

The Renoprotective Effect of SGLT2 Inhibitors in Patients with Type 2 Diabetes and Chronic Kidney Disease: A Real-World Cohort Study

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Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have shown potential in slowing chronic kidney disease (CKD) progression, yet their effectiveness in real-world settings warrants further validation. This retrospective cohort study utilized the Taipei Medical University Clinical Research Database (2008–2020) to assess renal outcomes among 4,202 patients with type 2 diabetes mellitus (T2DM) and CKD treated with SGLT2is (n=448), dipeptidyl peptidase-4 inhibitors (n=3,333), or thiazolidinediones (n=421). Following 1:4 propensity score matching, three renal endpoints were evaluated: sustained estimated glomerular filtration rate (eGFR) reduction $\geq 50\%$, progression to $\text{eGFR} \leq 15 \text{ mL/min/1.73m}^2$, and initiation of kidney replacement therapy. Cox proportional hazards models were applied to estimate risks. SGLT2i use was significantly associated with reduced risks of eGFR decline $\geq 50\%$ (adjusted hazard ratio [aHR] 0.60; 95% CI: 0.40–0.90) and progression to $\text{eGFR} \leq 15 \text{ mL/min/1.73m}^2$ (aHR 0.53; 95% CI: 0.33–0.85) compared with other glucose-lowering agents. Subgroup analyses indicated greater benefits among patients younger than 65 years, males, those with stage 3 CKD, and concurrent statin users. SGLT2is effectively decelerate renal function decline in T2DM with CKD under routine care, underscoring their potential as early therapeutic interventions for optimal renoprotection across clinically relevant subpopulations.

Introduction

Chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (T2DM) poses a significant global health challenge, affecting approximately 40% of individuals with diabetes and significantly contributing to morbidity and mortality worldwide. Recent epidemiological data shows that the prevalence of diabetes-related CKD is on the rise, with projections indicating an increase from 536.6 million affected individuals in 2021 to 783.2 million by 2045.^{1,2} This surge has serious implications for healthcare systems, particularly in regions with limited resources for kidney replacement therapy.

The pathophysiology of CKD in T2DM involves complex interactions between metabolic, hemodynamic, and inflammatory pathways. Chronic hyperglycemia initiates a series of events, including oxidative stress, the formation of advanced glycation end products, and the release of pro-inflammatory cytokines, leading to progressive damage to both glomeruli and tubules.^{3,4} Recent evidence suggests that endothelial dysfunction is a key factor in this process, characterized by impaired nitric oxide production and increased oxidative stress, which contribute to both microvascular and macrovascular complications.⁵

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have emerged as a promising class of therapies that offer benefits to the kidney. These medications work by reducing glucose reabsorption in the proximal tubule, which leads to increased glucose (glucosuria) and sodium (natriuresis) excretion.⁶ While evidence indicates that the benefits of SGLT2is extend beyond glycemic control through multiple mechanisms, including a reduction in intraglomerular pressure, oxidative stress, and inflammation,⁷ the diminishing glucosuric efficacy of SGLT2is with declining glomerular filtration rate⁸⁻¹⁰ has raised questions about their effectiveness in CKD.

To address these knowledge gaps, we conducted a real-world cohort study using comprehensive electronic health records to evaluate the comparative effectiveness of SGLT2is versus other glucose-lowering agents (dipeptidyl peptidase-4 inhibitors and thiazolidinediones) in patients with T2DM and CKD. Our study specifically aimed to assess the impact of SGLT2is on clinically meaningful renal outcomes in routine practice and identify patient characteristics associated with enhanced treatment response. This research addresses a critical need for real-

world evidence to guide clinical decision-making in the growing population of patients with diabetes and kidney disease.

Methods

Study design and study population

This retrospective cohort study utilized the Taipei Medical University Clinical Research Data (TMUCRD) database, which contains over four million patient records from 1998 to 2021 from three affiliated hospitals: Taipei Medical University Hospital, Wanfang Hospital, and Shuang Ho Hospital.¹¹ The study population comprised T2DM patients with CKD who had received at least one prescription for an antidiabetic medication between January 2008 and December 2020.

We excluded patients without precise demographic data (age and sex), those diagnosed with type 2 DM before age 40, those not prescribed SGLT2is, dipeptidyl peptidase-4 inhibitors (DPP4is), or thiazolidinediones (TZDs), those with less than 90 days of follow-up after diagnosis, those without baseline estimated glomerular filtration rate (eGFR) assessments, those who has CKD stage 5 or underwent KRT (Kidney Replacement Therapy) prior to their DM diagnosis, and those diagnosed with polycystic kidney disease or lupus nephritis. The Institutional Review Board at Taipei Medical University approved this study's ethical conduct (TMU-JIRB No.: N202304052). This study use of deidentified secondary data from the TMUCRD database, the requirement for informed consent was waived by the TMU Joint Institutional Review Board in accordance with the Human Subjects Research Act and institutional guidelines. All methods were performed in accordance with the relevant guidelines and regulations, including the principles of the Declaration of Helsinki and the ethical standards of the institutional.

Data extraction and cohort identification

An index date was set corresponding to the first prescription of antidiabetic agents (SGLT2is, DPP4is, or TZDs) following a T2DM diagnosis. We enrolled only patients prescribed antidiabetic agents for over 30 days within a year. The prevalence of T2DM was determined using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 250.0/250.2 and ICD, 10th Revision, CM (ICD-10-CM) code E11 in patients with at least two outpatient or inpatient visits. Established standards define CKD as a persistent eGFR below 60 mL/min/1.73 m² over three months.¹² We used the CKD-EPI creatinine formula to calculate eGFR from creatinine levels.¹³ Baseline eGFR was defined as the closest measurement to the index date, between 180 days before and 30 days after the index date.

