AJN
American Journal
of Nephrology

Novel Research Findings

Am J Nephrol
DOI: 10.1159/000542132

Received: August 25, 2024
Accepted: October 15, 2024
Published online: October 21, 2024

Comprehensive Evaluation of the Cardiovascular Protective Effects of Sodium-Glucose Cotransporter 2 Inhibitors in Patients with Advanced Chronic Kidney Disease: A Real-World Evidence

Chih-Chung Shiao[a] Ching-Wen Chiu[b, c] Yu-Ming Chang[a] Ming-Che Liu[d, e] Phung-Anh Nguyen[f, g, h, i] Thanh-Phuc Phan[j] Chia-Te Liao[k, l, m] Chih-Wei Huang[n, o] Christianus Heru Setiawan[p, q] Hui-Hsin Cheng[e] Min-Huei Hsu[i, r] Jason C. Hsu[f, g, h, j]

[a]Division of Nephrology, Department of Internal Medicine, Camillian Saint Mary's Hospital Luodong, Yilan, Taiwan; [b]School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [c]Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan; [d]Department of Urology, Taipei Medical University Hospital, Taipei, Taiwan; [e]Office of Human Research, Taipei Medical University, Taipei, Taiwan; [f]Clinical Data Center, Office of Data Science, Taipei Medical University, Taipei, Taiwan; [g]Research Center of Health Care Industry Data Science, College of Management, Taipei Medical University, Taipei, Taiwan; [h]Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan; [i]Graduate Institute of Data Science, College of Management, Taipei Medical University, Taipei, Taiwan; [j]International Ph.D. Program in Biotech and Healthcare Management, College of Management, Taipei Medical University, Taipei, Taiwan; [k]Division of Nephrology, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [l]Division of Nephrology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [m]TMU-Research Center of Urology and Kidney (TMU-RCUK), Taipei Medical University, Taipei, Taiwan; [n]International Center for Health Information Technology (ICHIT), Taipei Medical University, Taipei, Taiwan; [o]Taipei Medical University Ringgold Standard Institution – Center for Simulation in Medical Education, Taipei, Taiwan; [p]Ph.D. Program, School of Pharmacy, Taipei Medical University, Taipei, Taiwan; [q]Faculty of Pharmacy, Sanata Dharma University, Yogyakarta, Indonesia; [r]Office of Data Science, Taipei Medical University, Taipei, Taiwan

Keywords
SGLT2 inhibitors · Type 2 diabetes mellitus · Chronic kidney disease · Cardiovascular outcomes · 4-point major adverse cardiovascular events

Chih-Chung Shiao, Ching-Wen Chiu, Yu-Ming Chang, and Ming-Che Liu contributed equally to this work.
The article was not demonstrated in any prior presentation.

karger@karger.com
www.karger.com/ajn

Correspondence to:
Jason C. Hsu, jasonhsu@tmu.edu.tw

Karger

Abstract

Introduction: Diabetes, kidney disease, and cardiovascular disease have complex interactions and coexistences that significantly worsen a patient's overall health. Previous research results have shown that SGLT2i hypoglycemic drugs can not only effectively control blood sugar in diabetic patients but also protect the kidneys and heart. This study further focuses on diabetic patients with kidney disease to explore the effectiveness of using SGLT2i hypoglycemic drugs in avoiding heart-related complications or death. ***Methods:*** This is a multicenter retrospective cohort study using the Taipei Medical University Clinical Research Database (TMUCRD) as the data source. This study selected patients who suffered from both type 2 diabetes and chronic kidney disease from 1 January 2008 to 31 December 2020, as the research team. Integrated or separate 4-point major adverse cardiovascular events (4P-MACE) and mortality were the outcomes of this study. The Kaplan-Meier curves method and Cox proportional hazard regression analysis were used to explore the association between each influencing factor and the outcome. ***Results:*** A total of 5,005 patients with type 2 diabetes and CKD were included in this study, of which 524 patients were stably treated with SGLT2i, 3,952 patients were treated with DPP4i, and 529 patients were treated with TZD. The results showed that the SGLT2i user group had a significantly lower risk of 4P-MACE compared with the SGLT2i nonuser group (hazard ratio [HR]: 0.68, 95% CI [0.49, 0.95], $p = 0.024$). The SGLT2i group had a significantly lower risk of cardiovascular mortality compared with the DPP4i and TZD groups (HR: 0.37, 95% CI [0.21, 0.65], $p < 0.001$; HR: 0.42, 95% CI [0.20, 0.90], $p = 0.025$). ***Conclusion:*** This study found that for patients with both diabetes and kidney disease, SGLT2i is a better option than other oral hypoglycemic medications because it can significantly avoid the occurrence of heart-related complications. The results of this study can be used as a reference for clinical medication selection practice.

Introduction

Cardiovascular-kidney-metabolic syndrome (CKM syndrome) is a condition in which cardiovascular disease, kidney disease, and metabolic disorders such as diabetes coexist. There is a complex interaction between these conditions that results in a significant deterioration in the patient's overall health [1]. The prevalence of cardiovascular-kidney-metabolic syndrome is increasing with the aging of the population and changes in lifestyle, posing a huge challenge to the global medical system. More effective treatment strategies are a hot topic in recent clinical research. Approximately 40% of patients with type 2 diabetes will develop CKD during their lifetime, and some of these patients may even progress to end-stage renal disease (ESRD) [2]. These patients have a significantly higher risk of cardiovascular death and an increased risk of developing congestive heart failure (CHF) [3]. Furthermore, CKD treatment in patients with type 2 diabetes is complicated by changes in the clearance of medications, thereby exacerbating pharmacologic side effects [4]. Effective treatments for this population are particularly challenging, especially for those with severe renal impairment who are in the advanced stages of CKD or are on dialysis. In view of the serious impact of long-term hyperglycemia on glomerular function and considering the added complexity of inconsistent clearance of medications, the selection of hypoglycemic medications is quite important for this population.

