis codes for CKD stages 3–5, and no data on eGFR were used (Supplemental Table 1); the definition was based on a previously validated algorithm that showed sufficient accuracy to identify a population with CKD stages 3–5 (positive predictive value >80%).[25] We excluded individuals with a history of type 1 diabetes, secondary or gestational diabetes, kidney failure, nursing home admission, organ transplant, pancreatitis, cirrhosis, acute hepatitis, or multiple endocrine neoplasia type 2 (Supplemental Table 1).

Drug Exposure and Follow-Up

The study exposure was filled prescription for SGLT2i or GLP-1RA. Follow-up began on the day after cohort entry and continued in an "as-treated" approach until the earliest of treatment discontinuation or switch to a drug in the comparator class, outcome occurrence, death, end of continuous health plan enrollment, or end of available data, whichever occurred first. Discontinuation was defined as no prescription refill for the index exposure within 30 days after the termination of the last prescription's supply. We chose an as-treated follow-up approach as primary analysis to address the high rate of treatment discontinuation in routine care,[26] which reduces the exposure misclassification that occurs when intention-to-treat analyses are applied in observational studies.[20]

Study Outcomes

Safety outcomes included DKA, nonvertebral fractures, lower limb amputations, genital infections, hypovolemia, severe hypoglycemia, AKI, and severe urinary tract infections (UTI). We selected these outcomes on the basis of potential safety signals of SGLT2i previously identified in randomized trials or observational studies. The outcomes were identified using validated International Classification of Diseases-9/10-CM procedural and diagnosis codes (Supplemental Table 2). Validation studies for the claims-based algorithms for DKA, nonvertebral fractures, severe hypoglycemia, and AKI have shown positive predictive values >80%.[27–31] We adapted definition codes from previous studies for safety outcomes without validation studies (genital infections, lower limb amputations, and severe UTI).[32–34]

Covariates

Baseline characteristics were measured during 365 days before or on cohort entry. These included demographics, comorbid conditions, diabetes-specific complications, use of diabetes and non–diabetes-related drugs, and measures of health care use (Supplemental Table 1). To address potential confounding by frailty, we also used a claims-based frailty index.[35] Laboratory results were available for approximately 15% of the overall population (approximately 45% of patients in CDM and 5%–10% in IBM MarketScan). Race was self-reported in the claims data sources and not specifically collected for research purposes. There were no missing data for the other covariates (the absence of a diagnosis or procedure code was interpreted as the absence of a particular condition).

Statistical Analyses

We used 1:1 propensity score matching using the nearest neighbor method with a caliper of 0.01 of the propensity score to adjust for confounding.[36] We estimated the probability of receiving SGLT2i versus GLP-1RA as a function of >120 pre-exposure covariates using multivariable logistic regression. All covariates listed in Supplemental Table 1 were included in the propensity score model except for laboratory results, which were only available in a subset of patients. Covariate balance before and after matching was assessed using standardized mean differences.[37,38] Balance in laboratory results was also inspected to assess potential residual confounding by unmeasured factors because laboratory results were not included in the propensity score. For all outcomes, we calculated propensity score–matched numbers of events, incidence rates, incidence rate differences, and hazard ratios (HRs). The HRs and incidence rate differences with their 95% confidence intervals (CIs) were estimated in each data source and then pooled using a fixed effects meta-analysis. HRs were estimated using cause-specific Cox regression, and incidence rate differences using generalized linear regression with identity link function and normal error distribution.[39] We constructed cumulative incidence function plots with the Aalen–Johansen estimator, which does not overestimate

risks in the presence of the competing risk of death.[40] Analyses were performed using R version 3.6.2 and Aetion Evidence Platform v4.53.

Subgroup, Sensitivity, and *Post Hoc* Analyses

We performed subgroup analyses in the following prespecified strata: age (65–74 versus 75 years or older), sex, cardiovascular disease, heart failure, metformin use, insulin use, and sulfonylurea use. Within each subgroup, we re-estimated the propensity score and reperformed 1:1 propensity score matching. We also performed multiple sensitivity analyses. First, we defined treatment discontinuation as no prescription refill within 60 days (instead of 30 days). Second, to investigate the influence of informative censoring, we applied an intention-to-treat follow-up approach, where follow-up was continued for a maximum of 6 and 12 months regardless of treatment discontinuation or switch. We also performed three *post hoc* analyses. First, to address the potential for unmeasured confounding associated with risk for recurrence, we excluded individuals with prior nonvertebral fractures and lower limb amputations. Second, to investigate a potential effect of GLP-1RA on some of the study outcomes, we also compared SGLT2i with dipeptidyl peptidase-4 inhibitor (DPP4i). Third, we investigated the association between SGLT2i versus GLP-1RA with different types of nonvertebral fractures (hip and femur, humerus, pelvis, radius, and ulna).