We collected patient data on age and sex to establish baseline information. Age was recorded at the time of T2DM. Comorbidities, including dyslipidemia, heart failure (HF), hypertension, liver disease, and anemia along with the Charlson Comorbidity Index (CCI), were recorded one year before the index date. Additionally, we documented co-medications prescribed for over 30 days within the year preceding the index date. Furthermore, laboratory tests for glycated hemoglobin (HbA1c) and total cholesterol were conducted six months before the index date. Operational definitions of patient characteristics are available in Supplementary Table S1.

Follow-up and study outcomes

We divided all the enrolled patients into two main groups: those who were initially treated with SGLT2is (SGLT2is group) as the intervention group and those who were not (non-SGLT2is group) as the comparison group. In

addition, we also further categorized the non-SGLT2is group into DPP4is and TZDs subgroups. Follow-up for eligible patients continued until the patient's death, loss of follow-up, or December 31, 2021.

The primary endpoints included the decreasing of renal function, marked by a sustained eGFR reduction of $\geq 50\%$ from baseline, a decline in eGFR to ≤ 15 mL/min/1.73 m², and the initiation of any KRT after the index date (Supplementary Table S2). As defined in the study, KRT encompasses hemodialysis, peritoneal dialysis, and kidney transplantation, identified using specific order codes in the National Health Insurance Research Database (NHIRD).

Confounding mitigation and statistical analysis

We conducted a 1:4 propensity score matching (PSM) based on age, sex, and year of antidiabetic agents initiation (year of index date). This involved comparing the SGLT2is group with the non-SGLT2is group, as well as the SGLT2is group with the DPP4is and TZDs groups. The nearest neighbor matching algorithm was used to ensure equivalent pairings with a caliper of 0.1. Descriptive statistics were used to describe baseline patient characteristics. Continuous variables were reported as mean $\pm$ standard deviation (SD), while categorical variables were presented as frequencies and percentages (%). Standardized differences were calculated post-matching to evaluate covariate balance.

Kaplan-Meier survival curves were conducted to estimate the cumulative survival probabilities representing the time to the predefined study outcomes for each comparison treatment group over specified time intervals. The hazard ratio (HR) and the 95% confidence interval (CI) for the predefined study outcomes were conducted using Cox proportional hazards regression analysis. Adjusted HR (aHR) was constructed considering age, year of index date, CCI, eGFR, and HbA1c. Furthermore, we conducted subgroup comparisons between SGLT2is and non-SGLT2is using adjusted Cox hazards regression and visualized with forest plots. Subgroup analyses were based on demographics, comorbidities, and comedications. We only included subgroup data with at least a 15% representation to minimize selection bias.

All statistical tests were considered statistically significant at a P-value < 0.05 . Kaplan-Meier survival curves were plotted to visually depict the temporal progression of study outcomes across various treatment groups (Supplementary Figures S1-S3). All statistical computations and analyses were performed using R software version 4.2.3.

Fig. 1

Results

Participants characteristics

This study included 4,202 patients with T2DM and CKD who were prescribed SGLT2is (n=448), DPP4is (n=3,333), or TZDs (n=421). After conducting 1:4 PSM, we established three comparative cohorts: SGLT2is vs. DPP4is (448 vs. 1,426 patients), SGLT2is vs. TZDs (142 vs. 238 patients), and SGLT2is vs. combined non-SGLT2is (448 vs. 1,464 patients). The standardized differences for most baseline characteristics were less than 0.2, indicating well-balanced cohorts. Table 1 presents the baseline characteristics of the study cohorts after PSM.

Tbl. 1

The mean age was comparable across all comparisons, with SGLT2is users being slightly younger (69.5 ± 10.1 years) compared to DPP4is (71.7 ± 11.5 years), TZDs (71.2 ± 10.0 years), and overall non-SGLT2is (71.4 ± 11.4 years). The majority of patients were male (51.4-56.9%) across all groups. The year of index date in SGLT2is versus TZDs comparison demonstrated the most pronounced temporal disparity ($SD=0.548$). This substantial imbalance was characterized by inverse prescribing patterns: SGLT2is use was predominantly recent (2017-2020: 52.1%; 2012-2016: 40.8%; 2008-2011: 7.0%), while TZDs prescriptions were more heavily weighted toward earlier periods (2017-2020: 28.6%; 2012-2016: 52.1%; 2008-2011: 19.3%).

Regarding comorbidities, hypertension was the most prevalent condition across all groups (50.0-59.7%), followed by dyslipidemia (35.7-46.5%). Heart failure was present in approximately one-quarter of patients across all cohorts (21.0-25.0%). The mean CCI was lower in SGLT2is users compared to DPP4is (2.79 ± 1.48 vs. 3.58 ± 1.80 , $SD=0.480$) and overall non-SGLT2is (2.79 ± 1.48 vs. 3.49 ± 1.82 , $SD=0.420$), but similar to TZDs (2.91 ± 1.57 vs. 2.95 ± 1.50 , $SD=0.030$). Laboratory parameters revealed notably higher baseline eGFR levels in SGLT2is users compared to non-SGLT2is (44.7 ± 11.2 vs. 38.8 ± 12.0 mL/min/ $1.73m^2$, DPP4is (45.2 ± 10.7 vs. 39.3 ± 11.9 mL/min/ $1.73m^2$), and TZDs (45.2 ± 10.7 vs. 39.3 ± 11.9). Mean HbA1c levels were higher in SGLT2is users compared to DPP4is ($7.96 \pm 1.81\%$ vs. $7.46 \pm 1.57\%$, $SD=0.298$) and overall non-SGLT2is ($8.0 \pm 1.8\%$ vs. $7.5 \pm 1.6\%$, $SD=0.268$), although there was substantial missing data. Regarding concomitant medications, renin-angiotensin therapy was the most commonly prescribed medication across all groups (26.9-38.0%), followed by statins (20.2-31.2%) and antithrombotic agents (21.4-28.9%).

