Association between SGLT2 Inhibitors vs DPP4 Inhibitors and Renal Outcomes Among Patients with Type 2 Diabetes

Philip CM Au[1], Kathryn CB Tan[2], Bernard MY Cheung[2], Ian CK Wong[1,3,4], Hang-Long Li[2], Ching-Lung Cheung[1,3]

[1]Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

[2]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

[3]Laboratory of Data Discovery for Health (D24H), Hong Kong Science Park, Pak Shek Kok, Hong Kong.

[4]Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK.

Short title: SGLT2 inhibitors and renal outcomes

Keywords: albuminuria, diabetes, DPP4 inhibitor, eGFR, renal, SGLT2 inhibitor

Correspondence and reprint requests:

Ching-Lung Cheung, PhD (https://orcid.org/0000-0002-6233-9144)

Dept of Pharmacology and Pharmacy, 21 Sassoon Road, Pokfulam, Hong Kong

Email: lung1212@hku.hk; Tel: +852-3917-9462 Fax: +852-2816-2095

Funding support: N/A

Disclosure: The authors have no conflicts of interest to declare.

ABSTRACT

Context: Diabetic kidney disease is a major burden among diabetic patients. Sodium-glucose co-transporter 2 inhibitors (SGLT2is) were shown to reduce renal outcomes in clinical trials and real-world studies. However, head-to-head comparisons with individual classes of glucose-lowering agents warranted further investigation.

Objective: To investigate the associations between SGLT2is use versus dipeptidyl peptidase-4 inhibitors (DPP4is) use and 4 renal outcomes: end-stage renal disease (ESRD), albuminuria, acute renal failure (ARF), and the rate of eGFR change using a territory-wide electronic medical database in Hong Kong.

Design: A retrospective cohort study. The "prevalent new-user" design was adopted to account for previous exposure to study drugs. Propensity score matching was used to balance baseline characteristics.

Setting and participants: Electronic health data of type 2 diabetes patients using SGLT2is and DPP4is between 2015 and 2018 was collected.

Results: The matched cohort consisted of 6,333 SGLT2is users and 25,332 DPP4is users, with a median follow-up of 3.8 years. Compared to DPP4is, SGLT2is use was associated with lower risks of ESRD (HR: 0.51, 95% CI: 0.42-0.62; P<0.001) and ARF (HR: 0.59, 95% CI: 0.48-0.73; P<0.001), and a slower decline in eGFR. The associations remained significant among patients with or without rapid eGFR decline and patients who added or switched to SGLT2is from DPP4is. The association with albuminuria was inconsistent across analyses.

Conclusion: Compared to DPP4is, SGLT2is use was associated with reduced risks of ESRD and ARF, and a slower eGFR decline in a real-world setting. The associations remained significant in patients with or without pre-index rapid eGFR decline.

INTRODUCTION

Diabetic kidney disease (DKD) is associated with excess risks of all-cause and cardiovascular mortality and a major burden among patients with type 2 diabetes (T2D) (1). It is also one of the leading causes of end-stage renal disease (ESRD) in the US (2).

Sodium glucose co-transporter 2 inhibitors (SGLT2is) are one of the newer classes of glucose-lowering agents for T2D. Since their introduction, multiple large placebo-controlled clinical trials were conducted to study the pleiotropic properties of SGLT2is (3-8). These trials reported beneficial effects of SGLT2is against renal outcomes, including progression to albuminuria and ESRD. Since clinical trials tend to provide evidence on drug efficacy instead of drug effectiveness, to investigate the real-world effectiveness of the renal-protective effects of SGLT2is, the multinational CVD-REAL 3 study compared the use of SGLT2is with the use of other glucose-lowering agents on their effects on renal endpoints (9). The study showed that SGLT2is use was associated with a slower decline in estimated glomerular filtration rate (eGFR) and a reduced risk of ESRD. Very recently, a few real-world studies on the related topics were also published (10-12). However, inconsistent results were observed for composite renal disease progression, ESRD, and acute kidney injury. Notably, the effect of SGLT2is on the risk of microalbuminuria remained unstudied. Among these recent studies, only one study performed head-to-head comparisons (12) with individual classes of glucose-lowering agents. However, the results were inconsistent between analyses. The study also lacked sufficient size to examine the individual components of the renal composite outcome. Given that different associations with renal endpoints have been reported for different classes of glucose-lowering agents (13), it is important to have head-to-head comparisons, especially for dipeptidyl peptidase-4 inhibitors (DPP4is) since they are the most widely used second- or third-line antidiabetic medication in many parts of the world including the US (14) and Europe (15).

The present study aimed to investigate the associations between the use of SGLT2is versus the use of DPP4is and 4 renal outcomes: ESRD, albuminuria, acute renal failure (ARF), and the change in eGFR using a territory-wide representative electronic medical database in Hong Kong.

MATERIALS AND METHODS

Data Source

The Clinical Data Analysis and Reporting System (CDARS) is a territory-wide representative electronic medical database from the Hospital Authority (HA) of Hong Kong. The HA manages all 42 public hospitals and 120 public outpatient general and specialist clinics in Hong Kong. More than 90% of the known diabetes patients in Hong Kong are under the HA's care (16). The CDARS is ethnically homogeneous that about 92% of the population is Han Chinese (17). It stores clinical records from outpatient, emergency, and inpatient visits, including diagnosis, dispensing, clinical procedures and operations, laboratory tests, and death registry records. The ethical approval of this study has been granted by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref: UW 19-154).

