Research

# Sodium–glucose cotransporter 2 (SGLT2) inhibitors and risk of chronic kidney disease–mineral and bone disorders in patients with type 2 diabetes mellitus and stage 1–3 chronic kidney disease

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## Abstract

**Background:** In patients with type 2 diabetes mellitus and chronic kidney disease (CKD), sodium–glucose cotransporter 2 (SGLT2) inhibitors improve renal outcomes, but may transiently affect biochemical markers of CKD–mineral and bone disorders (CKD-MBD). We sought to evaluate the long-term risk of CKD-MBD associated with use of SGLT2 inhibitors in this patient population.

**Methods:** We conducted a retrospective cohort study, employing a target trial emulation framework and using electronic medical records of patients from 9 hospitals in Taiwan (2016–2023). We included adults with type 2 diabetes mellitus and stage 1–3 CKD who had newly started either an SGLT2 inhibitor or, as a comparison group, a glucagon-like peptide-1 receptor agonist (GLP-1 RA). The primary outcome was a composite of incident biochemical abnormalities (serum phosphate > 1.5 mmol/L, serum calcium < 2.1 mmol/L, serum intact parathyroid hormone [iPTH] > 6.9 pmol/L, or serum 25-hydroxyvitamin D < 49.9 nmol/L).

**Results:** The cohort included 13 379 patients receiving SGLT2 inhibitors ($n$ = 11 920) or GLP-1 RAs ($n$ = 1459) with a median follow-up of 3.3 years. Compared with GLP-1 RAs, SGLT2 inhibitors were associated with a lower cumulative incidence of the composite primary outcome (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.79–0.86), hyperphosphatemia (HR 0.83, 95% CI 0.76–0.91), hypocalcemia (HR 0.82, 95% CI 0.78–0.86), high serum iPTH levels (HR 0.66, 95% CI 0.57–0.78), and low serum 25-hydroxyvitamin D levels (HR 0.65, 95% CI 0.47–0.90).

**Interpretation:** Use of SGLT2 inhibitors was associated with a lower incidence of biochemical abnormalities related to CKD-MBD than GLP-1 RAs. These agents may be considered to reduce risk of CKD-MBD in patients with type 2 diabetes mellitus and stage 1–3 CKD.

Mineral and bone disorders (MBD) — characterized by hypocalcemia, hyperphosphatemia, and abnormalities in parathyroid hormone (PTH) and vitamin D metabolism — are observed in 50%–74% of patients with type 2 diabetes mellitus and chronic kidney disease (CKD).[1,2] Regular monitoring of biochemical abnormalities and bone diseases in patients with CKD is suggested for early detection of developing CKD-MBD.[3]

The 2024 American Diabetes Association guideline recommends that adults with type 2 diabetes mellitus and CKD be prescribed sodium–glucose cotransporter 2 (SGLT2) inhibitors to minimize progression of CKD, reduce risk of cardiovascular events, and reduce likelihood of admission to hospital for heart failure.[3] However, recent studies have suggested that SGLT2 inhibitors may affect phosphate homeostasis by stimulating the renal proximal tubular reabsorption of phosphate through type 2 sodium–phosphate cotransporters; they may also influence the regulation of the fibroblast growth factor 23, 1,25-dihydroxyvitamin D (1,25[OH]$_2$D), and PTH axis.[4,5] For example, de Jong and colleagues[5] found that dapagliflozin increased serum phosphate by 11% over 6 weeks among patients with a mean serum phosphate level of 1.1 (standard deviation 0.1) mmol/L at baseline. These observations raise concerns that these drugs influence the

regulators of bone and mineral homeostasis, but it remains unclear whether the transient effects of SGLT2 inhibitor use on these biochemical parameters signals a potential risk for developing CKD-MBD.

The hormonal and biochemical alterations that constitute CKD-MBD are part of the syndrome of complications associated with the progression of CKD.[6] The use of SGLT2 inhibitors has been found to reduce the risk of composite renal outcomes by 40% compared with placebo, which is superior to other current glucose-lowering therapies.[7] Given these favourable renal outcomes, SGLT2 inhibitors may lower the incidence of CKD-MBD, but this hypothesis is difficult to reconcile with the findings of transient alterations in bone and mineral homeostasis with SGLT2 inhibitor use. We therefore sought to evaluate risks of CKD-MBD associated with SGLT2 inhibitor use among patients with type 2 diabetes mellitus and stage 1–3 CKD.

## Methods

### Study design

We conducted a retrospective cohort study comparing new users of an SGLT2 inhibitor or, as an active comparator, a glucagon-like peptide-1 receptor agonist (GLP-1 RA). To enhance causal inference from the observational study design, we employed a target trial emulation framework.[8,9] We specified a hypothetical trial protocol — adapted from the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in CKD), and EMPA-KIDNEY (Empagliflozin in Patients with CKD) trials — to shape the study design and emulate the components of a trial by drawing on observational data (Appendix 1, Supplementary Figure 1 and Supplementary Table 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.240922/tab-related-content).[10–12] The key element of this framework was the coordination of eligibility criteria, treatment assignment, and commencement of follow-up, similar to a randomized controlled trial at randomization.[13] We emulated the placebo group in this hypothetical trial with new use of an active comparator that was expected to show no effect on the outcome of interest.[14] We chose GLP-1 RAs since these have pleiotropic effects similar to those of SGLT2 inhibitors, namely cardiovascular and renal benefits in the treatment of type 2 diabetes mellitus, and have similar temporal trends in use.[15–19] More importantly, GLP-1 RAs have no known association with CKD-MBD. This design allowed us to assess the strength of the association between SGLT2 inhibitors and the risk of CKD-MBD among patients with type 2 diabetes mellitus and stage 1–3 CKD.

### Data source

We used data from the Chang Gung Research Database (CGRD), which contains the anonymized electronic medical records of the 9 Chang Gung Memorial Hospitals that form the largest health care group in Taiwan.[20,21] The CGRD's diagnostic codes have been separately validated as disease definitions for clinical research,[22–27] and previous pharmacoepidemiologic studies have drawn on the CGRD as an important source of real-world data.[28–33]

### Study cohort

We included adult patients (aged > 18 yr) with type 2 diabetes mellitus and stage 1–3 CKD who were newly starting SGLT2 inhibitor or GLP-1 RA treatment in the period from 2016 to 2021. In Taiwan, these 2 drug classes were approved and reimbursed for second-line or third-line treatment of type 2 diabetes mellitus during the study period. The date of the first prescription for either drug served as the index date. We classified patients as having stage 1–3 CKD if they had an estimated glomerular filtration rate (eGFR) of 30–60 mL/min/1.73 $m^2$, or an eGFR greater than 60 mL/min/1.73 $m^2$ with a urine albumin-to-creatinine ratio greater than 3.4 mg/mmol (30 mg/g), based on the most recent laboratory data within 12 months before the index date.[34]

Our study applied similar major criteria for exclusion to those used in the DAPA-CKD, CREDENCE, and EMPA-KIDNEY trials.[10–12] We also excluded patients who had CKD-MBD events (i.e., any components of the study's primary composite outcome) during the 12 weeks preceding the index date,[11,12] to ensure the identified cases were incident cases. Appendix 1, Supplementary Table 2 and Supplementary Table 3 list the detailed exclusion criteria.