Renal deterioration outcomes

During the follow-up period, we analyzed three predefined indices of decreasing renal function progression: eGFR decline $\geq 50\%$, progression to eGFR <15 mL/min/ $1.73m^2$, and initiation of KRT. The SGLT2is groups demonstrated lower incidence rates across all endpoints compared to other treatment groups. The Kaplan-Meier survival analyses showed consistent separation patterns across all predefined study outcomes, demonstrating superior preservation of renal function in SGLT2is groups (log-rank $P < .01$) (Supplementary Figure S1-S3).

Tbl. 2

In the analysis of eGFR decline $\geq 50\%$, the SGLT2is group showed significantly lower risk compared to non-SGLT2is (aHR 0.63; 95% CI 0.42-0.94; $P = .02$), DPP4is (aHR 0.59; 95% CI 0.40-0.89; $P = .01$). The comparison with TZDs group showed a similar protective trend, though not reaching statistical significance (aHR 0.47, 95% CI 0.21-1.06, $P = .06$). For progression to CKD stage 5 (eGFR <15 mL/min/ $1.73m^2$), the SGLT2is group demonstrated significantly reduced risk compared to non-SGLT2is (aHR 0.55; 95% CI 0.34-0.88; $P = .01$) and DPP4is (aHR 0.53; 95% CI 0.33-0.86; $P = .01$). Although a similar trend was observed in comparison with TZDs (aHR 0.47; 95% CI 0.18-1.24), this difference did not reach statistical significance ($P = .13$).

Regarding kidney replacement therapy initiation, while unadjusted analyses showed significant risk reductions with SGLT2is treatment versus non-SGLT2is ($P < .05$), these associations were substantially attenuated after adjustment for confounding factors. The aHRs were 0.99 (95% CI 0.52-1.88; $P = .98$) versus non-SGLT2is, 0.91 (95% CI 0.48-1.73; $P = .78$) versus DPP4is, and 1.28 (95% CI 0.38-4.30; $P = .68$) versus TZDs.

Subgroup analysis

The forest plot illustrates the aHRs for eGFR decline $\geq 50\%$ and progression to eGFR <15 mL/min/ $1.73m^2$, revealing differential treatment effects of SGLT2is across various patient subgroups. Age-stratified analysis demonstrated

that younger patients (<65 years) derived more pronounced renoprotective benefits from SGLT2i therapy compared to older counterparts (≥65 years), with significantly lower risks for both eGFR decline ≥50% (aHR 0.51, 95% CI 0.26-1.00) and progression to eGFR <15 mL/min/1.73m² (aHR 0.25, 95% CI 0.10-0.63). Gender-specific analysis revealed that male participants experienced particularly robust treatment effects from SGLT2is, demonstrating substantially reduced risks for both eGFR decline ≥50% (aHR 0.38, 95% CI 0.20-0.73) and progression to eGFR <15 mL/min/1.73m² (aHR 0.41, 95% CI 0.19-0.89) compared to their female counterparts.

The protective effect of SGLT2is was also evident across various comorbid conditions. Patients with stage 3 CKD on SGLT2is exhibited lower aHRs of 0.57 (95% CI 0.34–0.95) for a ≥50% decline in eGFR and 0.40 (95% CI 0.17–0.92) for eGFR <15 mL/min/1.73m² compared to stage 4 CKD with aHRs of 0.83 (95% CI 0.43-1.64) and 0.73 (95% CI 0.40-1.32). Notably, concomitant statin therapy appeared to exhibit greater risk reductions of both eGFR decline ≥50% (HR 0.45, 95% CI 0.23-0.88) and progression to eGFR <15 mL/min/1.73m² (HR 0.31, 95% CI 0.13-0.74) compared to without statin, suggesting potential synergistic renoprotective effects between these therapeutic class with SGLT2is.

Fig. 2

Discussion

This study showed the effectiveness of SGLT2is in mitigating renal deterioration, including slowing renal function decline to reducing the incidence of end-stage kidney disease (ESKD) from real-world practice, especially when compared to DPP4is and non-SGLT2is. Our findings not only corroborate existing evidence but also extend current knowledge by identifying important subgroup-specific treatment effects of SGLT2is, notably more pronounced renoprotective effects observed in younger patients (<65 years), male, and on treatment with statin.

The evolution of evidence supporting SGLT2is use in kidney disease has been remarkable from the unexpected renal benefits observed in the EMPA-REG OUTCOME trial that focused on the effects of empagliflozin in patients with T2DM at high risk for cardiovascular events. Notably, the study revealed that the incidence of acute kidney failure was lower in the empagliflozin group compared to the placebo group.¹⁴ This unexpected finding prompted the CREDENCE research project, which targeted a diabetic population at high risk for kidney failure, and the results showed that the canagliflozin group experienced significantly lower rates of ESKD, doubling of serum creatinine, or renal or cardiovascular death compared to the placebo group.¹⁵ Subsequently, the DAPA-CKD Clinical Trials further investigated the renal protective effects of dapagliflozin in both diabetic and non-diabetic populations. Dapagliflozin was found to significantly reduce the risk of death from renal or cardiovascular causes, as well as a sustained decline in eGFR of at least 50%.¹⁶ Recently, the UK Kidney Association updated its guidelines in October 2023, offering comprehensive clinical practices for SGLT2is in type 2 DM patients with kidney disease. These guidelines detail the application of these inhibitors across different patient groups and provide recommendations for their implementation. It is noted that an eGFR of 20 mL/min/1.73m² is effective in individuals with albuminuric CKD across various populations, including those with and without type 2 DM.¹⁷ While our findings align with previous meta-analyses,¹⁸⁻²⁰ these findings differ from post-hoc analyses of randomized controlled trials (RCTs),^{14-16,21-23} which typically exclude patients with multiple comorbidities and have strict protocols that limit their applicability in real-world settings. RCTs adhere to a strict protocol to eliminate selection bias and ensure the treatment administered is the only difference between groups.