Many previous large randomized clinical trials (RCTs), including DAPA-CKD, EMPA-KIDNEY, CREDENCE, and SCORED, have consistently demonstrated the renal protective effect of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with type 2 diabetes and CKD [5–8]. Additionally, other studies have highlighted the benefits of SGLT2i in reducing the risk associated with cardiac and renal disease in patients with type 2 diabetes [6, 7, 9]. Based on these positive findings of SGLT2i on cardiovascular and renal health, the clinical use of SGLT2i has so far been expanded to include not only patients with type 2 diabetes but also patients with CKD with or without diabetes. Current international clinical guidelines recommend the use of SGLT2i in patients with an estimated glomerular filtration rate (eGFR) greater than 25 mL/min/1.73 m^2 [10]. Although SGLT2i has been widely used, the mechanisms behind these benefits are not fully understood.

Despite positive results from previous large randomized controlled trials, the use of SGLT2i in patients with type 2 diabetes and CKD still presents special challenges. These challenges are particularly acute for patients with severely impaired renal function or those receiving dialysis, as these conditions may hinder drug clearance and efficacy [11]. In clinical practice, SGLT2i remains useful in groups with eGFR below recommended thresholds or who are on dialysis, a group that has mostly been excluded from previous randomized controlled trials. Although the primary mechanism of SGLT2i (lowering blood glucose through glomerular filtration) theoretically become less effective as renal function worsens [12], the usefulness of SGLT2i in current practice makes a thorough evaluation of the effectiveness of SGLT2i in patients with advanced CKD even more necessary.

Although previous clinical trials have provided valuable findings, gaps remain in understanding the cardiovascular effects of SGLT2i in patients with type 2 diabetes and advanced CKD, including dialysis patients [5, 13–16]. To bridge this knowledge gap, we conducted a retrospective study designed to provide important implications for the comparative effectiveness of SGLT2i.

Materials and Methods

Data Source and Study Design

This study was a multicenter retrospective cohort study. The data source is the Taipei Medical University Clinical Research Database (TMUCRD), which includes the medical records of 4.3 million patients [17]. TMUCRD covers various types of de-identified clinical data from three medical centers in northern Taiwan (Taipei Medical University Hospital, Wanfang Hospital, Shuang-Ho Hospital), such as outpatient and inpatient, emergency, laboratory test results, and surgery and prescription and other information. The protocol for this study was reviewed and approved by the Human Research Ethics Committee of Taipei Medical University (TMU-JIRB No. N202304052), and the requirement for patient informed consent was waived due to the de-identification of the data.

This study included patients with CKD who were newly diagnosed with type 2 diabetes from January 2008 to December 2020. These patients had stable treatment with one of the following glucose-lowering drugs: SGLT2i, dipeptidyl peptidase 4 inhibitors (DPP4i), or thiazolidinediones (TZD). Due to the limited use of other glucose-lowering drugs as first-line treatments compared to SGLT2i, DPP4i, or TZD, our analysis primarily compared SGLT2i with non-SGLT2i treatments, specifically including only DPP4i and TZD users.

Exclusion criteria were: (1) Patients previously exposed to SGLT2i, DPP4i, or TZD within 1 year before the start of the study; (2) Patients lacking complete demographic data, such as age and gender; (3) Patients under 18 years of age at the start of the study; (4) Patients without any medical records before the study's start date; (5) Patients with less than 90 days of follow-up after their initial diabetes diagnosis; (6) Patients who had received a kidney transplant. We intentionally did not exclude patients with a history of cardiovascular disease (CVD) events. This inclusion allowed us to assess the incidence of CVD following treatment with SGLT2i, DPP4i, or TZD among individuals both with and without prior CVD.

In order to improve comparability between different groups and control for potential influencing factors, we used a propensity score matching (PSM) method of up to 1:4 to compare the SGLT2i user group and the nonuser group (using DPP4i or TZD drugs). Matching criteria include: gender, age, history of heart disease, Charlson Comorbidity Index (CCI), previous use of biguanides, sulfonylureas or alpha-glucosidase inhibitors, eGFR, and the year of use of hypoglycemic drugs.

Drug Exposure and Control Groups

The experimental group of this study is the SGLT2i user group, and the research subjects must stably continue SGLT2i for more than 30 days. The control group consisted of patients who had been stably and continuously using DPP4i or TZD for more than 30 days. We further subdivided the SGLT2i nonuser group based on the first prescription observed in the patient. If a patient used a TZD prescription before taking DPP4i, he was classified as the TZD group.

Measurement for Study Variables

We extracted clinical and biochemical data for analysis. The demographic data collected included gender, age at the index date, and the duration of type 2 diabetes at the index date. We identified prior comorbidities using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis or procedure codes (see online suppl. sTable 1; for all online suppl. material, see https://doi.org/10.1159/000542132). The Charlson Comorbidity Index (CCI) was calculated to assess the health status. We also gathered medication histories for glucose-lowering drugs and other baseline laboratory data, including eGFR, hemoglobin A1c (HbA1c), and lipid profiles.

The index date was defined as the date of the first prescription of SGLT2i, DPP4i, or TZD between 2008 and 2020. Type 2 diabetes was identified by at least one ICD code recorded during outpatient or inpatient visits, along with a prescription for antidiabetic drugs. CKD was defined as having a baseline eGFR of less than 60 mL/min/1.73 m^2 or undergoing dialysis [18].