Study Cohort

The study cohort consisted of diabetic patients prescribed with SGLT2is or DPP4is between 2015 (the year SGLT2is was first prescribed by the HA) and 2018. Patients who started SGLT2is, including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, were classified as "exposed". Patients who started DPP4is, including sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, and omarigliptin, but had not been prescribed with SGLT2is

before, were classified as “control”. Exclusion criteria were (Figure 1): 1) patients in the DPP4i control group with any use of SGLT2is before index date; 2) patients with DPP4i and SGLT2i initiated on the same date; 3) patients of type 1 diabetes (T1D); 4) patients with prescription records of index drugs for only 1 day; 5) patients with latest eGFR measurement <15 mL/min/1.73m^2 before index date; 6) patients who received dialysis or kidney transplant within 1 year before index date; 7) patients with no HbA1c measurement for the adjustment of pre-index diabetic control within 1 year before index date; and 8) patients with less than 2 eGFR measurements for the adjustment of the pre-index rate of eGFR change. To avoid short-term or acute changes, patients with the first and last available eGFR measurements less than 30 days apart were also excluded. For the analysis of albuminuria outcome, patients with urine albumin-to-creatinine ratio (UACR) ≥3 mg/mmol or 24-hour urine albumin ≥30 mg/day (18) within 1 year before index date were excluded. For the analysis of the rate of change eGFR, patients with less than 3 eGFR measurements during follow-up were excluded. T1D was defined according to a previous validation study (19): 1) the number of T1D diagnosis records to the number of T2D diagnosis records ratio ≥4 (19); 2) prescribed with insulin and no other glucose-lowering agents within the first year of diabetes diagnosis (19); or 3) age at diagnosis <30. eGFR was estimated using the new Asian modified CKD-EPI equation (20). For the 3 hard renal endpoints (ESRD, albuminuria, and ARF), the cohort was followed until the occurrence of study outcomes, the end of study (December 31, 2020), or death, whichever came first. For the change in eGFR, the cohort was followed until the end of 2 years follow-up, the end of study (December 31, 2020), discontinuation of index drug, or death, whichever came first. Discontinuation of index drug was defined as more than 90 days without a new prescription after the end date of the last prescription.

Outcomes

There were 4 outcomes of interest: 1) the first incidence of ESRD, 2) the first incidence of albuminuria, 3) the first incidence of ARF, and 4) the rate of change of eGFR over time. ESRD was defined as at least two consecutive laboratory measurements of eGFR <15 mL/min/1.73m^2, initiation of dialysis, or reception of kidney transplantation. Albuminuria was defined as urine albumin-to-creatinine ratio (UACR) ≥3 mg/mmol or 24-hour urine albumin ≥30 mg/day, followed by a second measurement within a 3- to 6-month period (18). ARF was defined as diagnosis coded by ICD-9-CM: 584.x in the accident and emergency (A&E) and the in-patient settings (21). For the change in eGFR, eGFR measurements were taken every 3 months after the start of follow-up for a maximum of 2 years. A measurement window of ±30 days was allowed. For patients with multiple eGFR measurements available within a measurement window, the measurement closest to the 3-month time point was selected.

"Prevalent New-User" Design

Since DPP4is were an older class of glucose-lowering agents and have been widely used before SGLT2is became available in Hong Kong, many patients who started SGLT2is were ongoing or previous DPP4is users. To account for the prior exposure to an active comparator, the present study adopted the "prevalent new-user" design (22). A detailed explanation of how the design was applied to the present study cohort has been mentioned elsewhere (23). In brief, the design matched study participants on the length of previous exposure to DPP4is in a time-dependent manner. For patients initiating SGLT2is without previous use of DPP4is (i.e., 0 day of previous exposure to DPP4is), they were matched with patients first initiating DPP4is. Compared to the traditional new-user design, the "prevalent new-user" design does not exclude patients with previous exposure to an active comparator. This "prevalent new-user" design allowed an

unbiased comparison between patients who switched to or added SGLT2is from DPP4is and patients who stayed on DPP4is.

Propensity Score (PS) Matching

The PS matching (24) was adopted to balance the baseline characteristics between the exposed and control groups. A wide range of 72 covariates, including eGFR and HbA1c measurements, pre-index rate of eGFR decline, albuminuria status, history of chronic kidney disease and acute renal failure, concurrent uses of other glucose-lowering agents, and history of other major comorbidities and related drug uses, were selected for PS calculation. The definition of each covariate was listed in Supplemental Table 1 (25). To account for the difference between patients who initiated SGLT2is/DPP4is as their first-ever anti-diabetic medication and those who did not, the medication history of individual classes of anti-diabetic drugs and the total number of different anti-diabetic drugs used were also included in the PS model. PS was calculated using conditional logistic regression stratified by the pairs matched in the "prevalent new-user" design. To reduce the risk of residual confounding (26), patients in the SGLT2is exposed group with PS <the 5th percentile and patients in the DPP4is control group with PS >the 95th percentile were trimmed. PS matching was done within each "prevalent new-user" matched pair using sequential greedy matching (27) with a calliper of 0.2 standard deviations (SD). The patients were matched 1:4 (SGLT2is:DPP4is) without replacement within and across "prevalent new-user" matched pairs. The balance of covariates post-PS matching was assessed by standardized mean difference (SMD). Covariates with SMD >0.1 were considered unbalanced and were adjusted in the subsequent regression analyses.