The pronounced efficacy of SGLT2is in younger populations observed in our study likely reflects multiple mechanisms. Enhanced urinary glucose excretion in younger patients may more effectively reduce hyperglycemia-related inflammation, providing superior kidney protection,^{24,25} explaining why they are more effective in stage 3 CKD than stage 4. Conversely, older patients, particularly those aged 65 and above, may reflect the impact of multiple comorbidities and polypharmacy on treatment effectiveness.²⁶⁻²⁸ The observed sex disparity in treatment response, favoring males, aligns with emerging evidence from other real-world cohorts that is in line with another real-world cohort study.²⁹ This finding may be explained by sex-specific differences in endothelial dysfunction and platelet response, where endothelial dysfunction in T2DM leads to inadequate release of nitric oxide (NO) and prostacyclin, potent platelet inhibitors.^{30,31} Recent experimental evidence suggests that the antithrombotic effects of canagliflozin and dapagliflozin, expressed as a decreased platelet activation index and an increased PECAM-1/thrombus ratio, more pronounced in male mice,³² potentially contribute to enhanced renoprotection. Furthermore, the stronger renoprotective effects of SGLT2is in males may also be influenced by differences in treatment duration and adherence rates, particularly because side effects such as urinary tract infections are more prevalent in women.^{33,34}

Our most clinically relevant finding is the enhanced efficacy of SGLT2is in patients receiving statin therapy. This synergistic effect likely reflects complementary mechanisms in reducing major vascular events in a wide range of individuals, including preventing or delaying progressive loss of kidney function.^{35,36} In addition to the strong cholesterol-lowering effect, statins also have various effects, including platelet inhibition, vasodilation, inflammation inhibition, and improvement of endothelial function,³⁷⁻³⁹ which contribute to the improvement of microcirculation function with SGLT2is. According to American College of Cardiology/American Heart Association (ACC/AHA),⁴⁰ all patients with T2DM and CKD to statin initiation may be reasonable. Patients with diabetes having CKD are statin eligible regardless of the estimated 10-year risk.⁴¹ Based on these insights, nephrologists should recognize the importance of early administration of SGLT2is in younger T2DM patients with CKD and add statin as pleiotropic medication. Further research is needed to identify sex that may compromise the renal protective properties of SGLT2is.

Conclusion

The strengths of our study include various outcome of renal disease from renal function decline to kidney failure incidence. We performed head-to-head analysis SGLT2is with DPP4is and TZDs directly in type 2 DM with CKD. We also analyzed subgroups to identify which factors most significantly impact the efficacy of SGLT2is. However, several limitations warrant mention. First, we did not monitor blood glucose and blood pressure post-index date, which can significantly influence study outcomes. Second, our study groups were defined based on administering antidiabetic agents for at least 30 days within a year, yet we did not assess treatment adherence or dosage, which could affect the results. Third, our data were sourced from three hospitals affiliated with Taipei Medical University, potentially limiting the generalizability of our findings to other populations or healthcare systems, particularly those in different geographical regions or with different healthcare infrastructures.

Abbreviations

ICD-9-CM= International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM= International Classification of Diseases, 10th Revision, Clinical Modification; T2DM= Type 2 Diabetes Mellitus; NSAIDS=

nonsteroidal anti-inflammatory drugs; eGFR= estimated glomerular filtration rate; SGLT2is= sodium-glucose cotransporter-2 inhibitors; DPP4is= dipeptidyl peptidase-4 inhibitors; TZDs= thiazolidinediones.

Declarations

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Competing interests

The author(s) declare no competing interests.

Author contributions

C.H.S. and W.C.K. conceptualized the study, performed the formal analysis, and drafted the original manuscript. C.H.S. and P.T.P. curated and managed the data. M.C.L. and C.T.L. developed the methodology and administered the project. N.P.A., P.T.P., and M.S.M. developed and implemented the software components. M.H.H. and H.H.C. validated the data and analytical results. M.S.M. and C.H.S. prepared the visualizations and figures. J.A.L., C.W.C., and C.W.H. provided essential resources and technical support. J.C.H. and C.C.S. secured funding, supervised the research activities, and contributed to the review and editing of the manuscript. All authors reviewed and approved the final manuscript.

Data availability

The datasets analysed during the current study are available from the corresponding author.

References

1. Ogurtsova, K. *et al.* IDF diabetes Atlas: Global estimates of undiagnosed diabetes in adults for 2021. *Diabetes Research and Clinical Practice* **183**, 109118 (2022). <https://doi.org/10.1016/j.diabres.2021.109118>
2. de Boer, I. H. *et al.* Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* **45**, 3075-3090 (2022). <https://doi.org/10.2337/dci22-0027>
3. Akhtar, M., Taha, N. M., Nauman, A., Mujeeb, I. B. & Al-Nabet, A. D. M. H. Diabetic Kidney Disease: Past and Present. *Advances in Anatomic Pathology* **27**, 87-97 (2020). <https://doi.org/10.1097/pap.0000000000000257>