Results

Study Population

We included a total of 96,128 individuals with CKD and type 2 diabetes, of whom 32,192 initiated SGLT2i and 63,936 GLP-1RA (Supplemental Figure 2). Although reasonably well balanced in baseline characteristics before propensity score matching, compared with GLP-1RA initiators, the SGLT2i group was slightly older, more likely to be male, and less likely to have obesity or CKD stage 4 (Table 1, Supplemental Table 3). They were also more likely to use metformin and DPP4i, but less likely to use insulin. After 1:1 propensity score matching 28,847 SGLT2i initiators to 28,847 GLP-1RA initiators, differences in patient characteristics were well balanced across treatment groups (see Supplemental Tables 4–6 for baseline characteristics in each database, Supplemental Figure 3 for propensity score distributions before and after propensity score matching). Laboratory results were also well balanced, except for a small difference in eGFR (2.6 ml/min per 1.73 m^2 higher for SGLT2i users) among the subset with available data. In the matched cohort, the mean age was 72 years, 56% were men, and 64% were White. Furthermore, 25% had heart failure, 90% had stage 3 CKD, 41% used metformin, and 27% used insulin. Among SGLT2i agents, empagliflozin was most commonly used (51%), followed by canagliflozin (35%) and dapagliflozin (14%) (Supplemental Table 7). The most used GLP-1RA agents were dulaglutide (40%), liraglutide (33%), and semaglutide (13%).

Safety of SGLT2i versus GLP-1RA

The mean on-treatment follow-up time was 7.5 months (median, 4.0 months). Most patients were censored due to treatment discontinuation (62%) or end of study period (23%) (Supplemental Table 8). In the 1:1 propensity score–matched cohort, SGLT2i compared with GLP-1RA were associated with a higher risk of nonvertebral fractures (HR, 1.30 [95% CI, 1.03 to 1.65]; incidence rate difference, 2.13 [95% CI, 0.28 to 3.97] events per 1000 person-years), lower limb amputations (HR, 1.65 [95% CI, 1.22 to 2.23]; incidence rate difference, 2.46 [95% CI, 1.00 to 3.92]), and genital infections (HR, 3.08 [95% CI, 2.73 to 3.48]; incidence rate difference, 41.26 [95% CI, 37.06 to 45.46]) (Figure 1). Similar risks of DKA (HR, 1.07 [95% CI, 0.74 to 1.54]; incidence rate difference, 0.29 [95% CI, −0.89 to 1.46]), hypovolemia (HR, 0.99 [95% CI, 0.86 to 1.14]; incidence rate difference, 0.20 [95% CI, −2.85 to 3.25]), hypoglycemia (HR, 1.08 [95% CI, 0.92 to 1.26]; incidence rate difference, 1.46 [95% CI, −1.31 to 4.23]), and severe UTI (HR, 1.02 [95% CI, 0.87 to 1.19]; incidence rate difference, 0.35 [95% CI, −2.51 to 3.21]) were observed, and a lower AKI risk (HR, 0.93 [95% CI, 0.87 to 0.99]; incidence rate difference, −6.75 [95% CI, −13.69 to 0.20]) was observed. Cumulative incidence curves (Figure 2) showed that the divergence for lower limb amputations, genital infections, and nonvertebral fractures occurred within the first 6 months of follow-up.

Subgroup, Sensitivity, and *Post Hoc* Analyses

Higher risks for lower limb amputations, genital infections, and nonvertebral fractures for SGLT2i versus GLP-1RA were observed across most subgroups of age, sex, cardiovascular disease, heart failure, and use of metformin, sulfonylurea, or insulin, although confidence intervals were wider (Figure 3).

The results were consistent when using a 60-day grace period after treatment discontinuation or switch (Supplemental Table 9). In both 180-day and 365-day intention-to-treat analyses, we observed elevated risks for genital infections (HR, 2.72; 95% CI, 2.40 to 3.09) and lower limb amputations (HR, 1.57; 95% CI, 1.13 to 2.19), but not for nonvertebral fractures (HR, 1.09; 95% CI, 0.82 to 1.44) (Supplemental Tables 10 and 11). Risks associated with SGLT2i versus GLP-1RA remained consistent after excluding individuals with prior nonvertebral fractures or lower limb amputations, with HRs of 1.32 (95% CI, 1.04 to 1.68) for nonvertebral fractures and 1.89 (95% CI, 1.34 to 2.67) for lower limb amputations (Supplemental Table 12). When comparing SGLT2i with DPP4i, the HR remained elevated for genital infections (HR, 2.75; 95% CI, 2.41 to 3.15), but not for lower limb amputations (HR, 1.13; 95% CI, 0.82 to 1.56) and fractures (HR, 0.87; 95% CI, 0.68 to 1.12) (Supplemental Table 12). The higher fracture risk for SGLT2i compared with GLP-1RA was driven by a higher risk of hip and femur fractures (HR, 1.62; 95% CI, 1.14 to 2.30) (Supplemental Table 13).

Discussion

In this large population-based study of individuals with CKD and type 2 diabetes treated in routine care, we found that SGLT2i use, as compared with GLP-1RA use, was associated with higher risks of lower limb amputations, genital infections, and nonvertebral fractures. No noticeable differences were observed for the other safety outcomes, including DKA, hypovolemia, hypoglycemia, and severe UTI. Findings were consistent across multiple sensitivity and subgroup analyses, although

Table 1. Selected baseline characteristics of patients with CKD and type 2 diabetes initiating treatment with SGLT2i versus GLP-1RA, before and after 1:1 propensity score matching in the pooled cohort