We followed patients from the start of exposure to an SGLT2 inhibitor or GLP-1 RA until occurrence of an outcome, last clinical visit, death, or Dec. 31, 2023 (end date in the database), whichever came first.

### Exposure

The exposure group included patients newly prescribed dapagliflozin, empagliflozin, ertugliflozin, or canagliflozin (SGLT2 inhibitors). The comparison group included those newly prescribed liraglutide, lixisenatide, semaglutide, or dulaglutide (GLP-1 RAs). Appendix 1, Supplementary Table 4 summarizes the Anatomical Therapeutic Chemical codes for the SGLT2 inhibitors and GLP-1 RAs.

### Outcomes

The study's primary outcome was the composite of incident biochemical abnormalities that are consistent with the presence of CKD-MBD,[35] including hyperphosphatemia (serum phosphate levels > 1.5 mmol/L [4.5 mg/dL]), hypocalcemia (serum calcium levels < 2.1 mmol/L [8.5 mg/dL]), high serum intact PTH (iPTH) levels (> 6.9 pmol/L [65 pg/mL]), or low serum 25-hydroxyvitamin D levels (< 49.9 nmol/L [20 ng/mL]), whichever was observed first. The composite outcome's individual components constituted the secondary outcomes.

### Positive and negative control outcome analyses

Previous studies have shown SGLT2 inhibitors to lower the incidence of hyperkalemia (*International Classification of Diseases, 10th Revision, Clinical Modification* E87.5 or serum potassium levels > 5.5 mmol/L) among patients with type 2 diabetes mellitus.[36,37] Furthermore, no differences have been observed in risk of all-cause death associated with SGLT2 inhibitors and GLP-1 RAs.[38] To determine the study's internal validity, we tested the occurrence of hyperkalemia and all-cause death as positive and negative control outcomes, respectively, to evaluate whether our study approach would reproduce known associations.

### Statistical analysis

We applied inverse probability of treatment weighting (IPTW) using propensity scores to balance the potential confounders between patients treated with SGLT2 inhibitors and those receiving GLP-1 RAs.[32] The potential confounders included comorbidities and comedications, laboratory information, and demographic characteristics.[5,10–12] To address the issue of missing laboratory data, we classified the absence of these measurements as no measurement. We included the baseline use of anti-osteoporotic medications and laboratory information indicative of hyperparathyroidism (e.g., serum iPTH) in the propensity score model to adjust for other important diseases or treatments that can affect bone metabolism. We estimated the propensity scores using multiple regression models incorporating clinical and biochemical variables (i.e., glycated hemoglobin [$HbA_{1c}$], eGFR, urine albumin-to-creatinine ratio, body mass index [BMI], serum phosphate, serum calcium, iPTH, 25-hydroxyvitamin D) comorbidities, and medications. We derived IPTW values as 1 divided by the propensity score for patients who received SGLT2 inhibitors and as 1 divided by the difference of 1 minus the propensity score) for patients who received GLP-1 RAs.[39] Appendix 1, Supplementary Table 5 and Supplementary Table 6 detail the baseline comorbidities and comedications. We trimmed the tails of the propensity score distribution below the first percentile of the observed propensity score for SGLT2 inhibitor users, and above the 99th percentile of the observed propensity score for GLP-1 RA users.[40] Since we adopted the active-comparator design, estimates generated by the propensity score with the IPTW approach represented the average treatment effects in the whole population.[41]

We used medians with interquartile ranges (IQRs) for continuous variables and numbers with percentages for categorical variables to summarize the characteristics at baseline. We used standardized mean differences (SMDs) to compare the baseline characteristics between patients who were receiving SGLT2 inhibitors and those who were receiving GLP-1 RAs, whereby the difference between the 2 groups was considered negligible if the SMD was between –0.1 and 0.1.[42] After IPTW adjustment, the incidence rates of the composite primary outcome were reported as the number of events per 1000 person-years.[43] To compare the cumulative incidences of the composite outcome with SGLT2 inhibitor or GLP-1 RA use in the IPTW-weighted cohort, we used Cox proportional hazards models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

To determine comparative risks for the composite outcomes using SGLT2 inhibitors and GLP-1 RAs in different subgroups of patients, we conducted subgroup analyses according to age (< 65 yr or ≥ 65 yr), sex (male or female), eGFR (30–59, 60–89, or ≥ 90 mL/min/1.73 $m^2$), and previous use of renin–angiotensin–aldosterone system inhibitors (yes or no). We reapplied propensity scores with IPTW to ensure that patient characteristics were well balanced between groups. We calculated *p* values for interactions using regression models that included a term representing the interaction between the subgroup variable and the treatment variable. We also conducted stratified analyses to examine the risk of CKD-MBD from individual SGLT2 inhibitors (empagliflozin, dapagliflozin, or canagliflozin). In Taiwan, ertugliflozin was granted approval in 2021 for type 2 diabetes mellitus management, which likely explains the low numbers of patients with this treatment. We therefore excluded ertugliflozin from the stratified analysis.

We conducted 5 sensitivity analyses to determine the robustness of the results of the primary analysis. First, we redefined hyperphosphatemia as serum phosphate levels greater than 1.8 mmol/L (5.5 mg/dL) or the initiation of specific hyperphosphatemia treatments (e.g., sevelamer carbonate, lanthanum carbonate, ferric citrate). We also redefined hypocalcemia as the initiation of calcitriol or specific hypocalcemia treatments (e.g., calcium gluconate, calcium chloride, calcium acetate, calcium carbonate, calcium aspartate). These new definitions identified more clinically important hyperphosphatemia or hypocalcemia events.[44,45] In a second sensitivity analysis, we applied on-treatment analysis to assess how much nonpersistence or switching medications after the index date influenced our study results.[34] We censored patients who did not refill their index drug prescription within 90 days, and those who switched their index drug to a different drug class during the period of follow-up. Our next analysis excluded any patients with fractures and ischemic heart disease at baseline, which could potentially indicate mineral metabolism disorders.[35] We conducted another sensitivity analysis whereby we extended the exclusion period of CKD-MBD history from 12 weeks to 1 year preceding the index date to further mitigate the effects of remote CKD-MBD events. Finally, we performed a sensitivity analysis using the robust variance estimator to address the potential impact of within-subject correlation in propensity scores with the IPTW approach.[46]

We conducted all analyses using SAS version 9.4 (SAS Institute).