Study Outcome Assessment

The primary outcomes of this study were the incidence rates of 4-point major adverse cardiovascular events (4P-MACE) after the index date. These were defined as the occurrence of any of the following during an inpatient visit: (1) acute myocardial infarction, (2) hemorrhagic or ischemic stroke, (3) CVD-related death, or (4) hospitalization

due to CHF [19]. The CVD-related death category was a composite measure that included various cardiovascular-related fatalities such as sudden death where a noncardiac cause could not be ruled out, as well as deaths due to myocardial infarction, heart failure, cardiogenic shock, cerebrovascular events, or aortic diseases. The incidence of these events was evaluated at intervals of 1 year, 3 years, and 5 years post-index date. All outcomes were identified through the ICD-9-CM and ICD-10-CM diagnosis or procedure codes as listed in online supplementary sTable 2. Secondary outcomes focused on the individual components of the primary 4P-MACE metric. Follow-up for patients commenced with the initiation of treatment using either SGLT2 inhibitors (SGLT2i) or non-SGLT2i medications and continued until the occurrence of a primary outcome event or all-cause mortality. The study period concluded on December 31, 2021.

Statistical Approach

Descriptive statistics were used to summarize the baseline clinical and biochemical characteristics of patients treated with SGLT2i and non-SGLT2i. For baseline clinical characteristics, continuous variables were presented either as median (95% confidence interval [CI]/interquartile range) or mean (standard deviation [SD]), and categorical variables were expressed as total number (percentage). To compare continuous variables, we used the two-tailed Mann-Whitney U test. For categorical variables, the two-tailed χ^2 test with Yates' correction was applied to 2×2 contingency tables.

The primary analyses involved Cox regression analysis and Kaplan-Meier survival curves to assess the hazard ratios (HRs) and 95% CIs for each study outcome. The multivariate Cox regression models were adjusted for factors including age, duration of type 2 DM, CCI, and eGFR. Kaplan-Meier survival curves, representing the time-to-event data for each treatment group over specified time intervals, were plotted to visualize differences between groups.

All hypothesis testing was conducted on a two-sided basis, with statistical significance set at $\alpha = 0.05$. All statistical analyses were performed using R statistical software, version 4.0 (R Project for Statistical Computing). The period for data analysis spanned from January 15, 2023 to August 30, 2023.

Results

After initially screening 133,910 patients diagnosed with type 2 diabetes, we excluded several subgroups: 53,847 patients who did not receive any antidiabetic medications; 87,405 patients treated with antidiabetics other than SGLT2i, DPP4i, or TZD; 316 patients under 18 years of age; 42,503 patients with follow-up durations shorter than 3 months; 31,045 patients without CKD; and 72 patients with the same initial prescription date for DPP4i or TZD (Fig. 1).

Among the 5,005 patients with type 2 diabetes and CKD included in the study, 524 were treated with SGLT2i (308 men [58.8%] and 216 women [41.2%]; mean [SD] age, 66.4 [11.2] years; mean eGFR, 46.5 mL/min/1.73 m^2; mean HbA1c, 8.05%). A total of 3,952 patients newly initiated treatment with DPP4i (2,063 men [52.2%] and 1,889 women [47.8%]; mean [SD] age, 72.6 [12.1] years; mean eGFR, 35.5 mL/min/1.73 m^2; mean HbA1c, 7.61%), and 529 patients started on TZD (301 men [56.9%] and 228 women [43.1%]; mean [SD] age, 69.2 [11.2] years; mean eGFR, 39.7 mL/min/1.73 m^2; mean HbA1c, 7.91%) (online suppl. sTable 3). Compared with non-SGLT2i users, SGLT2i users tended to be younger and comprised a larger proportion of males, and with significantly lower comorbidities compared with non-SGLT2i users. They also had higher eGFRs, worse HbA1c levels, and lower cholesterol compared with non-SGLT2i users. These results are shown in online supplementary sTable 4.

Following PSM, we identified 524 patients with stable use of SGLT2i compared to 2,096 patients with stable use of non-SGLT2i (Table 1). SGLT2i users and non-SGLT2is were well matched except for several variables including age (66.4 vs. 68.0 in SGLT2is vs. non-SGLT2is), CCI (2.71 vs. 2.87 in SGLT2is vs. non-SGLT2is), and eGFR (46.5 vs. 43.8 in SGLT2is vs. non-SGLT2is). These variables were further adjusted in Cox regression analysis. In sTable 5, we demonstrated that SGLT2i users had significantly lower incidence of 4P-MACE (8.0 vs. 12.1% in SGLT2is vs. non-SGLT2is) and cardiovascular death (2.7 vs. 7.5% in SGLT2is vs. non-SGLT2is) (online suppl. sTable 5).

Primary Analyses: 4P-MACE

Table 2 showed the event rates and HRs of study outcomes associated with using SGLT2is versus non-SGLT2is. In the adjusted model Cox regression analysis, SGLT2i also significantly lowered the incidence of 4P-MACE as compared with the use of non-SGLT2i (HR: 0.68, 95% CI [0.49, 0.95], $p = 0.024$). The cumulative incidence of 4P-MACE after the first prescription of non-SGLT2i including TZD also revealed significances (online suppl. sFig. 1a–c.