Characteristic	Before Propensity Score Matching			After 1:1 Propensity Score Matching		
	SGLT2i	GLP-1RA	SMD	SGLT2i	GLP-1RA	SMD
Total	32,192	63,936		28,847	28,847	
Demographics						
Age, mean (SD)	73 (7)	71 (7)	−0.16	72 (7)	72 (7)	0.00
Men, *n* (%)	18,452 (57)	32,061 (50)	−0.14	16,080 (56)	16,070 (56)	0.00
Race/ethnicity,[a] *n* (%)						
Asian	1719 (5)	1842 (3)	−0.12	1202 (4)	1162 (4)	−0.01
Black	3184 (10)	6442 (10)	0.01	2840 (10)	2874 (10)	0.01
Hispanic	2207 (7)	3650 (6)	−0.05	1888 (7)	1836 (6)	0.00
Other	1497 (5)	2528 (4)	−0.03	1280 (4)	1276 (4)	0.00
White	20,135 (63)	42,214 (66)	0.07	18,444 (64)	18,506 (64)	0.01
Burden of comorbidities						
Combined comorbidity score, mean (SD)[b]	4.07 (2.48)	4.14 (2.38)	0.03	4.03 (2.45)	4.06 (2.43)	0.01
Frailty score, mean (SD)[c]	0.20 (0.06)	0.21 (0.06)	0.17	0.21 (0.06)	0.21 (0.06)	0.00
Comorbidities, *n* (%)						
Hypertension	30,996 (96)	61,926 (97)	0.03	27,797 (96)	27,758 (96)	−0.01
Hyperlipidemia	28,753 (89)	57,081 (89)	0.00	25,732 (89)	25,678 (89)	−0.01
Cardiovascular disease[d]	19,204 (60)	37,233 (58)	−0.03	16,935 (59)	16,962 (59)	0.00
Acute myocardial infarction	1541 (5)	2395 (4)	−0.05	1222 (4)	1249 (4)	0.00
Coronary atherosclerosis	13,546 (42)	25,324 (40)	−0.05	11,823 (41)	11,955 (41)	0.01
Heart failure	8332 (26)	16,428 (26)	0.00	7236 (25)	7267 (25)	0.00
Ischemic stroke	4814 (15)	9054 (14)	−0.02	4218 (15)	4217 (15)	0.00
Peripheral arterial disease	6058 (19)	12,059 (19)	0.00	5361 (19)	5425 (19)	0.01
AKI	5362 (17)	12,292 (19)	0.07	4835 (17)	4896 (17)	0.01
CKD stage 3	29,339 (91)	53,125 (83)	0.24	26,086 (90)	26,104 (91)	0.00
CKD stage 4	2853 (9)	10,811 (17)	0.24	2761 (10)	2743 (10)	0.00
Urinary tract infection	5683 (18)	13,376 (21)	0.08	5228 (18)	5208 (18)	0.00
Kidney and urinary stone	2315 (7)	4982 (8)	0.02	2095 (7)	2093 (7)	0.00
Edema	6601 (21)	16,047 (25)	0.11	6102 (21)	6107 (21)	0.00
COPD	5554 (17)	11,274 (18)	0.01	4951 (17)	5028 (17)	0.01
Asthma	3080 (10)	6889 (11)	0.04	2809 (10)	2848 (10)	0.01
Fractures	655 (2)	1590 (3)	0.03	606 (2)	623 (2)	0.01
Falls	2175 (7)	4725 (7)	0.02	1943 (7)	1972 (7)	0.00
Diabetes-related conditions, *n* (%)						
Diabetic kidney disease	21,765 (68)	45,445 (71)	0.08	19,501 (68)	19,570 (68)	0.00
Diabetic retinopathy	5737 (18)	13,610 (21)	0.09	5265 (18)	5225 (18)	−0.01
Diabetic neuropathy	11,280 (35)	25,859 (40)	0.11	10,324 (36)	10,452 (36)	0.01
Diabetes with peripheral circulatory disorders	796 (3)	1684 (3)	0.01	716 (3)	732 (3)	0.00
Diabetic foot	1389 (4)	3677 (6)	0.07	1300 (5)	1309 (5)	0.00
Lower limb amputation	352 (1)	998 (2)	0.04	327 (1)	337 (1)	0.01
Hypoglycemia	5770 (18)	11,834 (19)	0.02	5089 (18)	5137 (18)	0.01
Diabetic ketoacidosis	121 (0.4)	259 (0.4)	0.00	104 (0.4)	100 (0.3)	−0.02
No. of distinct medications, mean (SD)	16 (6)	17 (7)	0.16	16 (6)	16 (6)	0.01
Diabetes medications on day of entry to cohort						
No. of antidiabetes drugs, mean (SD)	2 (1)	2 (1)	−0.11	2 (1)	2 (1)	0.00
Metformin, *n* (%)	14,063 (44)	18,617 (29)	−0.31	11,887 (41)	11,455 (40)	−0.03
Sulfonylureas, *n* (%)	12,374 (38)	22,349 (35)	−0.07	11,033 (38)	11,377 (39)	0.02
DPP-4 inhibitors, *n* (%)	9783 (30)	14,164 (22)	−0.19	8404 (29)	7757 (27)	−0.05
Insulin, *n* (%)	7488 (23)	26,224 (41)	0.39	7378 (26)	7934 (28)	0.04
Other medication use, *n* (%)						
ACE inhibitors or angiotensin II receptor blockers	26,282 (82)	51,546 (81)	−0.03	23,536 (82)	23,508 (82)	0.00
Beta blockers	19,572 (61)	39,597 (62)	0.02	17,482 (61)	17,501 (61)	0.00
Calcium channel blockers	14,467 (45)	29,410 (46)	0.02	12,985 (45)	12,880 (45)	−0.01
Loop diuretics	10,711 (33)	25,734 (40)	0.14	9780 (34)	9828 (34)	0.00
Statins	27,347 (85)	54,022 (85)	−0.01	24,414 (85)	24,383 (85)	0.00
Antiplatelets	6285 (20)	11,366 (18)	−0.04	5439 (19)	5425 (19)	0.00
Anticoagulants	4948 (15)	9767 (15)	0.00	4395 (15)	4381 (15)	0.00
Oral corticosteroids	6459 (20)	13,124 (21)	0.01	5771 (20)	5858 (20)	0.01
Antiosteoporosis agents	1754 (5)	3017 (5)	−0.03	1475 (5)	1480 (5)	0.00
Opioids	11,387 (35)	25,951 (41)	0.11	10,486 (36)	10,651 (37)	0.01
Health care utilization markers, mean (SD)						
No. of hospital days	1.66 (4.99)	1.72 (5.31)	−0.01	1.66 (5.41)	1.64 (5.19)	0.00
No. of emergency department visits	0.86 (1.99)	0.92 (2.04)	0.03	0.86 (1.97)	0.87 (2.09)	0.00
No. of internist visits	22.42 (26.93)	21.43 (26.10)	−0.04	22.03 (26.52)	22.18 (26.73)	0.01
No. of cardiologist visits	5.85 (10.80)	5.16 (9.65)	−0.07	5.50 (10.14)	5.52 (10.43)	0.00
No. of endocrinologist visits	1.70 (7.10)	2.46 (7.40)	0.10	1.81 (7.39)	1.80 (6.00)	−0.00
No. of nephrologist visits	1.90 (5.82)	2.51 (6.32)	0.10	1.97 (6.02)	1.97 (5.32)	0.00