### Ethics approval

The study protocol received approval from Chang Gung Medical Foundation's Institutional Review Board (no. 202400571B0).

## Results

We included 13 379 patients with type 2 diabetes mellitus and stage 1–3 CKD, of whom 11 920 were new users of SGLT2 inhibitors and 1459 were new users of GLP-1-RAs, with an overall median follow-up time of 3.3 years. After we applied IPTW by propensity scores, the effective sample sizes were 10 661 patients in the SGLT2 inhibitor group and 1307 patients in the GLP-1 RA group (Figure 1).

Some variables were not balanced between groups at baseline (i.e., sex, $HbA_{1c}$ level, eGFR, urine albumin-to-creatinine ratio, BMI, and serum phosphate and calcium levels), but this imbalance was fixed after IPTW adjustment. Patients treated with SGLT2 inhibitors (58.8% males) had a median age of 64.0 (IQR 55.0–71.0) years, eGFR of 68.0 (IQR 53.0–90.5) mL/min/1.73 $m^2$, urine albumin-to-creatinine ratio of 11.4 (IQR 5.0–32.4) mg/mmol, and $HbA_{1c}$ of 8.6% (IQR 7.6%–9.8%). The baseline characteristics for these cohorts and the propensity score distributions before and after IPTW adjustment are in Table 1 and Appendix 1, Supplementary Figure 2.

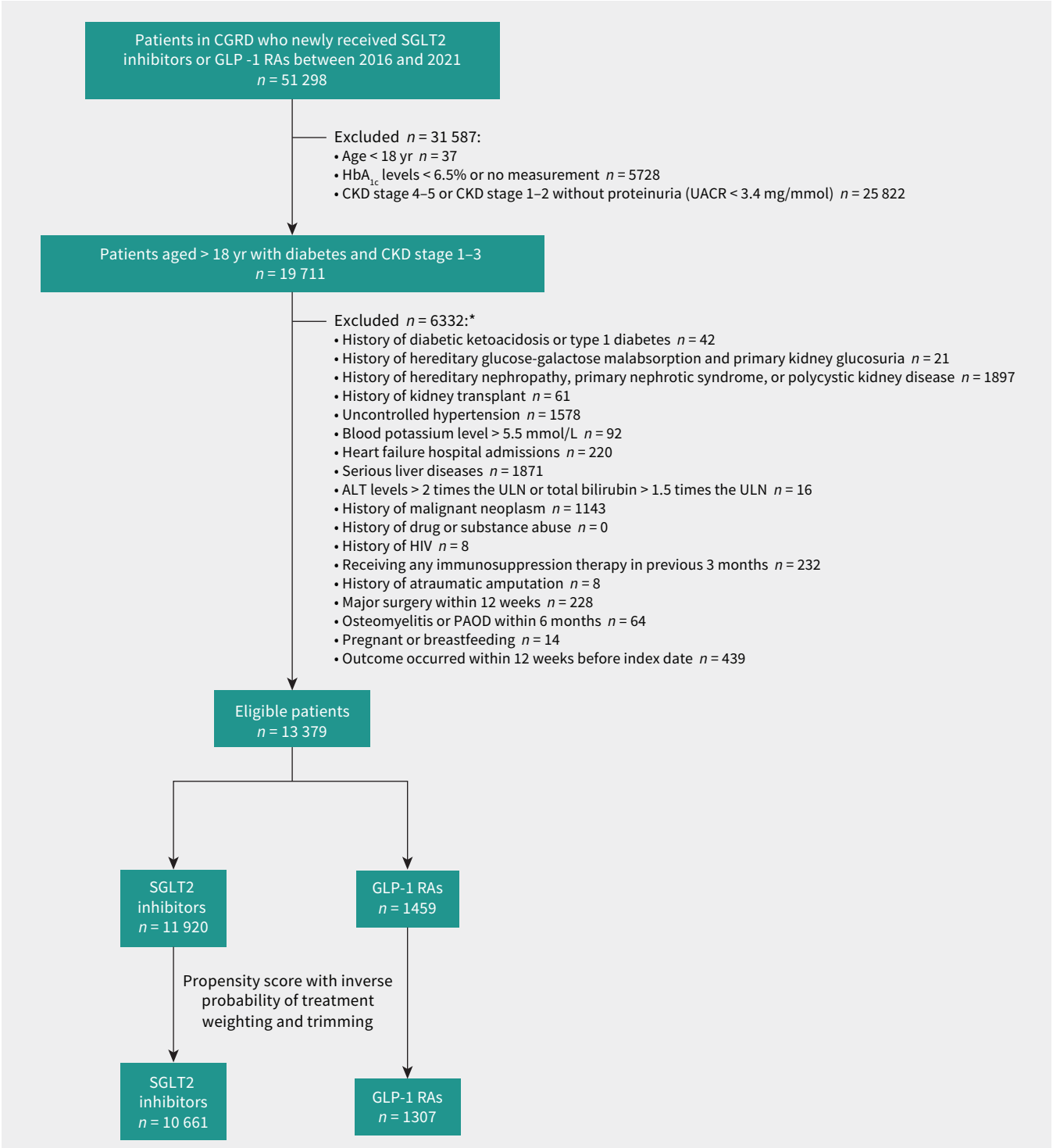


**Figure 1:** Flow diagram for patient inclusion in this study. See Related Content tab for accessible version. *The numbers represent the total number of patients who met the exclusion criteria. Numbers indicate the exact number of patients excluded because of each criterion, whereby some patients met multiple exclusion criteria. Note: ALT = alanine transaminase, CGRD = Chang Gung Research Database, CKD = chronic kidney disease, GLP-1 RAs = glucagon-like peptide 1 receptor agonists, $HbA_{1c}$ = glycated hemoglobin, PAOD = peripheral arterial occlusion disease, SGLT2 = sodium–glucose cotransporter 2, UACR = urine albumin-to-creatinine ratio, ULN = upper limit of normal.