Statistical analyses

Patient characteristics were presented as mean (SD) for continuous variables and as frequency (%) for categorical variables. Covariates with SMD>0.1 after PS matching were adjusted in all regression analyses. Hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazards regression. Proportional hazard assumption was tested and found no violation. Cumulative incidence differences (CIDs) at 1 and 2 years since follow-up were estimated using the method proposed by P.C. Austin (28). Survival probabilities were averaged across patients and cumulative incidence was estimated by 1-mean(survival probability). The 95% CIs for CID were estimated by the 2.5th and 97.5th percentiles of the sampling distribution of 500 bootstrap samples. The change in eGFR was modelled using linear mixed model. Measurement time (linear), treatment group (SGLT2i or DPP4i), and the interaction between measurement time and treatment group were included as fixed effects. Patients' id was included as random effect while allowing correlation between random intercepts and random slopes for the "measurement time" term. Statistically significant level was defined as a two-sided p-value ≤0.05.

Subgroup analyses

Two subgroup analyses were performed. The first one split the study cohort according to the rate of pre-index eGFR change. Rapid decline in eGFR was defined as >4% decline in eGFR per year (29), or as >5 mL/min/1.73m^2 decline in eGFR per year (according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline (30)), while non-rapid decline was defined as ≤4% decline in eGFR per year, or as ≤5 mL/min/1.73m^2 decline in eGFR per year, respectively. The pre-index percentage rate of eGFR decline was estimated per patient using linear least squares regression on the log-transformed eGFR measurements (non-log-transformed eGFR for absolute rate) within 1 year before index date. Interaction between SGLT2is use and status of rapid decline in eGFR was tested by adding the corresponding

interaction term to the Cox regression of the main analyses. The second subgroup analysis aimed to examine the effect of switching to or adding SGLT2is from DPP4is compared to staying on DPP4is without SGLT2is. The analysis included only patients with previous use or ongoing use of DPP4is at baseline (i.e., >0 day of previous exposure to DPP4is at baseline).

Sensitivity analyses

In addition to event occurrence, study end, and death, patients were censored upon discontinuation of index drugs. Discontinuation was defined as more than 90 days without a new prescription after the end date of the last prescription. To account for potential bias due to discontinuation censoring, HRs with 95% CIs were estimated using competing risk regression considering discontinuation censoring as competing event.

All statistical analyses were performed using R version 4.1.0.

RESULTS

Between 2015 and 2018, 9,895 patients first started SGLT2is and 93,481 patients first started or continued with DPP4is in the CDARS database. Each patient in the SGLT2is group was matched with patients in the DPP4is group according to the duration of previous exposure to DPP4is (±30 days) and the calendar period (±60 days) in a time-dependent manner. After screening for exclusion criteria, a "prevalent new-user" matched cohort of 8,597 SGLT2is patients and 83,010 DPP4is patients remained available for subsequent PS matching (Figure 1). The final 1:4 PS-matched cohort consisted of 6,333 patients in the SGLT2is group and 25,332 patients in the DPP4is group. All covariates showed SMD <0.1 after PS matching (Table 1 short version; Supplemental Table 2 full version (25)). At baseline, around 56% of

the patients were male. The mean age was 62. Around 90% of the patients had no history of CKD (defined as eGFR<60 mL/min/1.73m^2) and around 77% of the patients had normal albuminuria (defined as UACR <3 mg/mmol or 24-hour urine albumin <30 mg/day). The mean eGFR was around 86 mL/min/1.73m^2. Around 70% of the patients were in the low KDIGO risk group (defined as UACR <3 mg/mmol or 24-hour urine albumin <30 mg/day, and eGFR≥60 mL/min/1.73m^2 (30)). Among the SGLT2is group, 1.2% were canagliflozin, 71.3% were dapagliflozin, 27.4% were empagliflozin, and none were ertugliflozin.

Associations of SGLT2is with ESRD, ARF, and albuminuria

The cohort was followed for a median of around 3.8 years. No further adjustment in the statistical analyses was required as all covariates showed SMD <0.1. Compared to the use of DPP4is, the use of SGLT2is was significantly associated with reduced risks of ESRD (HR: 0.51, 95% CI: 0.42-0.62; P<0.001; Table 2) and ARF (HR: 0.59, 95% CI: 0.48-0.73; P<0.001; Table 2). The 1-year and 2-year CIDs were 0.36% (95% CI: 0.23-0.46) and 0.74% (95% CI: 0.50-0.95) for ESRD, and 0.25% (95% CI: 0.15-0.36) and 0.47% (95% CI: 0.29-0.65) for ARF, respectively (Table 2). The associations were stronger and remained significant in sensitivity analysis which patients were censored upon discontinuation of index drugs (Table 3). On the other hand, the association with albuminuria was statistically slightly non-significant in the main analysis (HR: 0.81, 95% CI: 0.64-1.01; P=0.065; Table 2) but became significant in the sensitivity analysis (HR: 0.50, 95% CI: 0.36-0.68; P<0.001; Table 3).