Table 1. (Continued)

Characteristic	Before Propensity Score Matching			After 1:1 Propensity Score Matching		
	SGLT2i	GLP-1RA	SMD	SGLT2i	GLP-1RA	SMD
No. of HbA1c tests ordered	3.00 (1.57)	3.12 (1.57)	0.08	3.02 (1.57)	3.02 (1.55)	0.00
No. of metabolic or creatinine tests ordered	4.86 (3.78)	5.22 (3.79)	0.10	4.88 (3.72)	4.90 (3.57)	0.01
No. of microalbuminuria/proteinuria tests ordered	1.58 (1.58)	1.70 (1.62)	0.07	1.60 (1.59)	1.59 (1.54)	−0.01

SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SMD, standardized mean difference; *n*, number of patients; COPD, chronic obstructive pulmonary disease; No., number of; DPP-4, dipeptidyl peptidase-4; ACE, angiotensin-converting enzyme; HbA1c, hemoglobin A1c.
[a]Pooled across Clinformatics Data Mart and Medicare databases.
[b]Based on Gagne *et al*.[51]
[c]Based on Kim *et al*.[35]
[d]Cardiovascular disease was defined as a composite of myocardial infarction, stable angina, acute coronary syndrome, coronary atherosclerosis, history of coronary procedure, heart failure, ischemic stroke, and peripheral vascular disease.

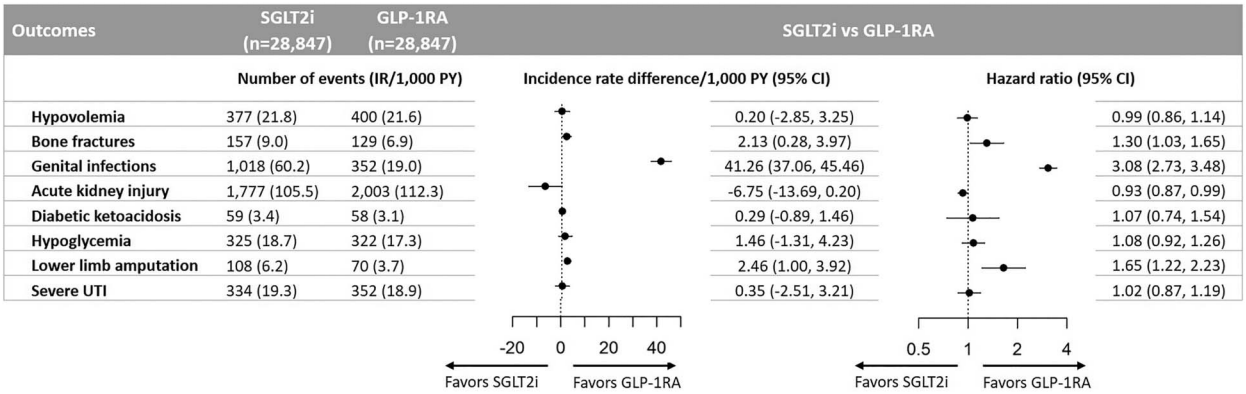

Figure 1. Number of events, incidence rates, incidence rate differences, and hazard ratios for safety outcomes, comparing SGLT2i versus GLP-1RA after 1:1 propensity score matching. CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; PY, person-year; SGLT2i, sodium-glucose cotransporter-2 inhibitors; UTI, urinary tract infection.

we did not identify an elevation in risk of lower limb amputations or fractures associated with SGLT2i when compared with the DPP4i class.