The composite primary outcome occurred in 2940 (24.7%) patients treated with SGLT2 inhibitors and 530 (36.3%) patients treated with GLP-1 RAs in the original cohort. After IPTW adjustment, the incidence rate of the composite outcome was lower among patients using SGLT2 inhibitors (75 per 1000 person-years, 95% CI 72–78) than among those using GLP-1 RAs (92 per 1000 person-years, 95% CI 89–95), resulting in an HR of 0.82 (95% CI 0.79–0.86) (Figure 2). The rate for biochemical measurements

**Table 1 (part 1 of 2): Baseline characteristics of the study cohort before and after inverse probability of treatment weighting***

| Characteristic | No. (%) of patients in original cohort† | | | No. (%) of patients after IPTW† | | |
|---|---|---|---|---|---|---|
| | SGLT2 inhibitors *n* = 11 920 | GLP-1 RAs *n* = 1459 | SMD‡ | SGLT2 inhibitors *n* = 10 661 | GLP-1 RAs *n* = 1307 | SMD‡ |
| Age, yr | | | | | | |
| Median (IQR) | 64.0 (56.0–71.0) | 64.0 (54.0–72.0) | 0.06 | 64.0 (55.0–71.0) | 63.0 (55.0–71.0) | 0.03 |
| 18–40 | 525 (4.4) | 96 (6.6) | | 512 (4.8) | 88 (6.7) | |
| 40–64 | 5616 (47.1) | 661 (45.3) | | 5085 (47.7) | 639 (48.9) | |
| > 65 | 5779 (48.5) | 702 (48.1) | | 5064 (47.5) | 582 (44.5) | |
| Sex | | | | | | |
| Female | 4592 (38.5) | 708 (48.5) | | 4392 (41.2) | 552 (42.2) | |
| Male | 7328 (61.5) | 751 (51.5) | 0.20 | 6269 (58.8) | 755 (57.8) | 0.02 |
| $HbA_{1c}$, % | | | | | | |
| Median (IQR) | 8.3 (7.4–9.6) | 9.4 (8.5–10.5) | 0.61 | 8.6 (7.6–9.8) | 8.8 (7.7–9.9) | 0.05 |
| 6.5–8 | 4802 (40.3) | 217 (14.9) | | 3486 (32.7) | 435 (33.3) | |
| 8–9.5 | 3950 (33.1) | 555 (38.0) | | 3913 (36.7) | 464 (35.5) | |
| > 9.5 | 3168 (26.6) | 687 (47.1) | | 3273 (30.7) | 408 (31.2) | |
| eGFR, mL/min/1.73 $m^2$ | | | | | | |
| Median (IQR) | 69.0 (53.3–90.1) | 60.0 (45.0–89.6) | 0.12 | 68.0 (53.0–90.5) | 72.5 (50.2–93.8) | –0.02 |
| ≥ 90 | 3070 (25.8) | 357 (24.5) | | 2761 (25.9) | 371 (28.4) | |
| 60–89 | 4228 (35.5) | 363 (24.9) | | 3571 (33.5) | 452 (34.6) | |
| 45–59 | 3362 (28.2) | 376 (25.8) | | 3145 (29.5) | 263 (20.1) | |
| 30–44 | 1260 (10.6) | 363 (24.9) | | 1183 (11.1) | 220 (16.8) | |
| UACR, mg/mmol | | | | | | |
| Median (IQR) | 11.4 (4.9–32.0) | 11.4 (5.3–34.0) | 0.22 | 11.4 (5.0–32.4) | 10.6 (4.3–30.2) | 0.08 |
| < 3.4 | 3 (< 0.1) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | |
| 3.4–33.9 | 5538 (46.5) | 545 (37.4) | | 4787 (44.9) | 629 (48.1) | |
| ≥ 33.9 | 1745 (14.6) | 192 (13.2) | | 1535 (14.4) | 193 (14.8) | |
| No measurement | 4634 (38.9) | 722 (49.5) | | 4339 (40.7) | 485 (37.1) | |
| BMI, kg/$m^2$ | | | | | | |
| Median (IQR) | 27.3 (24.7–30.5) | 28.2 (25.4–31.9) | 0.29 | 27.5 (24.8–30.8) | 28.0 (25.1–31.9) | 0.09 |
| < 24 | 1301 (11.0) | 163 (11.2) | | 1183 (11.1) | 144 (11.0) | |
| 24–30 | 3753 (31.5) | 493 (33.8) | | 3475 (32.6) | 374 (28.6) | |
| > 30 | 2021 (17.0) | 375 (25.7) | | 1994 (18.7) | 281 (21.5) | |
| No measurement | 4845 (40.6) | 428 (29.3) | | 4019 (37.7) | 510 (39.0) | |
| Phosphate, mmol/L | | | | | | |
| Median (IQR) | 1.1 (1.0–1.3) | 1.1 (1.0–1.3) | 0.16 | 1.1 (1.0–1.2) | 1.1 (1.0–1.3) | 0.06 |
| < 1.1 | 313 (2.6) | 71 (4.9) | | 309 (2.9) | 29 (2.2) | |
| 1.1–1.5 | 265 (2.2) | 60 (4.1) | | 245 (2.3) | 29 (2.2) | |
| No measurement | 11 342 (95.2) | 1328 (91.0) | | 10 117 (94.9) | 1249 (95.6) | |
| Calcium, mmol/L | | | | | | |
| Median (IQR) | 2.3 (2.2–2.4) | 2.3 (2.2–2.4) | 0.12 | 2.3 (2.2–2.4) | 2.3 (2.2–2.4) | 0.05 |
| 2.1–2.5 | 565 (4.7) | 111 (7.6) | | 522 (4.9) | 58 (4.4) | |
| > 2.5 | 9 (0.1) | 4 (0.3) | | 11 (0.1) | 1 (0.1) | |
| No measurement | 11 346 (95.2) | 1344 (92.1) | | 10 128 (95.0) | 1248 (95.5) | |
| iPTH, pmol/L | | | | | | |
| Median (IQR) | 3.8 (2.6–4.9) | 3.8 (3.3–5.9) | 0.00 | 4.8 (4.2–5.9) | 3.3 (3.3–3.8) | 0.00 |
| < 3.2 | 13 (0.1) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | |
| 3.2–6.9 | 22 (0.2) | 3 (0.2) | | 21 (0.2) | 1 (0.1) | |
| No measurement | 11 885 (99.7) | 1456 (99.8) | | 10 640 (99.8) | 1306 (99.9) | |