Secondary Analysis: Cardiovascular Death

SGLT2i significantly reduced risk of cardiovascular death than the non-SGLT2i (HR: 0.38, 95% CI [0.21, 0.65], $p < 0.001$), DPP4i (HR: 0.37, 95% CI [0.21, 0.65],

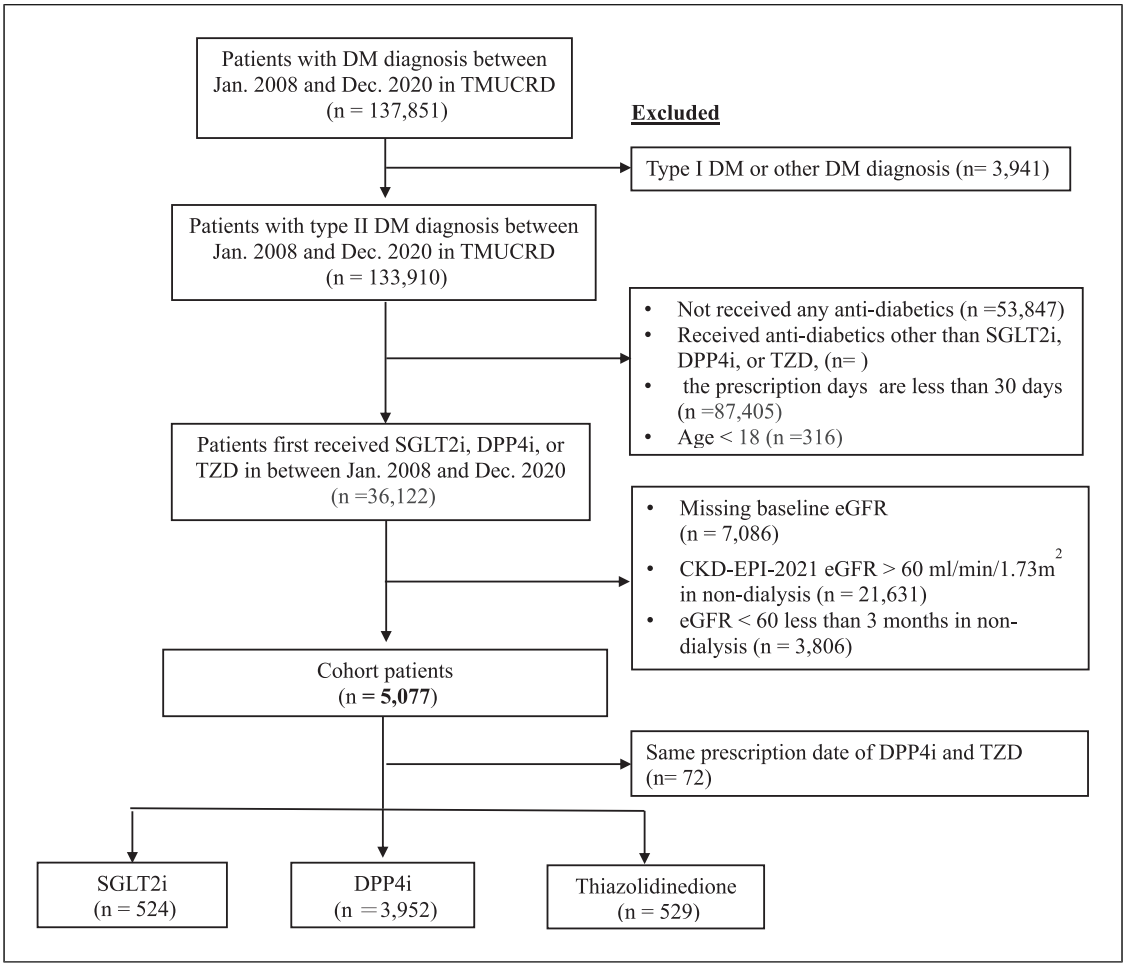

Fig. 1. Flowchart of study cohort selection.

$p < 0.001$), or TZD (HR: 0.42, 95% CI [0.20, 0.90], $p = 0.025$) (Table 3; online suppl. sFig. 2). However, SGLT2i did not show significance in reducing the risks of CHF hospitalization, MI, or stroke (online suppl. sTables 6–8; sFig. 3–5).

Subgroup Analysis

The subgroup analyses focusing on the incidence of 4P-MACE generally showed that SGLT2i use was associated with a significantly reduced risk of 4P-MACE compared to non-SGLT2i use among male patients (HR: 0.61, 95% CI [0.39, 0.95], $p = 0.031$) (online suppl. sTable 9). Additionally, among patients who had history of heart problems, those treated with SGLT2i exhibited a substantially lower risk of developing 4P-MACE than those treated with non-SGLT2i (HR: 0.38, 95% CI [0.15, 0.97], $p = 0.043$). To be noted, among patients who had no received dialysis, those treated with SGLT2i revealed a significantly lower risk of developing 4P-MACE than those treated with non-SGLT2i (HR: 0.71, 95% CI [0.50, 0.99], $p = 0.046$).

Discussion

Our study utilized an extensive database containing records from 3.5 million patients to provide a real-world analysis of the comparative effectiveness of SGLT2is relative to other oral antidiabetic drugs (OADs). The results indicated a significant reduction in the incidence of 4P-MACE among patients with type 2 diabetes and CKD treated with SGLT2is compared to those treated with non-SGLT2i, especially with TZDs. Furthermore, SGLT2is were also found to significantly decrease the incidence of cardiovascular mortality compared to DPP4is and TZDs.

Table 1. Baseline characteristics of study cohorts after propensity score matching*