To the best of our knowledge, this is the first study to comprehensively assess the safety profile of SGLT2i in routine care patients with CKD and type 2 diabetes. Assessing the incremental risk of safety outcomes such as fractures, lower limb amputations, and AKI associated with SGLT2i is important because the baseline risk of these complications in patients with CKD is markedly higher compared with adults without CKD.[12–15,41] The unclear safety profile of these drugs may be one of the contributors to the slow uptake of SGLT2i among patients with CKD,[5,6] despite clinical practice guidelines recommending these drugs as first-line therapy.[1,42]

Our results suggest potential higher risks for lower limb amputations and nonvertebral fractures in routinely cared populations associated with the use of SGLT2i, which were not observed in randomized trials investigating SGLT2i in patients with CKD and type 2 diabetes.[3,4] The absolute risk increase for these safety outcomes was small: 2.1 more lower limb amputations and 2.5 more fractures per 1000 people receiving SGLT2i versus GLP-1RA. In addition, SGLT2i were associated with 41 more genital infections per 1000 people. These findings need to be contextualized in light of the benefits of SGLT2i in this population because patients with CKD are at high cardiovascular and kidney risk. The reduction in the composite outcome of doubling of serum creatinine, kidney failure, cardiovascular, or kidney death was 18 events per 1000 person-years in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.[4] In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, the absolute reduction was 29 events per 1000 person-years for the composite of 50% eGFR decline, kidney failure, cardiovascular, and kidney death.[3] Finally, in the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY), the absolute reduction was 21 events per 1000 person-years for the composite of progression of kidney disease (defined as kidney failure, sustained eGFR <10 ml/min per 1.73 m^2, sustained 40% eGFR decline, or death from kidney causes) or cardiovascular death.

Our findings of an elevated risk of lower limb amputations are similar to those of the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, which found higher risks for canagliflozin versus placebo