Association between SGLT2is and the rate of eGFR change

The linear mixed regression was used to model the rate of change of eGFR. The interaction term between measurement time and treatment group was included as fixed effect to test the

difference in eGFR rates between the use of SGLT2is and the use of DPP4is. The eGFR measurements were taken in 3-months windows for 2 years. 5714 PS-matched pairs were excluded due to less than 3 eGFR measurements for at least one member in a pair. The resulting cohort consisted of 617 PS-matched pairs. The rate of change of eGFR among patients using SGLT2is was -0.060 mL/min/1.73m^2 per year (95% CI: -0.243 to 0.135), while the rate of change of eGFR among patients using DPP4is was -0.625 mL/min/1.73m^2 per year (95% CI: -0.712 to -0.536). There was a significant difference in the rate change of eGFR between SGLT2is and DPP4is ($P_{interaction}$<0.001).

Subgroup analyses

Subgroup analyses were performed for patients with or without rapid pre-index eGFR decline and patients with ongoing or previous use of DPP4is at baseline (Table 4). Between rapid decliners and non-rapid decliners (defined as >4% decline in eGFR), there was a significant difference in associations for ESRD ($P_{interaction}$=0.008), but not for ARF and albuminuria (all $P_{interaction}$>0.05, Table 4). There was no significant interaction between rapid and non-rapid decliners for ESRD, ARF, and albuminuria when the KDIGO definition was used (all $P_{interaction}$>0.05, Table 5). Except for albuminuria, the associations with ESRD and ARF remained significant for both rapid and non-rapid decliners.

For the second subgroup analysis including only patients with ongoing or previous use of DPP4is at cohort entry, the associations with ESRD (HR: 0.54, 95% CI: 0.43-0.69; P<0.001) and ARF (HR: 0.51, 95% CI: 0.39-0.69; P<0.001) remained significant with comparable effect sizes with the main analysis (Table 6). The association with albuminuria on the other hand remained slightly non-significant (P=0.068) (Table 6).

DISCUSSION

The present study investigated the associations between SGLT2is use and renal outcomes using a retrospective cohort with more than 30,000 diabetic patients from routine clinical practice in Hong Kong. The PS-matched cohort showed that the use of SGLT2is was significantly associated with reduced risks of ESRD and ARF, as well as a slower decline in eGFR compared to the use of DPP4is. The associations remained significant when patients were censored upon discontinuation of index drug, and in patients with rapid pre-index eGFR decline and patients without. Further subgroup analysis showed that there were also significant renal benefits for DPP4is users to add or switch to SGLT2is. The association with albuminuria was inconclusive.

SGLT2is has been shown to reduce renal outcomes in large placebo-controlled clinical trials (31). The multinational CVD-REAL 3 study further showed real-world evidence that SGLT2is were associated with a reduced risk of ESRD and a slower decline in eGFR compared to other glucose-lowering drugs (9). Recent population-based studies further investigated composite renal outcomes, eGFR reduction, ESRD, and acute kidney injury. However, the results were inconsistent (10-12). Notably, among these recent studies, only one provided head-to-head comparisons between SGLT2is and individual classes of glucose-lowering drugs (12). However, the results were not consistent between analyses and databases used. The limited study size also prevented further investigation of the individual components of the composite renal outcomes. The present study provided a more comprehensive investigation of a range of renal outcomes using DPP4is as the active comparator. Among the glucose-lowering drugs, DPP4is have been widely used as second- or third-line glucose-lowering drugs (32). Therefore, the use of DPP4is as an active comparator in the present study not only allowed a clinically meaningful comparison with SGLT2is but also prevented time-lagging bias (33).

Compared to previous studies, the strength of the present study was the use of the "prevalent new-user design" (22). Since DPP4is are an older class of glucose-lowering drugs, it was common for a patient to have previous exposure to DPP4is before the initiation of SGLT2is in our study cohort. Potential bias could arise from this previous exposure to an active comparator. To account for this issue, the traditional new-user design would exclude patients with previous exposure. The "prevalent new-user design" on the other hand addressed this issue by matching the length of previous exposure to DPP4is. This design did not require the exclusion of patients with previous exposure to an active comparator. Therefore, it allowed the study of adding or switching to SGLT2is from DPP4is, which could not be observed in the traditional new-user design. The present study adds to the knowledge about the use of SGLT2is and renal outcomes that there are significant renal benefits to adding or switching to SGLT2is for DPP4is users.

While the association between SGLT2is versus DPP4is and reduced risk of ARF has been reported in several observational studies (31), the association with the risk of albuminuria was less studied. In the present study, we could not observe a consistent association with albuminuria across analyses. A stronger and significant association was only observed when patients were censored upon discontinuation of index drug. This suggested that the association could be "diluted" in the intention-to-treat analyses since per-protocol approach would capture better the on-treatment effect of SGLT2is than intention-to-treat approach. In fact, stronger associations of SGLT2is were also observed for ESRD and ARF in the sensitivity analysis. Therefore, the slightly non-significant associations in the intention-to-treat analyses could be due to weaker associations which could not be captured by the smaller sample size after additional exclusion of patients with history of albuminuria.

Another strength of the study was the use of pre-index rate of eGFR change. The inclusion of both pre-index rate of eGFR change and the latest eGFR measurement in PS-matching allowed proper adjustment of patient's kidney function. Furthermore, there is a lack of SGLT2is studies examining subgroups of pre-index rate of eGFR change on renal outcomes. Rapid decliners are at a higher risk of progression to ESRD (34). It is clinically important to investigate the effect of SGLT2is against DKD progression among such high-risk group. Here we examined the associations among subgroups of patients with or without pre-index rapid eGFR decline using two different definitions for rapid decline. For both definitions, patients with or without rapid decline in eGFR both showed lower risks of ESRD and ARF for SGLT2is use. Interestingly, there was some evidence of an interaction between rapid decliner and SGLT2is use for ESRD. However, the evidence was not consistent. It would be of clinical importance if rapid decliners would benefit more from the use of SGLT2is. Further investigation is warranted.