4. Anders, H.-J., Huber, T. B., Isermann, B. & Schiffer, M. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nature Reviews Nephrology* **14**, 361-377 (2018). <https://doi.org/10.1038/s41581-018-0001-y>
5. Strain, W. D. & Paldanius, P. M. Diabetes, cardiovascular disease and the microcirculation. *Cardiovasc Diabetol* **17**, 57 (2018). <https://doi.org/10.1186/s12933-018-0703-2>
6. Liu, Z. et al. Impact of sodium glucose cotransporter 2 (SGLT2) inhibitors on atherosclerosis: from pharmacology to pre-clinical and clinical therapeutics. *Theranostics* **11**, 4502-4515 (2021). <https://doi.org/10.7150/thno.54498>
7. Bailey, C. J., Day, C. & Bellary, S. Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease. *Curr Diab Rep* **22**, 39-52 (2022). <https://doi.org/10.1007/s11892-021-01442-z>
8. Sugiyama, S. et al. Renoprotective Effects of Additional SGLT2 inhibitor Therapy in Patients With Type 2 Diabetes Mellitus and Chronic Kidney Disease Stages 3b-4: A Real World Report From A Japanese Specialized Diabetes Care Center. *J Clin Med Res* **11**, 267-274 (2019). <https://doi.org/10.14740/jocmr3761>
9. Layton, A. T. & Vallon, V. SGLT2 inhibition in a kidney with reduced nephron number: modeling and analysis of solute transport and metabolism. *Am J Physiol Renal Physiol* **314**, F969-f984 (2018). <https://doi.org/10.1152/ajprenal.00551.2017>
10. Scheen, A. J. Effects of glucose-lowering agents on surrogate endpoints and hard clinical renal outcomes in patients with type 2 diabetes. *Diabetes & Metabolism* **45**, 110-121 (2019). <https://doi.org/https://doi.org/10.1016/j.diabet.2018.10.003>
11. Chen, Y.-L. et al. Machine learning-based prediction of medication refill adherence among first-time insulin users with type 2 diabetes. *Diabetes Research and Clinical Practice* **207**, 111033 (2024). <https://doi.org/https://doi.org/10.1016/j.diabres.2023.111033>
12. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* **102**, S1-s127 (2022). <https://doi.org/10.1016/j.kint.2022.06.008>
13. Miller, W. G. et al. National Kidney Foundation Laboratory Engagement Working Group Recommendations for Implementing the CKD-EPI 2021 Race-Free Equations for Estimated Glomerular Filtration Rate: Practical Guidance for Clinical Laboratories. *Clin Chem* **68**, 511-520 (2022). <https://doi.org/10.1093/clinchem/hvab278>
14. Zinman, B. et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine* **373**, 2117-2128 (2015). <https://doi.org/10.1056/NEJMoa1504720>
15. Perkovic, V. et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* **380**, 2295-2306 (2019). <https://doi.org/10.1056/NEJMoa1811744>
16. Heerspink, H. J. L. et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* **383**, 1436-1446 (2020). <https://doi.org/10.1056/NEJMoa2024816>
17. Roddick, A. J. et al. UK Kidney Association Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease 2023 UPDATE. *BMC Nephrology* **24**, 310 (2023). <https://doi.org/10.1186/s12882-023-03339-3>
18. McGuire, D. K. et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol* **6**, 148-158 (2021). <https://doi.org/10.1001/jamacardio.2020.4511>
19. Toyama, T. et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. *Diabetes Obes Metab* **21**, 1237-1250 (2019). <https://doi.org/10.1111/dom.13648>

20. Neuen, B. L. et al. Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials. *Circulation* **145**, 1460-1470 (2022). <https://doi.org/10.1161/CIRCULATIONAHA.121.057736>
21. Chertow, G. M. et al. Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease. *J Am Soc Nephrol* **32**, 2352-2361 (2021). <https://doi.org/10.1681/ASN.2021020167>
22. Heerspink, H. J. L. et al. A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function. *Kidney Int* **101**, 174-184 (2022). <https://doi.org/10.1016/j.kint.2021.09.005>
23. The, E.-K. C. G. et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* **388**, 117-127 (2023). <https://doi.org/10.1056/NEJMoa2204233>
24. Yao, Y.-P. et al. Utilization of sodium-glucose cotransporter 2 inhibitors on dry eye disease severity in patients with type 2 diabetes mellitus. *International Journal of Medical Sciences* **20**, 1705-1710 (2023). <https://doi.org/10.7150/ijms.88720>
25. Nakamura, Y. et al. Better response to the SGLT2 inhibitor dapagliflozin in young adults with type 2 diabetes. *Expert Opin Pharmacother* **16**, 2553-2559 (2015). <https://doi.org/10.1517/14656566.2015.1101450>
26. van Poelgeest, E. P. et al. Diuretics, SGLT2 inhibitors and falls in older heart failure patients: to prescribe or to deprescribe? A clinical review. *European Geriatric Medicine* **14**, 659-674 (2023). <https://doi.org/10.1007/s41999-023-00752-7>
27. Rong, X. et al. Risk of hypovolemia associated with sodium-glucose cotransporter-2 inhibitors treatment: A meta-analysis of randomized controlled trials. *Front Cardiovasc Med* **9**, 973129 (2022). <https://doi.org/10.3389/fcvm.2022.973129>
28. Kambara, T. et al. Use of sodium-glucose cotransporter 2 inhibitors in older patients with type 2 diabetes mellitus. *Geriatr Gerontol Int* **18**, 108-114 (2018). <https://doi.org/10.1111/ggi.13149>
29. Siao, W.-Z., Lin, T.-K., Huang, J.-Y., Tsai, C.-F. & Jong, G.-P. The association between sodium-glucose cotransporter 2 inhibitors and incident dementia: A nationwide population-based longitudinal cohort study. *Diabetes and Vascular Disease Research* **19**, 14791641221098168 (2022). <https://doi.org/10.1177/14791641221098168>
30. Mahmoodian, R., Salimian, M., Hamidpour, M., Khadem-Maboudi, A. A. & Gharehbaghian, A. The effect of mild agonist stimulation on the platelet reactivity in patients with type 2 diabetes mellitus. *BMC Endocrine Disorders* **19**, 62 (2019). <https://doi.org/10.1186/s12902-019-0391-2>
31. Baaten, C. et al. Platelet Abnormalities in CKD and Their Implications for Antiplatelet Therapy. *Clin J Am Soc Nephrol* **17**, 155-170 (2022). <https://doi.org/10.2215/cjn.04100321>
32. Marcińczyk, N., Misztal, T., Chabielska, E. & Gromotowicz-Popławska, A. Sex-dependent effects of canagliflozin and dapagliflozin on hemostasis in normoglycemic and hyperglycemic mice. *Scientific Reports* **13**, 932 (2023). <https://doi.org/10.1038/s41598-023-28225-8>
33. Khan, S. et al. Frequency of Urinary Tract Infections in Type 2 Diabetic Patients Taking Dapagliflozin. *Cureus* **14**, e21720 (2022). <https://doi.org/10.7759/cureus.21720>
34. Limenta, M., Ho, C. S. C., Poh, J. W. W., Goh, S. Y. & Toh, D. S. L. Adverse Drug Reaction Profile of SGLT2 Inhibitor-Associated Diabetic Ketosis/Ketoacidosis in Singapore and their Precipitating Factors. *Clin Drug Investig* **39**, 683-690 (2019). <https://doi.org/10.1007/s40261-019-00794-5>
35. Jairoun, A. A., Ping, C. C. & Ibrahim, B. Statin therapy for patients with diabetic nephropathy: balance between safety and efficacy of statin treatment for patients with impaired kidney function. *Eur Rev Med Pharmacol Sci*