	SGLT2i (*N* = 524)	Non-SGLT2i (*N* = 2,096)	SD	*p* value
Age at index date, mean (SD), years	66.4 (11.2)	68.0 (12.0)	0.133	0.00539
Male, *N* (%)	308 (58.8)	1,216 (58.0)	0.015	0.789
Duration of diabetes at index date, mean (SD), days	852 (1,000)	887 (1,010)	0.035	0.47
Dialysis status, *N* (%)	25 (4.8)	98 (4.7)	0.004	1
CKD staging, *N* (%)				
Stage 3	429 (81.9)	1,679 (80.1)	0.112	0.122
Stage 4	59 (11.3)	236 (11.3)		
Stage 5	11 (2.1)	83 (4.0)		
ESRD	25 (4.8)	98 (4.7)		
Body mass index (BMI), kg/m^2				
Mean (SD)	27.0 (5.99)	26.8 (4.82)	0.046	0.755
Median [min, max]	26.7 [0.312, 43.5]	26.0 [16.0, 46.7]		
Missing, *N* (%)	459 (87.6)	1,789 (85.4)		
Comorbidities, *N* (%)				
Hyperlipidemia	243 (46.4)	966 (46.1)	0.006	0.945
Hypertension	296 (56.5)	1,226 (58.5)	0.041	0.434
Heart problem	67 (12.8)	333 (15.9)	0.083	0.114
Chronic pulmonary disease	9 (1.7)	69 (3.3)	0.101	0.0796
Renal disease	65 (12.4)	236 (11.3)	0.035	0.51
Peptic ulcer disease	18 (3.4)	94 (4.5)	0.054	0.346
Any malignancy	6 (1.1)	73 (3.5)	0.156	0.0079
Liver disease	35 (6.7)	117 (5.6)	0.046	0.392
Anemias	24 (4.6)	83 (4.0)	0.031	0.604
Charlson Comorbidity Index (CCI)				
Mean (SD)	2.71 (1.48)	2.87 (1.49)	0.103	0.0343
Median [min, max]	3.00 [0, 9.00]	3.00 [0, 8.00]		
GLDs prescribed in year before index date, *N* (%)				
Biguanides	195 (37.2)	729 (34.8)	0.051	0.321
Sulfonylureas	112 (21.4)	469 (22.4)	0.024	0.664
Alpha-glucosidase inhibitors	40 (7.6)	152 (7.3)	0.015	0.837
GLP-RAs	0 (0)	4 (0.2)	0.062	0.707
Insulins	63 (12.0)	250 (11.9)	0.003	1
Other	20 (3.8)	135 (6.4)	0.119	0.0297
Medication history in year before index date, *N* (%)				
Laxatives	38 (7.3)	173 (8.3)	0.039	0.489
Antithrombotic	157 (30.0)	516 (24.6)	0.120	0.0145
Antianemic agents	30 (5.7)	128 (6.1)	0.016	0.823
Cardiac therapy	67 (12.8)	159 (7.6)	0.174	<0.001
Diuretics	67 (12.8)	294 (14.0)	0.033	0.553
Purine derivatives	38 (7.3)	205 (9.8)	0.091	0.089
Beta-blocking agents	129 (24.6)	475 (22.7)	0.047	0.359
Calcium channel blockers	102 (19.5)	450 (21.5)	0.048	0.364
RAAS agents	189 (36.1)	692 (33.0)	0.061	0.233
Lipid-modifying agents	179 (34.2)	659 (31.4)	0.057	0.276
Antigout	54 (10.3)	201 (9.6)	0.027	0.637
Laboratory test, mean (SD)				
eGFR, mL/min/1.73 m^2	46.5 (15.4)	43.8 (15.5)	0.175	<0.001
HbA1C	8.05 (1.84)	7.66 (1.67)	0.224	<0.001
Missing, *N* (%)	245 (46.8)	412 (19.7)		
Fasting glucose, mg/dL	162 (62.3)	149 (62.4)	0.199	0.00337
Missing, *N* (%)	271 (51.7)	413 (19.7)		

Table 1 (continued)

	SGLT2i (*N* = 524)	Non-SGLT2i (*N* = 2,096)		SD	*p* value
Creatinine, mg/dL	1.55 (0.674)	1.80 (1.29)		0.247	<0.001
Missing, *N* (%)	242 (46.2)	245 (11.7)			
Total cholesterol, mg/dL	174 (43.1)	184 (54.7)		0.199	0.00476
Missing, *N* (%)	327 (62.4)	867 (41.4)			
Triglyceride, mg/dL	200 (141)	188 (144)		0.088	0.207
Missing, *N* (%)	292 (55.7)	292 (55.7)	577 (27.5%)		

GLD, glucose-lowering drugs; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SD, standard difference. *Propensity score matching is adjusted for age, gender, chronic kidney disease staging, previous heart problem, previous renal diseases, Charlson Comorbidity Index (CCI), past medication history of biguanides, sulfonylureas, or alpha-glucosidase inhibitors, eGFR, and prescription year of the glucose-lowering drugs (SGLT2i, DPP4i, or TZD).

Table 2. 4P-MACE outcomes in patients with SGLT2i or other hypoglycemic agents in propensity-matched cohort (1:4)

	Events, No.	Participant-years of follow-up	Incidence rate (events/100 participants)	Crude model		Adjusted model[1]	
				HR (95% CI)	*p* value	HR (95% CI)	*p* value
4P-MACE							
SGLT2i	42	2,842	8.0				
vs. non-SGLT2i	254	11,433	12.1	0.65 (0.47, 0.90)	0.010	0.68 (0.49, 0.95)	0.024
SGLT2i	42	2,842	8.0				
vs. DPP4i	253	11,430	12.1	0.65 (0.47, 0.91)	0.012	0.72 (0.52, 1.00)	0.053
SGLT2i	26	1,615	12.3				
vs. TZD	40	1,556	19.0	0.54 (0.34, 0.85)	0.008	0.56 (0.35, 0.88)	0.012

DPP4i, dipeptidyl peptidase 4 inhibitor; MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones. [1]Adjusted for age, duration of type 2 DM, Charlson Comorbidity Index (CCI), and eGFR.

Additionally, the subgroup analyses showed that male patients, those with a history of heart problems, and those without dialysis experienced significantly greater cardiovascular benefits from SGLT2i than non-SGLT2i. These findings underscore the potential of SGLT2is as a preferred therapeutic option for reducing cardiovascular risks in these high-risk population. To be noted, cardiovascular benefits of SGLT2i among patients with dialysis did not show significantly greater than non-SGLT2i. However, due to the relatively small sample size, the efficacy of SGLT2i in this patient population still remains unclear.