**Table 1 (part 2 of 2): Baseline characteristics of the study cohort before and after inverse probability of treatment weighting***

| Characteristic | No. (%) of patients in original cohort† | | | No. (%) of patients after IPTW† | | |
|---|---|---|---|---|---|---|
| | SGLT2 inhibitors *n* = 11 920 | GLP-1 RAs *n* = 1459 | SMD‡ | SGLT2 inhibitors | GLP-1 RAs | SMD‡ |
| 25-hydroxyvitamin D, nmol/L | | | | | | |
| Median (IQR) | 75.4 (58.7–106.8) | 79.4 (54.7–91.1) | 0.00 | 75.4 (59.4–103.8) | 54.7 (54.7–79.4) | 0.00 |
| 49.9–74.9 | 6 (0.1) | 1 (0.1) | | 11 (0.1) | 1 (0.1) | |
| > 74.9 | 9 (0.1) | 2 (0.1) | | 11 (0.1) | 1 (0.1) | |
| No measurement | 11 905 (99.9) | 1456 (99.8) | | 10 650 (99.9) | 1306 (99.9) | |
| Acute kidney injury | 221 (1.9) | 39 (2.7) | –0.06 | 203 (1.9) | 24 (1.8) | 0.00 |
| Asthma | 338 (2.8) | 47 (3.2) | –0.02 | 309 (2.9) | 41 (3.1) | –0.02 |
| Atrial fibrillation | 474 (4.0) | 42 (2.9) | 0.06 | 362 (3.4) | 39 (3.0) | 0.02 |
| Chronic obstructive pulmonary disease | 379 (3.2) | 41 (2.8) | 0.02 | 320 (3.0) | 31 (2.4) | 0.04 |
| Dyslipidemia | 7828 (65.7) | 999 (68.5) | –0.06 | 7026 (65.9) | 833 (63.7) | 0.05 |
| Fracture | 149 (1.3) | 19 (1.3) | 0.00 | 128 (1.2) | 14 (1.1) | 0.01 |
| Heart failure | 873 (7.3) | 72 (4.9) | 0.10 | 661 (6.2) | 76 (5.8) | 0.02 |
| Hypertension | 8125 (68.2) | 1021 (70.0) | –0.04 | 7249 (68.0) | 821 (62.8) | 0.11 |
| Hyperthyroidism | 183 (1.5) | 20 (1.4) | 0.01 | 149 (1.4) | 24 (1.8) | –0.03 |
| Hypothyroidism | 124 (1.0) | 26 (1.8) | –0.06 | 117 (1.1) | 12 (0.9) | 0.02 |
| Ischemic heart disease | 1412 (11.9) | 123 (8.4) | 0.11 | 1119 (10.5) | 118 (9.0) | 0.05 |
| Ischemic stroke | 775 (6.5) | 84 (5.8) | 0.03 | 661 (6.2) | 102 (7.8) | –0.06 |
| Peripheral arterial disease | 220 (1.9) | 39 (2.7) | –0.06 | 203 (1.9) | 24 (1.8) | 0.01 |
| Diabetes medications | | | | | | |
| Insulin | 2732 (22.9) | 860 (58.9) | –0.79 | 2964 (27.8) | 389 (29.8) | –0.04 |
| Metformin | 9425 (79.1) | 1051 (72.0) | 0.16 | 8337 (78.2) | 989 (75.7) | 0.06 |
| Sulfonylurea | 6703 (56.2) | 904 (62.0) | –0.12 | 6343 (59.5) | 757 (57.9) | 0.03 |
| α-Glucosidase inhibitor | 1840 (15.4) | 336 (23.0) | –0.19 | 1780 (16.7) | 225 (17.2) | –0.01 |
| Thiazolidinedione | 2092 (17.6) | 270 (18.5) | –0.02 | 1972 (18.5) | 259 (19.8) | –0.03 |
| DPP-4 inhibitor | 7817 (65.6) | 1111 (76.2) | –0.23 | 7377 (69.2) | 884 (67.6) | 0.03 |
| Meglitinide | 366 (3.1) | 106 (7.3) | –0.19 | 362 (3.4) | 34 (2.6) | 0.05 |
| ACE inhibitors or ARBs | 7727 (64.8) | 959 (65.7) | –0.02 | 6834 (64.1) | 770 (58.9) | 0.11 |
| Anticoagulants or antiplatelets | 4723 (39.6) | 568 (38.9) | 0.01 | 4083 (38.3) | 469 (35.9) | 0.05 |
| β-Blockers | 4193 (35.2) | 457 (31.3) | 0.08 | 3529 (33.1) | 369 (28.2) | 0.11 |
| Bisphosphonates | 56 (0.5) | 7 (0.5) | 0.00 | 53 (0.5) | 5 (0.4) | 0.01 |
| Calcium-channel blockers | 2906 (24.4) | 386 (26.5) | –0.05 | 2591 (24.3) | 290 (22.2) | 0.05 |
| Denosumab | 70 (0.6) | 13 (0.9) | –0.04 | 64 (0.6) | 10 (0.8) | –0.03 |
| Diuretics | 1898 (15.9) | 243 (16.7) | –0.02 | 1620 (15.2) | 196 (15.0) | 0.00 |
| Lipid-modifying agents | 8607 (72.2) | 1074 (73.6) | –0.03 | 7655 (71.8) | 886 (67.8) | 0.09 |
| NSAIDs | 2140 (18.0) | 284 (19.5) | –0.04 | 1930 (18.1) | 229 (17.5) | 0.02 |
| PPIs or H2 blockers | 2438 (20.5) | 323 (22.1) | –0.04 | 2164 (20.3) | 261 (20.0) | 0.01 |
| Systemic glucocorticoids | 920 (7.7) | 144 (9.9) | –0.08 | 853 (8.0) | 107 (8.2) | –0.01 |

ACE = angiotensin-converting enzyme, ARBs = angiotensin receptor blockers, BMI = body mass index, DPP-4 = dipeptidyl peptidase 4, eGFR = estimated glomerular filtration rate, GLP-1 RAs = glucagon-like peptide 1 receptor agonists, $HbA_{1c}$ = glycated hemoglobin, H2 = histamine 2 receptor, iPTH = intact parathyroid hormone, IPTW = inverse probability of treatment weighting, IQR = interquartile range, NSAIDs = nonsteroidal anti-inflammatory drugs, PPIs = proton-pump inhibitors, SGLT2 = sodium–glucose cotransporter 2, SMD = standardized mean difference, UACR = urine albumin-to-creatinine ratio.

*All variables in the table were included as covariates in regression models. The covariate assessment window was defined as the 1-year period preceding the index date (comorbidities and comedication uses) and 12 weeks preceding the index date (laboratory data) (Appendix 1, Supplementary Figure 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.240922/tab-related-content). If multiple laboratory tests were available, only the result from the laboratory test closest to the index date was included. The propensity-score model included age as a continuous variable; other laboratory information was included as categorical variables.