- 27**, 10595-10604 (2023). https://doi.org/10.26355/eurrev_202311_34339
36. Koya, D. & Campese, V. M. Statin use in patients with diabetes and kidney disease: the Japanese experience. *J Atheroscler Thromb* **20**, 407-424 (2013). <https://doi.org/10.5551/jat.16261>
37. Huang, B., Han, X., Pan, Y. & Chen, D. A systematic review and meta-analysis of the effect of high-intensity statin on coronary microvascular dysfunction. *BMC Cardiovasc Disord* **23**, 370 (2023). <https://doi.org/10.1186/s12872-023-03402-9>
38. Ray, K. K. & Cannon, C. P. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol* **46**, 1425-1433 (2005). <https://doi.org/10.1016/j.jacc.2005.05.086>
39. Wassmann, S. et al. Rapid effect of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition on coronary endothelial function. *Circ Res* **93**, e98-103 (2003). <https://doi.org/10.1161/01.Res.0000099503.13312.7b>
40. Grundy, S. M. et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **139**, e1082-e1143 (2019). <https://doi.org/doi:10.1161/CIR.0000000000000625>
41. Vega, G. L., Wang, J. & Grundy, S. M. Chronic kidney disease and statin eligibility. *J Clin Lipidol* **15**, 173-180 (2021). <https://doi.org/10.1016/j.jacl.2020.10.004>

Tables

Table 1. Patients’ baseline characteristics after PSM.

	SGLT2is vs. DPP4is			SGLT2is vs. TZDs			SGLT2is vs. non-SGLT2is		
	SGLT2i	DPP4i	SD	SGLT2i	TZDs	SD	SGLT2i	non-SGLT2is	SD
	(n=448)	(n=1,426)		(n=142)	(n=238)		(n=448)	(n=1,464)	
Age, years									
Mean (SD)	69.5 (10.1)	71.7 (11.5)	0.197	69.4 (10.3)	71.2 (10.0)	0.176	69.5 (10.1)	71.4 (11.4)	0.178
Year of index date									
2008-2011	10 (2.2%)	30 (2.1%)	0.16	10 (7.0%)	46 (19.3%)	0.548	10 (2.2%)	34 (2.3%)	0.142
2012-2016	90 (20.1%)	383 (26.9%)		58 (40.8%)	124 (52.1%)		90 (20.1%)	381 (26.0%)	
2017-2020	348 (77.7%)	1013 (71.0%)		74 (52.1%)	68 (28.6%)		348 (77.7%)	1049 (71.7%)	
Sex, n (%)									
Male	255 (56.9%)	786 (55.1%)	0.036	73 (51.4%)	135 (56.7%)	0.107	255 (56.9%)	806 (55.1%)	0.038
Female	193 (43.1%)	640 (44.9%)		69 (48.6%)	103 (43.3%)		193 (43.1%)	658 (44.9%)	
Comorbidities, n (%)									
Dyslipidemia	185 (41.3%)	663 (46.5%)	0.105	62 (43.7%)	85 (35.7%)	0.163	185 (41.3%)	658 (44.9%)	0.074
Hypertension	230 (51.3%)	852 (59.7%)	0.170	78 (54.9%)	119 (50.0%)	0.099	230 (51.3%)	858 (58.6%)	0.146
Heart failure	112 (25.0%)	335 (23.5%)	0.035	35 (24.6%)	50 (21.0%)	0.087	112 (25.0%)	342 (23.4%)	0.038
Liver disease	21 (4.7%)	74 (5.2%)	0.023	7 (4.9%)	4 (1.7%)	0.182	21 (4.7%)	72 (4.9%)	0.011
Anemias	18 (4.0%)	65 (4.6%)	0.027	5 (3.5%)	7 (2.9%)	0.033	18 (4.0%)	71 (4.8%)	0.04
Charlson Comorbidity Index									
Mean (SD)	2.79 (1.48)	3.58 (1.80)	0.480	2.91 (1.57)	2.95 (1.50)	0.03	2.79 (1.48)	3.49 (1.82)	0.42
Co-medications, n (%)									
Antithrombotic	122 (27.2%)	397 (27.8%)	0.014	41 (28.9%)	51 (21.4%)	0.172	122 (27.2%)	385 (26.3%)	0.021
Anti-anemic agents	23 (5.1%)	128 (9.0%)	0.150	7 (4.9%)	12 (5.0%)	0.005	23 (5.1%)	122 (8.3%)	0.128