The extensive scope of our dataset, which includes data from a diverse range of patient demographics, comorbidities, and concurrent medications, offers a depth of understanding that traditional RCTs are often unable to achieve. Given that diabetes management is a lifelong journey, our retrospective analysis facilitates the exploration of long-term trends and outcomes. This approach provides valuable insights into the durability and sustained effectiveness of various antidiabetic therapies. Critically, our study incorporates patients with advanced CKD, comparing the effectiveness of SGLT2is with other OADs.

By examining the long-term cardiovascular outcomes across a broad patient cohort, our aim is to highlight nuanced differences in treatment efficacy and safety profiles between SGLT2is and other OADs. DPP4is, known for their established cardiovascular safety, serve as a standard comparator in our study [20]. They are typically recommended as second-line or adjunct therapies in the treatment of type 2 diabetes, making them an appropriate benchmark for assessing the performance of other OAD classes. Furthermore, the cardiovascular risks

Table 3. Cardiovascular death outcomes in patients with SGLT2i or other hypoglycemic agents in propensity-matched cohort (1:4)

	Events, No.	Participant-years of follow-up	Incidence rate (events/100 participant-years)	Crude model		Adjusted model[1]	
				HR (95% CI)	*p* value	HR (95% CI)	*p* value
Cardiovascular death							
SGLT2i	14	3,001	2.7				
vs. non-SGLT2i	158	11,993	7.5	0.34 (0.19, 0.59)	<0.001	0.38 (0.21, 0.65)	<0.001
SGLT2i	14	3,001	2.7				
vs. DPP4i	160	11,932	7.6	0.32 (0.18, 0.57)	<0.001	0.37 (0.21, 0.65)	<0.001
SGLT2i	10	1,725	4.7				
vs. TZD	23	1,696	10.9	0.42 (0.20, 0.89)	0.023	0.42 (0.20, 0.90)	0.025

DPP4i, dipeptidyl peptidase 4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones. [1]Adjusted for age, duration of type 2 DM, Charlson Comorbidity Index (CCI), and eGFR.

or benefits associated with TZDs have not been definitively characterized, prompting their inclusion as comparators to provide a clearer picture of their clinical utility relative to SGLT2is and DPP4is.

Previous clinical trials have investigated the effects of SGLT2is on CVD prognosis in patients with type 2 diabetes and CKD. Notably, a meta-analysis of seven RCTs demonstrated that SGLT2is reduced the risk of 3-point major adverse cardiovascular events by 21% and hospitalization due to heart failure by 39% [21]. Prominent trials such as the CANVAS Program, DECLARE-TIMI 58, and EMPA-REG OUTCOME reported reductions in 3-point major adverse cardiovascular event of 30%, 8%, and 12%, respectively [14–16]. Focused studies on the effects of SGLT2is in patients with established CKD, such as EMPA-KIDNEY, DAPA-CKD, CREDENCE, and SCORED [5–8], have begun, with DAPA-CKD and EMPA-KIDNEY including both CKD patients with and without type 2 diabetes, showing cardiorenal benefits across these groups.

Given this robust evidence, recent KDIGO guidelines have elevated SGLT2is to a first-line therapy status for patients with type 2 diabetes and CKD [18]. This endorsement is supported by consistent findings across RCTs that highlight SGLT2is' effectiveness in managing blood glucose levels, reducing CKD progression, and lowering CVD incidence. However, the stringent inclusion criteria typically used in RCTs can limit the generalizability of these results to broader, real-world populations. This is particularly true for patients with advanced CKD or those on dialysis, where the pharmacokinetics of SGLT2is might diminish their effectiveness in managing cardiovascular outcomes. Moreover, the preference for SGLT2is over other hypoglycemic agents in clinical settings may not fully reflect the comparative effectiveness as seen in RCTs. Therefore, real-world studies that assess the cardiorenal effects of SGLT2is relative to other hypoglycemic agents like DPP4is or TZDs are crucial for confirming these benefits in everyday clinical practice.

DPP4is are frequently used as a comparator in studies involving SGLT2is, primarily because of their relatively neutral impact on hypoglycemia, weight gain, and CVDs. Extensive research, including multiple network meta-analyses [22, 23] and observational studies [24–31], has shown that SGLT2is reduce the risk of MACE more effectively than DPP4is in patients with type 2 diabetes. Despite these findings, patients with type 2 diabetes and CKD are often underrepresented in such studies. Yang et al. conducted a network meta-analysis that specifically evaluated CVD outcomes associated with SGLT2is, DPP4is, and other antidiabetic drugs in the type 2 diabetes and CKD patient population [32]. This analysis found that SGLT2is reduced cardiovascular risk by approximately 20% in this group. However, a direct comparison of SGLT2is and DPP4is in real-world settings remains scarce, indicating a significant gap in the current research landscape.

Therefore, our study utilized data from the database and found that SGLT2is significantly reduced cardiovascular mortality, though they did not show a significant reduction in the incidence of 4P-MACE or hospitalizations for CHF compared with DPP4is. These findings align with recent research, which also reported no significant differences in cardiovascular outcomes among patients with stage 3 CKD and type 2 diabetes when

comparing SGLT2is to DPP4is [33]. The inhibition of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) breakdown by DPP4is, which has been shown to markedly reduce the risk of MACE in type 2 diabetes patients, suggests that DPP4is may also offer a degree of cardiovascular protection in patients with type 2 diabetes and advanced CKD.