Nevertheless, there were limitations. First, the CDARS database does not contain lifestyle data. However, any clinically relevant effects should be captured via clinical diagnoses and conditions. Second, the present study used diagnosis records from A&E and in-patient departments instead of eGFR measurements to define ARF incidences. However, it has been shown in trials and observational studies that there is an immediate drop in eGFR, which would return to normal, for patients who first started SGLT2is (9, 35). Therefore, using eGFR measurements could misclassify this immediate drop as ARF incidence. Instead, using clinical diagnosis of ARF from A&E and in-patient records could ensure to include only the eGFR drop that required medical attention. Third, there was a potential by-indication bias. The need to add or switch to SGLT2is from DPP4is could be due to poor glycemic control or the presence

of comorbidities. These were often associated with worse clinical outcomes. Such bias would result in an increased risk of renal outcomes among SGLT2i users. However, this would not affect the overall conclusion of the present study. Even if existed, it would only under-estimate the beneficial effects of SGLT2is, rather than over-estimate them. Forth, the algorithm used to exclude T1D patients might not be able to distinguish all T1D patients from T2D patients. However, the bias should be negligible since T1D contributes only to a small proportion of the diabetes population. The exclusion of patients diagnosed before age 30 should be able to screen out the majority of T1D patients. Fifth, the cohort was only followed for a median of 3.8 years. The long-term associations of SGLT2is with renal outcomes would require further study.

In conclusion, among T2D patients, the use of SGLT2is was associated with reduced risks of ESRD and ARF, as well as a slower decline in eGFR compared to the use of DPP4is. There are significant renal benefits for DPP4is users to add or switch to SGLT2is. Lastly, patients with or without rapid eGFR decline would both benefit from the renal protective effects of SGLT2is against ESRD and ARF.

ACKNOWLEDGEMENTS: We express our gratitude to Mr Ricky Wong for his work and effort in data collection.

DATA AVAILABILITY: Restrictions apply to the availability of all data generated or analysed during this study to preserve patient confidentiality and because they were used under license by the Hospital Authority (HA) of Hong Kong, they are not publicly available.

Reference

1. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, de Boer IH. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol. 2013;24(2):302-8.
2. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ, Patel UD, Ratner RE, Whaley-Connell AT, Molitch ME. Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis. 2014;64(4):510-33.
3. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B, Investigators E-RO. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-34.
4. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, Wanner C. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):610-21.
5. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR, Group CPC. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-57.
6. Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, Barrett TD, Weidner-Wells M, Deng H, Matthews DR, Neal B. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol. 2018;6(9):691-704.
7. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjostrom CD, Toto RD, Langkilde AM, Wheeler DC, Committees D-CT, Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-46.
8. Heerspink HJL, Jongs N, Chertow GM, Langkilde AM, McMurray JJV, Correa-Rotter R, Rossing P, Sjostrom CD, Stefansson BV, Toto RD, Wheeler DC, Greene T, Committees D-CT, Investigators. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021;9(11):743-54.
9. Heerspink HJL, Karasik A, Thuresson M, Melzer-Cohen C, Chodick G, Khunti K, Wilding JPH, Garcia Rodriguez LA, Cea-Soriano L, Kohsaka S, Nicolucci A, Lucisano G, Lin FJ, Wang CY, Wittbrodt E, Fenici P, Kosiborod M. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Lancet Diabetes Endocrinol. 2020;8(1):27-35.
10. Nagasu H, Yano Y, Kanegae H, Heerspink HJL, Nangaku M, Hirakawa Y, Sugawara Y, Nakagawa N, Tani Y, Wada J, Sugiyama H, Tsuruya K, Nakano T, Maruyama S, Wada T, Yamagata K, Narita I, Tamura K, Yanagita M, Terada Y, Shigematsu T, Sofue T, Ito T, Okada H, Nakashima N, Kataoka H, Ohe K, Okada M, Itano S, Nishiyama A, Kanda E, Ueki K, Kashihara N. Kidney Outcomes Associated With SGLT2 Inhibitors Versus Other Glucose-Lowering Drugs in Real-world Clinical Practice: The Japan Chronic Kidney Disease Database. Diabetes Care. 2021;44(11):2542-51.
11. Schechter M, Melzer-Cohen C, Rozenberg A, Yanuv I, Chodick G, Karasik A, Kosiborod M, Mosenzon O. Cardiorenal outcomes with sodium/glucose cotransporter-2 inhibitors in patients with type 2 diabetes and low kidney risk: real world evidence. Cardiovasc Diabetol. 2021;20(1):169.
12. Alkabbani W, Zongo A, Minhas-Sandhu JK, Eurich DT, Shah BR, Alsabbagh MW, Gamble JM. Renal effectiveness and safety of the sodium-glucose cotransporter-2 inhibitors: a population-based cohort study. BMJ Open Diabetes Res Care. 2021;9(2).
13. Scheen AJ. Effects of glucose-lowering agents on surrogate endpoints and hard clinical renal outcomes in patients with type 2 diabetes. Diabetes Metab. 2019;45(2):110-21.
14. Fang M, Wang D, Coresh J, Selvin E. Trends in Diabetes Treatment and Control in U.S. Adults, 1999-2018. N Engl J Med. 2021;384(23):2219-28.