Cardiac stimulants	9 (2.0%)	16 (1.1%)	0.071	2 (1.4%)	0 (0%)	0.169	9 (2.0%)	19 (1.3%)	0.056
Diuretics	68 (15.2%)	240 (16.8%)	0.045	21 (14.8%)	32 (13.4%)	0.039	68 (15.2%)	249 (17.0%)	0.05
Beta blocker	99 (22.1%)	339 (23.8%)	0.040	33 (23.2%)	33 (13.9%)	0.243	99 (22.1%)	338 (23.1%)	0.024
Calcium channel blockers	85 (19.0%)	306 (21.5%)	0.062	36 (25.4%)	41 (17.2%)	0.199	85 (19.0%)	310 (21.2%)	0.055
Renin-angiotensin therapy	156 (34.8%)	517 (36.3%)	0.030	54 (38.0%)	64 (26.9%)	0.24	156 (34.8%)	523 (35.7%)	0.019
Statin	124 (27.7%)	444 (31.2%)	0.076	39 (27.5%)	48 (20.2%)	0.172	124 (27.7%)	438 (29.9%)	0.049
Lipid modifying agents	50 (11.2%)	158 (11.1%)	0.003	17 (12.0%)	20 (8.4%)	0.118	50 (11.2%)	161 (11.0%)	0.005
NSAIDS	5 (1.1%)	20 (1.4%)	0.026	1 (0.7%)	3 (1.3%)	0.056	5 (1.1%)	19 (1.3%)	0.017
Glucocorticoids	1 (0.2%)	21 (1.5%)	0.137	1 (0.7%)	5 (2.1%)	0.119	1 (0.2%)	22 (1.5%)	0.139
Antigout	49 (10.9%)	178 (12.5%)	0.048	16 (11.3%)	18 (7.6%)	0.127	49 (10.9%)	173 (11.8%)	0.028
Laboratory test, mean (SD)									
eGFR, mL/min/1.73m ²	44.7 (11.2)	38.8 (12.0)	0.511	45.2 (10.7)	39.3 (11.9)	0.527	44.7 (11.2)	38.8 (11.9)	0.512
HbA1c, %	7.96 (1.81)	7.46 (1.57)	0.298	7.68 (1.19)	7.97 (1.83)	0.194	8.0 (1.8)	7.5 (1.6)	0.268
Missing, n (%)	233 (52.0%)	286 (20.1%)		74 (52.1%)	124 (52.1%)		233 (52.0%)	330 (22.5%)	
Total Cholesterol, mg/dL	174 (45.9)	178 (53.8)	0.078	180 (43.5)	190 (45.6)	0.215	174 (45.9)	178 (52.5)	0.088
Missing, n (%)	291 (65.0%)	605 (42.4%)		89 (62.7%)	145 (60.9%)		291 (65.0%)	640 (43.7%)	

CCI, Charlson Comorbidity Index; HbA1c, Hemoglobin A1c; NSAIDS, nonsteroidal anti-inflammatory drugs; SD, Standardized Difference.

Table 2. Cox proportional hazards regression analysis for predefined indices of renal function progression.

	Event	Participant-years of follow up	Incidence rate (Events/100 participant-years)	Crude model		Adjusted model [¶]	
				HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
eGFR decline ≥50%							
SGLT2is	59	1355.19	13.17				
vs. non-SGLT2is	338	3931.66	23.13	0.51 (0.39, 0.67)	<0.001	0.63 (0.42, 0.94)	0.023
vs. DPP4is	331	3786.68	23.23	0.50 (0.38, 0.67)	<0.001	0.59 (0.40, 0.89)	0.011
SGLT2is	23	579.08	16.20				
vs. TZDs	82	904.39	21.64	0.44 (0.28, 0.70)	<0.001	0.47 (0.21, 1.06)	0.068
eGFR <15 mL/min/1.73m ²							
SGLT2is	37	1413.47	8.26				
vs. non-SGLT2is	311	3958.02	21.29	0.35 (0.25, 0.49)	<0.001	0.55 (0.34, 0.88)	0.014
vs. DPP4is	303	3808.74	21.26	0.35 (0.25, 0.49)	<0.001	0.53 (0.33, 0.86)	0.010
SGLT2is	12	628.77	8.45				
vs. TZDs	71	944.61	18.73	0.26 (0.14, 0.48)	<0.001	0.47 (0.18, 1.24)	0.126
Kidney replacement therapy							
SGLT2is	19	1460.34	4.24				
vs. non-SGLT2is	120	4388.69	8.21	0.46 (0.28, 0.74)	0.002	0.99 (0.52, 1.88)	0.975
vs. DPP4is	118	4223.12	8.28	0.46 (0.28, 0.75)	0.002	0.91 (0.48, 1.73)	0.779
SGLT2is	8	632.95	5.63				
vs. TZDs	33	1091.53	8.71	0.43 (0.20, 0.94)	0.033	1.28 (0.38, 4.30)	0.685

[¶] Adjusted for age, year of index date, CCI, eGFR, and HbA1c.

DPP4is, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; SGLT2is, sodium-glucose transporter-2 inhibitors; TZDs, thiazolidinediones.