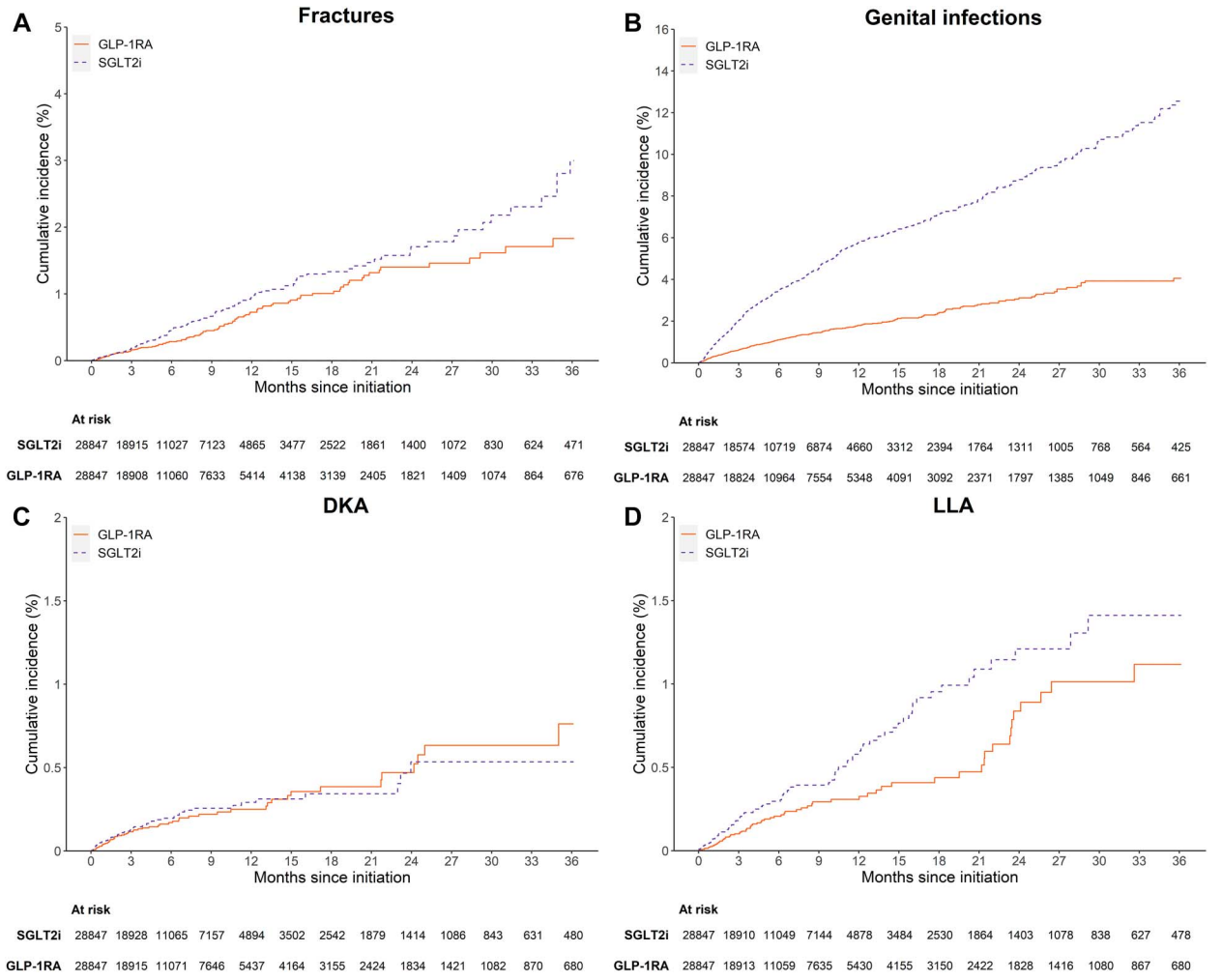

Figure 2. Cumulative incidence curves comparing SGLT2i versus GLP-1RA after 1:1 propensity score matching for specific outcomes. (A) Nonvertebral fractures, (B) genital infections, (C) diabetic ketoacidosis, and (D) lower limb amputations. DKA, diabetic ketoacidosis; LLA, lower limb amputations.

(incidence rate 6.3 versus 3.4 per 1000 patient-years; HR, 1.97; 95% CI, 1.41 to 2.75) among patients with type 2 diabetes at high cardiovascular risk.[43] Consistent with our findings, EMPA-KIDNEY found a trend toward a higher risk for lower limb amputations (incidence rate 4.3 versus 2.9 per 1000 patient-years; HR, 1.43; 95% CI, 0.80 to 2.57).[44] No elevated risks were observed in lower limb amputations in two other SGLT2i trials in patients with CKD. CREDENCE randomized 4401 patients with an eGFR between 30 and 90 ml/min per 1.73 m^2 and an albumin-to-creatinine ratio (ACR) of 300–5000 mg/g to canagliflozin versus placebo, and incidence rates were 12.3 versus 11.2 events per 1000 person-years, corresponding to a HR of 1.11 (95% CI, 0.79 to 1.56).[4] However, following the results of CANVAS, a protocol amendment was issued in May 2016 that asked investigators "to examine patient's feet at each trial visit and temporarily interrupt the assigned treatment in patients with any active condition that might lead to amputation."[4] Such monitoring practices may have contributed to the null finding observed in CREDENCE and may not be generally applied in routine clinical care. DAPA-CKD, which randomly assigned 4304 patients with an eGFR of 25–75 ml/min per 1.73 m^2 and ACR between 200 and 500 mg/g to dapagliflozin or placebo, also found no difference for amputations (incidence rate 1.6 versus 1.8 per 1000 patient-years; HR, 0.90; 95% CI, 0.57 to 1.41),[3] but found a much lower incidence rate than CANVAS, CREDENCE, or our study. Besides monitoring practices, differences in amputation risk may also be explained by differences in population characteristics: Our study population was on average 10 years older than those in CREDENCE and DAPA-CKD and had higher prevalence of cardiovascular disease (59% versus 37% in DAPA-CKD and 50% in CREDENCE). However, when comparing SGLT2i with the DPP4i class, the higher risk for lower limb amputations was attenuated. This may be due to larger confounding with DPP4i than GLP-1RA.

The higher risk of nonvertebral fractures in our study for SGLT2i versus GLP-1RA was similar in magnitude to that observed in the CANVAS Program (incidence rate 15.4 versus 11.9 per 1000 patient-years; HR, 1.26; 95% CI, 1.04 to 1.52).[43] However, higher risks were not observed in CREDENCE (incidence rate 11.8 versus 12.1 per 1000