Regarding TZDs, a systematic review and meta-analysis indicated that TZD users experienced a 7% reduction in the risk of cardiovascular death among patients with type 2 diabetes, which contrasts with a 14% reduction observed in SGLT2i users [34]. Additionally, Chan et al. [35] conducted an observational cohort study demonstrating that SGLT2is significantly lowered the risk of MACE in patients with type 2 diabetes and CKD. However, their study lacked a direct comparison of cardiovascular effectiveness between SGLT2is and other antidiabetic agents. In contrast, our study provided such comparative insights, revealing that SGLT2i users had a significantly lower risk of developing 4P-MACE and cardiovascular mortality compared to those using TZDs. These findings align with those of previous studies, highlighting the superior cardiovascular benefits of SGLT2is in this patient population.

Furthermore, the subgroup analyses revealed that patients with specific factors such as male, history of heart problems and without dialysis experienced significantly greater cardiovascular benefits from SGLT2i users compared to non-SGLT2i users within CKD. This finding suggests that while SGLT2is generally perform comparably to other antidiabetic agents, they may offer distinct advantages for certain populations. Real-world responses in patients with CKD can vary from those observed in RCTs, potentially due to differences in patient demographics, comorbid conditions, and treatment adherence. Especially in patients with ESRD or dialysis, who were mainly excluded from previous RCTs, our results demonstrated that cardiovascular effectiveness of SGLT2i was similar with non-SGLT2i. Given these variations, it is crucial to conduct further observational studies. By gathering more comprehensive real-world data, we can better tailor SGLT2i treatment approaches to meet the specific needs of different subgroups within the advanced CKD population.

Our study has several limitations. First, as a retrospective analysis, it is inherently constrained by potential data quality issues and selection bias. However, we demonstrated the clinical condition of SGLT2i application in patients with severe CKD and dialysis, who were not seen in the previous RCTs. Second, while the TMUCRD does not contain comprehensive blood pressure and smoking history information, we included hypertension and chronic pulmonary disease, associated with smoking exposure. Lastly, the scope of our database, while substantial, is still relatively limited in size and may not fully represent the broader, diverse population of patients with type 2 diabetes, and CKD. Nevertheless, we included all the stable SGLT2i users in our database as possible as we can to minimize the possible bias and provide comprehensive analysis. The proportion of SGLT2i use in Chinese population was consistent with previous publications [29, 31]. Despite the relatively smaller sample size compared to other antiglycemic agents, it remains crucial to explore the real-world effectiveness of SGLT2i in patients with T2DM and CKD.

Conclusion

Our results demonstrated a notable disparity in the occurrence of 4P-MACE in patients with type 2 diabetes and CKD between the use of SGLT2i and TZD. The cardiovascular benefits of SGLT2i were not significantly greater than non-SGLT2i in patients with ESRD or dialysis. However, among male patients or those with history of heart problems, SGLT2i showed greater effectiveness than non-SGLT2i. While RCTs contribute significantly to our understanding of diabetes treatments, a comprehensive retrospective study is essential to supplement and broaden these findings to real-world scenarios. We revealed nuanced insights into the relative advantages of SGLT2is versus other OADs in advanced CKD, ultimately guiding clinical practice and informing personalized treatment strategies for individuals with T2DM and advanced CKD.

Statement of Ethics

All data were anonymized and de-identified before the analysis. The protocol for this study was reviewed and approved by the Human Research Ethics Committee of Taipei Medical University (TMU-JIRB No. N202304052), and the requirement for patient informed consent was waived due to the de-identification of the data.

Conflict of Interest Statement

All authors have no conflicts of interest or financial ties to disclose.

Funding Sources

The research was supported by Saint Mary's Hospital Research Fund (SMHRF112001). The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Conception or design: Y.-M.C., M.-C.L., and J.C.H. Acquisition, analysis, or interpretation of data: C.-C.S., C.-W.C., P.-A.N., T.-P.P., C.H.S., M.-H.H., and H.-H.C. Drafting the work or revising: C.-C.S., C.-W.C., Y.-M.C., M.-C.L., C.-T.L., C.-W.H., and J.C.H. Final approval of the manuscript: Y.-M.C., M.-C.L., C.-T.L., C.-W.H., and J.C.H.

Data Availability Statement

The authors obtained data from the Taipei Medical University Clinical Research Database (TMUCRD). All data generated or analyzed during this study are included in the published article (and its online supplementary files). No applicable resources were generated or analyzed during the current study. Further inquiries can be directed to the corresponding author.