Figures

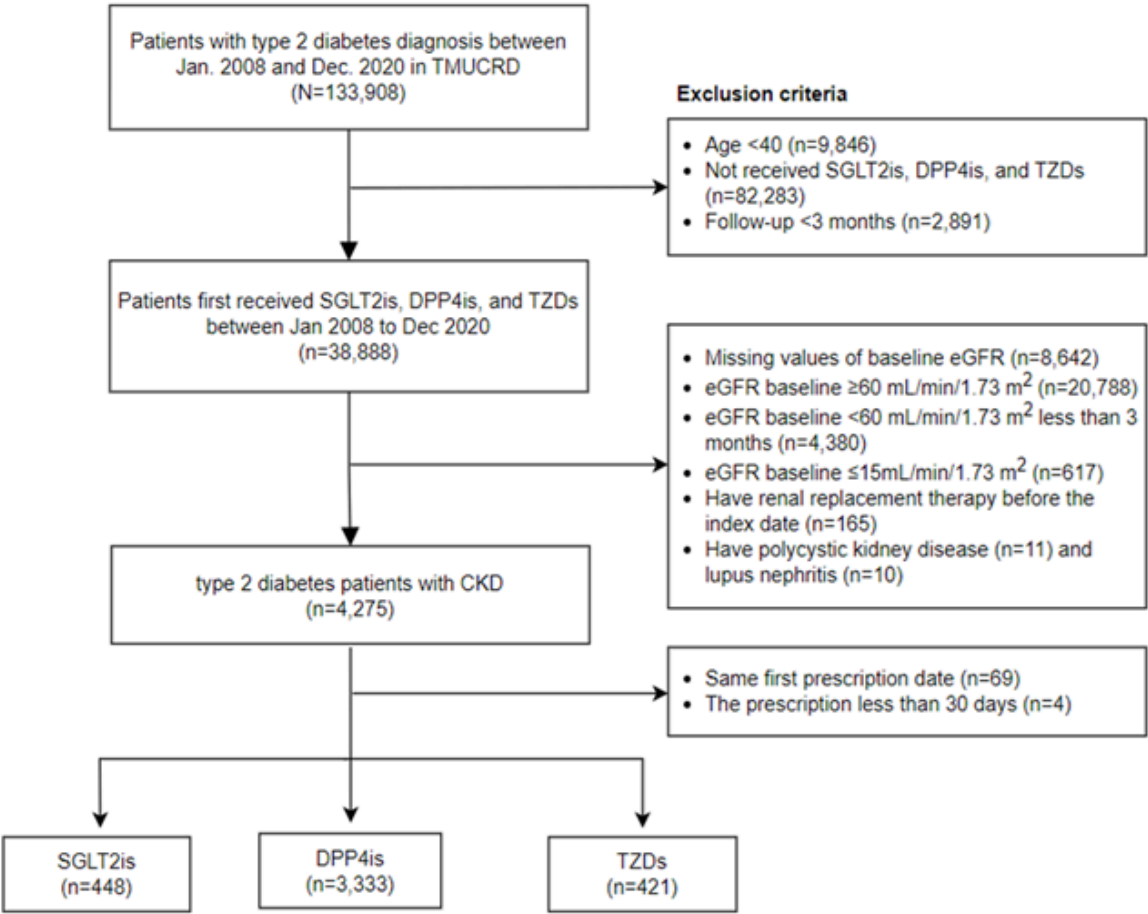


Figure 1

Flowchart of study cohort selection. CKD, chronic kidney disease; DPP4is, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; SGLT2is, sodium-glucose transporter-2 inhibitors; TZDs, thiazolidinediones

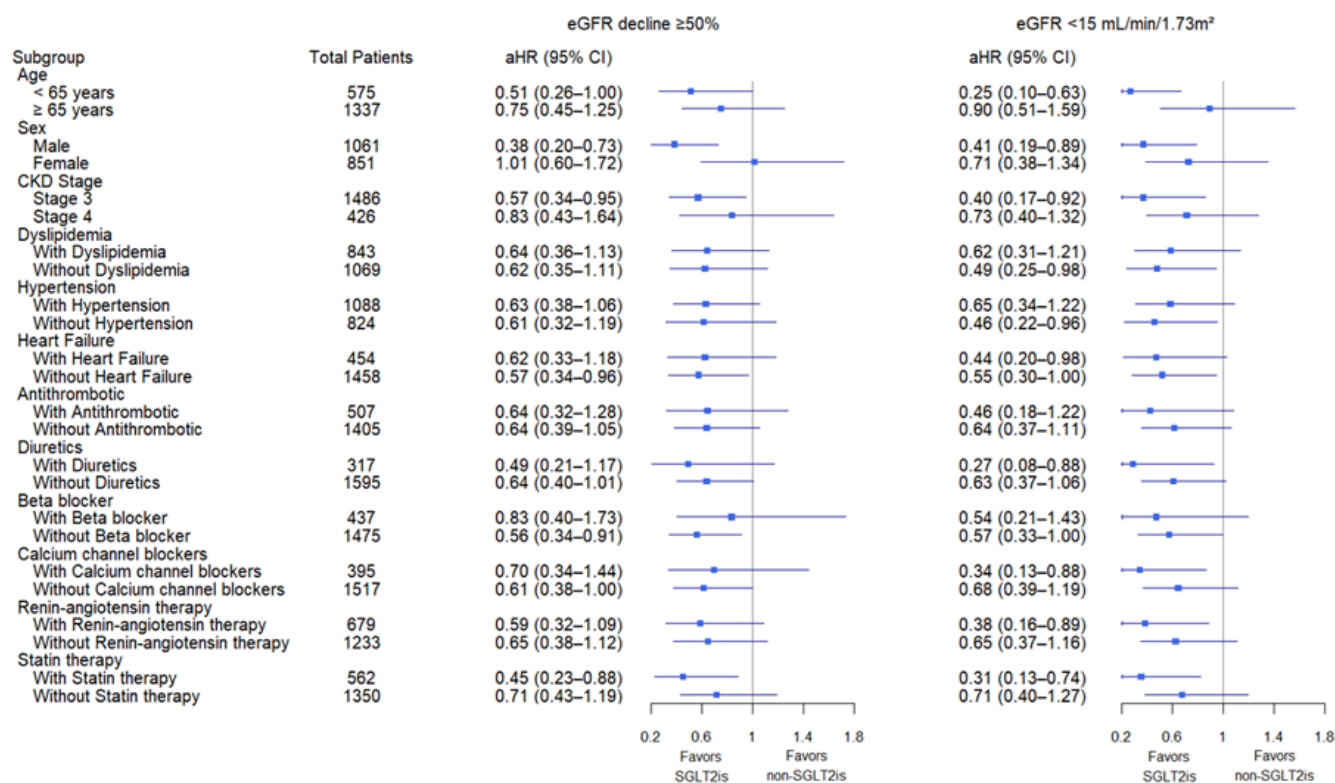


Figure 2

Forest plot of Adjusted Hazard Ratio for Subgroup. aHR, adjusted Hazard Ratio; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy

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