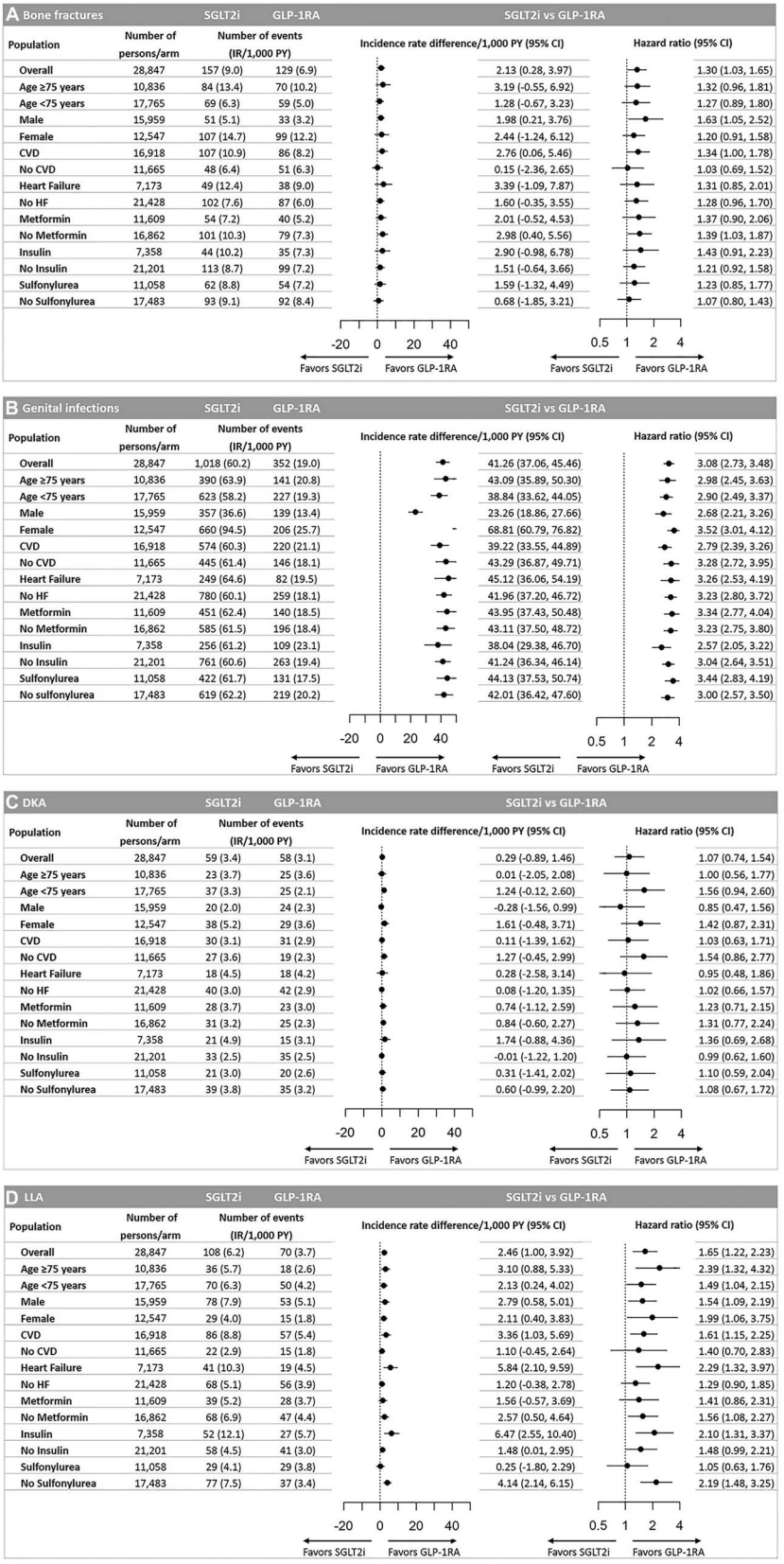

Figure 3. Comparative safety of SGLT2i versus GLP-1RA in subgroups after 1:1 propensity score matching for specific outcomes. (A) Nonvertebral fractures, (B) genital infections, (C) DKA, and (D) lower limb amputations. CVD, cardiovascular disease; HF, heart failure.

patient-years; HR, 0.98; 95% CI, 0.70 to 1.37)[4] or EMPA-KIDNEY (incidence rate 20.9 versus 19.3 per 1000 patient-years; HR, 1.08; 95% CI, 0.84 to 1.38).[44] Although the fracture risk in DAPA-CKD did not reach statistical significance, the relative risk was similar in magnitude to our study (incidence rate 4.0 versus 3.2 per 1000 person-years; risk ratio 1.23; 95% CI, 0.90 to 1.68).[3] One Canadian observational study assessed the risk of fractures for SGLT2i versus DPP4i but did not find higher risks for 180-day and 365-day intention-to-treat follow-up analyses, with HRs of 0.95 (95% CI, 0.79 to 1.13) and 0.88 (95% CI, 0.77 to 1.00), respectively.[45] Although we found higher fracture risks in as-treated analyses, these risks diminished in 180-day and 365-day intention-to-treat analyses. However, intention-to-treat analyses often lead to substantial exposure misclassification in observational studies, which typically bias findings toward the null and may falsely miss safety signals. The choice of comparator may also explain the discrepant findings. On the one hand, using DPP4i as the comparator group may increase confounding because these drugs have been shown not to influence cardiovascular or kidney outcomes and were prescribed in our study to older individuals with lower kidney function. On the other hand, GLP-1RA may be preferentially prescribed to more obese individuals, which may protect against hip fractures.[46] Therefore, our findings need to be replicated in future large-scale studies in patients with CKD.

The higher risk in genital infections with SGLT2i is consistent with previous trials[47] and observational studies,[32] although the incidence rate in our study is markedly higher than that observed in CREDENCE (94.5 in our study versus 12.6 per 1000 person-years in CREDENCE in the SGLT2i arm among women). Interestingly, we did not observe a higher risk of DKA (HR, 1.07; 95% CI, 0.74 to 1.54). Although CREDENCE found higher DKA risk in the SGLT2i arm (HR, 10.80; 95% CI, 1.39 to 83.65), no increased risk was observed in DAPA-CKD, in which no DKA events occurred in the dapagliflozin arm,[4] or EMPA-KIDNEY, in which only six events occurred in the empagliflozin arm.[44] In our study, only 26% of patients used insulin at baseline, compared with 66% in CREDENCE, and our population also had fewer diabetes-related complications such as retinopathy (18% versus 43%) or neuropathy (36% versus 49%), indicative of less advanced diabetes and potentially a greater proportion of insulin-resistant rather than insulin-deficient diabetes phenotypes.