†Unless indicated otherwise.

‡–0.1 < SMD value < 0.1 indicates no meaningful difference between the treatment groups. For continuous variables, the SMD value represents class-wide differences.

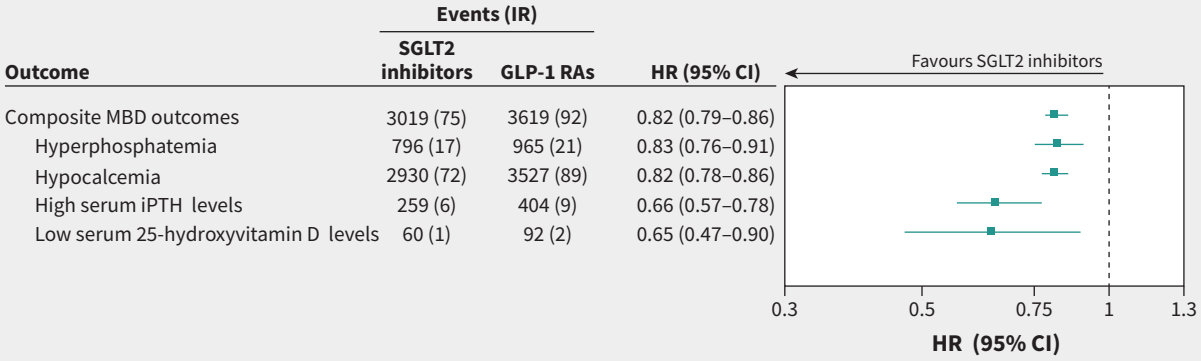


**Figure 2:** Hazard ratios for the composite primary outcome and its components for patients receiving sodium–glucose cotransporter 2 (SGLT2) inhibitors compared with those receiving glucagon-like peptide 1 receptor agonists (GLP-1-RAs), after application of propensity scores with inverse probability of treatment weighting. See Related Content tab for accessible version. Note: CI = confidence interval, HR = hazard ratio, iPTH = intact parathyroid hormone, IR = incidence rate per 1000 person-years, MBD = mineral and bone disorders.

**Table 2: Proportion of patients with biochemical measurements related to chronic kidney disease metabolic and bone disorders, and proportion with abnormal results, during follow-up**

| | Patients with biochemical measurements, % | | Patients with abnormal results among those with biochemical measurements, % | |
|---|---|---|---|---|
| **Measure** | **SGLT2 inhibitors** | **GLP-1 RAs** | **SGLT2 inhibitors** | **GLP-1 RAs** |
| **Original cohort** | | | | |
| Serum phosphate, calcium, iPTH, or 25-hydroxyvitamin D | 35.8 | 41.6 | 69.0 | 87.3 |
| Serum calcium | 35.0 | 41.2 | 68.6 | 85.9 |
| Serum iPTH | 5.5 | 8.7 | 38.2 | 51.7 |
| Serum phosphate | 26.9 | 31.5 | 23.0 | 35.9 |
| Serum 25-hydroxyvitamin D | 1.8 | 2.6 | 27.8 | 23.1 |
| **After IPTW** | | | | |
| Serum phosphate, calcium, iPTH, or 25-hydroxyvitamin D | 34.6 | 40.9 | 72.8 | 75.3 |
| Serum calcium | 33.8 | 40.5 | 72.5 | 74.1 |
| Serum iPTH | 5.3 | 8.6 | 41.5 | 39.5 |
| Serum phosphate | 25.6 | 30.7 | 26.2 | 26.7 |
| Serum 25-hydroxyvitamin D | 1.7 | 2.6 | 29.4 | 30.8 |

Note: GLP-1 RAs = glucagon-like peptide 1 receptor agonists, iPTH = intact parathyroid hormone, IPTW = inverse probability of treatment weighting, SGLT2 = sodium–glucose cotransporter 2.

related to CKD-MBD was around 15% lower among patients receiving SGLT2 inhibitors (34.6%) than among those receiving GLP-1 RAs (40.9%), and the effect size was consistent with the lower CKD-MBD risk among patients receiving SGLT2 inhibitors (Table 2). Measurement rates for $HbA_{1c}$ (GLP-1 RAs: 87.2% v. SGLT2 inhibitors: 86.2%) and eGFR (GLP-1 RAs: 97.7% v. SGLT2 inhibitors: 96.4%) indicated that overall biochemical testing rates were similar between the 2 groups. Individually, SGLT2 inhibitors were associated with reduced risks of incident hyperphosphatemia (HR 0.83, 95% CI 0.76–0.91), hypocalcemia (HR 0.82, 95% CI 0.78–0.86), high serum iPTH levels (HR 0.66, 95% CI 0.57–0.78), and low serum 25-hydroxyvitamin D levels (HR 0.65, 95% CI 0.47–0.90) (Figure 3). Results from the positive and negative control outcome analyses showed that SGLT2 inhibitor use was associated with a lower risk of incident hyperkalemia (HR 0.88, 95% CI 0.82–0.95), but no difference in risk of all-cause death (HR 1.11, 95% CI 0.73–1.69).

Results of subgroup analyses remained broadly consistent with those of the main analysis, suggesting that the risk of the primary outcome was lower when using SGLT2 inhibitors, except among patients with a high eGFR (Table 3). Patients taking SGLT2 inhibitors showed lower risk of the composite primary outcome than those taking GLP-1 RAs and those with eGFR levels of 60–89 mL/min/1.73 $m^2$ (HR 0.81, 95% CI 0.74–