15. Mardetko N, Nabergoj Makovec U, Locatelli I, Janez A, Kos M. Uptake of new antidiabetic medicines in 11 European countries. BMC Endocr Disord. 2021;21(1):127.
16. Lau IT. A Clinical Practice Guideline to Guide a System Approach to Diabetes Care in Hong Kong. Diabetes Metab J. 2017;41(2):81-8.
17. The Census and Statistics Department tGotHKSAR. Hong Kong 2016 Population By-census - Thematic Report : Ethnic Minorities 2016 [updated 29 Dec 2017. Available from: https://www.censtatd.gov.hk/en/EIndexbySubject.html?pcode=B1120100&scode=459.
18. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, Steffes MW, American Diabetes A. Nephropathy in diabetes. Diabetes Care. 2004;27 Suppl 1:S79-83.
19. Luk AOY, Ke C, Lau ESH, Wu H, Goggins W, Ma RCW, Chow E, Kong APS, So WY, Chan JCN. Secular trends in incidence of type 1 and type 2 diabetes in Hong Kong: A retrospective cohort study. PLoS Med. 2020;17(2):e1003052.
20. Wang J, Xie P, Huang JM, Qu Y, Zhang F, Wei LG, Fu P, Huang XJ. The new Asian modified CKD-EPI equation leads to more accurate GFR estimation in Chinese patients with CKD. Int Urol Nephrol. 2016;48(12):2077-81.
21. Cahn A, Melzer-Cohen C, Pollack R, Chodick G, Shalev V. Acute renal outcomes with sodium-glucose co-transporter-2 inhibitors: Real-world data analysis. Diabetes Obes Metab. 2019;21(2):340-8.
22. Suissa S, Moodie EE, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiol Drug Saf. 2017;26(4):459-68.
23. Au PCM, Tan KCB, Cheung BMY, Wong ICK, Wong Y, Cheung CL. Association between SGLT2 Inhibitors vs DPP-4 Inhibitors and Risk of Pneumonia Among Patients with Type 2 Diabetes. J Clin Endocrinol Metab. 2021.
24. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083-107.
25. Au PC. Data for: Association between SGLT2 Inhibitors vs DPP4 Inhibitors and Renal Outcomes Among Patients with Type 2 Diabetes. OSF repository. Deposited 7 February 2022;https://osf.io/cv2bw/?view_only=b82deca8aba9414a9f46dcc05f13234e.
26. Sturmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med. 2014;275(6):570-80.
27. Austin PC. A comparison of 12 algorithms for matching on the propensity score. Stat Med. 2014;33(6):1057-69.
28. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. J Clin Epidemiol. 2010;63(1):46-55.
29. Zoppini G, Targher G, Chonchol M, Ortalda V, Negri C, Stoico V, Bonora E. Predictors of estimated GFR decline in patients with type 2 diabetes and preserved kidney function. Clin J Am Soc Nephrol. 2012;7(3):401-8.
30. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group CPC. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1-150.
31. Sridhar VS, Rahman HU, Cherney DZI. What have we learned about renal protection from the cardiovascular outcome trials and observational analyses with SGLT2 inhibitors? Diabetes Obes Metab. 2020;22 Suppl 1:55-68.
32. Cahn A, Cernea S, Raz I. An update on DPP-4 inhibitors in the management of type 2 diabetes. Expert Opin Emerg Drugs. 2016;21(4):409-19.
33. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care. 2012;35(12):2665-73.
34. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, Arima H, Chadban SJ, Cirillo M, Djurdjev O, Green JA, Heine GH, Inker LA, Irie F, Ishani A, Ix JH, Kovesdy CP, Marks A, Ohkubo T,

Shalev V, Shankar A, Wen CP, de Jong PE, Iseki K, Stengel B, Gansevoort RT, Levey AS. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014;311(24):2518-31.
35. Kadowaki T, Nangaku M, Hantel S, Okamura T, von Eynatten M, Wanner C, Koitka-Weber A. Empagliflozin and kidney outcomes in Asian patients with type 2 diabetes and established cardiovascular disease: Results from the EMPA-REG OUTCOME((R)) trial. J Diabetes Investig. 2019;10(3):760-70.

Table 1. Baseline characteristics of the study cohort after PS matching (short version).