References

1 Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, et al. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a scientific statement from the American Heart Association. Circulation. 2023;148(20):1636–64. https://doi.org/10.1161/CIR.0000000000001186
2 Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016;12:73–81. https://doi.org/10.1038/nrneph.2015.173
3 Papademetriou V, Lovato L, Doumas M, Nylen E, Mottl A, Cohen RM, et al. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. Kidney Int. 2015;87(3):649–59. https://doi.org/10.1038/ki.2014.296
4 Bakris GL. Recognition, pathogenesis, and treatment of different stages of nephropathy in patients with type 2 diabetes mellitus. Mayo Clin Proc. 2011;86(5):444–56. https://doi.org/10.4065/mcp.2010.0713
5 Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med. 2021;384(2):129–39. https://doi.org/10.1056/NEJMoa2030186
6 Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46. https://doi.org/10.1056/NEJMoa2024816
7 The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388(2):117–27. https://doi.org/10.1056/NEJMoa2204233
8 Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306. https://doi.org/10.1056/NEJMoa1811744
9 Cherney DZI, Ferrannini E, Umpierrez GE, Peters AL, Rosenstock J, Carroll AK, et al. Efficacy and safety of sotagliflozin in patients with type 2 diabetes and severe renal impairment. Diabetes Obes Metab. 2021;23(12):2632–42. https://doi.org/10.1111/dom.14513
10 Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 inhibitors in patients with CKD: expanding indications and practical considerations. Kidney Int Rep. 2022;7(11):2546–7. https://doi.org/10.1016/j.ekir.2022.08.016
11 Shrishrimal K, Hart P, Michota F. Managing diabetes in hemodialysis patients: observations and recommendations. Cleve Clin J Med. 2009;76(11):649–55. https://doi.org/10.3949/ccjm.76a.09054
12 Cherney DZI, Cooper ME, Tikkanen I, Pfarr E, Johansen OE, Woerle HJ, et al. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. Kidney Int. 2018;93(1):231–44. https://doi.org/10.1016/j.kint.2017.06.017
13 Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med. 2020;383(15):1425–35. https://doi.org/10.1056/NEJMoa2004967
14 Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57. https://doi.org/10.1056/NEJMoa1611925
15 Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57. https://doi.org/10.1056/NEJMoa1812389
16 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28. https://doi.org/10.1056/NEJMoa1504720
17 Nguyen P-A, Hsu M-H, Chang T-H, Yang HC, Huang CW, Liao CT, et al. Taipei Medical University Clinical Research Database: a collaborative hospital EHR database aligned with international common data standards. BMJ Health Care Inform. 2024;31(1):e100890. https://doi.org/10.1136/bmjhci-2023-100890
18 Kidney Disease Improving Global Outcomes KDIGO Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98(4S):S1–115. https://doi.org/10.1016/j.kint.2020.06.019
19 Khera R, Schuemie MJ, Lu Y, Ostropolets A, Chen R, Hripcsak G, et al. Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM): a protocol for a series of multinational, real-world comparative cardiovascular effectiveness and safety studies. BMJ Open. 2022;12(6):e057977. https://doi.org/10.1136/bmjopen-2021-057977
20 Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA. 2019;321(1):69–79. https://doi.org/10.1001/jama.2018.18269
21 Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, 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. 2019;21(5):1237–50. https://doi.org/10.1111/dom.13648
22 Lee G, Oh SW, Hwang SS, Yoon JW, Kang S, Joh HK, et al. Comparative effectiveness of oral antidiabetic drugs in preventing cardiovascular mortality and morbidity: a network meta-analysis. PLoS One. 2017;12(5):e0177646. https://doi.org/10.1371/journal.pone.0177646

23 Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. JAMA. 2018;319(15):1580–91. https://doi.org/10.1001/jama.2018.3024
24 Filion KB, Lix LM, Yu OH, Dell'Aniello S, Douros A, Shah BR, et al. Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. BMJ. 2020;370:m3342. https://doi.org/10.1136/bmj.m3342
25 Xie Y, Bowe B, Gibson AK, McGill JB, Maddukuri G, Yan Y, et al. Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of kidney outcomes: emulation of a target trial using health care databases. Diabetes Care. 2020;43(11):2859–69. https://doi.org/10.2337/dc20-1890
26 Kohsaka S, Lam CSP, Kim DJ, Cavender MA, Norhammar A, Jørgensen ME, et al. Risk of cardiovascular events and death associated with initiation of SGLT2 inhibitors compared with DPP-4 inhibitors: an analysis from the CVD-REAL 2 multinational cohort study. Lancet Diabetes Endocrinol. 2020;8(7):606–15. https://doi.org/10.1016/S2213-8587(20)30130-3
27 Pasternak B, Wintzell V, Melbye M, Eliasson B, Svensson AM, Franzén S, et al. Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: scandinavian cohort study. BMJ. 2020;369:m1186. https://doi.org/10.1136/bmj.m1186
28 Patorno E, Goldfine AB, Schneeweiss S, Everett BM, Glynn RJ, Liu J, et al. Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study. BMJ. 2018;360:k119. https://doi.org/10.1136/bmj.k119
29 Peng ZY, Yang CT, Kuo S, Wu CH, Lin WH, Ou HT. Restricted mean survival time analysis to estimate SGLT2i-associated heterogeneous treatment effects on primary and secondary prevention of cardiorenal outcomes in patients with type 2 diabetes in taiwan. JAMA Netw Open. 2022;5(12):e2246928. https://doi.org/10.1001/jamanetworkopen.2022.46928
30 Persson F, Nyström T, Jørgensen ME, Carstensen B, Gulseth HL, Thuresson M, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: a multinational observational study. Diabetes Obes Metab. 2018;20:344–51. https://doi.org/10.1111/dom.13077
31 Yang CT, Peng ZY, Chen YC, Ou HT, Kuo S. Cardiovascular benefits with favorable renal, amputation and hypoglycemic outcomes of SGLT-2 inhibitors in type 2 diabetes from the Asian perspective: a population-based cohort study and systematic review. Front Endocrinol. 2022;13:836365. https://doi.org/10.3389/fendo.2022.836365
32 Yang Q, Lang Y, Yang W, Yang F, Yang J, Wu Y, et al. Efficacy and safety of drugs for people with type 2 diabetes mellitus and chronic kidney disease on kidney and cardiovascular outcomes: a systematic review and network meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2023;198:110592. https://doi.org/10.1016/j.diabres.2023.110592
33 Rhee JJ, Han J, Montez-Rath ME, Kim SH, Cullen MR, Stafford RS, et al. Cardiovascular outcomes associated with prescription of sodium-glucose co-transporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in patients with diabetes and chronic kidney disease. Diabetes Obes Metab. 2022;24(5):928–37. https://doi.org/10.1111/dom.14657
34 Shi Q, Nong K, Vandvik PO, Guyatt GH, Schnell O, Rydén L, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2023;381:e074068. https://doi.org/10.1136/bmj-2022-074068
35 Chan GC, Ng JK, Chow KM, Szeto CC. SGLT2 inhibitors reduce adverse kidney and cardiovascular events in patients with advanced diabetic kidney disease: a population-based propensity score-matched cohort study. Diabetes Res Clin Pract. 2023;195:110200. https://doi.org/10.1016/j.diabres.2022.110200