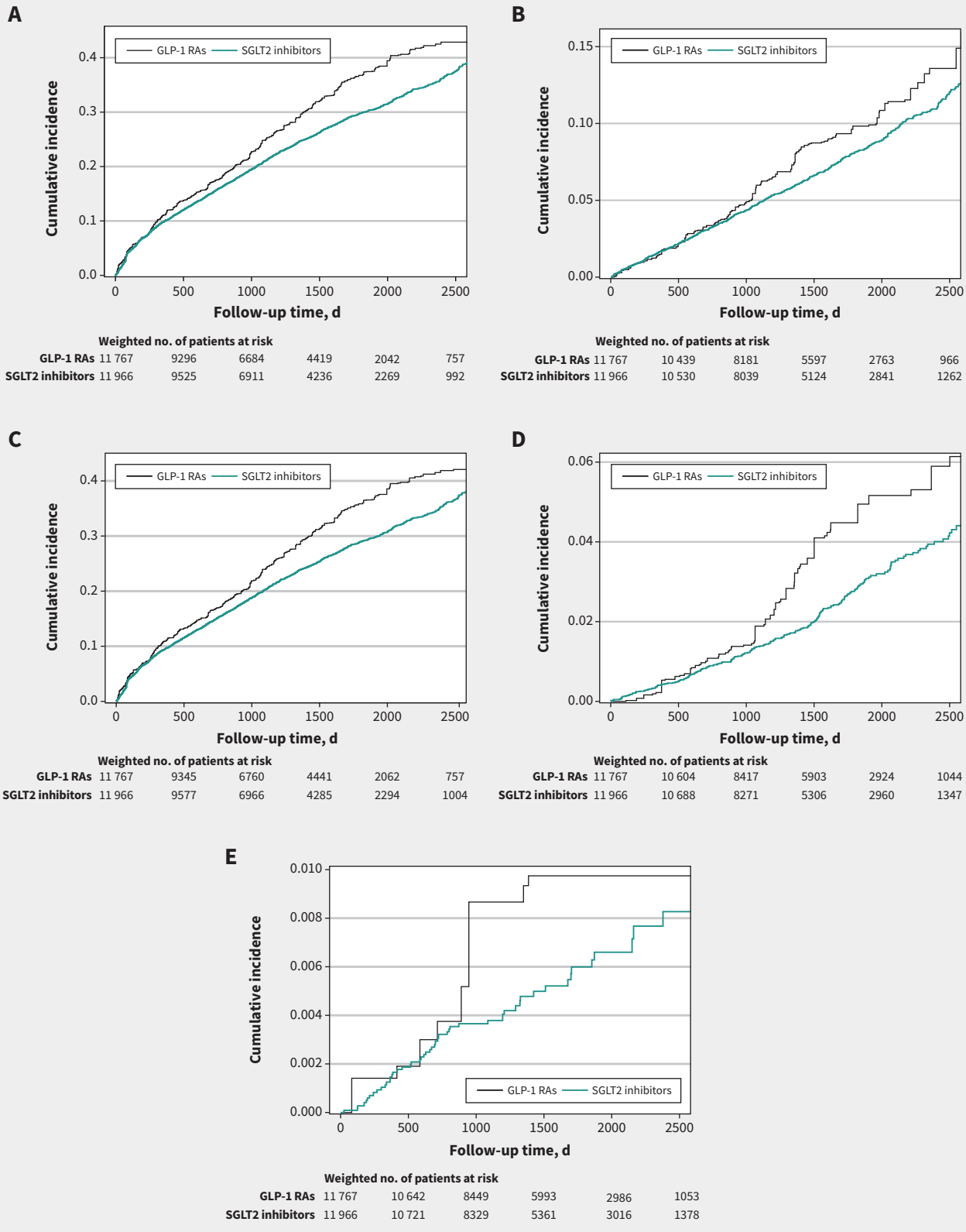


**Figure 3:** Survival curves for patients receiving glucagon-like peptide 1 receptor agonists (GLP-1-RAs) or sodium–glucose cotransporter 2 (SGLT2) inhibitors after application of propensity scores with inverse probability of treatment weighting, showing risk of (A) the composite outcome of all biochemical abnormalities related to chronic kidney disease metabolic and bone disorders, (B) hyperphosphatemia, (C) hypocalcemia, (D) high serum intact parathyroid hormone levels (> 6.9 pmol/L), and (E) low serum 25-hydroxyvitamin D levels (< 49.9 nmol/L) over time. The initial numbers (11 767 and 11 966) refer to the weighted numbers of patients at risk.

**Table 3: Effect of sodium–glucose cotransporter 2 (SGLT2) inhibitors, compared with glucagon-like peptide 1 receptor agonists (GLP-1-RAs), on the composite primary outcome within patient subgroups**

| Subgroup | No. of patients | Observed no. of events | Weighted no. of patients | Weighted no. of events | IR (95% CI) per 1000 person-years | HR (95% CI) | *p* value for interaction |
|---|---|---|---|---|---|---|---|
| Age | | | | | | | 0.5 |
| ≥ 65 yr | | | | | | | |
| SGLT2 inhibitors | 5779 | 1446 | 5667 | 1656 | 95 (90–100) | 0.88 (0.83–0.94) | |
| GLP-1 RAs | 702 | 228 | 5529 | 1847 | 108 (103–113) | Ref. | |
| < 65 yr | | | | | | | |
| SGLT2 inhibitors | 6141 | 1192 | 6269 | 1358 | 60 (57–63) | 0.75 (0.70–0.81) | |
| GLP-1 RAs | 757 | 213 | 6206 | 1788 | 80 (76–84) | Ref. | |
| Sex | | | | | | | 0.3 |
| Male | | | | | | | |
| SGLT2 inhibitors | 7328 | 1606 | 7190 | 1799 | 76 (72–79) | 0.82 (0.77–0.87) | |
| GLP-1 RAs | 751 | 233 | 6976 | 2106 | 92 (88–96) | Ref. | |
| Female | | | | | | | |
| SGLT2 inhibitors | 4592 | 1020 | 4777 | 1202 | 73 (69–77) | 0.84 (0.78–0.91) | |
| GLP-1 RAs | 708 | 210 | 4822 | 1474 | 87 (83–92) | Ref. | |
| eGFR | | | | | | | < 0.001 |
| ≥ 90 mL/min/1.73 m$^2$ | | | | | | | |
| SGLT2 inhibitors | 3070 | 421 | 2908 | 478 | 43 (40–47) | 1.06 (0.93–1.20) | |
| GLP-1 RAs | 363 | 60 | 2901 | 469 | 41 (37–45) | Ref. | |
| 60–89 mL/min/1.73 m$^2$ | | | | | | | |
| SGLT2 inhibitors | 4228 | 776 | 4062 | 851 | 59 (55–63) | 0.81 (0.74–0.89) | |
| GLP-1 RAs | 376 | 85 | 4086 | 1025 | 73 (68–77) | Ref. | |
| 30–59 mL/min/1.73 m$^2$ | | | | | | | |
| SGLT2 inhibitors | 4622 | 1391 | 4713 | 1639 | 120 (115–126) | 0.83 (0.77–0.88) | |
| GLP-1 RAs | 720 | 306 | 4506 | 1988 | 145 (139–151) | Ref. | |
| Receiving renin–angiotensin–aldosterone system inhibitors | | | | | | | 0.7 |
| Yes | | | | | | | |
| SGLT2 inhibitors | 7727 | 1805 | 7520 | 2073 | 80 (77–84) | 0.77 (0.73–0.82) | |
| GLP-1 RAs | 959 | 326 | 7147 | 2491 | 104 (100–108) | Ref. | |
| No | | | | | | | |
| SGLT2 inhibitors | 4193 | 787 | 4105 | 897 | 68 (64–73) | 0.87 (0.80–0.95) | |
| GLP-1 RAs | 500 | 128 | 4280 | 1127 | 78 (74–83) | Ref. | |

Note: CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio, IR = incidence rate, Ref. = reference category.