Our study has a number of limitations. First, despite the use of an active comparator design and adjustment for a large number of baseline characteristics through propensity score matching, we cannot rule out potential residual confounding. Nevertheless, laboratory measurements, which were not included in the propensity score, were adequately balanced between the SGLT2i and GLP-1RA groups. This is in line with the findings of a previous study showing that active comparator, new-user designs combined with adjustment for a large number of claims-based confounder proxies can ensure sufficient balance in characteristics that are unmeasured in claims data.[48] Second, we ascertained CKD using diagnosis codes, which has high specificity but low sensitivity,[25,49,50] and we did not have data on eGFR or albuminuria for all patients. Our results may therefore be generalizable to patients with diagnosed and recognized CKD, but not to all patients with an eGFR <60 ml/min per 1.73 m^2 or those with preserved kidney function and albuminuria. Third, we did not assess safety profiles of individual SGLT2i agents because our study was not powered to study individual agents. Finally, our study had a relatively short follow-up because a substantial proportion of patients discontinued the study medication and were therefore censored; specific reasons for discontinuation were not available in our databases. Nevertheless, the safety outcomes of interest occurred rapidly, within 6 months of follow-up, and our study was large enough to observe rare outcomes that had previously been reported in some but not all clinical trials but with greater precision than could be ascertained in those smaller cohorts.

In conclusion, in this large US cohort study of patients with CKD and type 2 diabetes treated in routine clinical practice, initiation of SGLT2i compared with GLP-1RA was associated with higher risks of lower limb amputations, genital infections, and nonvertebral fractures. The higher risk for lower limb amputations and nonvertebral fractures was not observed when using an alternative comparator, DPP4i. No differences were observed for DKA, hypovolemia, hypoglycemia, and severe UTI. Our study can help inform patient-physician decision making regarding risks and benefits before prescribing SGLT2i in this population but needs to be interpreted in light of its limitations, including residual confounding, short follow-up time, and the use of diagnosis codes to identify patients with CKD.

Disclosures

E. D'Andrea reports employment with and ownership interest in AbbVie Inc. and research funding from Bristol Myers Squibb. E. Patorno reports employment with Brigham and Women's Hospital and Harvard Medical School and is investigator of a research grant to the Brigham and Women's Hospital from Boehringer Ingelheim. D.J. Wexler reports consultancy for Novo Nordisk and serving as a Data Monitoring Committee Member for SOUL and FLOW trials. All remaining authors have nothing to disclose.

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Drs. E.L. Fu and J.M. Paik had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. E.L. Fu and J.M. Paik are the guarantors. Drs. E.L. Fu and J.M. Paik affirm that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

This study was approved with waiver of informed consent by the Brigham and Women's Hospital Institutional Review Board.

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Writing – original draft: Edouard L. Fu.
Writing – review & editing: Elvira D'Andrea, Edouard L. Fu, Julie M. Paik, Elisabetta Patorno, Deborah J. Wexler.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B653.

Supplemental Table 1. Definitions of inclusion and exclusion criteria.

Supplemental Table 2. Outcome definitions.

Supplemental Table 3. Full list of baseline characteristics in patients with CKD and type 2 diabetes, stratified by SGLT2i or GLP-1RA initiation in the pooled cohort.

Supplemental Table 4. Full list of baseline characteristics in patients with CKD and type 2 diabetes, stratified by SGLT2i or GLP-1RA initiation in CDM.

Supplemental Table 5. Full list of baseline characteristics in patients with CKD and type 2 diabetes, stratified by SGLT2i or GLP-1RA initiation in MarketScan.

Supplemental Table 6. Full list of baseline characteristics in patients with CKD and type 2 diabetes, stratified by SGLT2i or GLP-1RA initiation in Medicare.

Supplemental Table 7. Individual SGLT2i and GLP-1RA agents included in the analysis after 1:1 propensity score matching.

Supplemental Table 8. Follow-up and censoring reasons after 1:1 propensity score matching for the outcomes, genital infections and lower limb amputations, overall and stratified by SGLT2i or GLP-1RA initiation.

Supplemental Table 9. Number of events, incidence rates, hazard ratios, and incidence rate differences for safety outcomes, comparing SGLT2i versus GLP-1RA after 1:1 propensity score matching—sensitivity analysis applying a 60-day grace period after treatment discontinuation or switching.

Supplemental Table 10. Number of events, incidence rates, hazard ratios, and incidence rate differences for safety outcomes, comparing SGLT2i versus GLP-1RA after 1:1 propensity score matching—sensitivity analysis applying a 180-day intention-to-treat follow-up.

Supplemental Table 11. Number of events, incidence rates, hazard ratios, and incidence rate differences for safety outcomes, comparing SGLT2i versus GLP-1RA after 1:1 propensity score matching—sensitivity analysis applying a 365-day intention-to-treat follow-up.

Supplemental Table 12. Results from *post hoc* analyses in the 1:1 propensity score–matched cohort, excluding prior fractures and lower limb amputations, or changing the comparator group to DPP-4i.

Supplemental Table 13. Number of events, incidence rates, hazard ratios, and incidence rate differences for different types of nonvertebral fractures, comparing SGLT2i versus GLP-1RA after 1:1 propensity score matching.

Supplemental Figure 1. Overview of study design.

Supplemental Figure 2. Patient flow chart.

Supplemental Figure 3. Propensity score distribution before and after 1:1 propensity score matching, stratified by SGLT2i or GLP-1RA initiation.

Supplemental Figure 4. Comparative safety of SGLT2i versus GLP-1RA in subgroups after 1:1 propensity score matching for the specific outcomes (A) hypovolemia, (B) acute kidney injury, (C) hypoglycemia, and (D) severe urinary tract infections.

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