Covariates	**Group**		**SMD**
	DPP4i	SGLT2i	
n	25332	6333	
Male, n (%)	14070 (55.5)	3558 (56.2)	0.013
Age at index date, mean (SD)	61.76 (10.08)	61.52 (9.72)	0.024
Medication History (1 year prior), n (%)			
Cardiovascular			
Angiotensin-converting-enzyme inhibitors / angiotensin II receptor blockers	17782 (70.2)	4444 (70.2)	0.001
Antiarrhythmic agents	256 (1.0)	62 (1.0)	0.003
Anticoagulants	1216 (4.8)	319 (5.0)	0.011
Beta blockers	9949 (39.3)	2528 (39.9)	0.013
Calcium channel blockers	12693 (50.1)	3122 (49.3)	0.016
Cardiac glycosides	495 (2.0)	127 (2.0)	0.004
Loop diuretics	2014 (8.0)	539 (8.5)	0.02
Other diuretics	2795 (11.0)	660 (10.4)	0.02
Nitrates	3322 (13.1)	876 (13.8)	0.021
Peripheral vasodilators	118 (0.5)	38 (0.6)	0.018
Platelet inhibitors	8516 (33.6)	2215 (35.0)	0.029
Renal			
Phosphate binding agents	0 (0.0)	0 (0.0)	-
Glucose-lowering agents			
Metformin	22021 (86.9)	5553 (87.7)	0.023
Sulfonylureas	18305 (72.3)	4514 (71.3)	0.022
Thiazolidinediones	2779 (11.0)	567 (9.0)	0.067
Glucagon-like peptide-1 agonists	14 (0.1)	0 (0.0)	0.033
Acarbose	694 (2.7)	208 (3.3)	0.032
Meglitinides	0 (0.0)	0 (0.0)	<0.001
Insulin	3414 (13.5)	876 (13.8)	0.01
Diagnosis History (1 year prior), n (%)			
Renal			
Chronic kidney disease	2544 (10.0)	656 (10.4)	0.01
Acute renal failure	42 (0.2)	11 (0.2)	0.002
Albuminuria			0.027
Normal-	19715 (77.8)	4875 (77.0)	
Micro-	4269 (16.9)	1084 (17.1)	
Marco-	1348 (5.3)	374 (5.9)	

Rate of eGFR change (mL/min/1.73m^2 per year)	-1.70 (10.69)	-1.96 (8.44)	0.028
Low KDIGO risk	17942 (70.83)	4391 (69.34)	0.033
Biochemical parameters, mean (SD)			
HbA1c (mmol/mol)	69.22 (17.89)	70.38 (14.86)	0.07
HbA1c (%)	8.48 (1.64)	8.59 (1.36)	
eGFR (mL/min/1.73m^2)	86.46 (21.30)	86.45 (19.38)	<0.001

SMD: Standardized mean difference

Table 2. Associations between the use of SGLT2 inhibitors and the risks of ESRD, ARF and microalbuminuria.

Outcomes	Group	No. of subjects	No. of events	Total person-year	Median follow-up in year (IQR)	Hazard ratio (95% CI)	P	1-year CID (95% CI)	2-year CID (95% CI)
ESRD	DPP4i	25332	872	90786	3.7 (1.5)	1	<0.001	0.36% (0.23-0.46)	0.74% (0.50-0.95)
	SGLT2i	6333	112	23173	3.8 (1.5)	0.51 (0.42-0.62)			
ARF	DPP4i	25332	642	91057	3.7 (1.5)	1	<0.001	0.25% (0.15-0.36)	0.47% (0.29-0.65)
	SGLT2i	6333	98	23177	3.8 (1.5)	0.59 (0.48-0.73)			
Albuminuria	DPP4i	19352	439	69228	3.7 (1.5)	1	0.065	0.12% (-0.04-0.25)	0.21% (-0.07-0.45)
	SGLT2i	4838	90	17568	3.8 (1.5)	0.81 (0.64-1.01)			

ESRD: end stage renal disease, ARF: acute renal failure, DPP4i: dipeptidyl peptidase-4 inhibitor, SGLT2i: Sodium glucose co-transporter 2 inhibitors, IQR: inter quartile range, CI: confidence interval, CID: cumulative incidence differences.

Table 3. Sensitivity analysis for the associations between the use of SGLT2 inhibitors and the risks of ESRD, ARF and microalbuminuria.

Outcomes	Group	No. of subjects	No. of events	No. of competing events [a]	Total person-year	Median follow-up in year (IQR)	Hazard ratio (95% CI)	P
Censored upon discontinuation of index drugs.								
ESRD	DPP4i	25332	637	9540	70185	2.8 (2.2)	1	<0.001
	SGLT2i	6333	30	3791	12446	1.5 (2.4)	0.19 (0.13-0.27)	
ARF	DPP4i	25332	479	9596	70361	2.8 (2.2)	1	<0.001
	SGLT2i	6333	36	3783	12444	1.5 (2.4)	0.30 (0.22-0.42)	
Albuminuria	DPP4i	19352	356	7057	54124	2.9 (2.2)	1	<0.001
	SGLT2i	4838	44	2869	9502	1.5 (2.4)	0.50 (0.36-0.68)	

ESRD: end stage renal disease, ARF: acute renal failure, DPP4i: dipeptidyl peptidase-4 inhibitor, SGLT2i: Sodium glucose co-transporter 2 inhibitors, IQR: inter quartile range, CI: confidence interval.

[a] Censoring events due to discontinuation of index drugs.

Table 4. Subgroups by pre-index rate of eGFR change (defined as >4% decline in eGFR per year) for the association between the use of SGLT2 inhibitors and renal risks.