0.89) and 30–59 mL/min/1.73 m$^2$ (HR 0.83, 95% CI 0.77–0.88), but not patients with eGFR levels of 90 mL/min/1.73 m$^2$ or higher (HR 1.06, 95% CI 0.93–1.20). Moreover, we found that, compared with patients using GLP-1 RAs, those using empagliflozin (HR 0.82, 95% CI 0.77–0.87), canagliflozin (HR 0.88, 95% CI 0.78–1.00), or dapagliflozin (HR 0.82, 95% CI 0.76–0.88) had significantly lower risks of composite CKD-MBD outcomes (Appendix 1, Supplementary Table 7). The results remained consistent over a series of sensitivity analyses, confirming the robustness of our results (Appendix 1, Supplementary Table 8).

## Interpretation

Using a multi-institutional electronic medical records database and a target trial emulation framework, we found that use of SGLT2 inhibitors was associated with a lower risk of biochemical outcomes related to CKD-MBD than use of GLP-1 RAs. Consistent results from sensitivity analyses supported the robustness of these findings. The observed risk reduction was similar among those who received dapagliflozin, empagliflozin, and canagliflozin, suggesting a class effect of SGLT2 inhibitors.

Previous short-term studies have found that, compared with placebo, the use of canagliflozin or dapagliflozin led to elevated serum levels of phosphate, PTH, and fibroblast growth factor 23.[4,5] The possible mechanism behind these biochemical changes may be a sodium-driven increase in phosphate reabsorption within the proximal tubule of the kidney after initial use of SGLT2 inhibitors. However, these effects may be transient and subclinical,[5] since SGLT2 inhibitors do not significantly affect serum calcium levels or bone resorption and formation over months.[47] In addition, the results from the DAPA-CKD, CREDENCE, and EMPA-KIDNEY trials showed that, compared with placebo, SGLT2 inhibitors resulted in better cardiovascular and renal outcomes among participants with type 2 diabetes mellitus and CKD,[10–12] even though biochemical abnormalities related to CKD-MBD are associated with increased risk of major adverse cardiovascular and renal events among patients with CKD.[48] When we consider our findings with previous literature, it appears that initial SGLT2 inhibitor use may transiently and subclinically increase the regulators of bone and mineral homeostasis, but, in the long term, SGLT2 inhibitors may lower the risk of CKD-MBD among patients with type 2 diabetes mellitus and stage 1–3 CKD.

Furthermore, previous studies indicate that certain patient characteristics potentially modify the effects of treatment using SGLT2 inhibitors among patients with type 2 diabetes mellitus. A meta-analysis found that SGLT2 inhibitors had more substantial renal benefits among patients with lower eGFR levels than in those without reduced eGFR levels.[49] Similarly, our subgroup analyses revealed a reduction in CKD-MBD risk after SGLT2 inhibitor use among patients with lower kidney function (i.e., eGFR 60–89 mL/min/1.73 $m^2$ and eGFR 30–59 mL/min/1.73 $m^2$), but not among those with normal or higher kidney function (eGFR ≥ 90 mL/min/1.73 $m^2$). This observation is in line with the pathophysiology of CKD-MBD itself. Given that the increased risk of CKD-MBD in advanced CKD stages is primarily due to the kidney failing to appropriately excrete phosphate, subsequently leading to a series of biochemical abnormalities, the CKD-MBD risk reduction from SGLT2 inhibitors may occur only among patients with lower kidney function. Our findings suggest that physicians should account for the renal profile of patients with type 2 diabetes mellitus when considering SGLT2 inhibitors to prevent CKD-MBD.

### Limitations

Residual confounding in the analysis was a concern. However, we endeavoured to mitigate this bias by adjusting for potential confounders, such as measures of kidney function and glycemic levels. We did not include any data on over-the-counter drugs such as vitamins and mineral supplements paid for by patients.[50] The study database contains only data from Taiwan's largest multi-institutional health care system, so some patients may have been lost to follow-up or had missing data. However, the effect of such issues should be evenly distributed across groups. This, together with the active-comparator design, supports the reliability of our comparative risk estimates. Our study outcomes were based entirely on the biochemical abnormalities considered to be primary indicators for diagnosis and management of CKD-MBD among patients with CKD.[51] Other aspects of CKD-MBD, such as bone abnormalities or vascular calcification,[51] were not considered as study outcomes because these data are rarely recorded in secondary health care databases. In clinical practice in Taiwan, biochemical measurements related to CKD-MBD are not routinely monitored in patients with early-stage CKD. Physicians typically consider assessing these parameters only when signs or symptoms of CKD-MBD have already emerged. Consequently, differences in biochemical testing rates may arise between 2 treatment groups if the risk of CKD-MBD differs between them. To address this concern, we conducted a post hoc analysis to evaluate the measurement rates of $HbA_{1c}$ and eGFR, 2 critical laboratory parameters for monitoring disease progression in patients with type 2 diabetes mellitus and CKD. Our findings showed comparable measurement rates for $HbA_{1c}$ and eGFR between the 2 treatment groups, suggesting that the potential for surveillance bias in our study was minimal. Finally, we did not include patients with type 2 diabetes mellitus who had stage 4–5 CKD or those undergoing dialysis since SGLT2 inhibitors were not approved for this population during the study period.

## Conclusion

In this multi-institutional cohort study, patients with type 2 diabetes mellitus and stage 1–3 CKD who had newly started SGLT2 inhibitor treatment showed a reduced incidence of biochemical abnormalities related to CKD-MBD, compared with similar patients who started GLP-1 RA treatment. Although our findings suggest that treatment with SGLT2 inhibitors can mitigate the risk of CKD-MBD in such patients, further research, including randomized controlled trials, is warranted to establish more robust evidence.

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**Disclaimer:** The authors accept sole responsibility for the content and declare that it does not represent the official position of Chang Gung Medical Foundation. Chang Gung Medical Foundation of Taiwan provided the data used in this study from the Chang Gung Research Database. The interpretations and conclusions of the data reported in this article are not representative of the position of Chang Gung Medical Foundation.

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