Outcome	Subgroups	Group	No. of subjects	No. of events	Total person-year	Median follow-up in year (IQR)	Hazard ratio (95% CI)	P	$P_{interaction}$	1-year CID (95% CI)	2-year CID (95% CI)
ESRD	Rapid decline	DPP4i	8360	530	28815	3.6 (1.6)	1	<0.001	0.008	0.74% (0.49-0.97)	1.62% (1.08-2.06)
		SGLT2i	2090	62	7406	3.7 (1.5)	0.46 (0.35-0.60)				
	Non-rapid decline	DPP4i	16924	284	61532	3.7 (1.5)	1	0.009		0.09% (0.02-0.16)	0.21% (0.05-0.36)
		SGLT2i	4231	47	15583	3.8 (1.5)	0.66 (0.49-0.90)				
ARF	Rapid decline	DPP4i	8360	315	29129	3.6 (1.6)	1	0.002	0.280	0.35% (0.11-0.58)	0.67% (0.21-1.07)
		SGLT2i	2090	51	7418	3.7 (1.5)	0.63 (0.47-0.85)				
	Non-rapid decline	DPP4i	16924	293	61459	3.7 (1.5)	1	0.019		0.11% (0.01-0.21)	0.22% (0.03-0.39)
		SGLT2i	4231	51	15563	3.8 (1.5)	0.70 (0.52-0.94)				
Albuminuria	Rapid decline	DPP4i	6036	115	21050	3.6 (1.5)	1	0.781	0.885	0.03% (-0.19-0.25)	0.05% (-0.37-0.47)
		SGLT2i	1509	28	5357	3.7 (1.4)	0.94 (0.62-1.43)				
	Non-rapid decline	DPP4i	12928	298	46585	3.7 (1.5)	1	0.121		0.11% (-0.05-0.25)	0.22% (-0.10-0.48)
		SGLT2i	3232	59	11790	3.8 (1.5)	0.80 (0.61-1.06)				

ESRD: end stage renal disease, ARF: acute renal failure, DPP4i: dipeptidyl peptidase-4 inhibitor, SGLT2i: Sodium glucose co-transporter 2 inhibitors, IQR: inter quartile range, CI: confidence interval, CID: cumulative incidence differences.

Table 5. Subgroups by pre-index rate of eGFR change (defined as >5 mL/min/1.73m^2 decline in eGFR per year) for the association between the use of SGLT2 inhibitors and renal risks.

Outcome	Subgroups	Group	No. of subjects	No. of events	Total person-year	Median follow-up in year (IQR)	Hazard ratio (95% CI)	P	$P_{interaction}$	1-year CID (95% CI)	2-year CID (95% CI)
ESRD	Rapid decline	DPP4i	6060	385	20962	3.6 (1.6)	1	<0.001	0.078	0.88% (0.53-1.17)	1.64% (0.98-2.12)
		SGLT2i	1515	43	5374	3.7 (1.5)	0.42 (0.31-0.58)				
	Non-rapid decline	DPP4i	19100	441	69038	3.7 (1.5)	1	<0.001		0.16% (0.08-0.25)	0.39% (0.20-0.59)
		SGLT2i	4775	64	17539	3.8 (1.5)	0.59 (0.45-0.76)				
ARF	Rapid decline	DPP4i	6060	232	21180	3.6 (1.5)	1	0.001	0.113	0.43% (0.17-0.68)	0.91% (0.36-1.40)
		SGLT2i	1515	31	5385	3.7 (1.5)	0.53 (0.37-0.78)				
	Non-rapid decline	DPP4i	19100	367	69144	3.7 (1.5)	1	0.010		0.11% (0.03-0.20)	0.25% (0.06-0.43)
		SGLT2i	4775	67	17521	3.8 (1.5)	0.71 (0.54-0.92)				
Albuminuria	Rapid decline	DPP4i	4256	78	14787	3.6 (1.5)	1	0.690	0.611	0.04% (-0.15-0.28)	0.08% (-0.26-0.51)
		SGLT2i	1064	18	3779	3.7 (1.4)	0.90 (0.54-1.51)				
	Non-rapid decline	DPP4i	14676	334	52837	3.7 (1.5)	1	0.168		0.09% (-0.04-0.23)	0.18% (-0.08-0.45)
		SGLT2i	3669	69	13366	3.8 (1.5)	0.83 (0.64-1.08)				

ESRD: end stage renal disease, ARF: acute renal failure, DPP4i: dipeptidyl peptidase-4 inhibitor, SGLT2i: Sodium glucose co-transporter 2 inhibitors, IQR: inter quartile range, CI: confidence interval, CID: cumulative incidence differences.

Table 6. Subgroup analysis including only patients with ongoing or previous use of DPP4is.

Outcomes	Group	No. of subjects	No. of events	Total person-year	Median follow-up in year (IQR)	Hazard ratio (95% CI)	P	1-year CID (95% CI)	2-year CID (95% CI)
ESRD	DPP4i	15372	563	56140	3.8 (1.5)	1	<0.001	0.37% (0.23-0.52)	0.74% (0.47-1.03)
	SGLT2i	3843	77	14284	3.8 (1.4)	0.54 (0.43-0.69)			
ARF	DPP4i	15372	400	56357	3.8 (1.5)	1	<0.001	0.30% (0.17-0.42)	0.55% (0.32-0.77)
	SGLT2i	3843	53	14299	3.8 (1.4)	0.51 (0.39-0.69)			
Albuminuria	DPP4i	11904	293	43361	3.8 (1.5)	1	0.068	0.12% (-0.04-0.25)	0.21% (-0.07-0.45)
	SGLT2i	2976	57	10943	3.8 (1.4)	0.77 (0.58-1.02)			

ESRD: end stage renal disease, ARF: acute renal failure, DPP4i: dipeptidyl peptidase-4 inhibitor, SGLT2i: Sodium glucose co-transporter 2 inhibitors, IQR: inter quartile range, CI: confidence interval, CID: cumulative incidence differences.

Figure legends:

Figure 1. Flow diagram.